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Codex Alternus

A Research Collection of

Alternative and Complementary Treatments for
Schizophrenia, Bipolar Disorder and
Associated Drug-induced Side Effects

Alternative Mental Health Research

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Audience. *This paper is for adults with mental health issues and their supporters. The focus is on non-drug approaches since these are often given insufficient priority and may well offer the best hope for recovery. With this paper, readers can better understand, select and enact a set of approaches with their chosen mental healthcare providers and supporters that represent their unique recovery plan.*

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Disclaimer. *This paper is for educational purposes only and is not intended to replace the advice of health care practitioners. The views expressed in this paper are the author's. They do not necessarily represent those of the paper's reviewers and contributors or their affiliate organizations, nor does the publishing of this paper constitute endorsement by any person or group. Studies, information and links referenced in this paper may contain inaccuracies and such references do not represent endorsement by the author or associates. This paper is not intended to diagnose or prescribe treatment for any illness or disorder. Anyone already undergoing physician- prescribed therapy should seek the advice of their doctor before altering treatment. We make no claims of therapy efficacy for individual situations and although we have worked diligently, mistakes may be included.*

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Introduction

Codex Alternus is a research collection of citations and summaries of articles on alternative and complementary therapies for schizophrenia, bipolar disorders, and associated drug-induced side effects. It represents old, and new, novel and experimental therapies that researchers and clinicians may whant to utilize in their practicle or laboratory, or clinical trial. Laypersons, and patients may also benefit from therapies listed in the Codex if caution is taken, and proper research is conducted before utilizing chosen therapy. The Codex citations and summaries are set up by therapy class and disease category together. It has a table of contents and index included. Soon, there will be an added abreveations and symbols section, glossary, and authors index. Most of the citations at this time are from PubMed.

PubMed is a database of more than 23 million citations for biomedical literature from MEDLINE, life science journals, and online books. This document is a compilation of PubMed citations that meet the following criteria:

- **Time.** Citations occur between January 1930 to January 2015

- **Alternative psychiatric therapy focus.** Citations are for studies that demonstrate or suggest the efficacy of alternative and complementary psychiatric treatments—those treatments that fall outside the domains of pharmaceuticals, counseling, and other mainstream psychiatric therapies.

- **Psychiatric and EPS diagnoses.** The studies associated with the citations address one or more of the following psychiatric diagnoses: schizophrenia, schizoaffective disorder, typical psychosis and tardive psychosis, bipolar I disorder, bipolar II disorder, and extrapyramidal symptoms including tardive dyskenisia, orofacial dyskenisia, tardive dystonia, akathisia, parkinsonian--tremors, motor tics, and tremors.

- **Drug-induced Side Effects.** The studies include citations on alternative treatments for neuroleptic-malignant syndrome, metabolic syndrome, insulin resistance, cardiac disease prevention, sexual dysfunction prevention, weight gain prevention, polydipsia treatment, dyslipidemia treatment, homocysteine treatment, hypersalvation treatments, hyperprolactinemia treatments, and amenorrhea treatments, drug-induced constipation, GI upset, nausea and vomiting treatments, and valproic acid toxicity prevention.

- **Caution:** *The citations are for clinical trials and case studies with positive outcomes only. Due to the volume of this compilation this document does not review the negative criticisms some therapies may have received in some reported clinical trials or case studies in medical literature. Author suggest before a patient undertakes using any therapy listed in this document they should conduct their own research and consult a qualified holistic practitioner or integrative psychiatrist or integrative psychologist first.*

Schizophrenia affects approximately 24 million people worldwide and bipolar manic depression affects approximately 5.5 million people in the United States alone. The primary treatments are pharmaceutical drugs, and psychotherapy with little emphasis on alternative and complementary therapies.

Tradtionally in the mental hospitals, outpatient programs and day rehabilitation programs therapies such as art therapy, poetry, music therapy, exercise, weight lifting, tai chi, gardening, games, breathing exercises, sound therapy, progressive muscle relaxation, occupational therapy, family therapy, group reading therapy, and other psychological therapies are incorporated. Outside the traditional mental health system there are holistic psychiatrists, and integrative psychologists, naturopathic doctors, and nutrtionalists who have clientel who have psychotic disorders and prefer natural therapies. Many of these doctors are ortomolecular physcians in the United States and Canada. However, different cultures treat psychotic disorders differently. The Chinese use a lot of traditional herbal decoctions and acupuncture as well as Western medicine to treat schizophrenia.

Extrapyramidal symptoms can occur in up to 75% of patients who take typical antipsychotics with tardive dyskenisia occurring in up to about 20% of patients who take antipsychotics. The primary treatments of extrapyramidal symptoms are benzodiazepines for akathisia, anticholinergic medication for pseudoparkinsons, and acute dystonic reactions, and tetrabenazine, beta blockers, deep brain stimulation, and antipsychotic drug withdrawal for tardive dyskenisia. Natural medicines other than vitamin E are rarely used by physicians to treat extrapyramidal symptoms. Yet there are numerous natural remedies such as cholinergic supplements, antioxidants, amino acids, and osteopathic and chiropractic work that can be used to treat extrapyramidal symptoms including tardive dyskenisia. Therapies for these disorders are contained in this document.

Why we don't often hear of the majority of consumers using CAM therapies:

Most orthodox psychiatrists, general practitioners and psychologists who work in the field of mental health may only recommend, in clinical practice --a few of the natural therapies listed in this document. Though these clinicans may suggest the use of mind-body therapies, exercise, art therapy, poetry, music therapy, and dietary modifications, they often don not suggest the use of herbs and nutraceticals. Many orthodox mental health professionals may often not recommend the patient, or client take supplements in fear of drug interactions. Most often supplements taken with psychotropic drugs have few interactions. However, with herbs there can be some limited interactions, though most are generally safe.

These clinicans may have the fear of losing clientele due to the ease of procurement of supplements, which may alleviate symptoms w/o standard psychiatric intervention. However, often this lack of recommendations may have to do with the doctors own malpractice insurance which prohibits the prescribing of herbal remidies and supplements.These restrictions often are not in best interest in the recovery of the patient. Psychoeducation classes offered in the mental health day rehabilitation and outpatient services will not endorse, or educate their consumers on the benefits of using natural medicine. There are several reasons for this; fear of interactions, out of professional area of expertise and professional biases due to the fact their staff is trained in psychiatric nursing, social work, and psychology. Often some of these professionals will downplay the benefits to their consumers and suggest their consumers talk with their orthodox

allopathic physicians and psychiatrists before using supplements and herbal remidies. Often these doctors know nothing about nutrition or using natural medicine. Outpatient programs and day rehabilitation services sometimes may avoid natural medicine because of loyalty to members of their psychiatric business community who perform standard services and fund their non-profit groups and organizations. Often with some organizations there is pharmaceutical drug money being donated which pushes out the promotion of other competing therapies. Outpatient services, day rehabilitation services and inpatient psychiatric care will all often keep the patient deprived of critical lifesaving information and from getting quality medical care from integrative practitioners and holistic physicians which keeps the patient compliant to psychotropic drugs and standard services.

Drug compliance is often tied with the notion of patient and public safety which often implies alternatives and complementary medicine is not safe—yet there are few documented cases of tardive dyskenisia associated with the use of vitamins combined with psychotropics. Psychotropics deplete nutrients which are vital to mental health and are ordinarily supplemented safely. Psychotropics and nutrients work well together and combined with antioxidants this can reduce the toxic effects of the drugs making drug compliance safer. Many alternatives do not involve the use of supplements and herbs and should always be fully endorsed. These include; meditation, yoga, exercise, art therapy, music, creative writing, poetry, etc. Further, there are no cases of homicide directly induced by the use of drug-free therapies—yet there are hundreds of thousands of cases of violence, suicide and homicide associated with psychotropics.

More about the Codex Alternus:

The references listed contain conclusions or highlights of select articles on natural treatments and alternatives and complementary treatments that initially started with a selected PubMed search of over 355,000 citations. To complete the whole document additional research was needed to compile this selection of citations which took approximately 1800 hours to complete. This document contains nearly 750 citations and abstract and article summaries which will not be up dated until 2016. It is intended this compilation will be added to the upcoming book Codex Alternus.

This paper is primarily intended for the use by clinicians and researchers due to its complex language and lack of detail on how to use these therapies. It can be useful to those with psychiatric diagnosis and their supporters if further individual study is undertaken. It is a valuable resource for those seeking clinical efficacy of alternative treatments for schizophrenia and bipolar disorder that choose to not to use psychiatric drugs. This resource is also useful for those who are forced used psychiatric drugs, and are aware of iatrogenic harm, and are interested in methods in reducing harm, or treating dyskinesia's, dystonia, akathisia, atypical antipsychotic-induced weight gain, treating dopaminergic supersensitivity. However, some of these therapies have only been utilized in research settings—clinical outcome may vary, and clinical use may be limited for some therapies. Further, there are several therapies which can only be obtained by doctors' prescription and made in a compound pharmacy. Others may have to be ordered through special pharmacies or chemical suppliers. It is mostly advisable for many patients seeking use of supplemental and herbal forms of therapy to consult the advice of an experienced clinician before attempting to use these therapies. Further, some of these therapies have had negative clinical trials that have shown them insufficient in the majority of patients tested;

however they have demonstrated positive results in some clinical trials, and case reports, so they have been included in this document.

- **Intent of this document for clinicians and researchers;** this document was designed to inform clinicans and researchers on as many possible alternative and complementary options available to the professional as possible. It may further enhance the clinicians' therapeutic toolbox. Further research may be needed to evaluate each therapy and its safety and therapeutic efficacy. It may also aid a reference tool for researchers doing clinical trials and clinical research.

This document contains references to Ayurvedic medicine, Kampo medicine, and Chinese traditional medicine as well as alternative medicine used in the Western world such as orthomolecular medicine. Other non-invasive therapies such as neurofeedback, biofeedback, dark therapy, and sound therapy, etc. have been included. There are also neuroprotective treatments that can be found in current psychiatric and medical scientific literature, including treatment to reverse structural atrophy of the brain, and help reduce the oxidative damages of neuroleptic drugs. There is a very long section on natural herbal and peptide antipsychotics in the document. These are some of the many alternative and natural treatments that improve the outcome of schizophrenia and bipolar disorder that have been validated by scientific literature. All these and more are included in this document.

The author does not endorse any specific methods outlines in this document. To make best use of this document search Google Scholar or use your local public library, college library, or university medical school library to order the document you are interested in by interlibrary loan. Often this can be done from your home via the internet from the libraries home page via WoldCat and a library card ID number. If you have a medical school, or nursing school near your residence or place of business, it would be recommended if you are acquiring numerous articles to use their databases for free. They often only charge for copies and print outs. Some documents are written in a Chinese, German, Russian, French, Dutch, Spanish, etc., but most are English. These journal articles and case reports contain more information than what is listed in this document— dosages, contact names, e-mail addresses, supplier information, etc., etc. It may be in the future to have a Kindle version of Codex Alternus with hyperlinks to all 750 citations.

This document, even though it contains nearly 750 citations on alternative and complementary treatments, it has several weak areas in research. There are few citations on CAM medicine for schizophrenia on anxiety, insomnia, depression and substance abuse. These topics have to be researched separately. This document does not include family therapy, occupational therapy, nicotine therapies, CBT, web support based programs, psychoeducation, group therapy, or peer support citations. Chinese medical databases contain more information on traditional Chinese alternative and complementary medicine for schizophrenia and bipolar disorder. Hope everyone finds this document useful.

Half-way Therapies for Patients

The author wishes to recommend the use of many drug-free options for patients and to limit the use of psychotropic medications even though this document is full of integrative medicine. It is the author vision that the patients use of supplements, herbs, mind-body medicine and other CAM modalities combined with psychotropics can be seen as the "half-way" therapies to

achieving a totaling drug-free lifestyle (street drugs & pharmaceutical). These "half-way" therapies are ways of achieving total independence from the mental health system. This may be the only way to get some psychiatric patients started on a healthy lifestyle change that won't lead to immediate relapse from abrupt withdrawal from psychotropics. This may be a gradual appeal to a better way to change their life for the better with multiple treatment options. One patient may prefer the low-cost, but healthy use of yoga, and breathing techniques combined with a diet change and adjunctive multivitamin to psychotropics for treatment of their bipolar disorder. Another schizophrenic may prefer a gluten-free/casein free diet, with orthomolecular treatments with vitamins, and bright light therapy for their depressive episodes. The combinations are almost endless and the results are superior to monotherapy with psychotropics. This change in routine may lead some to a drug-free, healthy lifestyle, free from relapse. Let's all hope the "half-way" experience effects everyone on psychotropic drugs and leads to a drug-free lifestyle.

Schizophrenia Treatments

Vitamin Therapy

Vitamin B_1 (Thiamine)

Intravenous Vitamin B1 Supplementation Resolves Deficiency and Psychotic Symptoms

Sasaki, Takeshi, "[A case of thiamine deficiency with psychotic symptoms--blood concentration of thiamine and response to therapy]." Seishin Shinkeigaku Zasshi = Psychiatria Et Neurologia Japonica 112, no. 2 (2010): 97–110.

- *"We report the case of a 63-year-old woman with thiamine deficiency who showed auditory hallucinations, a delusion of persecution, catatonic stupor, and catalepsy but no neurological symptoms including oculomotor or gait disturbance. Brain MRI did not show high-intensity T2 signals in regions including the thalami, mamillary bodies, or periaqueductal area. Her thiamine concentration was 19 ng/mL, only slightly less than the reference range of 20-50 ng/mL. Her psychosis was unresponsive to antipsychotics or electroconvulsive therapy, but was ameliorated by repetitive intravenous thiamine administrations at 100-200 mg per day. However, one month after completing intravenous treatment, her psychosis recurred, even though she was given 150 mg of thiamine per day orally and her blood concentration of thiamine was maintained at far higher than the reference range. Again, intravenous thiamine administration was necessary to ameliorate her symptoms. The present patient indicates that the possibility of thiamine deficiency should be considered in cases of psychosis without neurological disturbance and high-intensity T2 MRI lesions. Also, this case suggests that a high blood thiamine concentration does not necessarily correspond to sufficient thiamine levels in the brain. Based on this, we must reconsider the importance of a high dose of thiamine administration as a therapy for thiamine deficiency. The validity of the reference range of the thiamine concentration, 20-50 ng/mL, is critically reviewed."*

Vitamin B_3 (Niacin, Nicotinic Acid)

Niacin Megavitamin Therapy Cures Young Schizophrenic Woman

Hoffer, A. "A Neurological Form of Schizophrenia." Canadian Medical Association Journal 108, no. 2 (January 20, 1973): 186 passim.

- *"A case is described of a young woman who first showed manifestations of schizophrenia in childhood. At the age of 13 years evidence was present of what was authoritatively diagnosed as a progressive degenerative cerebellar syndrome and her condition continued to deteriorate. Improvement commenced shortly after the institution of megavitamin therapy, notably nicotinic acid 3 grams daily. Her subsequent educational progress was satisfactory and her social rehabilitation is now complete. No medication other than nicotinic acid is required."*

Nicotinic Acid Reduces Hospital Readmission Rate

Hoffer A. Treatment of Schizophrenia with Nicotinic Acid: A ten year follow-up. Acta Psychiatrica Scandinavica, Volume 40, Issue 2, pages 171-189, June 1964

- *"The group which received nicotinic acid had the best record which showed most clearly in the total days of rehospitalization, i.e. about 11 days per patient per year. The comparison group required about 19 days per patient per year."*

Hoffer A. Nicotinic acid: An adjunct in the treatment of schizophrenia. Am J Psychiatry 1963 Aug; 120:171-3

- *"Of the first 16 patients treated in 1952, 75% have not required any further readmissions, 4 have between them had 6 brief readmissions and none now in the hospital. A comparison group of 27 did not fare so well. Of them 17 have required readmission 63 times. These 27 patients required 34 years of admissions over a ten-year period. The nicotinic acid group required only 1.4 years..*

Osmond H. Massive niacin treatment in schizophrenia. Review of a nine year study. Lancet, 1962 Feb 10; 1 (7224): 316-319

- *"Table IV shows the effect of niacin and other treatments on the time spent in the hospital. One way of summarizing this table would be to say that, during the four-year follow-up, patients who had never had nicotinic acid spent two-fifths of a year in hospital, while for those who received it the average was only a sixth of a year."*
- *"…Schizophrenics treated in Saskatchewan without niacin or nicotinamide had an equally gloomy prognosis (table III): over half were readmitted at least once within five years of discharge. But of those receiving this vitamin only about a sixth required readmission during the same period."*

Adequate Doses of Niacin Contribute to Recovery in Schizophrenic Patients

Hoffer, A., "Treatment of Schizophrenia with Nicotinic Acid and Nicotinamide." Journal of Clinical and Experimental Psychopathology 18, no. 2 (June 1957): 131–58.

- *"When used in adequate dosages, nicotinic acid and nicotinamide materially contribute to the recovery of schizophrenic patients."*

Niacin Augmentation Therapy for Rapid Resolution of Delusional Parasitosis

Prakash, Ravi, "Rapid Resolution of Delusional Parasitosis in Pellagra with Niacin Augmentation Therapy." General Hospital Psychiatry 30, no. 6 (December 2008): 581–84. doi:10.1016/j.genhosppsych.2008.04.011.

- *"We report a case of pellagra manifesting with delusional parasitosis in a man whose delusion resolved rapidly after he started niacin-augmentation therapy. This case may provide clues to the biological underpinnings of delusional parasitosis as well as niacin treatment as treatment option in similar cases."*

Vitamin B_6 (Pyridoxine)

Potentiation of Therapeutic Effects of Nicotinic Acid by Pyridoxine (vitamin B6) in Schizophrenia

Ananth JV. Potentiation of therapeutic effects of nicotinic acid by pyridoxine in chronic schizophrenics. The Canadian Psychiatric Association Journal, Volume 18(5), Oct 1973, 377-383

- *"Based on these findings it was hypothesized that the administration of pyridoxine will enhance the therapeutic effect of nicotinic acid in schizophrenic patients by opening up kynurenine cycle of tryptophan metabolism and thereby decreasing the formation of indoles.*
- *In this 48-week placebo-controlled study, the therapeutic effect of a combination of nicotinic acid and pyridoxine was compared with that of treatment with either nicotinic acid or pyridoxine alone. Of the three indices of therapeutic effects, global improvement in psychopathology (BPRS and NOSIE) scores was seen in all three groups; the number of days of hospitalization during the period of the clinical study was lower in both the nicotinic acid and combined treatment group; and only in the combined treatment group was the daily average dosage of phenothiazine medication decreased. Thus, improvement in all three indices was noted in the combined treatment group."*

Pyridoxine has an Antidepressant Effect (vitamin B6) in Schizophrenic Patients with Co-morbid Minor Depression

Shiloh R. Antidepressant effect of pyridoxine (vitamin B6) in neuroleptic-treated schizophrenic patients with co-morbid minor depression—preliminary open-label trial. Harefuah 2001 May;140(5):369-73,456.

- *"Two of nine patients (22%), characterized by higher initial HAM-D and SANS scores, and by older age and longer duration of illness, experienced marked improvements in depressive symptoms (235 and 28% decrease in HAM-D scores) following 4 weeks of pyridoxine administration. In one of these two, the improvement in depressive symptoms was accompanied by a parallel decrease in SANS scores."*

Vitamin B6 is Effective Monotherapy for Certain Types of Catatonic Schizophrenic-like Cases

Brooks, S. C., "An Unusual Schizophrenic Illness Responsive to Pyridoxine HCl (B6) Subsequent to Phenothiazine and Butyrophenone Toxicities." Biological Psychiatry 18, no. 11 (November 1983): 1321–28.

- *"This report describes the treatment of an 18-year-old male diagnosed (DSM II) as having an acute schizophrenic reaction, catatonic type (APA, 1968) in association with multiplex psychological findings which were partially congruous with several neuropsychobehavioral disorders. The patient did not demonstrate classical symptoms, in constellation, which could support a definitive diagnosis of an organic brain syndrome. The patient did demonstrate classical psychiatric symptoms supporting the clinical diagnosis of a schizophrenic disorder, however. Treatment with haloperidol (buturophenone) from 1-5 mg TID and, alternatively, trifluoperazine (phenothiazine) at 2 mg TID was unsuccessful because of the extrapyramidal side effects and the respective hepatotoxicities which occurred with both drugs. Pyridoxine HCI (vitamin B6) at 500 mg daily was therapeutically effective in eliminating the major schizophrenic reaction. Clinical relapse resulted with dose reduction to 250 mg daily, following full clinical recovery for 1 year, but was reinstituted again at 500 mg daily. The complex findings and clinical success with pyridoxine HCI in this case parallel a previously unreported case of an 11 year-old female with schizophrenia, catatonic type and minimal brain dysfunction who demonstrated initial trifluperazine and thiothixene intolerance but sequent responsiveness to pyridoxine HCI at 500 mg daily. Experience with both cases estimated the effective dosage of pyridoxine HCI at 500 mg daily to be 5-10 mg/kg per day."*

Vitamin B_9 (Folate, Folic Acid, and Methylfolate)

Methylfolate Significantly Improved Clinical and Social Recovery of Schizophrenic Patients

Godfrey, P. S., "Enhancement of Recovery from Psychiatric Illness by Methylfolate." Lancet 336, no. 8712 (August 18, 1990): 392–95.

- *"41 (33%) of 123 patients with acute psychiatric disorders (DSM III diagnosis of major depression or schizophrenia) had borderline or definite folate deficiency (red-cell folate below 200 micrograms/l) and took part in a double-blind, placebo-controlled trial of methylfolate, 15 mg daily, for 6 months in addition to standard psychotropic treatment. Among both depressed and schizophrenic patients methylfolate significantly improved clinical and social recovery. The differences in outcome scores between methylfolate and placebo groups became greater with time. These findings add to the evidence implicating disturbances of methylation in the nervous system in the biology of some forms of mental illness."*

Folate Supplementation May Be Good Management Modality for Clinical Improvement in Some Schizophrenic Patients with Genetic Defect

Kim, Tae Ho, "Serum Homocysteine and Folate Levels in Korean Schizophrenic Patients." Psychiatry Investigation 8, no. 2 (June 2011): 134–40. doi:10.4306/pi.2011.8.2.134.

- *"Some schizophrenia patients with high serum homocysteine levels may have the genetic defect of having low folate serum levels. In such cases, folate ingestion may be a good management modality for clinical improvement."*

Vitamin B_{12} (Cobalamin)

Chronic Psychosis Improves Dramatically with Short-term Antipsychotic Medication and Intramuscular Cobalamin Injections

Rajkumar, A. P., "Chronic Psychosis Associated with Vitamin B12 Deficiency." The Journal of the Association of Physicians of India 56 (February 2008): 115–16.

- *"B12 deficiency is widely prevalent and usually presents with haematologic and neuropsychiatric manifestations. Psychiatric symptoms seldom precede anaemia and present as the principal manifestation of B12 deficiency. A report an unusual presentation of long standing psychotic symptoms without anaemia in a 31 year old male, who presented to a tertiary care psychiatric facility. His physical examination revealed hyper pigmentation of extremities and posterior column involvement. Laboratory investigations confirmed normal haemoglobin and low serum B12 levels. He recovered dramatically with short term antipsychotic medication and intramuscular cobalamin supplementation. He remained asymptomatic and functionally independent at two years follow up."*

Three Patients Recovered Only on a Combination of B12 Supplementation and Psychiatric Medication

Bhat, Amritha S., "Psychiatric Presentations of Vitamin B 12 Deficiency." Journal of the Indian Medical Association 105, no. 7 (July 2007): 395–96.

- *"Vitamin B12 deficiency has been implicated in various psychiatric conditions for a long time. The association could be primary, secondary to the psychiatric disorder, or even just coincidental. However, left untreated, the deficiency can delay or preclude recovery. Hence early recognition is important, especially when the traditional manifestations of B12 deficiency like anaemia, macrocytosis or spinal cord symptoms are not prominent. Three cases are presented here where vitamin B12 deficiency and psychiatric*

symptomatology were coexistent, and the patients recovered only on a combination of B12 supplementation and psychiatric medication."

Patient Recovers from Schizophrenia-like Psychotic Episode with Oral Cobalamin Supplementation and Short Course Antipsychotic Treatment

Kuo, Shin-Chang,"Schizophrenia-like Psychotic Episode Precipitated by Cobalamin Deficiency." General Hospital Psychiatry 31, no. 6 (December 2009): 586–88. doi:10.1016/j.genhosppsych.2009.02.003.

- *"Although cobalamin deficiency is widely known and usually presents with hematologic and neuropsychiatric manifestations, the psychiatric symptoms are not usually the predominant manifestation. We describe a young single male vegetarian who developed a cobalamin-induced psychotic episode without preceding neurologic manifestations and without any hematologic symptoms. He recovered after a short course of antipsychotics and oral cobalamin supplementation and remained asymptomatic and functionally independent at 1 year of follow-up."*

Psychosis is Eliminated by Vitamin B12 Replacement Therapy

Masalha, R., "Cobalamin-Responsive Psychosis as the Sole Manifestation of Vitamin B12 Deficiency." The Israel Medical Association Journal: IMAJ 3, no. 9 (September 2001): 701–3.

- *"Treatment for vitamin B12 deficiency is described as simple, uncomplicated and very helpful, especially when the deficiency is diagnosed early and the appropriate treatment instituted promptly. Our patients were treated with anti-psychotic drugs for 2 months with- out any benefit and the treatment was stopped. After substitution with intra-muscular injections of hydroxycobala-min, the effect was observed within 6±8 weeks after initiation of therapy. Similarly, the two patients described by Evans et al. [5] also showed improvement after several weeks, even though their initial response was more dramatic. Both our patients are currently receiving oral hydroxycobalamin (300 g/day), and after a year of follow-up have maintained their mental health. The therapeutic protocol we used was entirely empirical, as there are no controlled studies or recommendations of optimal therapy for dietary vitamin B12 deficiency. We con- tend however, that prevention would have been the most effective approach."*

Vitamin B Complex

Schizophrenic Patients with Hyperhomocysteinemia Benefit from the Addition of B Vitamins

Levine, Joseph, "Homocysteine-Reducing Strategies Improve Symptoms in Chronic Schizophrenic Patients with Hyperhomocysteinemia." Biological Psychiatry 60, no. 3 (August 1, 2006): 265–69. doi:10.1016/j.biopsych.2005.10.009.

- *"Homocysteine levels declined with vitamin therapy compared with placebo in all patients except for one noncompliant subject. Clinical symptoms of schizophrenia as measured by the Positive and Negative Syndrome Scale declined significantly with active treatment compared with placebo. Neuropsychological test results overall, and Wisconsin Card Sort (Categories Completed) test results in particular, were significantly better after vitamin treatment than after placebo. A subgroup of schizophrenic patients with hyperhomocysteinemia might benefit from the simple addition of B vitamins."*

Correction of Essential Fatty Acids and B vitamin Status Reduces Psychiatric Symptoms and Cardiovascular Disease

Kemperman, R. F. J.,"Low Essential Fatty Acid and B-Vitamin Status in a Subgroup of Patients with Schizophrenia and Its Response to Dietary Supplementation." Prostaglandins, Leukotrienes, and Essential Fatty Acids 74, no. 2 (February 2006): 75–85. doi:10.1016/j.plefa.2005.11.004.

- *"We conclude that a subgroup of patients with schizophrenia has biochemical EFA deficiency, omega3/DHA marginality, moderate hyperhomocysteinemia, or combinations. Correction seems indicated in view of the possible relation of poor EFA and B-vitamin status with some of their psychiatric symptoms, but notably to reduce their high risk of cardiovascular disease."*

Folate Plus Vitamin B12 Supplementation Can Improve Negative Symptoms of Schizophrenia

Roffman, Joshua L., "Randomized Multicenter Investigation of Folate plus Vitamin B12 Supplementation in Schizophrenia." JAMA Psychiatry 70, no. 5 (May 2013): 481–89. doi:10.1001/jamapsychiatry.2013.900.

- *"Folate plus vitamin B12 supplementation can improve negative symptoms of schizophrenia, but treatment response is influenced by genetic variation in folate absorption. These findings support a personalized medicine approach for the treatment of negative symptoms."*

Vitamin C

Vitamin C Improves Outcome of Schizophrenia

Dakhale G.N. Supplementation of vitamin C with atypical antipsychotics reduces oxidative stress and improves the outcome of schizophrenia. Psychopharmacology (2005) 182:494-498

- *"BPRS change scores at 8 weeks improved statically significant with vitamin C as compared to placebo."*

Vitamin D

Vitamin D Supplementation May Reduce the Incidence of Schizophrenia

McGrath, John. "Is It Time to Trial Vitamin D Supplements for the Prevention of Schizophrenia?" Acta Psychiatrica Scandinavica 121, no. 5 (May 2010): 321–24. doi:10.1111/j.1600-0447.2010.01551.x.

- *"Based on the accumulating evidence linking hypovitaminosis D and schizophrenia, and the potential that a simple, safe and cheap nutritional supplement could reduce the incidence of this disorder, I argue that we should move to randomized controlled trials promptly. In light of the substantial burden of disability associated with schizophrenia, we should undertake these studies with a sense of urgency."*

Preventing Vitamin D Deficiency during Early Life May Prevent Schizophrenia

McGrath, John, "Vitamin D Supplementation during the First Year of Life and Risk of Schizophrenia: A Finnish Birth Cohort Study." Schizophrenia Research 67, no. 2–3 (April 1, 2004): 237–45. doi:10.1016/j.schres.2003.08.005.

- *"Vitamin D supplementation during the first year of life is associated with a reduced risk of schizophrenia in males. Preventing hypovitaminosis D during early life may reduce the incidence of schizophrenia."*

Vitamin D Supplementation in Deficient Schizophrenic Patients Should Be Considered

Yüksel, Rabia Nazik, "Correlation between Total Vitamin D Levels and Psychotic Psychopathology in Patients with Schizophrenia: Therapeutic Implications for Add-on Vitamin D Augmentation." Therapeutic Advances in Psychopharmacology 4, no. 6 (December 2014): 268–75. doi:10.1177/2045125314553612.

- *"Even though important factors for vitamin D synthesis were similar, there was severe vitamin D deficiency in patients presenting with an acute episode, significantly different from those in remission. Is vitamin D deficiency the result or the cause of an acute episode? Our results contribute to the idea that vitamin D deficiency and schizophrenia may have interactions with an unknown pathway. Present data points out a possible*

influence at a genomic level. Future trials may investigate this association with longer follow up. We recommend that, serum vitamin D levels should be measured in patients with schizophrenia especially in long term care. Appropriate further treatment with add-on vitamin D supplements and diets that are rich in vitamin D should be considered."

Vitamin D Supplementation is recommended in Schizophrenia Patients, Particularly Those with Elevated Proline

Clelland, James D., "Vitamin D Insufficiency and Schizophrenia Risk: Evaluation of Hyperprolinemia as a Mediator of Association." Schizophrenia Research 156, no. 1 (June 2014): 15–22. doi:10.1016/j.schres.2014.03.017.

- *"Although definitive causality cannot be confirmed, these findings strongly support vitamin D supplementation in patients, particularly for those with elevated proline, who may represent a large subgroup of the schizophrenia population."*

Dietary and Nutrition

Fasting

Preplanned Fasting Dietary Treatment of Schizophrenia Results in Complete Disappearance on Symptoms

Boehme, D. H. "Preplanned Fasting in the Treatment of Mental Disease: Survey of Current Soviet Literature." Schizophrenia Bulletin 3, no. 2 (1977): 288–96.

- *"This constituted the smallest group of patients, eight of whom had suffered from their disease between 5 and 10 years. Four of the eight patients experienced total disappearance of their symptoms during preplanned fasting. Their symptomatology consisted of moderate depression with a background of slight emotional defect. In general it was found that the results in those patients who had experienced significant improvements were quite impressive—after treatment, a majority of such patients were capable of attending institutions of higher learning, working in their specialty, and even of acquiring academic degrees. In 30 percent recurrence was observed within 2 years of treatment; this recurrence, however, responded to a new course of therapy. In the opinion of Nikolajew (19696), treatment should not be repeated earlier than 6 months after termination of the first course."*

Fasting Dietetic Therapy Results in Considerable Improvement of Schizophrenic and Manic-depressive Patients

Polishchuk, Iu I. "[Fasting-diet therapy of elderly patients with borderline mental disorders]." Zhurnal Nevropatologii I Psikhiatrii Imeni S.S. Korsakova (Moscow, Russia: 1952) 91, no. 4 (1991): 101–4.

- *"During the fasting dietetic therapy (FDT), 89 patients aged 46 to 75 years with mental disorders of nonpsychotic character (neurosis-like, neurotic and affective) were examined. The time-course of changes in the clinical status of patients with cerebral atherosclerosis, essential hypertension, slow-progredient schizophrenia, cyclothymia and manic-depressive psychosis, neuroses and lingering neurotic reactions during the FDT is described. The beneficial results in the form of considerable improvement and improvement of the mental status were attained in 83.2% of the patients. The elderly patients were found to tolerate FDT well. Side effects and somatic complications were recorded in 6 patients and were not serious. Based on the data obtained the FDT can be recommended for use on a wider basis in the management of elderly patients with borderline mental disorders."*

Fruits and Vegetables

Dietary Improvement in Schizophrenia

McCreadie RG. Dietary improvement in people with schizophrenia: randomized controlled trial. Br J Psychiatry 2005 Oct; 187:346-51

- *"People with schizophrenia make poor dietary choices. Aims were to measure the impact of giving free fruits and vegetables for 6 months on eating habits in schizophrenia. Conclusions: The diet of people with schizophrenia improved when they were given free fruits and vegetables but this was not sustained after withdrawal of intervention. A support group added no benefit."*

Gluten-free Diet

Gluten-free Diet Shows Improvement in Some Schizophrenics in Hospital Setting

Rice, J. R., "Another Look at Gluten in Schizophrenia." The American Journal of Psychiatry 135, no. 11 (November 1978): 1417–18.

- *"After the gluten phase, 1 patient of 16 demonstrated severe regression below baseline on the Brief Psychiatric Rating Scale and clinical observations. She has had paranoid schizophrenia since she was 15 years old and has been in the South Carolina State Hospital for 14 years. She is now 29 years old. While she was ingesting excess gluten, she became severely agitated, uncooperative, and paranoid. We had to discontinue the gluten drink and give her intramuscular medication for three days because she became uncooperative and refused to take hen oral medications. During the gluten- free diet phase, 2 patients improved in their levels of functioning above baseline on the Brief*

Psychiatric Rating Scale and clinical observations. One of these patients was the woman already described; she showed improvement in level of functioning and de- creased level of paranoid ideation. We were able to reduce her medications substantially. She continued on a gluten-free diet after this study, but despite her improvement she was never able to develop insight in- to her illness. She discontinued her diet whenever she was not closely observed and therefore had to remain in the hospital. The other patient showed no remarkable regression during the gluten phase, but her level of functioning above baseline improved substantially on the Brief Psychiatric Rating Scale and clinical observations during the gluten-free diet. She had been in a state hospital for over 13 years, with a diagnosis of chronic schizophrenia, undifferentiated type. Because of her improvement we were able to discharge her from the hospital and send her home to her family."

Schizophrenics Improve Faster on a Gluten Free/Dairy Free Diet

Dohan FC. Relapsed schizophrenics: more rapid improvement on a milk-and cereal free diet. Br J Psychiatry 1969 May; 115(522):595-6

- *"Relapsed schizophrenic men randomly assigned to a milk-and cereal free diet on admission to a locked ward were released to an open ward considerably more rapidly than those assigned a high-cereal diet. When gluten was secretly added to the cereal-free diet the difference did not occur. Release of non-schizophrenic patients was not related to diet. These findings support the hypotheses that ingestion of cereals may be pathogenic for those with the genotype for schizophrenia."*

Dohan FC. Relapsed schizophrenics: Earlier discharged from the hospital after cereal-free, milk-free diet. Am J Psychiatry 130;6, June 1973

- *"During the first 90 days after admission to the hospital, those schizophrenics assigned to the CFMF diet were discharged more than twice as fast as those in the HC (high cereal) control group. In contrast to the beneficial effects of the CFMF diet, the relapsed schizophrenics on the CFMF diet to which wheat gluten was added (without the February 2, 2015knowledge of staff or patients) were not discharged from hospital significantly faster than their temporal controls on the HC diet."*

Gluten Free Diet Causes Disappearance of Psychiatric Symptoms

De Santis A. Schizophrenic symptoms and SPECT abnormalities in a coeliac patient: regression after a gluten-free diet. J Internal Medicine 1997;242:421-423

- *"A 33 year-old patient, with pre-existing diagnosis of 'schizophrenic' disorder, came to our observation for severe diarrhea and weight loss. Use of SPECT, demonstrated hypoperfusion of the left frontal brain area, without evidence of structural cerebral abnormalities. Jejunal biopsy showed villous atrophy. Antiendomysial antibodies were present. A gluten-free diet was started, resulting in disappearance of psychiatric*

symptoms, and normalization of histological duodenal findings and of the SPECT pattern….the SPECT demonstrating a dysfunction of the frontal cortex disappearing after a gluten free diet."

Improvement in Schizophrenic Patients on a Gluten Free Diet

Cade R. Autism and Schizophrenia: Intestinal Disorders Nutritional Neuroscience, Vol. 3, pp. 52-72, 2000

- *"….with a gluten-casein free diet alone. Patients 1 and 6 showed significant improvement after only two months on the diet. After four months on the diet, all seven patients had improved and there was a statistically significant improvement for the group as a whole comparing control with experimental values."*

Kraft BD. Schizophrenia, gluten and low-carbohydrate, ketogenic diets. Nutr Metab (Lond) 2009 Feb 26;6-10

- *A case report of a 70 year old schizophrenic with severe medical problems who used a ketogenic diet. "Over the course of 12 months, C.D. has continued the low-carbohydrate, ketogenic diet and has had no recurrence of auditory or visual hallucinations. She has also continued to lose weight and experience improvements in her energy level. She acknowledged having 2-3 isolated episodes of dietary non-compliance that lasted several days, where she ate pasta, bread, and cakes around the holidays: however she had no recurrence of her hallucinations.*

Pacheco A. A pilot study of the ketogenic diet in schizophrenia. Am J Psychiatry 121, May 1965, pp. 1110-1

- *"The average scores showed a statistically significant decrease in symptomology after 2 weeks on the ketogenic diet. The third rating taken one week after discontinuing the diet, showed that in 7 out of 10 patients there was a slight to fairly large increase in symptomology."*

Hypocaloric Diet

Hypocaloric Diet Increases BDNF Levels in Schizophrenic Patients

Guimarães, Lísia Rejane, "Serum Levels of Brain-Derived Neurotrophic Factor in Schizophrenia on a Hypocaloric Diet." Progress in Neuro-Psychopharmacology & Biological Psychiatry 32, no. 6 (August 1, 2008): 1595–98. doi:10.1016/j.pnpbp.2008.06.004.

- *"Serum BDNF levels were significantly higher in patients on the HD (p=0.023). Additional research examining the interaction among patterns of nutritional food behavior and underlying physiopathology may result in insights upon which evidence-based*

decisions regarding dietary interventions can be made in people identified with major psychiatric disorders, such as schizophrenia."

Low Protein, Imbalanced Amino Acid Diet

Treatment of Psychosis and Tardive Dyskinesia with Low Protein, Imbalanced Amino Acid Dietary Intervention

Aschheim E. Dietary control of psychosis. Medical Hypotheses (1993) 41, 327-328

- *"The purposed dietary intervention derives from established animal work dealing with the feeding of diets in which the essential amino acid (EAA) composition has been modified so as to produce a defined imbalance. It has been demonstrated that when animals are kept on a low but adequate protein diet balanced in terms of EAAs the addition of extra amount of single amino acids induces a deficiency of other EEAs…It is likely the biochemical effects of this treatment will become apparent in a matter of hours because amino acids, in contrast to carbohydrates and fats are not stored in the body. Consequently, the change in psychiatric presentation may become noticeable with-in a short time."*

Low Tryptophan Diet

Effect of Low Tryptophan Diet as an Adjunct to Neuroleptic Therapy in Schizophrenia

Rosse RB. Effect of a low-tryptophan diet as an adjuvant to conventional neuroleptic therapy in schizophrenia. Clinical Neuropharmacology Vol. 15, No. 2, pp. 129-141

- *"Authors Summary; Dietary manipulations of TRP have been shown to alter levels of 5-HT, kynurenic acid, and quinolinic acid. Conceivably, decreasing dietary ingestion of TRP would (a) diminish central serotonergic transmission due to a reduction of presynaptic stores of 5-HT, (b) relieve antagonism of NMDA-mediated neural transmission by decreasing levels of kynurenic acid, and (c) reduce exitotoxin levels of quinolinic acid. As reviewed above, a reduction in serotonergic transmission and alternation of glutamatergic transmission at a specific receptor subclass may be associated with salutary therapeutic effects in patients with schizophrenia.*
- *In this investigation, we examined the safety and adjunctive therapeutics effects of 4-day TRP-deficient diet on the behavioral symptomology of schizophrenic patients maintained on a stable dose of their conventional antipsychotic medications.*
- *Interestingly, however, some of the behavioral rating measures (BPRS, CGI) reached statistical significance in the last 2 days of the diet, suggesting a beneficial adjuvant effect for the low-TRP that was not immediate but delayed a few days.*

- *Potentially, the most important finding of this study is improved performance on the Stroop Color and Word Test during the diet phase that largely dropped off during the post-diet phase.*

Milk with A2 Genetic Variant

Attenuation of Schizophrenic Symptoms Using Milk Containing A2 Genetic Variant

Bell SJ. Health implications of milk containing beta-casein with the A2 genetic variant. Crit Rev Food Sci Nutr 2006;46(1):93-100

- *"Furthermore, consumption of milk with A2 variant may be associated with less severe symptoms of autism and schizophrenia"*

Probiotics Lactobacillus GG

Culturelle Probiotics Lactobacillus GG Can Cure Schizophrenia by Reducing Clostridia

Shaw, William. "Increased Urinary Excretion of a 3-(3-Hydroxyphenyl)-3-Hydroxypropionic Acid (HPHPA), an Abnormal Phenylalanine Metabolite of Clostridia Spp. in the Gastrointestinal Tract, in Urine Samples from Patients with Autism and Schizophrenia." Nutritional Neuroscience 13, no. 3 (June 2010): 135–43. doi:10.1179/147683010X12611460763968.

- *"High doses of the GG strain of Lactobacillus acidophilus have been used to control C. difficile. L. acidophilus therapy has no reported toxicity, and treatment with L. acidophilus GG of individuals with an elevated concentration of 3-(3-hydroxyphenyl)-3-hydroxy- propionic acid in their urine markedly reduces the con- centration of 3-(3-hydroxyphenyl)-3-hydroxypropionic acid in subsequent urine samples (unpublished data). Bolte20reportedamarkeddecreaseinsymptomsof autism in children treated with antibiotics effective against Clostridia, indicating treatment of abnormal microbial overgrowth may be a promising new therapy for the treatment of autism in individuals with this abnormality. The observation that elevated amounts of this compound in urine samples were associated with mental illnesses in general was made 50 years ago but has been completely ignored since then. Significant decreases in symptoms of schizophrenia, tic disorders, depression, chronic fatigue syndrome, and attention deficit hyperactivity have been reported by the attending physicians (personal communications, see Addendum) following antimicrobial treatment of individuals with elevated urinary concentrations of this compound, indicating that this compound may be of importance to many other mental diseases In addition to autism but also indicating that these probable Clostridia species are not specific for the etiology of autism or other diseases."*

Sugar

Sugar Improves Memory Function of Patients with Schizophrenia

Newcomer, J. W., "Glucose-Induced Increase in Memory Performance in Patients with Schizophrenia." Schizophrenia Bulletin 25, no. 2 (1999): 321–35.

- *"Previous investigations have found that increasing circulating glucose availability can increase memory performance in rodents, healthy humans, and individuals with dementia of the Alzheimer's type. In this study, patients with schizophrenia, healthy control subjects, and controls with bipolar affective disorder were tested using double-blind treatment with either 50 g anhydrous dextrose plus 4 mg sodium saccharin (for "taste") or 23.7 mg saccharin alone, followed by cognitive testing on a complex battery. At this glucose dose, verbal memory performance on a paragraph recall task was increased during the glucose condition relative to the saccharin condition in the patients with schizophrenia; this effect was not detected in either the psychiatric or normal controls. The results provide preliminary support for the hypothesis that memory performance can be improved in patients with schizophrenia by increasing circulating glucose availability and suggest the importance of further evaluation of therapeutic manipulations of glucose availability."*

Fatty Acids

The Use of GLA & LA to Differentiate Between Temporal Lobe Epilepsy and Schizophrenia

Vaddadi KS. The use of gamma-linolenic acid and linoleic acid to differentiate between temporal lobe epilepsy and schizophrenia. Prostaglandins Med 1981 Apr;6(4):375-9

- *"Three long-stay, hospitalized schizophrenics who failed to respond adequately to conventional drug therapy were treated with gamma-linolenic acid and linoleic acid in the form of evening primrose oil. They became substantially worse and electroencephalographic features of temporal epilepsy became apparent. In all three the clinical state dramatically improved when carbamazepine, the conventional therapy for temporal lobe epilepsy was introduced. It can be extremely difficult to distinguish on clinical grounds between schizophrenia and temporal lobe epilepsy, and electroencephalographic studies do not always reveal an abnormality in the temporal lobe syndrome, unless additional procedure such as sphenoidal electroencephalography is undertaken. A trial of therapy with gamma-linolenic acid may prove of considerable value in distinguishing between these two states, so allowing specific therapy to be introduced."*

Ethyl Eicosapentaenoic Acid (EPA)

EPA Has Procognitive Effects in Patients with Schizophrenia

Reddy, R., "Reduction in Perseverative Errors with Adjunctive Ethyl-Eicosapentaenoic Acid in Patients with Schizophrenia: Preliminary Study." Prostaglandins, Leukotrienes, and Essential Fatty Acids 84, no. 3–4 (April 2011): 79–83. doi:10.1016/j.plefa.2010.12.001.

- *"The 27 patients, with a mean duration of illness of 4.2 years, were all receiving atypical antipsychotics; treatment remained unchanged for the study. Perseverative errors - the key measure derived from WCST - were significantly reduced from the baseline mean of 28.2 to 18.4 errors at week 24. Positive symptoms also improved significantly. There were no correlations between EPA levels and any clinical or other neuropsychological measures. These findings suggest that an EPA has procognitive effects for patients with schizophrenia, but controlled trials are required."*

Omega 3

Omega-3 Fatty Acids as Psychotherapeutic Agent for Pregnant Schizophrenic Patient

Su KP. Omega-3 fatty acids as a psychotherapeutic agent for a pregnant schizophrenic patient. Eur Neuropsychopharmacol 2001 Aug;11(4):295-9

- *"Because of the potential adverse events and teratogenesis of antipsychotic drugs, it is important to find a safe and effective treatment for pregnant women with severe mental illness. The membrane hypothesis of schizophrenia provides a rationale to treat symptoms of schizophrenia with omega-3 PUFAs. We report a 30-year-old married woman with chronic schizophrenia, who experienced an episode of acute exacerbation of psychotic symptoms during pregnancy. After entering into an opening trial of omega-3 PUFAs momotherapy, she showed a dramatic improvement in both positive and negative symptoms of schizophrenia and a significant increase of omega-3 composition in erythrocyte membrane. There were no adverse effects in this treatment. Thus, omega-3 PUFAs could be both beneficial and therapeutic to pregnant schizophrenic women."*

Omega-3 Fatty Acids Have Much Clinical Potential in the Treatment of Schizophrenia

Emsley, Robin, "Clinical Potential of Omega-3 Fatty Acids in the Treatment of Schizophrenia." CNS Drugs 17, no. 15 (2003): 1081–91.

- *The phospholipids in the neuronal membranes of the brain are rich in highly unsaturated essential fatty acids (EFAs). It has been hypothesized that abnormalities of phospholipid metabolism are present in patients with schizophrenia and that the EFAs omega-3 polyunsaturated fatty acids, and eicosapentaenoic acid (EPA) in particular, may have a role in treating this illness. Considerable preclinical and clinical evidence provides support for this proposal. An epidemiological study reported a better outcome for patients with schizophrenia in countries where the diet is rich in unsaturated fatty acids.*

Evidence of abnormalities of EFAs has been found in erythrocyte membranes and cultured skin fibroblasts of patients with schizophrenia, and abnormal retinal function and niacin skin flush tests (markers of omega-3 polyunsaturated fatty acid depletion) have also been reported. Case reports and an open-label clinical trial reported efficacy for EPA in schizophrenia. Four randomized, controlled trials of EPA versus placebo as supplemental medication have now been reported. Two of these trials showed significant benefit with EPA on the positive and negative symptom scale total scores, whereas the other two did not show any effects on this primary efficacy measure. One study also reported a beneficial effect on dyskinesia. In the only published trial in which EPA was used as monotherapy versus placebo in schizophrenia, some evidence was found to suggest antipsychotic activity. Taken together, there is considerable evidence to suggest abnormalities of EFAs in cell membranes of patients with schizophrenia, and there is preliminary evidence that EPA is an effective adjunct to antipsychotics.

Omega-3 Fatty Acids May Change Hemispheric Imbalance in Schizophrenic Patients

Richardson, A. J., "Laterality Changes Accompanying Symptom Remission in Schizophrenia Following Treatment with Eicosapentaenoic Acid." International Journal of Psychophysiology: Official Journal of the International Organization of Psychophysiology 34, no. 3 (December 1999): 333–39.

- *"As measured by the Schedules for the Assessment of Positive Symptoms and Negative Symptoms, a marked reduction in his symptoms was first apparent at 2-month follow-up; further improvement followed, so that at the 6-month point few symptoms remained. Corresponding to his clinical improvement, the patient's performance on the pegboard task at 3-month follow-up had shifted from a strong right-hand advantage to near symmetry, owing to a marked improvement in his left-hand scores. On retest at 6 months this change in asymmetry was also maintained. These findings suggest that treatment with certain fatty acids may have significant benefits in the management of schizophrenia. They are also consistent with existing evidence that an Active syndrome of schizophrenia reflects a left over right hemispheric imbalance which is functional in nature, and can therefore change with symptom remission."*

Supplemental Omega-3 Fatty Acids May Increase the Efficacy of Antipsychotics

Jamilian, Hamidreza, "Randomized, Placebo-Controlled Clinical Trial of Omega-3 as Supplemental Treatment in Schizophrenia." Global Journal of Health Science 6, no. 7 Spec No (2014): 38466.

- *"We found that supplemental omega-3 might increase efficacy of conventional antipsychotics in decreasing symptoms of schizophrenia. Low price, rare adverse*

reactions and availability of omega-3 made this substance a potential supplement in improved treatment of schizophrenia."

Omega-3 Fatty Acids Have Low Risk of Harm and Clinicians Should Add Supplements to Drug Regimens

Akter, K., "A Review of the Possible Role of the Essential Fatty Acids and Fish Oils in the Aetiology, Prevention or Pharmacotherapy of Schizophrenia." Journal of Clinical Pharmacy and Therapeutics 37, no. 2 (April 2012): 132–39. doi:10.1111/j.1365-2710.2011.01265.x.

- *"Despite the limited evidence that supplements ameliorate symptoms of schizophrenia, given the low risk of harm, some clinicians might opt to add omega-3 polyunsaturated fatty acid to current drug regimens in hope of better symptomatic control in schizophrenia."*

Omega-3 Fatty Acid Supplementation Can Improve Behavioral Aspects and Reduce Cognitve Deterioration

Marano, G., "Omega-3 Fatty Acids and Schizophrenia: Evidences and Recommendations." La Clinica Terapeutica 164, no. 6 (2013): e529–37.

- *"Schizophrenia is a brain disease that represents a not rare condition, in fact the lifetime risk of developing schizophrenia is widely accepted to be around 1 in 100. Schizophrenia clinically manifests with acute episodes which are associated with hallucinations, delirium, behavioral disorders and a variable range of chronic persistent symptoms, which can be debilitating. The causes of schizophrenia are not clearly understood. It seems that genetic factors may produce a vulnerability to schizophrenia, along with environmental factors that contribute in a different way from individual to individual. In this context schizophrenia constitutes the outcome of a complex interaction between multiple genes and environmental risk factors, none of which on its own causes the disorder itself. Antipsychotic medications represent the first line of psychiatric treatment for schizophrenia. But there is a growing body of evidence that omega-3 fatty acids can prevent the disease or at least mitigate the course and symptoms. Probably, an appropriate dietary supplementation can play a partially therapeutic effect, even in more severe patients, improving some behavioral aspects and, mainly, reducing the cognitive deterioration. In this context the role of omega-3 fatty acids as a treatment for schizophrenia will strengthen the thrust of researchers and clinicians to the integrated approach to the prevention and cure of a disease that for more than a century challenging researchers."*

Amino Acids

D-alanine

D-alanine is a Promising Approach for the Pharmacotherapy of Schizophrenia

Tsai, Guochuan E., "D-Alanine Added to Antipsychotics for the Treatment of Schizophrenia." Biological Psychiatry 59, no. 3 (February 1, 2006): 230–34. doi:10.1016/j.biopsych.2005.06.032.

- *"The significant improvement with the D-alanine further supports the hypothesis of hypofunction of NMDA neurotransmission in schizophrenia and strengthens the proof of the principle that NMDA-enhancing treatment is a promising approach for the pharmacotherapy of schizophrenia."*

Lower Plasma Alanine Levels Correlate to More Severe Positive Symptoms

Hatano, Tokiko, "Plasma Alanine Levels Increase in Patients with Schizophrenia as Their Clinical Symptoms Improve-Results from the Juntendo University Schizophrenia Projects (JUSP)." Psychiatry Research 177, no. 1–2 (May 15, 2010): 27–31. doi:10.1016/j.psychres.2010.02.014.

- *"Eighty-one Japanese patients with schizophrenia and 50 age- and gender-matched healthy controls were studied. Plasma alanine levels were measured twice, during the acute stage and during the remission stage, using high-performance liquid chromatography. On admission, lower plasma alanine levels in patients with schizophrenia were accompanied by more severe schizophrenic symptoms, especially positive symptoms. The plasma alanine levels in patients with schizophrenia increased significantly from the time of admission to discharge, when they were significantly higher than control levels. An increase in plasma alanine levels from the acute stage to the remission stage of schizophrenia was correlated with improvement in symptoms. Drug-naïve patients did not show a significant difference in plasma alanine levels when compared with healthy controls. The measurement of plasma alanine levels may be a therapeutic marker for schizophrenia."*

D-Amino Oxidase Inhibitors

D-Amino Acid Oxidase Inhibitors Could Be Useful for Reducing the Dose of D-serine to Improve Psychosis or Cognitive Deficits

Smith, Sean M., "The Therapeutic Potential of D-Amino Acid Oxidase (DAAO) Inhibitors." The Open Medicinal Chemistry Journal 4 (2010): 3–9. doi:10.2174/1874104501004020003.

- *"Nevertheless, these findings suggest that DAAO inhibitors could be useful clinically for reducing the dose of D-serine necessary to improve psychosis or cognitive deficits associated with schizophrenia. As a result, the coadministration of DAAO inhibitors with D-serine could ameliorate some of the side effects associated with the administration of high doses of D-serine, such as nephrotoxicity."*

D-Amino Oxidase Inhibitor Could Enhance the Oral Bioavailability of D-alanine

Mao Horio, "Effects of D-Amino Acid Oxidase Inhibitor on the Extracellular D-Alanine Levels and the Efficacy of D-Alanine on Dizocilpine-Induced Prepulse Inhibition Deficits in Mice" The Open Clinical Chemistry Journal, 2009, 2, 16-21

- *"In this study, we found that administration of DAAO inhibitor CBIO could enhance the oral bioavailability of D-alanine in mice, and that co-administration of D-alanine with CBIO significantly increased the extracellular D-alanine levels in the mouse frontal cortex as compared with Dalanine alone group. In conclusion, co-administration of Dalanine and a DAAO inhibitor would be a new approach for the treatment of schizophrenia."*

Adjunctive D-Amino Acid Oxidase Inhibitors Increase the Levels of D-serine in the Brain

Sacchi, Silvia, "D-Amino Acid Oxidase Inhibitors as a Novel Class of Drugs for Schizophrenia Therapy." Current Pharmaceutical Design 19, no. 14 (2013): 2499–2511.

- *"Several findings have linked low levels of D-serine to schizophrenia: D-serine concentrations in serum and cerebrospinal fluid have been reported to be decreased in schizophrenia patients while human DAAO activity and expression are increased; oral administration of D-serine improved positive, negative, and cognitive symptoms of schizophrenia as add-on therapy to typical and atypical antipsychotics. This evidence indicates that increasing NMDA receptor function, perhaps by inhibiting DAAO-induced degradation of D-serine may alleviate symptoms in schizophrenic patients. Furthermore, it has been suggested that co-administration of D-serine with a human DAAO inhibitor may be a more effective means of increasing D-serine levels in the brain. Here, we present an overview of the current knowledge of the structure-function relationships in human DAAO and of the compounds recently developed to inhibit its activity (specifically the ones recently exploited for schizophrenia treatment)."*

Sodium Benzoate is a DAAO Inhibitor that Produced Significant Improvement in PANSS Total Score in Schizophrenic Patients

Lane, Hsien-Yuan, "Add-on Treatment of Benzoate for Schizophrenia: A Randomized, Double-Blind, Placebo-Controlled Trial of D-Amino Acid Oxidase Inhibitor." JAMA Psychiatry 70, no. 12 (December 2013): 1267–75. doi:10.1001/jamapsychiatry.2013.2159.

- *"Benzoate produced a 21% improvement in PANSS total score and large effect sizes (range, 1.16-1.69) in the PANSS total and subscales, Scales for the Assessment of Negative Symptoms-20 items, Global Assessment of Function, Quality of Life Scale and Clinical Global Impression and improvement in the neurocognition subtests as recommended by the National Institute of Mental Health's Measurement and Treatment Research to Improve Cognition in Schizophrenia initiative, including the domains of processing speed and visual learning. Benzoate was well tolerated without significant adverse effects."*

Glycine

Glycine Augmentation May Ameliorate Depressive and Extrapyramidal Symptoms in Schizophrenic Patients

Strzelecki, Dominik "[Augmentation of antipsychotics with glycine may ameliorate depressive and extrapyramidal symptoms in schizophrenic patients--a preliminary 10-week open-label study]." Psychiatria Polska 47, no. 4 (August 2013): 609–20.

- *"Glycine augmentation of antipsychotic treatment may reduce the severity of depressive and extrapyramidal symptoms. Glycine use was safe and well tolerated."*

High Dose Glycine Results in Significant Reduction in Negative Symptoms

Heresco-Levy, U., "Efficacy of High-Dose Glycine in the Treatment of Enduring Negative Symptoms of Schizophrenia." Archives of General Psychiatry 56, no. 1 (January 1999): 29–36.

- *"Glycine treatment was well tolerated and induced increased glycine (P=.001) and serine (P=.001) serum levels. Glycine administration resulted in (1) a significant (P<.001) 30%+/-16% reduction in negative symptoms, as measured by the PANSS, and (2) a significant (P<.001) 30%+/-18% improvement in the BPRS total scores. The improvement in negative symptoms was unrelated to alterations in extrapyramidal effects or symptoms of depression. Low pretreatment glycine serum levels significantly predicted (r= 0.80) clinical response."*

Adjunctive Glycine Therapy Induced a Significant Reduction in Negative, Depression, and Cognitive Symptoms

Heresco-Levy, U., "Double-Blind, Placebo-Controlled, Crossover Trial of Glycine Adjuvant Therapy for Treatment-Resistant Schizophrenia." The British Journal of Psychiatry: The Journal of Mental Science 169, no. 5 (November 1996): 610–17.

- *"Glycine was well tolerated, resulted in significantly increased serum glycine levels and induced a mean 36 (7%) reduction in negative symptoms ($P < 0.0001$). Significant improvements were also induced in depressive and cognitive symptoms. The greatest reduction in negative symptoms was registered in the patients who had the lowest baseline serum glycine levels."*

Glycine Treatment May Be Effective for Neuroleptic-resistant Negative Symptoms in Schizophrenia

Javitt, D. C., "Amelioration of Negative Symptoms in Schizophrenia by Glycine." The American Journal of Psychiatry 151, no. 8 (August 1994): 1234–36.

- *"Phencyclidine induces a psychotomimetic state by blocking neurotransmission at N-methyl-D-aspartic acid (NMDA) receptors. In a double-blind, placebo-controlled fashion, 14 medicated patients with chronic schizophrenia were treated with glycine, a potentiator of NMDA-receptor-mediated neurotransmission. Significant improvement in negative symptoms occurred in the group given glycine but not in the group given placebo, suggesting that potentiation of NMDA-receptor-mediated neurotransmission may represent an effective treatment for neuroleptic-resistant negative symptoms in schizophrenia."*

Glycine Therapy Reduced Muscle Stiffness and Extrapyramidal Dysfunction in Schizophrenic Patients on Conventional Neuroleptics

Rosse, R. B., "Glycine Adjuvant Therapy to Conventional Neuroleptic Treatment in Schizophrenia: An Open-Label, Pilot Study." Clinical Neuropharmacology 12, no. 5 (October 1989): 416–24.

- *"In an open-label study, glycine was administered orally (10.8 g/day in three divided doses) to six chronically psychotic patients, as an adjunct to conventional neuroleptic therapy, for periods extending from 4 days to 8 weeks. Glycine was administered in an effort to facilitate endogenous glutamatergic transmission at the level of the N-methyl-D-aspartate (NMDA) receptor complex, since a glutamatergic deficiency in the pathophysiology of schizophrenia has been postulated. Therapeutic efficacy was assessed with standardized psychiatric rating scales. Beneficial effects on behavioral symptomatology were observed in two patients, whereas two others worsened. In one of the two responders, clinical deterioration occurred after glycine withdrawal consistent with a positive adjuvant effect in this patient. However, glycine rechallenge in this*

patient was not associated with the clinical improvement seen during the initial glycine period. Clinical worsening was not observed after glycine discontinuation in the second responder. Glycine administration reduced neuroleptic-induced muscle stiffness and extrapyramidal dysfunction in three of the six patients. All patients tolerated the clinical trial. The limited penetrability of glycine across the blood-brain barrier is a major limitation of this approach to facilitating glutamatergic transmission at the level of the NMDA receptor complex."

Glycine Administration Reduces Positive and Negative Symptoms Significantly

Strzelecki, Dominik, "[Changes in positive and negative symptoms, general psychopathology in schizophrenic patients during augmentation of antipsychotics with glycine: a preliminary 10-week open-label study]." Psychiatria Polska 45, no. 6 (December 2011): 825–37.

- *"After 6 weeks of glycine administration we observed statistically significant improvement in positive (PANSS P subscale, -7.8%, $p < 0.05$), negative symptoms (N subscale, -16.1%, $p < 0.001$), general psychopathology (G subscale, -12.2%, $p < 0.001$) and PANSS total score (T, -12.8%, $p < 0.001$). 2 weeks after the end of glycine augmentation mental status remained stable."*

Glycine was Associated with Reduced Symptoms and Improved Cognitive Function

Woods, Scott W., "Glycine Treatment of the Risk Syndrome for Psychosis: Report of Two Pilot Studies." European Neuropsychopharmacology: The Journal of the European College of Neuropsychopharmacology 23, no. 8 (August 2013): 931–40. doi:10.1016/j.euroneuro.2012.09.008.

- *"We conclude that glycine was associated with reduced symptoms with promising effect sizes in two pilot studies and a possibility of improvement in cognitive function. Further studies of agents that facilitate NMDA receptor function in risk syndrome patients are supported by these preliminary findings."*

Adjunctive High-Dose Glycine Provides a Significant Reduction in Negative Symptoms

Javitt, D. C., "Adjunctive High-Dose Glycine in the Treatment of Schizophrenia." The International Journal of Neuropsychopharmacology / Official Scientific Journal of the Collegium Internationale Neuropsychopharmacologicum (CINP) 4, no. 4 (December 2001): 385–91. doi:doi:10.1017/S1461145701002590.

- *"Glycine treatment was associated with an 8-fold increase in serum glycine levels, similar to that observed previously. A significant 34% reduction in negative symptoms was observed during glycine treatment. Serum antipsychotic levels were not significantly*

altered. Significant clinical effects were observed despite the fact that the majority of subjects were receiving atypical antipsychotics (clozapine or olanzapine). As in earlier studies, improvement persisted following glycine discontinuation."

High-Dose Glycine Significantly Improves Negative Symptoms in Schizophrenia

Heresco-Levy U. High-dose glycine added to olanzapine and risperidone for the treatment of schizophrenia. Biol Psychiatry 2004 Jan 15;55(2):165-71

- *"The negative symptoms improvement remained significant even following covaration for changes in other symptom clusters and extrapyramidal side effects."*

D-phenylanine

D-phenylanine is a Enkephalinase Inhibitor Which Can Treat Endorphin Deficiency States in Schizophrenia

Ehrenpreis, S. "D-phenylalanine and Other Enkephalinase Inhibitors as Pharmacological Agents: Implications for Some Important Therapeutic Application." Acupuncture & Electro-Therapeutics Research 7, no. 2–3 (1982): 157–72.

- *"A number of compounds have been shown to inhibit the degradation of enkephalins. As expected, these compounds produce naloxone reversible analgesia and potentiate the analgesia produced by enkephalins and by acupuncture. One of these, D-phenylalanine, is also anti-inflammatory. D-phenylalanine has proven to be beneficial in many human patients with chronic, intractable pain. It is proposed the enkephalinase inhibitors may be effective in a number of human "endorphin deficiency diseases" such as depression, schizophrenia, convulsive disorders and arthritis. Such compounds may alleviate other conditions associated with decreased endorphin levels such as opiate withdrawal symptoms."*

D-serine

High Dose D-serine is Effective for Both Persistent Symptoms and Neurocognitive Dysfunction

Kantrowitz, Joshua T., "High Dose D-serine in the Treatment of Schizophrenia." Schizophrenia Research 121, no. 1–3 (August 2010): 125–30. doi:10.1016/j.schres.2010.05.012.

- *"These findings support double-blind investigation of D-serine at doses> or =60 mg/kg/d, and suggest effectiveness in treatment of both persistent symptoms and neurocognitive dysfunction."*

D-serine Resulted in Significant Improvements as an Add-on Pharmacotherapy for Schizophrenia

Heresco-Levy U. D-serine efficiency as add-on pharmacotherapy to risperidone and olanzapine for treatment-refractory schizophrenia. Biol Psychiatry 2005 Mar 15:57(6):577-85

- *"D-serine administration induced increased serine serum levels and resulted in significant improvements in negative, positive, cognitive, and depression symptoms, as measured by the Positive and Negative Syndrome Scale."*

D-serine as an Adjunct to Antipsychotic Therapy

Nunes, Emerson A., "D-serine and Schizophrenia: An Update." Expert Review of Neurotherapeutics 12, no. 7 (July 2012): 801–12. doi:10.1586/ern.12.65.

- *"A summary of the relevant animal data, as well as genetic studies and clinical trials examining D-serine as an adjunct to standard antipsychotic therapy, is provided in this article. Together, the evidence suggests that research on the next generation of antipsychotic agents should include studies on increasing brain levels of D-serine or mimicking its action on the NMDA receptor."*

Adjunctive D-serine Revealed Significant Improvements in Positive, Negative, and Cognitive Symptoms

Tsai, G., "D-serine Added to Antipsychotics for the Treatment of Schizophrenia." Biological Psychiatry 44, no. 11 (December 1, 1998): 1081–89.

- *"Patients who received D-serine treatment revealed significant improvements in their positive, negative, and cognitive symptoms as well as some performance in WCST. D-serine levels at week 4 and 6 significantly predicted the improvements. D-serine was well tolerated and no significant side effects were noted."*

L-carnosine

L-carnosine Merits Further Consideration as Adjunctive Treatment to Improve Executive Dysfunction in Schizophrenia

Chengappa, K. N. Roy, "A Preliminary, Randomized, Double-Blind, Placebo-Controlled Trial of L-Carnosine to Improve Cognition in Schizophrenia." Schizophrenia Research 142, no. 1–3 (December 2012): 145–52. doi:10.1016/j.schres.2012.10.001.

- *"The L-carnosine group performed significantly faster on non-reversal condition trials of the set-shifting test compared with placebo but reversal reaction times and errors were*

not significantly different between treatments. On the strategic target detection test, the L-carnosine group displayed significantly improved strategic efficiency and made fewer perseverative errors compared with placebo. Other cognitive tests showed no significant differences between treatments. Psychopathology scores remained stable. The carnosine group reported more adverse events (30%) compared with the placebo group (14%). Laboratory indices remained within acceptable ranges. These preliminary findings suggest that L-carnosine merits further consideration as adjunctive treatment to improve executive dysfunction in persons with schizophrenia."

L-lysine

L-Lysine is a Therapeutic Adjunctive Therapy in Patients with Chronic Schizophrenia

Zeinoddini, Atefeh, "L-Lysine as an Adjunct to Risperidone in Patients with Chronic Schizophrenia: A Double-Blind, Placebo-Controlled, Randomized Trial." Journal of Psychiatric Research, September 6, 2014. doi:10.1016/j.jpsychires.2014.08.016.

- *"The present study demonstrated that l-lysine can be a tolerable and efficacious adjunctive therapy for improving negative and general psychopathology symptoms in chronic schizophrenia. However, the safety and efficacy of higher doses of l-lysine and longer treatment periods still remain unknown."*

L-Lysine is an Efficient adjunctive Therapy Improving Negative and General Psychopathology

Zeinoddini, Atefeh, "L-Lysine as an Adjunct to Risperidone in Patients with Chronic Schizophrenia: A Double-Blind, Placebo-Controlled, Randomized Trial." Journal of Psychiatric Research, September 6, 2014. doi:10.1016/j.jpsychires.2014.08.016.

- *"The present study demonstrated that l-lysine can be a tolerable and efficacious adjunctive therapy for improving negative and general psychopathology symptoms in chronic schizophrenia. However, the safety and efficacy of higher doses of l-lysine and longer treatment periods still remain unknown.*

L-lysine Patients Showed a Significant Decrease in Positive Symptoms

Wass, Caroline, "L-Lysine as Adjunctive Treatment in Patients with Schizophrenia: A Single-Blinded, Randomized, Cross-over Pilot Study." BMC Medicine 9 (2011): 40. doi:10.1186/1741-7015-9-40.

- *"Four-week L-lysine treatment of 6 g/day caused a significant increase in blood concentration of L-lysine that was well tolerated. Patients showed a significant decrease in positive symptoms as assessed by PANSS in addition to self-reported symptom*

improvement by three patients. The NO-signaling pathway is an interesting, potentially new treatment target for schizophrenia; however, the effects of L-lysine need further evaluation to decide the amino acid's potentially beneficial effects on symptom severity in schizophrenia."

L-theanine

L-theanine Relieves Positive, Activation, and Anxiety Symptoms in Patients with Schizophrenia

Ritsner MS. L-theanine relieves positive, activation, and anxiety symptoms in patients with schizophrenia and schizoaffective disorder: an 8 week, randomized, double-blind, placebo-controlled, 2-center study. J Clin Psychiatry 2011 Jan;72(1):34-42

- *"40 patients completed the study protocol. Compared with placebo, L-theanine augmentation was associated with reduction of anxiety (P= .015; measured by the HARS scale) and positive (P= .009) and general psychopathology (P<.001) scores (measured by PANSS 3-dimensional model). According to the 5-dimension model of psychopathology, L-theanine produced significant reductions on PANSS positive (P= .004) and activation factor (P= .006) scores compared to placebo." ….L-theanine augmentation of antipsychotic therapy can ameliorate positive, activation and anxiety symptoms in schizophrenia and schizoaffective disorder patients, "*

L-theanine has Antipsychotic and Possibly Antidepressant Effects

Wakabayashi C. Behavioral and molecular evidence for psychotropic effects in L-theanine. Psychopharmacology (Berl) 2012 Feb;219(4):1099-109

- *"Our results suggest that L-theanine has antipsychotic-like and possibly antidepressant-like effects. It exerts these effects, at least in part, through induction of BDNF in the hippocampus and the agonistic action of L-theanine on the NMDA receptor."*

L-tryptophan (Tryptophan)

Tryptophan May Be Useful in the Treatment of Aggressive Schizophrenics

Morand, C., "Clinical Response of Aggressive Schizophrenics to Oral Tryptophan." Biological Psychiatry 18, no. 5 (May 1983): 575–78.

- *"However, tryptophan may be useful in treating aggressive symptoms in patients with poor impulse control who were characterized in this study as having high Buss-Durkee scores, high lifetime aggression frequency, and normal GSRs. Although aggressive behavior has been linked to many neurotransmitters the present study indicates that 5HT can be manipulated in a simple way through administration of the nontoxic dietary 5HT*

precursor, tryptophan, to modulate aggressive symptomology. We are reporting these preliminary results now in the hope of encouraging other further studies."

Tryptophan Has a Beneficial Effect on Memory in Schizophrenia

Levkovitz, Yechiel, "Effect of L-Tryptophan on Memory in Patients with Schizophrenia." The Journal of Nervous and Mental Disease 191, no. 9 (September 2003): 568–73. doi:10.1097/01.nmd.0000087182.29781.e0.

- *"Compared with placebo, l-tryptophan had a beneficial effect on memory functions but not on the patients' psychotic state or on the side effects of medications. These preliminary results suggest the possibility of using serotonin precursor to enhance memory function in schizophrenia."*

5-hydroxtryptophan

L-5HTP Attenuates Amphetamine Induced Positive Psychotic Symptoms

Irwin MR. L-5-hydroxtryptophan attenuates positive psychotic symptoms induced by D-amphetamine. Psychiatric Res 1987 Dec;22(4):283-9

- *"Pre-administration with 5HTP significantly antagonized amphetamine-elicited elevations in thought disturbance, activation, and hallucinations."*

Peptides

Amylin Peptide

Amylin Peptide May Be a Potential Target for Antipsychotic Medication Research

Baisley, Sarah K., "Antipsychotic-like Actions of the Satiety Peptide, Amylin, in Ventral Striatal Regions Marked by Overlapping Calcitonin Receptor and RAMP-1 Gene Expression." The Journal of Neuroscience: The Official Journal of the Society for Neuroscience 34, no. 12 (March 19, 2014): 4318–25. doi:10.1523/JNEUROSCI.2260-13.2014.

- *"Coinfusion of AC187 (20 μg), an antagonist for AMY1-R, blocked the ability of amylin to normalize AMPH-induced PPI disruption, showing the specificity of AcbSh amylin effects to the AMY1-R. Intra-AcbSh AC187 on its own disrupted PPI in a haloperidol-reversible manner (0.1 mg/kg). Thus, AMY1-R may be a potential target for the development of putative antipsychotics or adjunct treatments that oppose metabolic side effects of current medications. Moreover, AMY1-Rs may represent a novel way to modulate activity preferentially in ventral versus dorsal striatum."*

Caerulein Diethylamine

Ceruletide Has Long Acting Antipsychotic Effects on Schizophrenics

Moroji, T., "Antipsychotic Effects of Ceruletide (caerulein) on Chronic Schizophrenia." Archives of General Psychiatry 39, no. 4 (April 1982): 485–86.

- *"Our clinical observations indicate that ceruletide—whatever its mechanism—may have a long-acting antipsychotic effect in schizophrenia and, as they differ from conventional neuroleptics, CCK-like peptides could be a useful and effective antipsychotic drug."*

Caerulein Has Rapid Action and Long Lasting Effects in Certain types of Schizophrenia

Moroji, T., "Antipsychotic Effects of Ceruletide in Chronic Schizophrenia. An Appraisal of the Long-Term, Intermittent Medication of Ceruletide in Chronic Schizophrenia." Annals of the New York Academy of Sciences 448 (1985): 518–34.

- *"Based on the above findings, caerulein, a decapeptide chemically related to CCK-8, may have therapeutic efficacy in certain types(s) of chronic schizophrenia with rapidity of action and long duration. Caerulein also appears to be applicable to clinical practice with high safety. Before classed as a therapeutic agent, however, there are a great number of urgent problems to be resolved, like the confirmation of clinical utility in double-blind controlled trials and the safety of long-term administration."*

Caerulein Diethylamine Has Therapeutic Value in the Treatment of Schizophrenia

Itoh, H., "Clinical Study on the Psychotropic Effects of Caerulein--an Open Clinical Trial in Chronic Schizophrenic Patients." The Keio Journal of Medicine 31, no. 3 (October 1982): 71–95.

- *"An open clinical trial of caerulein diethylamine, a cholecystokinin analogue, was performed in a total of 58 chronic schizophrenic patients maintained on drugs such as antipsychotic agents without dosage modification. The neuro peptide medication by intramuscular route produced a clinical improvement in 20 cases and was eventually assessed to have been of therapeutic value in 23 cases. Clinical responses to the medication observed in the present series included: subjective changes in mood mostly to become feeling "fine" or "refreshed in the head", improvement in contact, increased spontaneity and objective behavioral changes such as restlessness and excitement. These features of clinical responses observed in respect of mental condition seem to indicate that the drug affects emotion and exerts an analeptic effect as its principal clinical effects. The clinical effects were remarkably long sustained for 1-2 weeks after a single i.m. dose in most responders. Feeling of facial warmth and lassitude as well as symptoms of the gastrointestinal system were encountered as attendant symptoms in 6 cases."*

Caerulein Has Long Lasting Antipsychotic Activity in Chronic Schizophrenia

Moroji, T., "Antipsychotic Effects of Caerulein, a Decapeptide Chemically Related to Cholecystokinin Octapeptide, on Schizophrenia." International Pharmacopsychiatry 17, no. 4 (1982): 255–73.

- *"Caerulein, a decapeptide chemically related to CCK-8, was administered intramuscularly to 20 patients with chronic schizophrenia in two different doses of 0.3 and 0.6 microgram/kg. BPRS ratings were made before and 3 weeks after the injection. The neuroleptic therapy was not discontinued, but both drug and dose were not changed at least 3 weeks before the first injection and during the study period. Clinically obvious and statistically significant improvement in psychotic symptoms occurred shortly after the injection of caerulein. The greatest change occurred 1--2 weeks later. There was an evident correlation between the observed changes and the dose injected. Our findings suggest that caerulein has a long-acting, antipsychotic activity in chronic schizophrenia. Furthermore, our findings suggest the involvement of CCK-like peptides in the pathogenesis of schizophrenia."*

Cholecystokinn-Octapeptide

Cholecystokinin Peptides (CCK-8, CCK-33) Have Shown Therapeutic Effect in Numerous Clinical Trials

Nair, N. P., "Cholecystokinin Peptides, Dopamine and Schizophrenia--a Review." Progress in Neuro-Psychopharmacology & Biological Psychiatry 9, no. 5–6 (1985): 515–24.

- *"In man there is endrocrinological evidence for an inhibitory effect of CCK-33 and CCK-8 on DA function. However, alternate explanations are possible. CSF CCK-IR is unchanged or decreased in schizophrenia. Autopsy investigations have shown significant decreases, increases or no change in brain CCK-IR concentrations and a decrease in CCK-33 binding in schizophrenia. Eight of 11 clinical trials with CER, CCK-8 or CCK-33 have shown a therapeutic effect in schizophrenia; only two of these eight trials have been double blind studies. The three controlled investigations which have shown no effect have used only small patient populations. None of the trials have used an active placebo."*

Cholecystokinn-Octapetide Has Definite Antipsychotic Properties

Nair, N. P., "Cholecystokinin-Octapeptide in Chronic Schizophrenia: A Double-Blind Placebo-Controlled Study." Progress in Neuro-Psychopharmacology & Biological Psychiatry 8, no. 4–6 (1984): 711–14.

- *"It is concluded that CCK-8 has definite antipsychotic properties in patients with chronic schizophrenia. Clinical trials in neuroleptic-free patients are warranted."*

Desenkephalin-Gamma-Enorphin (DE gamma E)

Desenkephalin-Gamma-Endorphin and Ceruletide were both Effective as Neuroleptics in Schizophrenic Patients

Verhoeven, W. M., "A Comparative Study on the Antipsychotic Properties of Desenkephalin-Gamma-Endorphin and Ceruletide in Schizophrenic Patients." Acta Psychiatrica Scandinavica 73, no. 4 (April 1986): 372–82.

- *"The neuropeptides desenkephalin-gamma-endorphin (DE gamma E) and ceruletide were administered intramuscularly to patients with schizophrenic psychoses following a double-blind placebo-controlled design, including a total of 44 subjects. Neuroleptic medication was continued during the experimental period, which was started with one placebo injection for all patients. One week later subjects received a single intramuscular injection with 3 mg DE gamma E, 40 micrograms ceruletide or placebo. After an interval of 10 days, the patients received six similar injections over a period of 2 weeks. Treatment with either peptides resulted in a decrease of psychotic symptomatology as compared to placebo treatment. The beneficial effect of the peptides lasted at least 2 weeks after the experimental treatment period. Of the 14 patients treated with placebo only, three showed a slight response. Of the 30 patients treated with the neuropeptides, eight did not respond (DE gamma E: 3; ceruletide: 5), eight had a slight response (DE gamma E: 6; ceruletide: 2) and 14 responded moderately or markedly (DE gamma E: 6; ceruletide: 8). No obvious difference between the effects of the two neuropeptides was found, besides a somewhat earlier onset of the effect of ceruletide. Patients presenting relatively less negative psychotic symptoms were particularly susceptible to treatment with either peptide. Apart from slight and short-lasting gastrointestinal complaints after the first injections with ceruletide in some patients, no side effects were observed."*

Des-Enkephalin-Gamma-Endorphin has Antipsychotic Properties in Treatment of Schizophrenia

Verhoeven, W. M., "Antipsychotic Properties of Des-Enkephalin-Gamma-Endorphin in Treatment of Schizophrenic Patients." Archives of General Psychiatry 39, no. 6 (June 1982): 648–54.

- *"Animal experiments have shown that the gamma-endorphin fragment des-enkephalin-gamma-endorphin (DE gamma E; beta-lipotropin 66-77) is the shortest sequence with neuroleptic-like activity with potency comparable to des-tyrosine-gamma-endorphin. We postulated that DE gamma E may be an endogenous peptide implicated in psychopathologic disease, particularly schizophrenia. To investigate the purported antipsychotic action of DE gamma E, 23 patients with different types of relapsing schizophrenia were treated with DE gamma E dissolved in saline or placebo. Neuroleptic medication was continued during the experimental period. In the first single-blind trial,*

two patients were treated with 1 mg of DE gamma E and two with 10 mg of DE gamma E intramuscularly (IM) daily for ten days. In the second double-blind placebo-controlled trial 13 patients were treated with 3 mg of DE gamma E IM daily for ten days and six received placebo. Of the 17 patients treated with DE gamma E, two did not respond, 11 had a slight to moderate effect, and four responded markedly. No side effects were observed. The response to DE gamma E appeared to be negatively correlated with the dosage of neuroleptic medication and the duration of the last psychotic episode. These results support the hypothesis that disturbances in gamma-endorphin fragmentation might contribute to the pathogenesis of schizophrenic psychoses."

DTgammaE

DTgammaE has Neuroleptic-like Activity in Schizophrenia

Verhoeven, W. M., "Improvement of Schizophrenic Patients Treated with [des-Tyr1]-Gamma-Endorphin (DTgammaE)." Archives of General Psychiatry 36, no. 3 (March 1979): 294–98.

- *"It was postulated from animal experiments that gamma-endorphin and, in particular, the nonopiate-like peptide [des-Tyr1]-gamma-endorphin (DTgammaE, beta-lipotropin [beta-LPH]62-77) have neurolepic-like activity. To test this, 14 patients with long-lasting, relapsing schizophrenic or schizoaffective psychosis resistant to conventional neuroleptics were treated with DTgammaE. An open design was used first for six patients (study 1) and a double-blind, crossover design for the other eight (study 2). In study 1, all neuroleptic medication was discontinued and 1 mg of DTgammaE zinc phosphate was given daily intramuscularly for about seven days. In study 2, six patients were maintained with neuroleptic therapy and two patients were drug free; all eight received daily intramuscular injections of 1 mg of nonlasting DTgammaE in saline and solution for eight days. There was transient or semipermanent improvement in both studies in which the psychotic symptoms diminished or even disappeared. In study 2, there was a slight but significant improvement with the first treatment. Improvement continued and by day 4, the psychotic symptoms had almost disappeared. No toxic side effects were noted. These effects of DTgammaE may be a consequence of the normalization of beta-endorphin homeostasis in the brain."*

DTgammaE has Effective Pharmalogical Action in Schizophrenic Patients

Meltzer, H. Y., "Effect of (Des-Tyr)-Gamma-Endorphin in Schizophrenia." Psychiatry Research 6, no. 3 (June 1982): 313–26.

- *"Des-tyrosine-gamma-endorphin (DT gamma E), a derivative of gamma-endorphin, which has been reported to have some neuroleptic-like properties in man, was administered to eight hospitalized schizophrenic patients (six chronic, one subacute, one*

acute) in an open study. Following an initial drug-free period, patients were given DT gamma E for 12 days in doses ranging from 1 to 10 mg/day. Two of the patients were markedly improved after receiving DT gamma E. The improvement was sustained for 2 months in one subjects, while the other deteriorated to pretreatment status within 48 hours of the discontinuation of DT gamma E. Of the other six patients, one showed moderate improvement, three showed minimal improvement, and two showed no change. Improvement was mainly in the area of social functioning; change in positive psychotic symptoms was less noticeable. The positive results obtained in this study in some subjects could have been nonspecific effects, rather than pharmacological action, since social functioning, the main area of improvement, may be especially sensitive to expectancy effects in open trials. Nevertheless, further study of DT gamma E in acute schizophrenics for longer periods appears indicated."

Gamma-Endorphin

Pharmacological Actions of Gamma-Type Endorphins are Similar to Neuroleptics

Van Praag, H. M., "The Treatment of Schizophrenic Psychoses with Gamma-Type Endorphins." Biological Psychiatry 17, no. 1 (January 1982): 83–98.

- *"The pharmacological actions of γ-type endorphins show similarities to those of the neuroleptics. Two fragments of γ-endorphin (β-LPH 61-77) were therefore tested in patients with schizophrenic and schizoaffective psychoses who had shown an insufficient response to neuroleptics. The fragments were DTγE (β-LPH 62-77) and DEγE (β-LPH 66-77). Some of the patients studied responded favorably to this treatment. "*

Glycomacropeptide

Dietary Glycomacropeptide: A Novel Nutritional Treatment for Manic and Psychotic Disorders

Badawy A. Novel nutritional treatment for manic and psychotic disorders: a review of tryptophan and tyrosine depletion studies and the potential of protein-based formulations using glycomacropeptide. Psychopharmacology (2013) 228: 347-358

- *"A palatable alternative lacking Trp, Tyr and Phe has been identified in the whey protein fraction caseino-glycomacropeptide (c-GMP). The absence of these three aromatic amino acids renders GMP suitable as a template for seven formulations for separate and combined depletion or loading and placebo control. The absence of Phe and Tyr enables GMP to provide a unique nutritional therapy of manic and psychotic disorders by inhibition of cerebral dopamine synthesis and release and possibly also by enhancing glutamatergic function, in general, and in patients resistant to antipsychotic medication, in particular."*

Thymalin

Thymic Peptide Thymalin was Therapeutic in Schizophrenic Patients with Immune Abnormalities

Govorin, N. V., "[Use of thymic peptide thymalin in the complex treatment of therapy-resistant schizophrenia]." Zhurnal Nevropatologii I Psikhiatrii Imeni S.S. Korsakova (Moscow, Russia: 1952) 90, no. 3 (1990): 100–103.

- *"The thymic peptide thymaline combined with psychotropic drugs was used in the treatment of 36 therapeutically resistant patients with pronounced immune abnormalities. Such a policy favoured considerable enhancement of the treatment efficacy which manifested itself by the elimination or amelioration of psychic disorders, appreciable activation of patients and reduction of neuroleptic complications. The positive dynamics in the patients' status always correlated with the normalization of immune abnormalities, with this being seen to a greater degree in cases of the secondary "pharmacogenic" resistance and resistance because of the "pathological ground". On the one hand, the studies demonstrated wide potentialities of the use of thymaline in the treatment of the resistant patterns of schizophrenia. On the other hand, they showed the heterogeneity of immune abnormalities in patients with different varieties of resistance."*

Hormones

DHEA

DHEA Improves Negative Symptoms in Schizophrenia

Strous RD. Dehydroepiandrosterone augmentation in the management of negative, depressive, and anxiety symptoms in schizophrenia. Arch Gen Psychiatry 2003 Feb;60(2): 133-41

- *"Increases in DHEA and DHEA-S levels were correlated with improvement in negative symptoms (P<.05), but not with improvement in depressive and anxiety symptoms."*

Strous RD. Dehydroeplandrosterone (DHEA) augmentation in the management of schizophrenia symptomology. Essent Psychopharmacol 2005;6(3):141-7

- *"In the authors study, administering DHEA to patients with schizophrenia who had moderate to severe negative symptoms and who were maintained on antipsychotic medications induced significant improvement, more so in women and corresponding to increased plasma levels of DHEA and DHEA-S."*

DHEA Treatment is Associated with Significant Improvement in Cognitive Function

Ritsner MS. Improvement of sustained attention and visual and movement skills, but not clinical symptoms, after dehydroepiandrosterone augmentation in schizophrenia: a randomized, double-blind, placebo-controlled crossover trial. J Clin Psychopharmacol 2006 Oct;26(5);495-9

- *Compared to placebo, DHEA administration did not produce significant improvement in clinical symptoms, side effects, and quality-of-life scores. However, 6 weeks of DHEA administration (but not placebo) was associated with a significant improvement in Positive and Negative Symptom Scale ratings compared with baseline. Furthermore, 6 weeks of DHEA treatment was associated with significant improvement in cognitive functions of visual sustained attention and visual and movement skills compared with placebo conditions."*

Estrogen (Oestrogen)

Adjunctive Estrogen Treatment Showed a Significant Decrease in Positive and Negative Symptoms

Ghafari, Emel, "Combination of Estrogen and Antipsychotics in the Treatment of Women with Chronic Schizophrenia: A Double-Blind, Randomized, Placebo-Controlled Clinical Trial." Clinical Schizophrenia & Related Psychoses 6, no. 4 (January 2013): 172–76. doi:10.3371/CSRP.GHFA.01062013.

- *"The combination of conjugated estrogens with antipsychotic treatment showed a significant decrease in positive ($p=0.003$), negative ($p<0.001$), general ($p<0.001$) and total ($p<0.001$) PANSS scores over 4 weeks. Estrogen may be an effective adjuvant agent in the treatment of women with chronic schizophrenia."*

Further Exploration of Adjunctive Estrogen Treatment in Men in Schizophrenia is Warranted

Kulkarni, Jayashri, "The Role of Estrogen in the Treatment of Men with Schizophrenia." International Journal of Endocrinology and Metabolism 11, no. 3 (2013): 129–36. doi:10.5812/ijem.6615.

- *"Findings do, however, suggest that further exploration of a therapeutic role for adjunctive estradiol treatment in men with schizophrenia is warranted. The development of the new estrogen compounds - Selective Estrogen Receptor Modulators (SERMs) which do not cause feminisation - opens up the possibility of using a different type of estrogen for a longer period of time at higher doses. Estrogen could therefore prove to be an important component in the treatment of psychotic symptoms in men with schizophrenia. This review explains the scientific rationale behind the estrogen hypothesis*

and how it can be clinically utilised to address concerns unique to the care of men with schizophrenia."

Kulkami J. Estrogens and men with schizophrenia: is there a case for adjunctive therapy? Schizophr Res 2011 Feb;125(2-3):278-83

- *"Results demonstrated for estradiol participants a more rapid reduction in general psychopathology that occurred in the context of greater increases in serum estrogen levels and reductions in FSH and testosterone levels."*

Oestrogen to Added to Antipsychotics Reduces Psychosis in Women and Men

Kulkarni, Jayashri. "Oestrogen--a New Treatment Approach for Schizophrenia?" The Medical Journal of Australia 190, no. 4 Suppl (February 16, 2009): S37–38.

- *"The oestrogen protection hypothesis proposes that oestrogen has a protective effect against onset of schizophrenia. In support of this: Epidemiological studies have shown that young women are less likely to develop schizophrenia than men of the same age, and women are more likely to develop late-onset schizophrenia after menopause. Clinical studies have shown higher psychotic symptoms in perimenopausal women, and women at the low oestrogen phase of the menstrual cycle. Animal studies provide further evidence in support of the oestrogen protection hypothesis. Three randomised double-blind placebo-controlled trials and an open-label study showed that adding oestradiol to women's usual antipsychotic medications was associated with significant abatement of schizophrenia symptoms. A small study of men with schizophrenia who received oral oestradiol valerate also showed a significant abatement in psychotic symptoms. Although oestrogen appears to be a useful treatment for schizophrenia, further research is required to determine the correct dose and duration of use of oestradiol. New types of oestrogen compounds may provide a safer, non-feminising approach for the treatment of schizophrenia."*

Grigoriadis S. The role of estrogen in schizophrenia:implications for schizophrenia practice guidelines for women. Can J Psychiatry. 2002 Jun;47(5):437-42

- *"Estrogen has been used effectively as an adjunctive treatment in women with schizophrenia. Estrogen may also play a preventive role in TD."*

Kulkarni J. Estrogen in severe mental illness: a potential new treatment approach. Arch Gen Psychiatry 2008 Aug; 65(8):955-60

- *"Estradiol appears to be a useful treatment for women with schizophrenia and may provide a new adjunctive therapeutic option for severe mental illness."*

Hormone Replacement Therapy

Adjunctive Hormone Replacement Therapy May Help Reduce Negative Symptoms in Schizophrenia

Lindamer, L. A., "Hormone Replacement Therapy in Postmenopausal Women with Schizophrenia: Positive Effect on Negative Symptoms?" Biological Psychiatry 49, no. 1 (January 1, 2001): 47–51.

- *"Our results suggest that the use of hormone replacement therapy in conjunction with antipsychotic medication in postmenopausal women with schizophrenia may help reduce negative, but not positive, symptoms."*

Leptin

Leptin Supplementation May Reduce Positive Symptoms in Schizophrenics by Reducing Cortisol and Oxidative Stress

Venkatasubramanian, Ganesan, "Neuropharmacology of Schizophrenia: Is There a Role for Leptin?" Clinical Chemistry and Laboratory Medicine: CCLM / FESCC 48, no. 6 (June 2010): 895–96. doi:10.1515/CCLM.2010.158.

- *"Thus, it is possible that the magnitude of the central nervous system effects of leptin might be proportionate to its peripheral concentration wsummarized in (1)x. Moreover, ample evidence supports a neuroprotective effect of leptin (3). Of interest, leptin receptors are found in the cerebral cortex, hippocampus, basal ganglia, hypothalamus, brainstem, and cerebellum (3). In addition, gray matter concentrations in the anterior cingulate gyrus, inferior parietal lobule and cerebellum increased significantly following replacement therapy with leptin in genetically leptin deficient subjects (4). Even in healthy elderly subjects, a significant positive correlation was observed between plasma leptin concentrations and the right hippocampus (5). It is important to note that schizophrenia patients demonstrate deficits in these brain regions summarized in (1)x that have been shown to be influenced by leptin in the above-mentioned studies (3–5). Moreover, these brain regions, especially the limbic brain circuit regions, such as the hippocampus, have been shown to underlie the genesis of positive symptoms in schizophrenia. Hippocampal volume deficits can be caused by high cortisol concentrations and an aberrant hyperactive hypothalamic-pituitary-adrenal (HPA) axis. The resultant hypercortisolemia has been proposed as one of the contributing factors in the pathogenesis of schizophrenia (6). Interestingly, leptin can potentially reduce HPA axis hyperactivity by inhibiting the release of corticotrophin releasing hormone in the hypothalamus (7). Thus, leptin might have an indirect protective effect on the hippocampus by ameliorating hypercortisolemia (7), as well as a direct protective effect by reducing oxidative stress (8). Critically, both hypercortisolemia as well as oxidative stress have been shown to be associated with positive symptoms in schizophrenia. In this context, the significant positive correlation between baseline serum leptin concentrations and improvements in*

positive symptoms supports the possibility of a neuroprotective and anti-apoptotic effects of leptin that facilitate clinical improvements in schizophrenia"

Oxytocin

Oxytocin Has Psychotropic Effects Which Can Be Utilized for Psychosis Treatment

Bakharev, V. D., "[Psychotropic properties of oxytocin]." Problemy Ėndokrinologii 30, no. 2 (April 1984): 37–41.

- *"Oxytocin neurotropic qualities were investigated in "reserpine depression" tests under ethanol and levomepromazine anesthesia, phenamine depression, haloperidol catatonia and swimming of experimental animals in the cylinder. Twenty seven patients with schizophrenia were treated with the hormone mentioned, injected intravenously and/or intranasally, using a double blind control test. The activating psychotropic oxytocin effects were revealed, allowing one to utilize it as a therapeutic means for psychosis treatment."*

Adjunctive Oxytocin Efficaciously Improves Positive Symptoms of Schizophrenia

Modabbernia, Amirhossein, "Intranasal Oxytocin as an Adjunct to Risperidone in Patients with Schizophrenia : An 8-Week, Randomized, Double-Blind, Placebo-Controlled Study." CNS Drugs 27, no. 1 (January 2013): 57–65. doi:10.1007/s40263-012-0022-1.

- *"Oxytocin as an adjunct to risperidone tolerably and efficaciously improves positive symptoms of schizophrenia. In addition, effects on negative and total psychopathology scores were statistically significant, but likely to be clinically insignificant. The interesting findings from the present pilot study need further replication in a larger population of patients."*

Oxytocin May Represent a Novel Adjunctive Treatment for Patients with Schizophrenia.

De Berardis, Domenico, "The Role of Intranasal Oxytocin in the Treatment of Patients with Schizophrenia: A Systematic Review." CNS & Neurological Disorders Drug Targets 12, no. 2 (March 2013): 252–64.

- *"Some authors report that intranasal oxytocin administration to schizophrenic patients may reduce symptomatology. The aim of the present paper was to review studies investigating symptomatology, social cognition and emotion recognition changes in DSM-IV-TR schizophrenic patients, after administration of intranasal oxytocin at different doses. Literature search was conducted in March, 2012. PubMed and Scopus databases were used to find studies for inclusion in the systematic review. Oxytocin may represent an important novel adjunctive treatment for patients with schizophrenia.*

However, some limitations of current studies cannot be overlooked and further investigations are certainly needed."

Oxytocin Enhances the Effectiveness of Cognitive Skills Training When Administered Before Training

Davis, Michael C.,"Oxytocin-Augmented Social Cognitive Skills Training in Schizophrenia." Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology 39, no. 9 (August 2014): 2070–77. doi:10.1038/npp.2014.68.

- *"This study provides initial support for the idea that OT enhances the effectiveness of training when administered shortly before social cognitive training sessions. The effects were most pronounced on empathic accuracy, a high-level social cognitive process that is not easily improved in current social cognitive remediation programs."*

Oxytocin Administration Improves Schizophrenic Patients Ability to Recognize Emotions

Averbeck, B. B., "Emotion Recognition and Oxytocin in Patients with Schizophrenia." Psychological Medicine 42, no. 2 (February 2012): 259–66. doi:10.1017/S0033291711001413.

- *"In the first experiment we found that patients with schizophrenia had a deficit relative to controls in recognizing emotions. In the second experiment we found that administration of oxytocin improved the ability of patients to recognize emotions. The improvement was consistent and occurred for most emotions, and was present whether patients were identifying morphed or non-morphed faces. These data add to a growing literature showing beneficial effects of oxytocin on social-behavioral tasks, as well as clinical symptoms."*

Intranasal Oxytocin Exhibits Antipsychotic Properties and Has a Greater Reduction of Symptoms Compared to Placebo

Feifel D. Adjunctive intranasal oxytocin reduces symptoms in schizophrenic patients. Biol Psychiatry 2010;68:678-680

- *"We found that 3 weeks of intranasal oxytocin given adjunctive to standard antipsychotic medications, caused significantly greater reductions in schizophrenia symptoms at the end point compared with placebo. This result supports our hypothesis that oxytocin exhibits antipsychotic properties and validates preclinical studies, case reports, and less well controlled clinical studies suggesting oxytocin's ability to ameliorate symptoms of schizophrenia"*

Oxytocin is Effective for Social Cognition Improvements in Schizophrenia

Gibson, Clare M., "A Pilot Six-Week Randomized Controlled Trial of Oxytocin on Social Cognition and Social Skills in Schizophrenia." Schizophrenia Research 156, no. 2–3 (July 2014): 261–65. doi:10.1016/j.schres.2014.04.009.

- *"The current study explored whether oxytocin can improve social cognition and social skills in individuals with schizophrenia using a six-week, double-blind design. Fourteen participants with schizophrenia were randomized to receive either intranasal oxytocin or a placebo solution and completed a battery of social cognitive, social skills and clinical psychiatric symptom measures. Results showed within group improvements in fear recognition, perspective taking, and a reduction in negative symptoms in the oxytocin group. These preliminary findings indicate oxytocin treatment may help improve certain components of functioning in schizophrenia. Implications for the treatment of social functioning in schizophrenia are discussed."*

Intranasal Oxytocin Improves Verbal Memory in People with Schizophrenia

Feifel, David, "Adjunctive Intranasal Oxytocin Improves Verbal Memory in People with Schizophrenia." Schizophrenia Research 139, no. 1–3 (August 2012): 207–10. doi:10.1016/j.schres.2012.05.018.

- *"We found no evidence for an amnestic effect and, in fact, significantly better performance with oxytocin on several subtests of the CVLT; namely total Recall trials 1-5 (p=0.027), short delayed free recall (p=0.032) and total recall discrimination (p=0.020). In contrast we found no difference between placebo and oxytocin on LNS performance. This is the first report we are aware of documenting a beneficial effect of oxytocin on cognition in schizophrenia. Though from a small sample (n=15), these data both offset past concerns about oxytocin's amnestic effects, and may auger another potential benefit in addition to the already-demonstrated salutary effects on other components of the illness."*

Pregnenolone

Pregnenolone Treatment Reduces Severity of Negative Symptoms in Schizophrenia

Ritsner, Michael S., "Pregnenolone Treatment Reduces Severity of Negative Symptoms in Recent-Onset Schizophrenia: An 8-Week, Double-Blind, Randomized Add-on Two-Center Trial." Psychiatry and Clinical Neurosciences 68, no. 6 (June 2014): 432–40. doi:10.1111/pcn.12150.

- *"Thus, add-on pregnenolone reduces the severity of negative symptoms in recent-onset schizophrenia and schizoaffective disorder, especially among patients who are not treated with concomitant mood stabilizers. Further studies are warranted."*

Pregnenolone May Be a Novel Candidate for Treatment of Negative Symptoms in Schizophrenia

Marx, C. E., "Pregnenolone as a Novel Therapeutic Candidate in Schizophrenia: Emerging Preclinical and Clinical Evidence." Neuroscience 191 (September 15, 2011): 78–90. doi:10.1016/j.neuroscience.2011.06.076.

- *"Treatment with adjunctive pregnenolone significantly decreased negative symptoms in patients with schizophrenia or schizoaffective disorder in a pilot proof-of-concept randomized controlled trial, and elevations in pregnenolone and allopregnanolone post-treatment with this intervention were correlated with cognitive improvements [Marx et al. (2009) Neuropsychopharmacology 34:1885-1903]. Another pilot randomized controlled trial recently presented at a scientific meeting demonstrated significant improvements in negative symptoms, verbal memory, and attention following treatment with adjunctive pregnenolone, in addition to enduring effects in a small subset of patients receiving pregnenolone longer-term [Savitz (2010) Society of Biological Psychiatry Annual Meeting New Orleans, LA]. A third pilot clinical trial reported significantly decreased positive symptoms and extrapyramidal side effects following adjunctive pregnenolone, in addition to increased attention and working memory performance [Ritsner et al. (2010) J Clin Psychiatry 71:1351-1362]. Future efforts in larger cohorts will be required to investigate pregnenolone as a possible therapeutic candidate in schizophrenia, but early efforts are promising and merit further investigation. This article is part of a Special Issue entitled: Neuroactive Steroids: Focus on Human Brain."*

Low-Dose Pregnenolone Augmentation Demonstrated Significant Reduction of Positive Symptoms and Cognitive Function

Ritsner, Michael S., "Pregnenolone and Dehydroepiandrosterone as an Adjunctive Treatment in Schizophrenia and Schizoaffective Disorder: An 8-Week, Double-Blind, Randomized, Controlled, 2-Center, Parallel-Group Trial." The Journal of Clinical Psychiatry 71, no. 10 (October 2010): 1351–62. doi:10.4088/JCP.09m05031yel.

- *"Low-dose PREG augmentation demonstrated significant amelioration of positive symptoms and EPS and improvement in attention and working memory performance of schizophrenia and schizoaffective disorder patients. Further double-blind controlled studies are needed to investigate the clinical benefit of pregnenolone augmentation."*

Pregnenolone May Be a Promising Therapeutic Agent for Negative Symptoms in Schizophrenia

Marx, Christine E., "Proof-of-Concept Trial with the Neurosteroid Pregnenolone Targeting Cognitive and Negative Symptoms in Schizophrenia." Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology 34, no. 8 (July 2009): 1885–1903. doi:10.1038/npp.2009.26.

- *"Pregnenolone may be a promising therapeutic agent for negative symptoms and merits further investigation for cognitive symptoms in schizophrenia."*

Pregnenolone Ameliorates Visual Attention Deficits in Schizophrenia

Kreinin, Anatoly, "Adjunctive Pregnenolone Ameliorates the Cognitive Deficits in Recent-Onset Schizophrenia." Clinical Schizophrenia & Related Psychoses, February 4, 2014, 1–31. doi:10.3371/CSRP.KRBA.013114.

- *"Pregnenolone augmentation demonstrated significant amelioration of the visual attention deficit in recent-onset SZ/SA. Long-term, large-scale studies are required to obtain greater statistical significance and more confident clinical generalization."*

Secretin (peptide hormone)

Gastrointestinal Peptide Secretin Produces Clinically Meaningful Reductions in Symptoms in Several Schizophrenic Patients

Sheitman, Brian B., "Secretin for Refractory Schizophrenia." Schizophrenia Research 66, no. 2–3 (February 1, 2004): 177–81. doi:10.1016/S0920-9964(03)00068-9.

- *"In preliminary uncontrolled studies, intravenous injection of the gastrointestinal peptide secretin produced improvements in the symptoms of autism. Because of the phenotypic overlap between autism and some aspects of schizophrenia, we performed a pilot study of secretin for treatment refractory schizophrenia. Twenty-two patients were randomized to a single intravenous dose of porcine secretin or placebo. Patients were evaluated with the Positive and Negative Symptom Scale for Schizophrenia (PANSS) and the Clinical Global Impression Scale (CGI) at baseline, 2 days after secretin infusion and weekly for 4 weeks. There were no statistically significant differences between drug- and placebo-treated patients with repeated measures analysis of variance (ANOVA). However, several patients treated with secretin experienced clinically meaningful, but transient, reductions in symptoms and a greater percentage of patients treated with secretin were rated as improved with the CGI. Further study of brain hypocretins and molecules affecting this system are warranted in schizophrenia."*

Gastrointestinal Peptide Secretin is a Novel Adjunctive Treatment Strategy in Schizophrenic Patients with Autistic Features

Alamy, Sayed S., "Secretin in a Patient with Treatment-Resistant Schizophrenia and Prominent Autistic Features." Schizophrenia Research 66, no. 2–3 (February 1, 2004): 183–86. doi:10.1016/j.schres.2003.07.003.

- *"Secretin, a gastrointestinal (GI) peptide, may offer therapeutic benefit in autism. Autistic features can also be present in schizophrenia and a recent study suggested a role for adjunctive secretin in treatment-resistant schizophrenia. The current report describes one patient with undifferentiated schizophrenia and prominent autistic features who received a single dose of secretin and demonstrated substantial yet transient improvement. The case illustrates the potential role of secretin as a novel adjunctive treatment strategy in schizophrenic patients with autistic features."*

Administration of Gastrointestinal Peptide Secretin Improves Eye-Blink Conditioning in Schizophrenic Patients

Bolbecker, Amanda R., "Secretin Effects on Cerebellar-Dependent Motor Learning in Schizophrenia." The American Journal of Psychiatry 166, no. 4 (April 2009): 460–66. doi:10.1176/appi.ajp.2008.08040597.

- *"Eye-blink conditioning was significantly improved at 2 and 24 hours after secretin administration but not after treatment with placebo. These results are consistent with evidence of intracellular signaling abnormalities in the pathophysiology of schizophrenia and indicate a possible role for secretin in modulating cerebellar-mediated classically conditioned learning. If cerebellar abnormalities in individuals with schizophrenia are associated with fundamental mechanisms and symptoms of the disorder, as suggested by the cognitive dysmetria model, then cerebellar-targeted treatments may provide a novel approach to treatment for schizophrenia."*

Testosterone

Testosterone Gel Augmentation in Male Schizophrenics Improves Depression and Negative Symptoms

Ko, Young-Hoon, "Short-Term Testosterone Augmentation in Male Schizophrenics: A Randomized, Double-Blind, Placebo-Controlled Trial." Journal of Clinical Psychopharmacology 28, no. 4 (August 2008): 375–83. doi:10.1097/JCP.0b013e31817d5912.

- *"Results indicated a significant improvement of negative symptoms in both the last observation carried forward and the completer analyses and a nonsignificant trend for the improvement of depressive symptoms in completers. There were no significant changes in serum hormone levels except total and free testosterone. The findings of this study*

suggest that testosterone augmentation may be a potential therapeutic strategy in patients with schizophrenia."

Thyroid Hormone Treatment

Thyrotropin-Releasing Hormone Shows Some Improvement in Schizophrenic Patients

Kobayashi, K., K. "Effects of Thyrotropin-Releasing Hormone in Chronic Schizophrenic Patients." Acta Medica Okayama 34, no. 4 (September 1980): 263–73.

- *"The effects of oral and intravenous thyrotropin-releasing hormone (TRH) were studied in 11 male, chronic schizophrenic inpatients in an open trial and a double-blind, crossover design. The general beneficial effects of TRH as assessed on the Brief Psychiatric Rating Scale were not obtained, although improvement of contact, apathy and emotional rapport was observed in a few patients. Serum prolactin, L-triiodothyronine and thyroxine were assayed throughout the study. Since the effects of TRH on behavior were not related to changes in these endocrine factors, the mechanism of action might be independent of its original functions on the pituitary-thyroid axis."*

Triiodothyronine May Be Possible Associated with Better Cognitive Function and Less Extrapyramidal Symptoms in Chronic Schizophrenia

Ichioka, Shugo, "Triiodothyronine May Be Possibly Associated with Better Cognitive Function and Less Extrapyramidal Symptoms in Chronic Schizophrenia." Progress in Neuro-Psychopharmacology & Biological Psychiatry 39, no. 1 (October 1, 2012): 170–74. doi:10.1016/j.pnpbp.2012.06.008.

- *"These findings suggest that BDNF, free T_3, and prolactin may be associated with cognitive function and/or extrapyramidal symptoms in patients with chronic schizophrenia. Notably, free T_3 may be possibly associated with better cognitive function and less extrapyramidal symptoms, although our cross-sectional study could not reveal a causal relationship."*

Intravenous Protrelin (thyrotropin-releasing hormone) caused a Significant Decrease in Psychotic Symptoms in Schizophrenic Patients

Prange, A. J. "Behavioral and Endocrine Responses of Schizophrenic Patients to TRH (protirelin)." Archives of General Psychiatry 36, no. 10 (September 1979): 1086–93.

- *"We studied the effects of intravenous protirelin (thyrotropin-releasing hormone) in 17 schizophrenic patients and 17 normal subjects. A total of 12 patients received protirelin, 0.5 mg, and, on another occasion, niacin, 2 mg, in a double-blind, crossover design. Both behavioral and endocrine data were collected. Five patients received protirelin in an open*

trial; only endocrine data were collected. Protirelin caused about a 50% prompt decrease in psychotic symptoms. Patients then tended slowly to experience a relapse. Side effects were about as infrequent after protirelin as after niacin. We assayed serum prolactin (PRL), growth hormone (GH), thyroid-stimulating hormone (TSH), L-triiodothyronine (T3) and thyroxine (T4). Free T4 (FT4) index was calculated. The values for PRL, GH, and TSH at baseline and after protirelin stimulation were normal. Patients showed lower T3 values at baseline, but a brisker T3 response to protirelin, than controls. Their FT4 indices were higher at baseline. Patients showed diminished T4 binding sites rather than increased total T4. The causes of these alterations in thyroid dynamics are unidentified."

Other Natural Compounds

Ampullosporin A

Ampullosporin A has Characteristics of an Atypical Neuroleptic Drug

Berek, I., "Ampullosporin A, a Peptaibol from Sepedonium Ampullosporum HKI-0053 with Neuroleptic-like Activity." Behavioural Brain Research 203, no. 2 (November 5, 2009): 232–39. doi:10.1016/j.bbr.2009.05.012.

- *"The potential neuroleptic-like effect of ampullosporin A, a new peptaibol, isolated from the fungus Sepedonium ampullosporum HKI-0053, was characterized using specific behavioural models and methods. Ampullosporin A (amp) disrupted the retrieval of a well-trained conditioned reaction and normalized the behavioural effects of subchronic ketamine treatment in the social interaction test in a dose which showed only inconsiderable side effects. The experiments demonstrated that the substance did not antagonize the apomorphine (apo) induced hyperactivity. On the other hand, the locomotor stimulation induced by the NMDA receptor antagonist MK-801 was nearly completely suppressed by ampullosporin A, supposing interactions with the glutamatergic system. Binding studies demonstrated no interaction with dopaminergic D(1) and D(2) receptors. However, amp can alter the activity of glutamate receptors. The results resemble characteristics of an atypical neuroleptic drug. But further experiments are necessary to validate the suggested neuroleptic-like activity."*

Ampullosporin A Belongs to a Group of Neuroleptic-like Compounds

Krügel, Hans, "Transcriptional Response to the Neuroleptic-like Compound Ampullosporin A in the Rat Ketamine Model." Journal of Neurochemistry 97 Suppl 1 (April 2006): 74–81. doi:10.1111/j.1471-4159.2005.03621.x.

- *"Our results suggest the possibility that Ampullosporin A belongs to the group of neuroleptic-like compounds, inducing massive changes in neurotransmitter receptor*

composition, calcium signaling cascades and second messenger systems, and leading to the plastic reorganization of brain tissue, metabolic pathways and synapses."

Deanol (Deaner)

Deanol Works Well with an Antipsychotic in the Treatment of Schizophrenia

Barsa, J. A., "Deanol (deaner) in the Treatment of Schizophrenia." The American Journal of Psychiatry 116 (September 1959): 255–56.

- *"From this study, it can be concluded that deanol, when combined with a tranquilizer containing a potent antipsychotic action is of definite value in the treatment of schizophrenia. Not only does its stimulating effect counteract the excessive sedation and lethargy produced by the tranquilizer, but its own ant-psychotic effect is additive to that of the tranquilizer."*

Deanol was Effective in 25% Institutionalized Female Schizophrenics

Barsa, J. A.,"Deanol (deaner) in the Treatment of Schizophrenia." The American Journal of Psychiatry 116 (September 1959): 255–56.

- *"Deanol was used in 100 institutionalized female schizophrenics. It was moderately effective in 25%, producing increased interest in milieu, work and recreation, and decreasing somatic delusional trends, depression, retardation, and mutism. Side actions were minimal, and all were controlled by dosage regulation."*

Deaner Produces Dramatic Responses in Some Cases of Schizophrenia

Toll, N. "Deaner an Adjunct for Treatment of Schizoid and Schzophrenic Patients." The American Journal of Psychiatry 115, no. 4 (October 1958): 366–67.

- *"Despite the small number of patients included in this study, certain clinical impressions were formed: Deaner appears to merit further study in those conditions where CNS stimulation is needed. Its freedom from serious side-effects, and the dramatic response produced in some cases suggest that the drug is worthy of trial, especially in schizoid and schizophrenic patients who have not responded to other therapies."*

Flavonoids

The Use of Flavonoids in Schizophrenia and Other Neurodegenerative Diseases

Grosso, C., "The Use of Flavonoids in Central Nervous System Disorders." Current Medicinal Chemistry 20, no. 37 (2013): 4694–4719.

- *"This review will give emphasis to the benefits of flavonoids found in the diet in the treatment of Alzheimer's disease, Parkinson's disease, epilepsy, depression, and schizophrenia. The antioxidant effect of several flavonoids, as well as their effects not related with antioxidant activity, in the above mentioned diseases will be reviewed. Aspects concerning structure-activity relationships, but also the bioavailability of these compounds in the brain will be referred."*

Folinic Acid

Folinic Acid Treatment Causes Disappearance of Hallucinations in Schizophrenic Patients

Ramaekers, V. T., "Folinic Acid Treatment for Schizophrenia Associated with Folate Receptor Autoantibodies." Molecular Genetics and Metabolism 113, no. 4 (December 2014): 307–14. doi:10.1016/j.ymgme.2014.10.002.

- *"Assessment of FR auto-antibodies in serum is recommended for schizophrenic patients. Clinical negative or positive symptoms are speculated to be influenced by the level and evolution of FRα antibody titers which determine folate flux to the brain with up- or down-regulation of brain folate intermediates linked to metabolic processes affecting homocysteine levels, synthesis of tetrahydrobiopterin and neurotransmitters. Folinic acid intervention appears to stabilize the disease process."*

Galantamine

Galantamine as Adjunctive Treatment is Effective in Resistant Schizophrenia

Allen, Trina B., "Galantamine for Treatment-Resistant Schizophrenia." *The American Journal of Psychiatry* 159, no. 7 (July 2002): 1244–45.

- *"Controlled double-blind trials of galantamine as an ad- junctive treatment for schizophrenia are currently underway. These two patients were both very heavy smokers and had shown a favorable therapeutic response to clozapine that could not be matched by treatment with any other currently available antipsychotic. Both of these attributes (smoking and clozapine response) may signal that nicotinic pathophysiology contributed to their illnesses and that an agent such as galantamine that can augment nicotinic function may be a useful treatment.".*

Diminished Expression of Nicotinic Receptors Determine Response to Galantamine in the Treatment of Apathy for Schizophrenia

Arnold, David S., "Adjuvant Therapeutic Effects of Galantamine on Apathy in a Schizophrenia Patient." The Journal of Clinical Psychiatry 65, no. 12 (December 2004): 1723–24.

- *"Conceivably, galantamine's greatest therapeutic benefit will be observed in schizophrenia patients with diminished expression of nicotinic acetylcholine receptors in selected regions of the brain. Abnormal variants of the promoter region for the α_7 nicotinic acetylcholine receptor located on chromosome 15 may be a mechanism for its diminished expression in selected brain areas. Diminished expression of normal receptor protein would encourage exploration of strategies to improve the transduction of the acetylcholine signal, such as galantamine use. Of course, only future double-blind, placebo-controlled trials can substantiate the suggestions of therapeutic efficacy of adjuvant galantmine administration, especially for such targets as negative symptoms, apathy, and mood. It might be informative to randomize subjects in these future studies according to smoking status and genetic profiles of promoter variants that regulate expression of the α_7 nicotinic acetylcholine receptor subunit. It is possible that the smoking status of the patient who responded contributed to his therapeutic response to galantamine."*

Adjunctive Galantamine Improves Negative Symptoms in Patient with Treatment Refractory Schizophrenia

Rosse, Richard B.,"Adjuvant Galantamine Administration Improves Negative Symptoms in a Patient with Treatment-Refractory Schizophrenia." Clinical Neuropharmacology 25, no. 5 (October 2002): 272–75.

- *"Because of the demonstration of a selective alpha nicotinic receptor abnormality in patients with schizophrenia, galantamine was added to the stable regimen of atypical and other antipsychotic medications in a 43-year-old man manifesting severe and persistent positive and negative symptoms, as well as mood disturbance and cognitive dysfunction. Galantamine is an inhibitor of acetylcholinesterase and a positive allosteric modulator of nicotinic cholinergic receptors (with a FDA-approved indication for the treatment of patients with mild to moderate Alzheimer disease (AD) under the trade name Reminyl). Galantamine HBr was initiated at a dose of 4 mg po BID, which was maintained for the first week of adjuvant therapy, and eventually was increased to 12 mg po BID during the final weeks of his 2-month trial. Remarkably, within 1 week of its initiation, there was a dramatic and clinically significant decrease of negative symptoms, as reflected in formal ratings on the Scale for the Assessment of Negative Symptoms. Moreover, within a few days of galantamine discontinuation, negative symptoms worsened, returning to the baseline level of severity. In addition to targeting memory dysfunction in AD, acetylcholinesterase inhibitors may have an expanded range of targets and clinical indications, including behavioral and psychotic symptoms. Galantamine is distinguished from other acetylcholinesterase inhibitors by its positive allosteric modulatory properties,*

improving the efficiency of transduction of the acetylcholine signal at nicotinic receptors."

Galantamine Shows Some Improvement in Attention and Speech of Schizophrenic Patients with Cognitive Impairement

Ochoa, Enrique L. M., "Galantamine May Improve Attention and Speech in Schizophrenia." Human Psychopharmacology 21, no. 2 (March 2006): 127–28. doi:10.1002/hup.751.

- *"After 34 days the patient showed a remarkable improvement in working memory and delayed recall, though he continued to show impairment in the other examined domains. Negative symptom ratings on the SANS also revealed improvement of attention and speech."*
- *"At the time of his discharge, 20 days after admission, his thought processes were more organized and he was able to maintain a coherent conversation. Speech and attention showed marked improvements with less gains in anhedonia, affective flattening, avolition or apathy."*

Adjunctive Galantamine Improves Cognition in Schizophrenic Patients Stabilized on Antipsychotic

Schubert, Max H., "Galantamine Improves Cognition in Schizophrenic Patients Stabilized on Risperidone." Biological Psychiatry 60, no. 6 (September 15, 2006): 530–33. doi:10.1016/j.biopsych.2006.04.006.

- *"Adjunctive treatment with galantamine improves memory and attention in patients with schizophrenia who are stabilized on risperidone, providing the opportunity to improve functional outcome in these patients."*

Guanosine

Guanosine has Potential Antipsychotic Properties

Schmidt, André P., "Guanosine and Its Modulatory Effects on the Glutamatergic System." European Neuropsychopharmacology: The Journal of the European College of Neuropsychopharmacology 18, no. 8 (August 2008): 620–22. doi:10.1016/j.euroneuro.2008.01.007.

- *Although the mechanism of action of guanosine and its modulatory effects on MK-801-induced behavioral disturbances are not completely elucidated, these findings point to a potential antipsychotic property of guanosine. This may be especially important in targeting psychotic symptoms that are not generally treated with currently available*

antipsychotics. Moreover, the neuroprotective and neurotrophic effects of guanosine may also be advantageous for the treatment of schizophrenia and other brain diseases.

Harmine

Harmine a Forgotten Treatment for Catatonic Schizophrenia

Hostiuc, Sorin, "Harmine for Catatonic Schizophrenia. A Forgotten Experiment." Schizophrenia Research 159, no. 1 (October 2014): 249–50. doi:10.1016/j.schres.2014.08.006.

- *"Harmine was found in the 1920's to have a possible use in the treatment of Parkinsonism (Beringer, 1929). As in schizophrenic catatonia muscle rigidity was one of the most important symptoms, Tomescu designed an experiment to test whether Harmine could be used as a potential therapeutic agent for catatonic schizophrenia with it, by using three patients with this disease. A dosage of 0.03–0.04 cg was found to be optimal. In the first patient injecting 0.03 cg Harmine caused a complete disappearance of the rigidity after an hour, with free passive movements in the upper limbs and only a slight residual rigidity in the lower limbs. Moreover, this dosage had positive effects on negativity, as the patient started saying a few words, and asked for his favorite foods. The patient was able to reveal various information from his past but also information from the time he was admitted (from the time he has been in a catatonic state). The symptoms reemerged gradually a few hours after the treatment; however the patient remained in an ameliorated state for a few days. After this initial success, Tomescu treated the patient for 25 days with Harmine, obtaining the same effects as those from the initial experiment. The patient was cooperative, with an almost complete remission of negativity, no muscle rigidity, and a significant increase in weight. The effects of the drug completely disappeared at 5–6 days after discontinuing it. On the second patient he obtained a complete remission of the muscle rigidity and negativity with a dosage of 0.04 cg. Moreover, the use of the drug on a longer period of time (20 days) had effects on his affectivity as he showed signs of falling in love with a nurse. The effect diminished significantly after 2–3 days. On the third patient similar results were obtained at a dosage of 0.04 cg; the use of the drug on a longer period of time (20 days) caused him to want to leave the hospital and stay with his family. The study concluded that, even if Harmine had a purely symptomatic effect, it Schizophrenia Research 159 (2014) 249–250 did cause significant improvement of the symptoms and of the quality of life. The experiments were not continued due to the prohibitive costs of Harmine (Tomescu and Russu, 1930). The effect disappeared in about five days. "*

Huperzine

Huperzine A Demonstrated Beneficial Effects in Treating Cognitive and Negative Symptom Clusters in Schizophrenia

Zhang, Zhang-Jin, "Huperzine A as Add-on Therapy in Patients with Treatment-Resistant Schizophrenia: An Open-Labeled Trial." Schizophrenia Research 92, no. 1–3 (May 2007): 273–75. doi:10.1016/j.schres.2007.02.005.

- *"In conclusion, this pilot trial demonstrated the beneficial effects of HupA in treating cognitive and negative symptom clusters of schizophrenia and it may deserve to be further tested in larger-scale, controlled trials."*

Indole Alkaloids

Indole Alkaloid Alstonine was found to possess a Antipsychotic Profile

Costa-Campos L. Antipsychotic-like profile of alstonine. Pharmacology Biochemistry and Behavior, Vol. 60, No.1,pp. 133-141, 1998

- *"An ethnopharmacological study in Nigeria has led to the investigation of a plant-based extract used by traditional psychiatrists with anecdotal antipsychotic-like effects. This extract was later found to bear antipsychotic profile (Elisabetsky et al., unpublished results) using a behavioral approach similar to the present study. Phytochemical studies have identified alstonine as one of the major components of this extract. The following study investigates the putative antipsychotic profile of alstonine using behavioral and neurochemical strategies."*

Alstonine is a Potential Innovative Antipsychotic

Linck, Viviane M., "Alstonine as an Antipsychotic: Effects on Brain Amines and Metabolic Changes." Evidence-Based Complementary and Alternative Medicine: eCAM 2011 (2011): 418597. doi:10.1093/ecam/nep002.

- *"Alstonine is an indole alkaloid identified as the major component of a plant-based remedy used in Nigeria to treat the mentally ill. Alstonine presents a clear antipsychotic profile in rodents, apparently with differential effects in distinct dopaminergic pathways. The aim of this study was to complement the antipsychotic profile of alstonine, verifying its effects on brain amines in mouse frontal cortex and striatum. Additionally, we examined if alstonine induces some hormonal and metabolic changes common to antipsychotics. HPLC data reveal that alstonine increases serotonergic transmission and increases intraneuronal dopamine catabolism. In relation to possible side effects, preliminary data suggest that alstonine does not affect prolactin levels, does not induce gains in body weight, but prevents the expected fasting-induced decrease in glucose levels. Overall, this study reinforces the proposal that alstonine is a potential innovative antipsychotic, and that a comprehensive understanding of its neurochemical basis may open new avenues to developing newer antipsychotic medications."*

L-stepholidine (Stepholidine)

Stepholidine Shows Antipsychotic Effects in Animal Model of Schizophrenia

Elenbroek BA. Effects of (-)stepholidine in animal models for schizophrenia. Acta Pharmacol Sin 2006 Sep;27(9):1111-8

- *"The data showed that SPD showed antipsychotic-like effects in both the prepulse inhibition paradigm and in the paw test. Moreover, the results of the paw test suggest that SPD has an atypical character with relatively small potency to induce extrapyramidal symptoms."*

Natesan S. The antipsychotic potential of l-stepholidine—a naturally occurring dopamine receptor D1 agonist and D2 antagonist. Psychopharmacology (Berl) 2008 Aug; 199(2):275-89

- *"Thus, l-stepholidine shows efficacy like an "atypical" antipsychotic in traditional animal models predictive of antipsychotic activity and shows in vitro and vivo D91) agonism, and, if its rapid elimination does not limit its actions, it could provide a unique therapeutic approach to schizophrenia."*

Stepholidine Improves both Negative and Positive Symptoms of Schizophrenia

Yang, Kechun, "The Neuropharmacology of (-)-Stepholidine and Its Potential Applications." Current Neuropharmacology 5, no. 4 (December 2007): 289–94. doi:10.2174/157015907782793649.

- *"(-)-Stepholidine (SPD), a natural product isolated from the Chinese herb Stephania, possesses dopamine (DA) D1 partial agonistic and D2 antagonistic properties in the nigrostriatal and mesocorticolimbic DAergic pathways. These unique dual effects have suggested that SPD can effectively restore previously imbalanced functional linkage between D1 and D2 receptors under schizophrenic conditions, in which, SPD improves both the negative and positive symptoms of schizophrenia. SPD also relieves the motor symptoms of Parkinson's disease (PD) when co-administered with Levodopa. Furthermore, SPD exhibits neuroprotective effects through an antioxidative mechanism and slows down the progression of neuronal degeneration in the substantia nigra (SN) of PD patients and/or animal models. Therefore, SPD is a novel, natural compound with potentially therapeutic roles in the treatment of schizophrenia and/or PD."*

L-Stepholidine is a Potential Neurotransmitter Stabilizer and Promising Drug Canidate for Treatment of Schizophrenia

Guo, Yang, "Evaluation of the Antipsychotic Effect of Bi-Acetylated L-Stepholidine (l-SPD-A), a Novel Dopamine and Serotonin Receptor Dual Ligand." Schizophrenia Research 115, no. 1 (November 2009): 41–49. doi:10.1016/j.schres.2009.08.002.

- *"Taken together, these results indicate that l-SPD-A was not only effective against the hyperactivity, but also improved the sensorimotor gating deficit, social withdrawal and cognitive impairment in an animal model of schizophrenia. The present data suggest that l-SPD-A, a potential neurotransmitter stabilizer, is a promising novel candidate drug for the treatment of schizophrenia."*

L-Stepholidine is a Potential Agent for Treatment of Drug Addiction as Well as Schizophrenia

Mo, Jiao, "Recent Developments in Studies of L-Stepholidine and Its Analogs: Chemistry, Pharmacology and Clinical Implications." Current Medicinal Chemistry 14, no. 28 (2007): 2996–3002.

- *"This unique pharmacological profile made dihydroxyl-THPBs such as l-stepholidine (l-SPD) potential agents in the treatment of drug addiction, Parkinson's disease, and especially, schizophrenia. Clinical studies have shown that co-administration of l-SPD with a typical antipsychotic drug significantly enhances the therapeutic effects and remarkably reduces the tardive dyskinesia induced by the typical antipsychotic drug used with schizophrenic patients. Moreover, l-SPD alone was shown to have therapeutic value without inducing significant extrapyramidal side effects and also seemed to reduce the negative symptoms of schizophrenia. This is confirmed in experimental studies using animal models of schizophrenia, in which l-SPD improved social interaction and cognitive function, inhibited hyperactivity in schizophrenic animals. This review discusses the chemistry, pharmacology and clinical implications of l-THPBs in the drug development for psychosis and neurobiological diseases."*

Manassantin A

Manassantin A is a Potential Neuroleptic Agent form the Plant Saururus Cernuus

Rao, K. V., "Preliminary Evaluation of Manassantin A, a Potential Neuroleptic Agent from Saururus Cernuus." Pharmacological Research Communications 19, no. 9 (September 1987): 629–38.

- *"Manassantin A (MNS-A), a novel dineolignan isolated from Saururus cernuus was evaluated for its central depressant effects. Intraperitoneal (IP) administration of MNS-A to mice at nontoxic doses caused a decrease in spontaneous motor activity and inhibition of amphetamine-induced stereotypy, with an ED50 of 0.21 +/- 0.02 mg/kg for its*

antiamphetamine activity. Doses of MNS-A up to the LD50 did not produce catalepsy and ptosis as were observed with haloperidol used as a reference drug. The compound caused a dose-dependent hypothermia, while haloperidol was not very effective in this test. Potentiation of pentobarbital-sleeping time was observed to be of comparable degree with both drugs. In spite of the higher toxicity (acute LD50 5.4 +/- 0.2 mg/kg, IP) than that shown by haloperidol, the somewhat selective neuroleptic profile of MNS-A makes it an interesting candidate for more detailed studies."

N-acetylcysteine

N-acetylcysteine in Beneficial for Treatment Resistant Schizophrenia

Bulut, Mahmut, "Beneficial Effects of N-Acetylcysteine in Treatment Resistant Schizophrenia." The World Journal of Biological Psychiatry: The Official Journal of the World Federation of Societies of Biological Psychiatry 10, no. 4 Pt 2 (2009): 626–28. doi:10.1080/15622970903144004.

- *"Poor response to antipsychotics is still an important problem in the treatment of many schizophrenia patients. N-acetylcysteine (NAC) is a compound that exerts anti-oxidant and scavenging actions against reactive oxygen species. This paper reports a case of poorly responsive schizophrenia patient who improved considerably with add-on NAC 600 mg/day. The NAC might work through activating cysteine-glutamate antiporters or reducing in nitric oxide (NO) metabolites, free radicals and cytokines or through both of these mechanisms."*

N-acetylcysteine is a Safe and Effective Augmentation Strategy for Schizophrenia

Berk, Michael, "N-Acetyl Cysteine as a Glutathione Precursor for Schizophrenia--a Double-Blind, Randomized, Placebo-Controlled Trial." Biological Psychiatry 64, no. 5 (September 1, 2008): 361–68. doi:10.1016/j.biopsych.2008.03.004.

- *"These data suggest that adjunctive NAC has potential as a safe and moderately effective augmentation strategy for chronic schizophrenia."*

N-acetylcysteine Improves Positive and Negative Symptoms in the Long-term

Berk M. N-Acetyl-Cysteine as a glutathione precursor for schizophrenia-a double blind, randomized, placebo-controlled trial. Biol Psychiatry 2008;64:361-368

- *"Improvement was seen on the CGI-I at 2 weeks and the CGI-S at 4 weeks, while improvement on the PANSS and a trend for improvement on the BAS emerged only toward 24 weeks of treatment."*

N-acetylcysteine Improves Poorly Responsive Schizophrenic Patient

Bulut M. Beneficial effects of N-acetylcysteine in treatment resistant schizophrenia. World J Biol Psychiatry 2009;10(4 Pt 2):626-8

- *"This paper reports a case of a poorly responsive schizophrenia patient who improved considerably with add-on NAC 600 mg/day."*

N-Acetylcysteine is a Potential Therapeutic Agent for Hallucinations and Psychosis from Hallucinogen use in Schizophrenia

Lee, Mei-Yi, "N-Acetylcysteine Modulates Hallucinogenic 5-HT(2A) Receptor Agonist-Mediated Responses: Behavioral, Molecular, and Electrophysiological Studies." Neuropharmacology 81 (June 2014): 215–23. doi:10.1016/j.neuropharm.2014.02.006.

- *"These findings implicate NAC as a potential therapeutic agent for hallucinations and psychosis associated with hallucinogen use and schizophrenia."*

N-acetylcysteine is a Safe and Effective Augmentative Strategy for Alleviating Negative Symptoms of Schizophrenia

Farokhnia, Mehdi, "N-Acetylcysteine as an Adjunct to Risperidone for Treatment of Negative Symptoms in Patients with Chronic Schizophrenia: A Randomized, Double-Blind, Placebo-Controlled Study." Clinical Neuropharmacology 36, no. 6 (December 2013): 185–92. doi:10.1097/WNF.0000000000000001.

- *NAC add-on therapy showed to be a safe and effective augmentative strategy for alleviating negative symptoms of schizophrenia.*

Oleanolic Acid

Oleanolic Acid Could Be a Candidate for the Treatment of Positive Symptoms, Sensorimotor Gating Disruption and Cognitive Impairments in Schizophrenia

Park, Se Jin, "Oleanolic Acid Attenuates MK-801-Induced Schizophrenia-like Behaviors in Mice." Neuropharmacology 86C (July 2, 2014): 49–56. doi:10.1016/j.neuropharm.2014.06.025.

- *"These results suggest that oleanolic acid could be a candidate for the treatment of several symptoms of schizophrenia, including positive symptoms, sensorimotor gating disruption, and cognitive impairments."*

Rubidium Chloride

Overall Low-dose Effect of Rubidium Chloride was Beneficial in Schizophrenia

Chouinard, G., "The Effect of Rubidium in Schizophrenia." Communications in Psychopharmacology 1, no. 4 (1977): 373–83.

- *"The nature of the dose-response relationship for the BPRS total score suggests that the overall effect of 1g of rubidium on schizophrenia was beneficial. There was evidence, however, that the 2g dose of rubidium was exacerbating the symptoms of anxiety and depression. Since animal studies point to a specific capacity of rubidium to increase norepinephrine turnover, one might hypothesize that the beneficial effect of the 1g dose on withdrawal retardation may be caused by an increase in cerebral norepinephrine. In the same way, the increase in hostile suspiciousness and anxious depression among patients receiving 2g of rubidium may be related to an excess of cerebral norepinephrine. Further investigation is required to determine whether this drug can be of value in the treatment of schizophrenia and, if so, what the therapeutic dose range would be."*

SAMe

SAMe Reduces Aggressive Behavior and Increases Quality of Life for Schizophrenic Patients

Strous, Rael D., "Improvement of Aggressive Behavior and Quality of Life Impairment Following S-Adenosyl-Methionine (SAM-E) Augmentation in Schizophrenia." European Neuropsychopharmacology: The Journal of the European College of Neuropsychopharmacology 19, no. 1 (January 2009): 14–22. doi:10.1016/j.euroneuro.2008.08.004.

- *"S-adenosyl-methionine (SAM-e), functions as a primary methyl group donor for several metabolic compounds. Since SAM-e is involved in several metabolic processes, its administration may have a role in the amelioration of several disorders. In addition, SAM-e increases catechol-O-methyltransferase (COMT) enzyme activity, which may ameliorate aggressive symptoms in certain patients. We have therefore investigated the efficacy of SAM-e in managing schizophrenia symptomatology in patients with the low activity COMT polymorphism. Eighteen patients with chronic schizophrenia were randomly assigned to receive either SAM-e (800 mg) or placebo for 8 weeks in double-blind fashion. Results indicated some reduction in aggressive behavior and improved quality of life following SAM-e administration. Female patients showed improvement of depressive symptoms. Clinical improvement did not correlate with serum SAM-e levels. Two patients receiving SAM-e exhibited some exacerbation of irritability. This preliminary pilot short-term study cautiously supports SAM-e as an adjunct in management of aggressive behavior and quality of life impairment in schizophrenia."*

Sarcosine

Sarcosine Treatment Can Benefit Schizophrenic Patients Treated with Antipsychotics

Tsai, Guochuan, "Glycine Transporter I Inhibitor, N-Methylglycine (sarcosine), Added to Antipsychotics for the Treatment of Schizophrenia." Biological Psychiatry 55, no. 5 (March 1, 2004): 452–56. doi:10.1016/j.biopsych.2003.09.012.

- *"Sarcosine treatment can benefit schizophrenic patients treated by antipsychotics including risperidone. The significant improvement with the sarcosine further supports the hypothesis of N-methyl-D-aspartate receptor hypofunction in schizophrenia. Glycine transporter-1 is a novel target for the pharmacotherapy to enhance N-methyl-D-aspartate function."*

Sarcosine is Supported for Benefit of General Psychiatric Symptoms and Depression in Schizophrenia

Lane H Y. Sarcosine or D-serine add-on treatment for acute exacerbation of schizophrenia. Arch Gen Psychiatry, 2005;62:1196-1204

- *"The evidence most strongly supports the benefit of sarcosine for general psychiatric symptoms and depression and possible benefit for negative symptoms (blunted effect and alogia) but not for positive symptoms during acute phase."*

Sarcosine was Superior to Placebo as an Add-on for the Treatment of Schizophrenia

Lane HY. A randomized, double –blind, placebo-controlled comparison study of sarcosine (N-methlglycine) and D-serine add-on treatment for schizophrenia. Int J Neuropsychopharmacolgy 2010 May; 13(4):451-60

- *"Treatment group x treatment duration interaction analysis by multiple linear regression showed that sarcosine was superior to placebo at all four outcome measures of Positive and Negative Syndrome Scale (PANSS)…., Scale for the Assessment of Negative Symptoms (SANS), Quality of Life (QOL) and Global Assessment of Functioning (GAF). However, D-serine did not differ in effect significantly from placebo in any measure."*

Sarcosine is Superior to D-serine as Add-on Treatment in Schizophrenia

Lane, Hsien-Yuan, "Sarcosine or D-serine Add-on Treatment for Acute Exacerbation of Schizophrenia: A Randomized, Double-Blind, Placebo-Controlled Study." Archives of General Psychiatry 62, no. 11 (November 2005): 1196–1204. doi:10.1001/archpsyc.62.11.1196.

- *"This first short-term treatment study on NMDA receptor-enhancing agents suggests that sarcosine, superior to D-serine, can benefit not only patients with long-term stable disease but also acutely ill persons with schizophrenia. This finding indicates that a glycine transporter 1 inhibitor may be more efficacious than NMDA-glycine site agonists*

for adjuvant treatment of schizophrenia, at least during the acute phase. Further studies are needed."

Sarcosine Can Benefit Schizophrenic Patients on Antipsychotics

Tsai, Guochuan, "Glycine Transporter I Inhibitor, N-Methylglycine (sarcosine), Added to Antipsychotics for the Treatment of Schizophrenia." Biological Psychiatry 55, no. 5 (March 1, 2004): 452–56. doi:10.1016/j.biopsych.2003.09.012.

- *"Sarcosine treatment can benefit schizophrenic patients treated by antipsychotics including risperidone. The significant improvement with the sarcosine further supports the hypothesis of N-methyl-D-aspartate receptor hypofunction in schizophrenia. Glycine transporter-1 is a novel target for the pharmacotherapy to enhance N-methyl-D-aspartate function."*

Gly T 1 Inhibitor Sarcosine is more efficacious than NMDA/glycine site agonist D-serine in the Treatment of Schizophrenia

Lane, Hsien-Yuan, "A Randomized, Double-Blind, Placebo-Controlled Comparison Study of Sarcosine (N-Methylglycine) and D-serine Add-on Treatment for Schizophrenia." The International Journal of Neuropsychopharmacology / Official Scientific Journal of the Collegium Internationale Neuropsychopharmacologicum (CINP) 13, no. 4 (May 2010): 451–60. doi:10.1017/S1461145709990939.

- *"However, D-serine did not differ significantly from placebo in any measure. Sarcosine treatment was better than D-serine in effect sizes for all outcome measures. Sarcosine also surpassed placebo in most of the measures of five PANSS factors and five SANS subscales. All treatments were well tolerated. These findings suggest that the GlyT-1 inhibitor is more efficacious than the NMDA/glycine site agonist in treatment for schizophrenia, including life quality and global function, at the dosages tested."*

Sarcosine Works Primarily Well in Antipsychotic-naive Schizophrenic Patients

Lane, Hsien-Yuan, "Sarcosine (N-Methylglycine) Treatment for Acute Schizophrenia: A Randomized, Double-Blind Study." Biological Psychiatry 63, no. 1 (January 1, 2008): 9–12. doi:10.1016/j.biopsych.2007.04.038.

- *"Although patients receiving the 2-g daily dose were more likely to respond, it requires further clarification whether the effect is limited to the antipsychotic-naive population. Future placebo- or active-controlled, larger-sized studies are needed to fully assess sarcosine's effects."*

Traditional Herbal Remedies (Overview)

Bangladesh Medicinal Plants

Formulations of Medicinal Plants used in Bangladesh to Treat Schizophrenia-like Psychosis

Ahmed, Md Nasir, "Traditional Knowledge and Formulations of Medicinal Plants Used by the Traditional Medical Practitioners of Bangladesh to Treat Schizophrenia like Psychosis." Schizophrenia Research and Treatment 2014 (2014): 679810. doi:10.1155/2014/679810.

- *"The aim of the present study was to conduct an ethnomedicinal plant survey and documentation of the formulations of different plant parts used by the traditional medical practitioners of Rangamati district of Bangladesh for the treatment of schizophrenia like psychosis. It was observed that the traditional medical practitioners used a total of 15 plant species to make 14 formulations. The plants were divided into 13 families, used for treatment of schizophrenia and accompanying symptoms like hallucination, depression, oversleeping or insomnia, deterioration of personal hygiene, forgetfulness, and fear due to evil spirits like genies or ghost. A search of the relevant scientific literatures showed that a number of plants used by the medicinal practitioners have been scientifically validated in their uses and traditional medicinal knowledge has been a means towards the discovery of many modern medicines. Moreover, the antipsychotic drug reserpine, isolated from the dried root of Rauvolfia serpentina species, revolutionized the treatment of schizophrenia. So it is very much possible that formulations of the practitioner, when examined scientifically in their entireties, can form discovery of lead compounds which can be used as safe and effective antipsychotic drug to treat schizophrenia."*

Herbal Extracts

Article on Neuroleptic Herbs used in Animal Models of Psychosis

Zhang-Jin Zhang. Therapeutic effects of herbal extracts and constituents in animal models of psychiatric disorders.

- *"Authors Summary; This article contains a section with numerous neuroleptic herbs that have been tested in animal models of psychosis."*

Herbal PAK1 Blockers

Herbal PAK1 Blockers Berberine, Propolis, and Curcumin May Be Therapeutic for the Treatment of Schizophrenia

Maruta, Hiroshi. "Herbal Therapeutics That Block the Oncogenic Kinase PAK1: A Practical Approach towards PAK1-Dependent Diseases and Longevity." Phytotherapy Research: PTR 28, no. 5 (May 2014): 656–72. doi:10.1002/ptr.5054.

- *"Accordingly, it is presumed that PAK1 is abnormally activated in the brain of schizophrenia patients with DISC1 mutation, and that in principle, anti-PAK1 drugs could suppress schizophrenia as well. In fact, according to a recent review (Kulkarni and Dhir, 2010), among PAK1-blockers, berberine, at least, appears to suppress schizophrenia as well as other PAK1-dependent neuronal disorders such as depression. Thus, it would be worth testing the therapeutic effect on DISC1-induced schizophrenia of other natural PAK1-blockers such as propolis and curcumin."*

Mexican Medicine Plants

Mexican Medicine Plants Include Plants with Antipsychotic Properties

Jiménez-Olivares, E. "[Pre-Columbian indigenous psychopharmacology]." Neurología, Neurocirugía, Psiquiatría 19, no. 1 (1978): 40–52.

- *"A careful review has been carried out on texts concerning Mexican medicine plants, especially on texts obtained directly from the XVI century Indian reports. The plants utilized for psychiatric purposes have been separated from the huge group of 1 500 medicine plants used by the prehispanic Indians, and have been found about 150 plants which have been classified in the modern way of antipsychotic, antidepressant, minor tranquilizer, hallucinogens, sedatives, hypnotics, brain tonics, stimulants and anticonvulsants. The intention in making this research is to awake the interest of the people in the experimenting field; as experiments have been effected only on hallucinogen up to now, and if these have proved to possess the effects caused to the Indians, supposedly large part of the other plants have the effects according to the indications they have mentioned."*

Traditional Western Herbal Remedies

Cannabinoids

Cannabinoids May Be Useful for the Treatment of Schizophrenia

Coulston, Carissa M., "Cannabinoids for the Treatment of Schizophrenia? A Balanced Neurochemical Framework for Both Adverse and Therapeutic Effects of Cannabis Use." Schizophrenia Research and Treatment 2011 (2011): 501726. doi:10.1155/2011/501726.

- *"Recent studies have found that cannabinoids may improve neuropsychological performance, ameliorate negative symptoms, and have antipsychotic properties for a subgroup of the schizophrenia population. These findings are in contrast to the*

longstanding history of adverse consequences of cannabis use, predominantly on the positive symptoms, and a balanced neurochemical basis for these opposing views is lacking. This paper details a review of the neurobiological substrates of schizophrenia and the neurochemical effects of cannabis use in the normal population, in both cortical (in particular prefrontal) and subcortical brain regions. The aim of this paper is to provide a holistic neurochemical framework in which to understand how cannabinoids may impair, or indeed, serve to ameliorate the positive and negative symptoms as well as cognitive impairment. Directions in which future research can proceed to resolve the discrepancies are briefly discussed."

Cannabidiol Alleviates Psychosis by Anadamide Deactivation

Leweke, F. M., "Cannabidiol Enhances Anandamide Signaling and Alleviates Psychotic Symptoms of Schizophrenia." Translational Psychiatry 2 (2012): e94. doi:10.1038/tp.2012.15.

- *"The results suggest that inhibition of anandamide deactivation may contribute to the antipsychotic effects of cannabidiol potentially representing a completely new mechanism in the treatment of schizophrenia."*

Cannabidiol Shows Potential for Antipsychotic Treatment

Schubart, C. D., "Cannabidiol as a Potential Treatment for Psychosis." European Neuropsychopharmacology: The Journal of the European College of Neuropsychopharmacology 24, no. 1 (January 2014): 51–64. doi:10.1016/j.euroneuro.2013.11.002.

- *"Evidence from several research domains suggests that CBD shows potential for antipsychotic treatment."*

Cannabidiol a Safe and Well Tolerated Alternative Antipsychotic Drug

Zuardi, A. W., "Cannabidiol, a Cannabis Sativa Constituent, as an Antipsychotic Drug." Brazilian Journal of Medical and Biological Research = Revista Brasileira De Pesquisas Médicas E Biológicas / Sociedade Brasileira De Biofísica ... [et Al.] 39, no. 4 (April 2006): 421–29. doi:/S0100-879X2006000400001.

- *"A high dose of delta9-tetrahydrocannabinol, the main Cannabis sativa (cannabis) component, induces anxiety and psychotic-like symptoms in healthy volunteers. These effects of delta9-tetrahydrocannabinol are significantly reduced by cannabidiol (CBD), a cannabis constituent which is devoid of the typical effects of the plant. This observation led us to suspect that CBD could have anxiolytic and/or antipsychotic actions. Studies in animal models and in healthy volunteers clearly suggest an anxiolytic-like effect of CBD.*

The antipsychotic-like properties of CBD have been investigated in animal models using behavioral and neurochemical techniques which suggested that CBD has a pharmacological profile similar to that of atypical antipsychotic drugs. The results of two studies on healthy volunteers using perception of binocular depth inversion and ketamine-induced psychotic symptoms supported the proposal of the antipsychotic-like properties of CBD. In addition, open case reports of schizophrenic patients treated with CBD and a preliminary report of a controlled clinical trial comparing CBD with an atypical antipsychotic drug have confirmed that this cannabinoid can be a safe and well-tolerated alternative treatment for schizophrenia. Future studies of CBD in other psychotic conditions such as bipolar disorder and comparative studies of its antipsychotic effects with those produced by clozapine in schizophrenic patients are clearly indicated."

Cannabidiol is a Well Tolerated Alternative Treatment for Schizophrenia

Deiana, Serena. "Medical Use of Cannabis. Cannabidiol: A New Light for Schizophrenia?" Drug Testing and Analysis 5, no. 1 (January 2013): 46–51. doi:10.1002/dta.1425.

- *"Evidence suggests that CBD can ameliorate positive and negative symptoms of schizophrenia. Behavioural and neurochemical models suggest that CBD has a pharmacological profile similar to that of atypical anti-psychotic drugs and a clinical trial reported that this cannabinoid is a well-tolerated alternative treatment for schizophrenia."*

Cannabidiol Has Pharmacological Profile Similar to That of Atypical Antipsychotic Drugs

Zuardi AW. A critical review of the antipsychotic effects of cannabidiol: 30 years of a translational investigation. Curr Pharm Des 2012; 18(32):5131-40

- *"Subsequent studies have demonstrated that CBD has antipsychotic effects as observed using animal models and in healthy volunteers. Thus, this article provides a critical review of the research evaluating antipsychotic potential of this cannabinoid. CBD appears to have pharmacological profile similar to that of atypical antipsychotic drugs as seem using behavioral and neurochemical techniques in animal models. Additionally, CBD, prevented human experimental psychosis and was effective in open case reports and clinical trials in patients with schizophrenia with remarkable safety profile."*

Emodin Rubarb

Emodin Rubarb Extract Ameliorates Neurobehavioral Deficits and Might Be A Novel Class of Pro-drug for Antipsychotic Medication

Mizuno, M., "The Anthraquinone Derivative Emodin Ameliorates Neurobehavioral Deficits of a Rodent Model for Schizophrenia." Journal of Neural Transmission (Vienna, Austria: 1996) 115, no. 3 (2008): 521–30. doi:10.1007/s00702-007-0867-5.

- *"We conclude that emodin can both attenuate EGF receptor signaling and ameliorate behavioral deficits. Therefore, emodin might be a novel class of a pro-drug for anti-psychotic medication."*

Gentianine

Gentianine Exhibits Significant Antipsychotic Activity with Minimal Toxicity

Bhattacharya, S. K., "Letter: Chemical Constituents of Gentianaceae. XI. Antipsychotic Activity of Gentianine." Journal of Pharmaceutical Sciences 63, no. 8 (August 1974): 1341–42.

- *"Gentianine exhibited significant antipsychotic activity in the battery of tests accepted for arriving at such a conclusion (17). It has the added advantage of its minimal toxicity. The alkaloid, bearing a skeleton (lactonic monoterpene) different from those of known antipsychotic agents, is thus of potential importance as an antipsychotic drug. "*

Ginseng

Ginseng Significantly Improves Working Memory in Schizophrenic Patients

Chen EY. HT1001, a proprietary North American ginseng extract, improves working memory in schizophrenia: a double-blind, placebo-controlled study. Phyther Res 2012 Aug;26(8):1166-72

- *"Visual working memory was significantly improved in the HT1001 group, but not in the placebo group. Furthermore, extrapyramidal symptoms were significantly reduced after 4 weeks treatment with HT1001, whereas no difference in extrapyramidal effects was observed in the placebo group. These results provide a solid foundation for the further investigation of HT1001 as an adjunct therapy in schizophrenia, as an improvement in working memory and a reduction in medication related side effects has considerable potential to improve functional outcome in this population."*

American Ginseng Posses Antipsychotic-like Properties which May Be Beneficial in Negative and Cognitive Symptoms in Schizophrenia

Chatterjee M. Evaluation of the antipsychotic potential of Panax quinquefolium in ketamine induced experimental psychosis model in mice. Neurochem Res 2012 Apr;37(4):759-70

- *"Overall our findings suggest that PQ possesses antipsychotic like properties, which may lead to future studies with its specific constitutes which may particularly be beneficial in predominant negative and cognitive symptoms of schizophrenia."*

Glory Bower Leaf

Glory Bower Leaf Extract Alleviates Hyperlocomotion and Improve Sensorimotor Gating Deficit Supporting a Therapeutic Role in Schizophrenia

Chen, Hon-Lie, "Clerodendrum Inerme Leaf Extract Alleviates Animal Behaviors, Hyperlocomotion, and Prepulse Inhibition Disruptions, Mimicking Tourette Syndrome and Schizophrenia." Evidence-Based Complementary and Alternative Medicine: eCAM 2012 (2012): 284301. doi:10.1155/2012/284301.

- *"Previously, we found a patient with intractable motor tic disorder, a spectrum of Tourette syndrome (TS), responsive to the ground leaf juice of Clerodendrum inerme (CI). Here, we examined the effect of the ethanol extract of CI leaves (CI extract) on animal behaviors mimicking TS, hyperlocomotion, and sensorimotor gating deficit. The latter is also observed in schizophrenic patients and can be reflected by a disruption of prepulse inhibition of acoustic startle response (PPI) in animal models induced by methamphetamine and NMDA channel blockers (ketamine or MK-801), based on hyperdopaminergic and hypoglutamatergic hypotheses, respectively. CI extract (10-300 mg/kg, i.p.) dose-dependently inhibited hyperlocomotion induced by methamphetamine (2 mg/kg, i.p.) and PPI disruptions induced by methamphetamine, ketamine (30 mg/kg, i.p.), and MK-801 (0.3 mg/kg, i.p.) but did not affect spontaneous locomotor activity, rotarod performance, and grip force. These results suggest that CI extract can relieve hyperlocomotion and improve sensorimotor gating deficit, supporting the therapeutic potential of CI for TS and schizophrenia."*

Herbal Self-Heal (Heal All)

Herbal Self-Heal (Heal All) could be Useful for Treating Schizophrenia Because it Ameliorates PPI and Attention Defects

Park, Se Jin, "Prunella Vulgaris Attenuates Prepulse Inhibition Deficit and Attention Disruption Induced by MK-801 in Mice." Phytotherapy Research: PTR 27, no. 12 (December 2013): 1763–69. doi:10.1002/ptr.4929.

- *"These results suggest that EEPV could be useful for treating schizophrenia because EEPV ameliorates prepulse inhibition disruption and attention deficits induced by MK-801."*

Maytenus Obtusifola

Maytenus Obtusifola Extract Posses Neuroleptic-like Properties

de Sousa DP. Neuroleptic-like properties of the chloroform extract of Maytenus obtusifolia MART. Roots. Biol Pharm Bull 2005 Feb;28(2):224-5

- *"The results suggest that chloroform extract of Maytenus obtusifolia MART. possesses neuroleptic-like properties."*

Mistletoe

Mistletoe has Sedative, Antiepileptic and Antipsychotic Activity in Animals

Gupta G. Sedative, antiepileptic and antipsychotic effects of Viscum album L. (Loranthaceae) in mice and rats. J Ethnopharmacol 2012 Jun 14;141(3):810-6

- *"The results obtained in present study suggested that title plant exhibited sedative, antiepileptic and antipsychotic activity in mice and rats."*

Myricitrin

Natural Chemical Compound Myricitrin Exerts Antipsychotic-like Effects in Animal Models

Pereira, M., I. P. Siba, "Myricitrin, a Nitric Oxide and Protein Kinase C Inhibitor, Exerts Antipsychotic-like Effects in Animal Models." Progress in Neuro-Psychopharmacology & Biological Psychiatry 35, no. 7 (August 15, 2011): 1636–44. doi:10.1016/j.pnpbp.2011.06.002.

- *"Thus, myricitrin exhibited an antipsychotic-like profile at doses that did not induce catalepsy, and this effect may be related to nitrergic action."*

Pedersen CA. Intranasal oxytocin reduces psychotic symptoms and improves Theory of Mind and social perception in schizophrenia. Schizophrenia Res 2011 Oct;132(1):50-3

- *"PANSS scores declined significantly and several social cognition measures improved significantly or near significantly in oxytocin but not placebo."*

Palicourea Marcgravii

Leaf Palicourea Marcgravii Leaf Extract Has Antipsychotic-like Properties

Górniak, S. L., "Effects of a Palicourea Marcgravii Leaf Extract on Some Dopamine-Related Behaviors of Rats." Journal of Ethnopharmacology 28, no. 3 (March 1990): 329–35.

- *"The effects of a Palicourea marcgravii leaf extract on some dopamine-related behaviors were studied in rats. The extract given subcutaneously decreased both spontaneous locomotion and rearing frequencies of rats observed in open-field studies and increased their periods of immobility. The extract was also able to produce a rightward displacement of the apomorphine dose-response curve for stereotyped behavior and decrease the maximum response possible. Although the extract (1.87 g/kg subcutaneously) was unable to produce true catalepsy by itself, it potentiated that induced by haloperidol. These results with the extract can be interpreted to be due to a direct blocking action for the extract on a mesostriatal dopamine receptor or to an indirect effect on dopamine pathways through central cholinergic activation."*

Phytocannabinoid Δ9-Tetrahydrocannabivarin

Phytocannabinoid Δ9-Tetrahydrocannabivarin Has Therapeutic Potential for ameliorating some of the Negative, Cognitive and Positive Symptoms of Schizophrenia

Cascio, Maria Grazia, "The Phytocannabinoid, Δ9-Tetrahydrocannabivarin, Can Act through 5-HT1A Receptors to Produce Anti-Psychotic Effects." British Journal of Pharmacology, November 1, 2014, n/a – n/a. doi:10.1111/bph.13000.

- *"Our findings suggest that THCV can enhance 5-HT1A receptor activation, and that some of its apparent anti-psychotic effects may depend on this enhancement. We conclude that THCV has therapeutic potential for ameliorating some of the negative, cognitive and positive symptoms of schizophrenia."*

St. John's Wort

St. John's Wort Extract Reverses Changes in Auditory Evoked Potentials in Humans

Murck, Harald, "Hypericum Extract Reverses S-Ketamine-Induced Changes in Auditory Evoked Potentials in Humans - Possible Implications for the Treatment of Schizophrenia." Biological Psychiatry 59, no. 5 (March 1, 2006): 440–45. doi:10.1016/j.biopsych.2005.07.008.

- *"S-ketamine lead to a significant decrease in the N100-P200 peak to peak (ptp) amplitude after the placebo treatment, whereas ptp was significantly increased by S-ketamine infusion in the LI160 treated subjects. The ODT and the cognitive testing revealed no significant effect of ketamine-infusion and therefore no interaction between treatment groups. AEP measures are sensitive means to assess the effect of low dose ketamine.*

Provided that ketamine mimics cognitive deficits in schizophrenia, LI160 might be effective to treat these symptoms."

Traditional African Medicine

Crassocephalum Bauchiense Leaf

Crassocephalum Bauchiense Leaf Extract Has Antipsychotic and Sedative Properties

Sotoing Taïwe, Germain, "Antipsychotic and Sedative Effects of the Leaf Extract of Crassocephalum Bauchiense (Hutch.) Milne-Redh (Asteraceae) in Rodents." Journal of Ethnopharmacology 143, no. 1 (August 30, 2012): 213–20. doi:10.1016/j.jep.2012.06.026.

- *"The results show that the antipsychotic and sedative properties of Crassocephalum bauchiense are possibly mediated via the blockade of dopamine D-2 receptors and GABAergic activation, respectively. However, pharmacological and chemical studies are continuing in order to characterize the mechanism(s) responsible for these neuropharmacological actions and also to identify the active substances present in the extracts of Crassocephalum bauchiense."*

Jobelyn

Jobelyn Exhibits Antipsychotic-like Activity

Omogbiya IA. Jobelyn® pretreatment ameliorates symptoms of psychosis in experimental models. J Basic Clin Physiol Pharmacol 2013;24(4):331-6

- *"Taken together, these findings suggest that JB exhibits antipsychotic-like activity, devoid of the adverse effect of cataleptic behavior, and may offer some beneficial effects in the symptomatic relief of psychotic ailments."*

Lonchocarpus Cyanescens

Lonchocarpus Cyanescens Extracts Posses Phytochemically Constitutes with Antipsychotic Property

Sonibare MA. Antipsychotic property of aqueous and ethanolic extracts of Lonchocarpus cyanescens (Schumach and Thonn.) Benth. (Fabaceae) in rodents.

- *"Taken together, these findings suggest that the extracts possess phytochemically active constituents with antipsychotic property. Thus, this investigation provides evidence that*

may justify the ethnomedicinal applications of Lonchocarpus cyanescens as the major constitute of the recipe used for the management of psychosis in Nigeria."

Arowona IT. Antipsychotic property of solvent-partitioned fractions of Lonchocarpus cyanescens leaf extract in mice. J Basic Clin Physiol Pharmacol 2013 Dec 19: 1-6

- *"These findings suggest that EAF contains the major active constitute(s) mediating the antipsychotic property of LC and further support it use for the management of psychosis in traditional medicine."*

Ragleaf

Ragleaf Extract Has Sedative and Antipsychotic Effects

Sotoing Taiwe G. Antipsychotic and sedative effects of the leaf extract of Crassocephalum bauchiense (Hutch.) Milne-Redh (Asteraceae) in rodents. J Ethnopharmacol 2012 Aug 30;143(1): 213-20

- *"The results show that the antipsychotic and sedative properties of Crassocephalum bauchiense are possibly mediated via the blockade of dopamine D-2 receptors and GABAergic activation, respectively."*

Securinega Virosa Root Bark

Securinega Virosa Root Bark Has Antipsychotic Potential

Magaji, M. G., "Evaluation of the Antipsychotic Potential of Aqueous Fraction of Securinega Virosa Root Bark Extract in Mice." Metabolic Brain Disease 29, no. 1 (March 2014): 161–65. doi:10.1007/s11011-014-9483-x.

- *"These results suggest that the residual aqueous fraction of methanol root bark extract of Securinega virosa contains biological active principle with antipsychotic potential."*

Traditional African Healers

Traditional Healers have a High Rate of Success in Treating Cases of Schizophrenia in African People

Wessels, W. H. "The Traditional Healer and Psychiatry." The Australian and New Zealand Journal of Psychiatry 19, no. 3 (September 1985): 283–86.

- *"Successful psychiatric treatment for rural Africans should incorporate their traditional belief that illness should be viewed in terms of magical, social, physical and religious*

parameters. Traditional healers divide illness into those of natural causation and those of traditional cultural aetiology which are peculiar to African people. Natural illness includes epilepsy, familial/genetic disorders, mental retardation and schizophrenia. Traditional, cultural disorders often cause difficulties for Western-trained psychiatrists because sorcery, spirit possession and ancestral worship are central to their aetiology and treatment as practised by traditional healers. They, in a state of altered consciousness, use a process of divination to determine why and from whom the misfortune originated. With this in mind, reputable traditional healers were consulted in therapy-resistant cases of culture-bound syndromes in Africans. Their high rate of success in treating these cases was notable. More recognition should be given to the reputable traditional healers."

Traditional Ayurvedic Medicine (India)

Alstonia Scholaris and Bacopa Monniera

Extracts of Alstonia Scholaris and Bacopa Monniera Posses Neuroleptic Activity

Jash, Rajiv, "Ethanolic Extracts of Alstonia Scholaris and Bacopa Monniera Possess Neuroleptic Activity due to Anti-Dopaminergic Effect." Pharmacognosy Research 6, no. 1 (January 2014): 46–51. doi:10.4103/0974-8490.122917.

- *"The result of the study indicated a significant reduction of amphetamine-induced stereotype and conditioned avoidance response for both the extracts compared with the control group, but both did not have any significant effect in phencyclidine-induced locomotor activity and social interaction activity. However, both the extracts showed minor signs of catalepsy compared to the control group. The study also revealed that the neuroleptic effect was due to the reduction of the dopamine concentration in the frontal cortex region of the rat brain. The results largely pointed out the fact that both the extract may be having the property to alleviate the positive symptoms of schizophrenia by reducing the dopamine levels of dopaminergic neurons of the brain. The estimation of dopamine in the two major regions of brain indicated the alteration of dopamine levels was the reason for the anti-psychotic activity as demonstrated by the different animal models."*

Ayurvedic Mixtures

Ayurvedic Medicine for Schizophrenia

Agarwal V. Ayurvedic medicine for schizophrenia. Cochrane Database Syst Rev 2007 Oct 17;(4):CD006867

- *"….Ayurevedic treatment, in the case a complex mixture of many herbs, is compared with chlorpromazine in acutely ill people with schizophrenia, it is equally, but skewed*

data seems to favor the chlorpromazine group. Ayurevedic medication may have some effects for treatment of schizophrenia…."

Ayurvedic Herbs Regulate RGS4 Protein Found in Schizophrenia Establishing a Remedy

Preenon Bagchi*, "Establishing an in-silico ayurvedic medication towards treatment of Schizophrenia". International Journal of Systems Biology, ISSN: 0975–2900, Volume 1, Issue 2, 2009, pp-46-50

- *"RGS4 protein responsible for Schizophrenia is taken from NCBI's Entrez database; its 3D structure is determined by homology modelling. Ashwagandha, Sarpagandha and Mandukparni (Thankuni) were selected from Indian Ayurvedic medication. Their active component's 3D structures were established. Their combination is found to dock with RGS4 protein, hence establishing a remedy."*

Report on Several Ayurvedic Herbs Binding Assays for the NMDA Receptor

Preenon Bagchi, "Identification of Novel Drug Leads for NMDA Receptor Implicated In Schizophrenia from Indian Traditional Herbs" International conference on Intelligent Systems, Data Mining and Information Technology (ICIDIT'2014), April 21-22, 2014 Bangkok (Thailand)

- *"Schizophrenia is a major debilitating disorder worldwide. Schizophrenia is a result of multi-gene mutation and psycho-social factors. Mutated amino acid sequences of N-Methyl-D- Aspartate (NMDA) have been implicated as factors causing schizophrenia which were retrieved from the National Centre for Biotechnology Information (NCBI). 3D structure of the above receptor was determined by using protein threading technique. Several ayurvedic herbs are implicated as causative factors for schizophrenia. The phyto-compounds information of the above herbs was retrieved from various literature studies. The pharmacophore hypothesis was generated for the reported inhibitors. The phytochemical compounds were screened against the NMDA receptor. Novel ligands were shortlisted based on their fitness & docking score. These shortlisted ligands can be considered for binding assay studies with cell lines with the NMDA receptor in in-vitro."*

- *"NMDA: The phytocompounds picroside II, wedelolactone, 7-o-methylwogonin and isoformononetin having the best fitness score, docking score and most interactions with the NMDA receptor are considered for binding assay studies with NMDA receptor in-vitro."*

Brahmi (Bacopa Monnieri)

Brahmi (Bacopa monnieri) Resulted in Reduction of Psychopathology in Schizophrenic Patient

Sarkar, Sukanto, "Add-on Effect of Brahmi in the Management of Schizophrenia." Journal of Ayurveda and Integrative Medicine 3, no. 4 (October 2012): 223–25. doi:10.4103/0975-9476.104448.

- *"Brahmi(Bacopa monnieri), an Ayurvedic herb has primarily been used to enhance cognitive ability, memory and learning skills. We present a case study of schizophrenia in which add-on Brahmi extracts 500 mg/day for a period of one month resulted in reduction in psychopathology without any treatment-emergent adverse effect. Although preliminary, our case study suggests therapeutic efficacy of add-on Brahmi in schizophrenia, thus opening up a new dimension of its role in alternative medicines."*

Brahmyadiyoga

Brahmyadiyoga is an Ayurvedic Drug Compound that is Successful in Treating Schizophrenia

Ramu, M. G., "A Pilot Study of Role of Brahmyadiyoga in Chronic Unmada(schizophrenia)." Ancient Science of Life 2, no. 4 (April 1983): 205–7.

- *"Brahmyadiyoga a compound drug was used on fourteen Chronic Unmada patients suffering from 2 years to 8 years between the ago range of 18 to 40 years of either sex. The dose of the drug was 8 gms. to 16 gms. for three months. Assessments were done independently by Ayurvedic physician, Psychiatrist and Clinical Psychologist. Seven out of 10 patients who underwent treatment for three months and all the four patients who took the drug for two months improved."*

Indian Spurgetree Leaves

Indian Spurgetree Leaves Extract Has Anti-anxiety, Antipsychotic and Anti-consultant Activity

Bigoniya, Papiya, "Psychopharmacological Profile of Hydro-Alcoholic Extract of Euphorbia Neriifolia Leaves in Mice and Rats." Indian Journal of Experimental Biology 43, no. 10 (October 2005): 859–62.

- *"These results indicated anti-anxiety, anti-psychotic and anti-convulsant activity of E. neriifolia leaf extract in mice and rats. Phytochemical study showed the presence of steroidal saponin, reducing sugar, tannins, flavonoids in the crude leaf extract"*

Neuroleptic plant extracts

Mono Ingredient Herbal Neuroleptic Has Similar Effect as Marketed Formulations

Samanta M. K. Development of mono ingredient herbal neuroleptic tablet for better psychiatric therapy. Indian J Pharm Sci, 2005, 67(1):51-56

- *"A tablet containing A. calamus, W. somnifera, and G. glabra" "….three neuroleptic plant extracts were used for the formulation based on ayurvedic neuroleptic formulations and available literatures. …It was found that these formulations containing three plant extracts were having similar effects as those of marketed formulations. The prepared tablet formulation has not shown any drug induced parkinsonian syndrome or any other relevant side effects, wereas the synthetic drug, chlorpromazine showed maximum pyramidal side effects."*

Tinospora Cordifolia

Guduchi Standard Extract Has Antipsychotic Activity

Jain, Bindu Nee Giri, "Antipsychotic Activity of Aqueous Ethanolic Extract of Tinospora Cordifolia in Amphetamine Challenged Mice Model." Journal of Advanced Pharmaceutical Technology & Research 1, no. 1 (January 2010): 30–33.

- *"The results in SLA showed that the hydro alcoholic extract of the stems of Tinospora cordifolia at a dose level of 250 mg/kg and 500 mg/kg showed no significant antipsychotic activity in amphetamine induced hyperactivity in mice when compared to standard. Extract alone treated group at a dos level of 250 mg/kg and 500 mg/kg showed a decreased in locomotor activity when compared to the control. The plant extract increased the DAD(2) receptor binding in a dose dependent manner in treated mice compared to the control group."*

Traditional Asian/Chinese/Kampo Medicine

Acupuncture

Acupuncture Reduces Hallucinations in Patient with Schizophrenia

Bosch, Peggy, "A Case Study on Acupuncture in the Treatment of Schizophrenia." Acupuncture in Medicine: Journal of the British Medical Acupuncture Society 32, no. 3 (June 2014): 286–89. doi:10.1136/acupmed-2014-010547.

- *"This report describes the use of acupuncture as an add on treatment for a patient with chronic schizophrenia. The 63-year-old woman suffered from persistent hallucinations and even physical pain as a result of the hallucination of a black bird that kept pecking*

her back. The patient received 12 weekly acupuncture treatments. A clinical diagnostic interview and psychological testing (on sleep quality, depression, and on positive and negative symptoms) were conducted before, immediately after and 3 months after the acupuncture treatment. The results of the diagnostic interview gave important insights into the treatment effects. The patient experienced improved daily functioning and noticed a change in hallucinations. Although the hallucinations still occurred, she felt less disturbed by them. Interestingly, pain decreased markedly. In addition, the results showed that the overall score of the positive and negative symptoms did not change immediately; however, a decrease in symptoms occurred 3 months after acupuncture treatment. Moreover, the patient described an immediate improvement in sleep; this was confirmed by a daytime sleepiness questionnaire. The patient was not able to complete a (longer) test on sleep quality beforehand but did so after the treatment period. Finally, a delayed improvement in the depression scale was found. Although larger clinical intervention studies on acupuncture and schizophrenia are needed, the results of this case study indicate that acupuncture may be beneficial as an add on treatment tool in patients with schizophrenia."

Acupuncture Plus Antipsychotic Therapy Shows Significant Effects for Schizophrenia

Lee MS. Acupuncture for schizophrenia: a systematic review and meta-analysis. Int J Clin Pract 2009 Nov;63(11):1622-33

- *"Thirteen RTC's, all originating from China, met the inclusion criteria. One RTC reported significant effects of electro-acupuncture plus drug therapy for improving auditory hallucinations and positive symptoms compared to sham EA plus drug therapy. Four RTCs showed significant effects of acupuncture for response rate compared with antipsychotic drugs. Seven RTCs showed significant effects of acupuncture plus antipsychotic therapy for response rate compared with antipsychotic drug therapy. Two RTCs tested laser acupuncture on hallucinations against sham laser acupuncture. One RTC found beneficial effects of laser acupuncture on response rate, Brief Psychiatric Rating Scale and clinical global index compared with sham laser."*

Acupuncture (Aricular)

Aricular Acupuncture is Recommended for the Treatment of Auditory Hallucinations

Shi Zx. Observation on the curative effect of 120 cases of auditory hallucination treated with aricular acupuncture. Journal of Traditional Chinese Medicine , 9(3): 176-178, 1989

- *"We have treated auditory hallucination with different kinds of psychosis, mainly using auricular acupuncture and yielding certain cumulative effect. We also noted there is no significant difference in curative effects among groups of simple auricular acupuncture, aricular plus body acupuncture and aricular acupuncture plus chlorpromazine. Therefore, we recommend auricular acupuncture for treating hallucinations."*

Acupuncture (electro)

Electroacupuncture for Treatment of Schizophrenia Has a Higher Clinical Response Rate Than Sham

Jing Cheng. Electro-acupuncture verses sham electro-acupuncture for auditory hallucinations in patients with schizophrenia: a randomized controlled trial. Clin Rehabil 2009 Jul;(7):579-88

- *"The clinical response rates in electro-acupuncture and sham electro-acupuncture group were 43.3% and 13.3% respectively."*

Electroacupuncture Plus Antipsychotic Shows Higher Compliance in Treating Schizophrenia

Feng-Ju Y. Short-term curative effect of electroacupuncture as adjunctive treatment on schizophrenia. Zhongguo Zhong Xi Yi Zhi 2006 Mar;26(3):253-5

- *"With effect equal to CZ (clonzapine), combination of CZ and EA shows higher compliance in treating schizophrenia….*

Electroacupuncture Plus Antipsychotic Requires less Drug

Zhuge DY . Comparison between electro-acupuncture with chlorpromazine and chlorpromazine alone in 60 schizophrenic patients. Zhongguo Zhong Xi Yi Jie He Za Zhi 1993 Jul;13(7):408-9,388

- "*The result showed the total curative effects of the two groups were similar. However, the marked effects appeared earlier in combined therapy than using chlorpromazine alone, less chlorpromazine was needed."*

Bacopa Monnieri

Bacopa Monnieri May Recover Cognitive Deficit

Piyabhan, Pritsana,"Cognitive Enhancement Effects of Bacopa Monnieri (Brahmi) on Novel Object Recognition and VGLUT1 Density in the Prefrontal Cortex, Striatum, and Hippocampus of Sub-Chronic Phencyclidine Rat Model of Schizophrenia." Journal of the Medical Association of Thailand = Chotmaihet Thangphaet 96, no. 5 (May 2013): 625–32.

- *"Cognitive deficit observed in PCP-administered rats was mediated by VGLUT1 reduction in prefrontal cortex, striatum, CA1 and CA2/3. Interestingly, Brahmi could recover this cognitive deficit by increasing VGLUT1 in CA1 and CA2/3 to normal."*

Betel Nut

Chewing Betel Nut is Associated with Lower Positive and Negative Symptoms in People with Schizophrenia

Sullivan, R. J., "Effects of Chewing Betel Nut (Areca Catechu) on the Symptoms of People with Schizophrenia in Palau, Micronesia." The British Journal of Psychiatry: The Journal of Mental Science 177 (August 2000): 174–78.

- *"Betel chewers with schizophrenia scored significantly lower on the positive (P = 0.001) and negative (P = 0.002) sub-scales of the PANSS than did non-chewers. There were no significant differences in extrapyramidal symptoms or tardive dyskinesia. Betel chewing is associated with milder symptomatology and avoidance of more harmful recreational drugs. These initial results indicate that longitudinal research is merited."*

Male High Consumption of Betel Had Significantly Lower Positive Symptoms than Non-betel Users

Coppola, Maurizio, "Potential Action of Betel Alkaloids on Positive and Negative Symptoms of Schizophrenia: A Review." Nordic Journal of Psychiatry 66, no. 2 (April 2012): 73–78. doi:10.3109/08039488.2011.605172.

- *"Male high consumption of betel had significantly lower positive symptoms than low consumers or non-betel users."*

Schizophrenic Betel Chewers Had Significantly Milder Positive Symptoms than Low Consumption Chewers

Sullivan, Roger J., "The Effects of an Indigenous Muscarinic Drug, Betel Nut (Areca Catechu), on the Symptoms of Schizophrenia: A Longitudinal Study in Palau, Micronesia." The American Journal of Psychiatry 164, no. 4 (April 2007): 670–73. doi:10.1176/appi.ajp.164.4.670.

- *"Male high-consumption betel chewers had significantly milder positive symptoms than low-consumption chewers over 1 year. Betel chewing was not associated with global health, social functioning, or movement disorders. Betel chewing was associated with tobacco use but not with cannabis or alcohol."*

Binding Essays

Binding Essays of Natural Products to Treat Psychotic Illness

In-Won Chung. Pharmacologic Profile of Natural Products Used to Treat Psychotic Illnesses. Psychopharmacology Bulletin 31:139-145, 1995

- *"Authors Summary; In this article there are 31 extracts prepared from natural products frequently used to treat psychotic illnesses were identified from prescriptions in the Korean Tongeuibogam. The screening assays determined the receptor binding of each natural product used to treat psychotic illness."*

Blood Stasis Treatments

Chinese Medical Treatment to Relieve Blood Stasis in Schizophrenia

Wang B. Traditional Chinese medical treatment to invigorate blood and relieve stasis treatment of schizophrenia: comparison with antipsychotic treatment. Psychiatry Clin Neurosci 1996 Dec;52 Suppl:S329-30

- *"Traditional Chinese medicine is superior to antipsychotic drugs in the effects of anti-anxiety-depression and antipsychomotor inhibition, but is less effective in controlling psychomotor excitation compared with antipsychotic drugs"*

Zhu YZ. Clinical study of shuizhi-dahuang mixture in treating schizophrenics with blood stasis syndrome. Zhongguo Zhong Xi Yi Jie He Za Zhi 1996 Nov;16(11):646-8

- *A clinical study of 67 female schizophrenics was conducted. Thirty two patients of them treated with Shuizhi (leech)-Dahuang (rhubarb) mixture mainly with low dosage of antipsychotic drugs (combined therapy group). The results showed that their overall therapeutic effects were similar and the combined therapy group could reduce the dosages of antipsychotic drugs and its side effects, and tended to normalize the hemorheologic indices."*

Zhang JZ. Xuefu zhuyu decoction in treating blood stasis syndrome of schizophrenia. Zhongguo Zhong Xi Yi Jie He Za Zhi 1993 Jul; 13(7):397-401

- *"The clinical and experimental study of 66 schizophrenics were conducted. Based on mental symptoms, four-diagnostic method of TCM and hemorheology, it presented preliminarily the clinical and experimental criteria for schizophrenia. The combined therapy of Xuefu Zhuyu Decoction and low dosage of antipsychotic drug could relive the mental symptoms and the abnormal hemorhelogic index normalized. Its therapeutic index was higher than that of the control group."*

Chinese Herbal Remedies

Chinese Herbal Medicine for Schizophrenia

Rathbone J. Chinese herbal medicine for schizophrenia: Cochrane systematic review of randomized trials. Br J Psychiatry 2007 May;190:379-84

- *"Results suggest that combing Chinese herbal medicine with antipsychotics is beneficial"*

Daotan

Modified Daotan Decoction Improves Negative Symptoms in Schizophrenia

Liu JL. Clinical observation on effect of modified Daotan Decoction combined with small dose risperidone in treating chronic schizophrenia. Zhongguo Zhong Xi Yi Jie He Za Zhi 2007 Mar;27(3):208-10

- *"There was no significant difference in the overall efficiency between the two groups, but the improvement of the negative symptoms, illness provocation and general psychopathologic condition was significantly better in the treatment group than that in the control group respectively (P< 0.05)."*

Gastrodia Elata

Gastrodia Elata Has Antipsychotic Effects in PCP-induced Schizophrenia-like Psychosis

Shin, E.-J., "Effects of Gastrodia Elata Bl on Phencyclidine-Induced Schizophrenia-like Psychosis in Mice." Current Neuropharmacology 9, no. 1 (March 2011): 247–50. doi:10.2174/157015911795017263.

- *"In conclusion, our finding suggests that 5-HT1A receptor agonistic properties of GE offer potential therapeutic advantages in response to PCP-induced schizophrenia-like psycho- sis, although many details of the GE-mediated effect(s) re- main to be determined."*

Ginkgo Biloba (and Shuxening)

Ginkgo Biloba May Enhance the Effectiveness of Antipsychotic Drugs and Reduce Their Extrapyramidal Side Effects

Zhang, X. Y., "A Double-Blind, Placebo-Controlled Trial of Extract of Ginkgo Biloba Added to Haloperidol in Treatment-Resistant Patients with Schizophrenia." The Journal of Clinical Psychiatry 62, no. 11 (November 2001): 878–83.

- *"EGb treatment may enhance the effectiveness of antipsychotic drugs and reduce their extrapyramidal side effects."*

Ginkgo Biloba Was Effective for Positive Symptoms in Refractory Schizophrenia

Knable, Michael B. "Extract of Ginkgo Biloba Added to Haloperidol Was Effective for Positive Symptoms in Refractory Schizophrenia." Evidence-Based Mental Health 5, no. 3 (August 2002): 90.

- *"In patients with chronic, refractory schizophrenia, extract of Ginkgo biloba added to haloperidol was more effective than placebo added to haloperidol in treating positive symptoms."*
- *" Unintentionally, two experiments were performed. One woman, had been doing very well on the above combination, discontinued the salt supplement while remaining on the maintenance dose of lithium carbonate. 4 weeks later she became nauseated and dizzy and complained of strange ill-deined feelings and general weakness shortly after taking each dose. A second patient was started on lithium carbonate without salt supplements and had similar symptoms 1 ½ weeks after treatment was started. These side-effects disappeared when sodium chloride supplements were started. We conclude that sodium chloride supplements may diminish the side effects frequently reported with lithium carbonate treatment. Further investigations are indicated."*

Ginkgo is Effective as an Add-on Therapy for Schizophrenia

Singh, Vidhi, "Review and Meta-Analysis of Usage of Ginkgo as an Adjunct Therapy in Chronic Schizophrenia." The International Journal of Neuropsychopharmacology / Official Scientific Journal of the Collegium Internationale Neuropsychopharmacologicum (CINP) 13, no. 2 (March 2010): 257–71. doi:10.1017/S1461145709990654.

- *"Ginkgo as an add-on therapy to antipsychotic medication produced statistically significant moderate improvement (SMD=-0.50) in total and negative symptoms of chronic schizophrenia. Ginkgo as add-on therapy ameliorates the symptoms of chronic schizophrenia. The role of antioxidants in pathogenesis of schizophrenia has also been explored."*

Ginkgo Biloba Reduces Positive Symptoms in Patients with Schizophrenia

Atmaca M. The effect of extract of gingko biloba addition to olanzapine on therapeutic effect and antioxidant enzyme levels in patients with schizophrenia. Psychiatry and Clinical Neurosciences (2005),59. 652-656

- *"At the evaluation of week 8, a significant difference in mean Scale for the Assessment of Positive Symptoms (SAPS) scores but not in Scale for the Assessment of Negative Symptoms between groups was found."*

Ginkgo Biloba as an Add-on Produced Statistically Significant Improvement in Negative Symptoms

Singh V. Review and meta-analysis of usage of gingko as an adjunct therapy in chronic schizophrenia. Int J Neuropsychopharmacol 2010 Mar;13(2):257-71

- *"Ginkgo as an add-on therapy to antipsychotic medication produced statistically significant moderate improvement (SMD=0.50) in total and negative symptoms of chronic schizophrenia. Ginkgo as an add-on therapy ameliorates the symptoms of chronic schizophrenia. The role of antioxidants in the pathogenesis of schizophrenia has also been explored."*

Ginkgo Biloba is Useful for Enhancing the Effect of Clozapine on Negative Symptoms in Schizophrenia

Doruk A. A placebo-controlled study of extract of ginkgo biloba added to clozapine in patients with treatment-resistant schizophrenia. Int Clin Psychopharmacol 2008 Jul;23(4):223-7

- *"These preliminary data suggested that EGb was found useful for enhancing the effect of clozapine on negative symptoms in patients with treatment resistant schizophrenia"*

Shuxening Presented Better Therapeutic Effect for Schizophrenia than Control

Lou HC. Therapeutic effect of shuxening combining neuroleptics for the treatment of chronic schizophrenia—double blind study. Zhongguo Zhong Xi Yi Jie He Za Zhi 1997 Mar;17(3): 139-42

- *"SXN presented a better therapeutic effect for chronic schizophrenics than the control group when rated with traditional global rating method as well, in which 44.98% marked improvement was obtained in the SXN group compared to 20.98% in the control group."*

Huang Qi

Huang Qi Injection Has a Definite Prevention of Hospital Infection in Patients with Chronic Schizophrenia

Zhang, Bing-ru, "[Effects of injection of Huangqi injectio into Zusanli (ST 36) on immune function in the patient of schizophrenia]." Zhongguo Zhen Jiu = Chinese Acupuncture & Moxibustion 26, no. 9 (September 2006): 625–28.

- *"Injection of Huangqi Injectio into Zusanli (ST 36) has definite effect for prevention of the hospital infection in inpatients of chronic schizophrenia, and SIL-2R is a valuable index for investigation of the hospital of infection."*

Jieyu Anshen

Jieyu Anshen Decoction has a Definite and Quick Effect in Treating Schizophrenia

Zeng DZ. Clinical observation on effect of Jieyu Anshen Decoction combined with aripiprazole in treating chronic schizophrenia. Zhongguo Zhong Xi Yi Jie He Za Zhi 2007 Apr;27(4):358-61

- *"JAD combined with aripiparazole has definite effect in treating chronic schizophrenia, shows advantages of quickly initiating effect, high safety and with no harm for increasing adverse reactions, so it is better than using aripiprazole alone."*

Jinkoh-eremol and Agarospirol

Jinkoh-eremol and Agarospirol from Agarwood is Considered a Neuroleptic

Okugawa, H., "Effect of Jinkoh-Eremol and Agarospirol from Agarwood on the Central Nervous System in Mice." Planta Medica 62, no. 1 (February 1996): 2–6. doi:10.1055/s-2006-957784.

- *"Agarwood (Jinkoh in Japanese), one of the Oriental medicines, is used as a sedative. The benzene extract of this medicine showed a prolonged effect on the hexobarbital-induced sleeping time, and hypothermic effects in terms of rectal temperature, a suppressive effect on acetic acid-writhing, and a reduction of the spontaneous motility in mice. By repeated fractionation, oral administration in mice, and pharmacological screening, the active principles, jinkoh-eremol and agarospirol, were obtained from the benzene extract. They also gave positive effects on the central nervous system by peritoneal and intracerebroventricular administration. They decreased both methamphetamine- and apomorphine-induced spontaneous motility. The level of homovanillic acid in the brain was increased by them, while the levels of monoamines and other metabolites were unchanged. Similar results were seen in chlorpromazine-administered mice. Therefore, jinkoh-eremol and agarospirol can be considered to be neuroleptic."*

Kidney Yang

Warm-Supplementing Kidney Yang Enhances Cognitive Performance in Schizophrenia

Guo, Xin, "WSKY, a Traditional Chinese Decoction, Rescues Cognitive Impairment Associated with NMDA Receptor Antagonism by Enhancing BDNF/ERK/CREB Signaling." Molecular Medicine Reports, December 12, 2014. doi:10.3892/mmr.2014.3086.

- *"The results of the present study indicated that WSKY enhances cognitive performance via the upregulation of BDNF/ERK/CREB signaling, and that WSKY has potential therapeutic implications for cognitive impairment of schizophrenia."*

Warm Supplementing Kidney Yang Capsule Improves Cognitive and Social Function in Schizophrenia

Chen ZH. Effects of warm-supplementing kidney yang (WSKY) capsule added on risperidone on cognition in chronic schizophrenic patients: a randomized, double-blind, placebo-controlled, multi-center clinical trial. Hum Psychopharmacol 2008 Aug;23(6)"465-70

- *"WSKY capsule added on risperidone may improve cognitive function, social function of the chronic schizophrenics patients, and the WSKY safely during treatment"*

Kodo Millet

Kodo Millet Extract Has Tranquillizing Effects on Psychotic Patients

Deo, V. R. "STUDY OF PASPALUM SCROBICULATUM EXTRACT IN FORTY PSYCHOTIC PATIENTS." Psychopharmacologia 5 (February 12, 1964): 228–33.

- *"The dried ethanol extract of the husk of Paspalum scrobiculatum grain was given to psychotic patients. The trial was conducted by the double blind control, cross over method. The extract has been found to exert definite tranquillizing effect on patients. The only side effects noticed were tremors and rigidity, which were revesible. However, clinical trial with larger doses and for a longer period is necessary to access its efficacy and safety in psychiatric patients."*

Kodo Millet Has Tranquillizing Effect on Acutely Disturbed Schizophrenic Patients

Deo, V. R., "Effect of Paspalum Scrobiculatum Extract on Acutely Disturbed Schizophrenic Patients. A Prelimiinary Report." Psychopharmacologia 2 (1961): 295–96.

- *"As the clinical condition improved within 4 days after starting the extract and mostly relapsed equally rapidly after discontinuing the same, the observed effects cannot be attributed to chance alone. Considering the type of clinical disorder, the short duration of treatment and the expected degree of improvement, double-blind technique was not thought necessary during this initial phase of trial. On the other hand clinical effects of the neuropharmacological agents should be interpreted very cautiously. Thus the present results appear only to be encouragingly suggestive of the tranquillizing effect of the extract of P. scrobiculatum. Futher work in progress."*

Kodo Millet Produces Tranquility and Beneficial Effects for Schizophrenic Patients

Deo, V. R. "Tranquillizing Action of a Crystalline Fraction of Paspalum Scrobiculatum Extract in Fourteen Psychotic Patients." Indian Journal of Medical Sciences 25, no. 6 (June 1971): 389–91.

- *"A crystalline fraction BZ5 obtained from the dried alcoholic extract of Paspalum scrobiculatum was orally administered for about 11 days to 14 acutely agitated psychotic patients of whom 11 suffered from schizophrenia. (2) It produced tranquility and other beneficial effects in 9 schizophrenic patients. (3) Signs of Parkinsonism were not noticed in this study but reversible hypotension was seen in 3 patients. (4) Like the dried alcoholic ex- tract, BZ5 produced its beneficial effects only in schizophrenic patients."*

Noni

Noni Posses Antipsychotic-like Activity Can Be Utilized in the Treatment of Psychiatric Disorders

Pandy V. Antipsychotic-like activity of noni (Norinda citrifolia Linn.) in mice. BMC Complement Altern Med 2012 Oct 19; 12:186

- *" The present study results demonstrated the antidopaminergic effect of Morinda citrifolia Linn. In mice, suggesting that noni has antipsychotic-like activity which can be utilized in the treatment of psychiatric disorders."*

Schisandria Chinensis Bail

Schisandria Chinensis Bail showed Effectiveness as Antipsychotic in a Group of Schizophrenics

Panossian A. Pharmacology of Schisandria Chinensis Bail: An overview of Russian research and uses in medicine. Journal of Ethhopharmacology 118(2008) 183-212

- *"Galant et. al. (1957) claimed total recovery in psychosis following a trial involving the administration of SSP over a period of ten days (0.5g, three times daily) to 36 patients (19 with schizophrenia, 6 with reactive psychosis, 4 with alcoholic psychosis, 3 with involutional depression, and 4 with psychopathology) presenting astheno-depressive syndrome. However, in the treatment showed no effect in psychopathology, whilst in schizophrenic group, six patients recovered, seven patients improved, and six (the hardest) cases the treatment was ineffective."*

Shell Ginger

Shell Ginger May Be a Promising Treatment for Schizophrenia

De Araújo, Fernanda Yvelize Ramos, "Inhibition of Ketamine-Induced Hyperlocomotion in Mice by the Essential Oil of Alpinia Zerumbet: Possible Involvement of an Antioxidant Effect." The Journal of Pharmacy and Pharmacology 63, no. 8 (August 2011): 1103–10. doi:10.1111/j.2042-7158.2011.01312.x.

- *"The results suggest antipsychotic and antioxidant effects for the EOAZ that may have promising efficacy for the treatment of schizophrenia."*

Spanish Plum

Spanish Plum Has Antipsychotic Effects in Animals

Ayoka, Abiodun O., "Sedative, Antiepileptic and Antipsychotic Effects of Spondias Mombin L. (Anacardiaceae) in Mice and Rats." Journal of Ethnopharmacology 103, no. 2 (January 16, 2006): 166–75. doi:10.1016/j.jep.2005.07.019.

- *"The extracts decreased the amphetamine/apomorphine-induced stereotyped behaviour, which suggest that these extracts possess antidopaminergic activity. The effect of the extracts on hexobarbitone-induced sleeping time was blocked by flumazenil a GABA(A) antagonist, indicating that the extracts contain GABA(A) agonists. These results suggest that the leaves extracts of Spondias mombin possess sedative and antidopaminergic effects."*

White Mulberry

White Mulberry Extract Posses Antidoparmeinergic Activity

Yadav AV. Anti-dopaminergic effect of the methanolic extract of Morbus alba L. leaves. Indian J Pharmacol 2008 Oct;40(5):221-6

- *"The results suggest that the methanolic extract of Morbus alba L. possesses antidopaminergic activity. Further neurochemical investigation can explore the mechanism of action of the plant drug with respect to dopaminergic functions and help to establish the plant as an antipsychotic agent."*

Yokukansan (Yi-gan san)

Yokukansan is a Potential Adjunctive Treatment Strategy for Treatment-Resistant Schizophrenia

Miyaoka, Tsuyoshi, "Efficacy and Safety of Yokukansan in Treatment-Resistant Schizophrenia: A Randomized, Double-Blind, Placebo-Controlled Trial (a Positive and

Negative Syndrome Scale, Five-Factor Analysis)." Psychopharmacology, June 13, 2014. doi:10.1007/s00213-014-3645-8.

- *"The results of the present study indicate YKS to be a potential adjunctive treatment strategy for treatment-resistant schizophrenia, particularly to improve excitement/hostility symptoms."*

Provides Highly Significant Improvement in Psychotic Symptoms

Miyaoka T. Yokukansan (TJ-54) for the treatment of very-late-onset schizophrenia-like psychosis: an open label study. Phytomedicine 2013 may 15;20(7):654-8

- *"A highly significant ($p<0.001$) improvement on all measures of psychotic symptomology was observed in all patients. TJ-54 was very well tolerated by the patients, and no clinically significant adverse effects were observed. Scores on all abnormal movement scales did not differ significantly prior to and after TJ-54 treatment."*

Yi-gan san is Effective for the Treatment of Visual Hallucinations

Miyaoka T. Yi-gan san for the treatment of Charles bonnet syndrome (visual hallucinations due to vision loss): an open-label study. Clin Neuropharmacol 2011 Jan-Feb;34(1):24-7

- *"Yi-gan san may be effective and safe therapy to control visual hallucinations in patients with CBS and should be further tested in double-blind, placebo controlled trials."*

Yi-gan san Decreases Positive and Negative Symptoms in Schizophrenia

Miyaoka T. Yi-gan san as adjunctive therapy for treatment-resistant schizophrenia: an open-label study. Clin Neuropharmacol 2009 Jan-Feb;32(1):6-9

- *"A significant decrease was observed at 2 weeks and at 4 weeks in each Positive and Negative Syndrome Scale for Schizophrenia subscale score in the YGS group, but not observed in the control group."*

Kampo Yokukansan Alkaloid Geissoschizine Methyl Ether May Be a New Set of Candidates for Atypical Antipsychotics

Ueda T. Geissoschizine methyl ether has third-generation antipsychotic-like actions at the dopamine and serotonin receptors. Eur J Pharmacol 2011 Dec 5;671(1-3):79-86

- *"GM and GM derivatives may compromise a new set of candidates for atypical antipsychotics."*

Yokukansan and its Ingredients have Antipsychotic Effects

Yu, Chuan-Hsun, "Yokukansan and Its Ingredients as Possible Treatment Options for Schizophrenia." Neuropsychiatric Disease and Treatment 10 (2014): 1629–34. doi:10.2147/NDT.S67607.

- *"Yokukansan (TJ-54), also called yi-gan san in Chinese, is a traditional herbal medicine with evident therapeutic effect for neuropsychiatric disorders. There are several open-label clinical studies upholding the possibility of using yokukansan to treat schizophrenia or schizophrenia-like psychosis. Evidence from animal studies and neurobiology also sheds light on the antipsychotic implications of yokukansan and its ingredients. Nevertheless, correlations between the experimental environment and clinical settings may be complicated by a number of confounders. Clinical trials with more sophisticated designs are required to fill the gap between the experimental environment and clinical settings."*

Yokukansan Treatment Improves Cognitive Functions in Patient with Schizophrenia

Sakamoto, Shinji, "Adjunctive Yokukansan Treatment Improved Cognitive Functions in a Patient with Schizophrenia." The Journal of Neuropsychiatry and Clinical Neurosciences 25, no. 3 (2013): E39–40. doi:10.1176/appi.neuropsych.12070166**.**

- *"Yokukansan, a traditional Asian herbal medicine, isreportedtobesafeandeffectivefor behavioral and psychological symptoms of dementia in random- ized, controlled trials, and is widely prescribed for patients with dementia in Japan.1 A recent open- label study indicates that adjunctive yokukansan administration in treatment-resistant schizophrenia improved the positive and negative symptoms of schizophrenia.2 In this report, we present a case of schizophrenia in which adjunctive yokukansan treatment dramatically improved severe cognitive dysfunction."*

Drugs

Adenosine

Adenosine Augmentation Therapies May Be Used in the Future of Psychiatry

Shen, Hai-Ying, "Adenosine Augmentation Ameliorates Psychotic and Cognitive Endophenotypes of Schizophrenia." The Journal of Clinical Investigation 122, no. 7 (July 2, 2012): 2567–77. doi:10.1172/JCI62378.

- *"An emerging theory of schizophrenia postulates that hypofunction of adenosine signaling may contribute to its pathophysiology. This study was designed to test the*

"adenosine hypothesis" of schizophrenia and to evaluate focal adenosine-based strategies for therapy. We found that augmentation of adenosine by pharmacologic inhibition of adenosine kinase (ADK), the key enzyme of adenosine clearance, exerted antipsychotic-like activity in mice. Further, overexpression of ADK in transgenic mice was associated with attentional impairments linked to schizophrenia. We observed that the striatal adenosine A2A receptor links adenosine tone and psychomotor response to amphetamine, an indicator of dopaminergic signaling. Finally, intrastriatal implants of engineered adenosine-releasing cells restored the locomotor response to amphetamine in mice overexpressing ADK, whereas the same grafts placed proximal to the hippocampus of transgenic mice reversed their working memory deficit. This functional double dissociation between striatal and hippocampal adenosine demonstrated in Adk transgenic mice highlights the independent contributions of these two interconnected brain regions in the pathophysiology of schizophrenia and thus provides the rationale for developing local adenosine augmentation therapies for the treatment of schizophrenia."

Aspirin

Aspirin Therapy Reduces the Symptoms of Schizophrenia

Laan, Wijnand, "Adjuvant Aspirin Therapy Reduces Symptoms of Schizophrenia Spectrum Disorders: Results from a Randomized, Double-Blind, Placebo-Controlled Trial." The Journal of Clinical Psychiatry 71, no. 5 (May 2010): 520–27. doi:10.4088/JCP.09m05117yel.

- *"Aspirin given as adjuvant therapy to regular antipsychotic treatment reduces the symptoms of schizophrenia spectrum disorders. The reduction is more pronounced in those with the more altered immune function. Inflammation may constitute a potential new target for antipsychotic drug development."*

Adjunctive Aspirin Reduces Symptoms of Schizophrenia

Laan W. Adjuvant aspirin therapy reduces symptoms of schizophrenia spectrum disorders: results from a randomized, double-blind, placebo-controlled trial. J Clin Psychiatry 2010 May;71(5):520-7

- *"Aspirin given as adjunctive therapy to regular antipsychotic treatment reduces the symptoms of schizophrenia spectrum disorders."*

Exercise, Aerobics, and Sports

Aqua Therapy

Aqua-Therapy Proven Successful Rehabilitation for Physically Disabled Schizophrenic Patient

Kacavas, J. J., "The Use of Aqua-Therapy with Geriatric Patients." American Corrective Therapy Journal 31, no. 2 (April 1977): 52–59.

- *"Aqua-Therapy, has proven to be a highly effective means of rehabilitation for physically disabled patient. In the treatment and care of the aged patient, situations occur for which there are no immediate solutions. This indicates the need for carefully planned research followed through by an organized treatment program. As a case in point we would like to consider a patient, who for many years was a supervisory problem for many of our staff members, doctors, and therapists. This particular patient, in his early seventies, had stamina of a much younger person. This schizophrenic patient who not direct his energy in a socially acceptable manner would often physically abuse himself to gain attention. He did this to the point where he was not only causing physical damage, but created great uneasiness among other patients on the ward. Two alternatives the ward staff had were to keep him heavily tranquilized to a point where he would remain quiet for several hours, or to work with this man in some constructive ways to channel his energy. The gymnasium offered a number of outlets, such as bicycling, running, calisthenics, etc., but he still would not tire that easily. The patient also had access to apparatus on which he could injure himself unless carefully supervised. The swimming pool and Aqua-Therapy Program became an ideal means of treatment. While the patient was in the water he had no real means to intentionally harm himself since he was a good swimmer and was kept busy diving off the board and swimming to the shallow end. The water temperature of eighty-five degrees and air temperature of ninety-five degrees Fahrenheit provided resistance to his movements, thus fatiguing him while providing effective means of exercise. The patient would usually enter the pool in a very restless state but after a half-hour program of swimming, diving and underwater exercises, he quieted down to the point where he would actually sit down and converse with the therapist. Through Aqua-Therapy he became more manageable and sociable with other patients."*

Sports

Soccer Practice is a very Effective Add-on Treatment for Schizophrenic Patients

Battaglia, Giuseppe, "Soccer Practice as an Add-on Treatment in the Management of Individuals with a Diagnosis of Schizophrenia." Neuropsychiatric Disease and Treatment 9 (2013): 595–603. doi:10.2147/NDT.S44066.

- *"After the training period, the TG showed a relevant decrease by 4.6% in bodyweight (BW) and body mass index compared to baseline. Conversely, the CG showed an increased BW and body mass index by 1.8% from baseline to posttest. Moreover, after 12 weeks we found that control patients increased their BW significantly when compared to trained patients (Δ = 5.4%; $P < 0.05$). After the training period, comparing the baseline TG's Short Form-12-scores to posttest results, we found an improvement of 10.5% and 10.8% in physical component summary and mental component summary, respectively. In addition, performances on the 30 meter sprint test and slalom test running with a ball in the TG improved significantly ($P < 0.01$) from baseline to posttest when compared to CG. Soccer practice appears able to improve psychophysical health in individuals with diagnosis of schizophrenia. Indeed, our study demonstrated that programmed soccer physical activity could reduce antipsychotic medication-related weight gain and improve SRHQL and sports performance in psychotic subjects."*

Sports are Effective Treatments, Improve Self-esteem, Body Awareness and Increase Overall Physical Activity

Längle, G.,"[Role of sports in treatment and rehabilitation of schizophrenic patients]." Die Rehabilitation 39, no. 5 (October 2000): 276–82. doi:10.1055/s-2000-7863.

- *"The literature on the role of sports in the treatment and rehabilitation of schizophrenic patients is meagre and no systematic interdisciplinary review of the subject exists. This article reviews the existing literature and summarizes the relevant research findings. It also discusses practical experiences derived from a model project designed to study the role of sports in the management of chronically ill psychiatric patients, which showed that social interaction as well as the ability to organize time and leisure activities improved as did self-esteem, body awareness, and overall physical activity. Sports activities as part of the care of chronically ill psychiatric patients are effective as well as cost-effective and should receive more attention in both practice and research."*

Sports in the Treatment of Schizophrenic Patients is Therapeutic as Well as Cost Effective

Langle G. Role of sports in the treatment and rehabilitation of schizophrenic patients. Rehabilitation (Stuttg). 2000 Oct;39(5):276-82

- *"Sports activities as part of the care of chronically ill psychiatric patients are effective as well as cost-effective and should receive more attention in both practice and research."*

Takahashi H. Effects of sports participation on psychiatric symptoms and brain activations during sports observation in schizophrenia. Translational Psychiatry (2012) 2, e96

- *"Compared with baseline, activation of the body-selective extrastriate body area (EBA) in the posterior temporal-occipitial cortex during observation of sports related actions was increased in the program group. In this group, increase in EBA activation was associated with improvement in general psychopathology scale of PANSS. Sports participation had a positive effect not only on weight gain but also on psychiatric symptoms in schizophrenia. EBA might mediate these beneficial effects of sports participation. Our findings merit further investigation of neurobiological mechanisms underlying the therapeutic effect of sports for schizophrenia."*

Football Teams are Forms of Therapy for Psychiatric Hospitals

Nolot, Franck, Christian Védie, "Football and Psychosis." The Psychiatrist 36, no. 8 (August 1, 2012): 307–9. doi:10.1192/pb.bp.112.038570.

- *"Summary "After 25 years of promoting football in psychiatric hospitals, the authors highlight the potential benefits of sport and physical activity in treating people diagnosed with psychosis. A number of clinical cases are used to illustrate the benefits to individual people as well as to the collective and the institution."*

Exercise

High Aerobic Intensity Training Rehabilitation Improved Physical Capacity and Reduced the Risk of Cardiovascular Disease

Heggelund, Jørn, "Effects of High Aerobic Intensity Training in Patients with Schizophrenia: A Controlled Trial." Nordic Journal of Psychiatry 65, no. 4 (September 2011): 269–75. doi:10.3109/08039488.2011.560278.

- *"VO(2peak) and net mechanical efficiency of walking improved significantly by 8 weeks of HIT. HIT should be included in rehabilitation in order to improve physical capacity and contribute risk reduction of CVD."*

Aerobic Exercise May Help Reduce Psychopathological Symptoms and Improve Cognitive Skills in Depressive and Schizophrenic Patients

Oertel-Knöchel, Viola, "Effects of Aerobic Exercise on Cognitive Performance and Individual Psychopathology in Depressive and Schizophrenia Patients." European Archives of Psychiatry and Clinical Neuroscience, February 2, 2014. doi:10.1007/s00406-014-0485-9.

- *"In sum, the effects for the combined training were superior to the other forms of treatment. Physical exercise may help to reduce psychopathological symptoms and improve cognitive skills. The intervention routines employed in this study promise to add*

the current psychopathological and medical treatment options and could aid the transition to a multidisciplinary approach. However, a limitation of the current study is the short time interval for interventions (6 weeks including pre- and post-testing)."

High Aerobic Intensity Training Improves Physical Capacity and Reduces the Risk of Cardiovascular Disease

Heggelund, Jørn, "Effects of High Aerobic Intensity Training in Patients with Schizophrenia: A Controlled Trial." Nordic Journal of Psychiatry 65, no. 4 (September 2011): 269–75. doi:10.3109/08039488.2011.560278.

- *"VO(2peak) and net mechanical efficiency of walking improved significantly by 8 weeks of HIT. HIT should be included in rehabilitation in order to improve physical capacity and contribute risk reduction of CVD."*

Exercise Therapy Can Have Healthful Physical and Mental Effects for Individuals with Schizophrenia

Gorczynski P. Exercise therapy for schizophrenia. Cochrane Database Syst Rev 2010 May 12;(5):CD004412

- *"…..results indicated that regular exercise programs are possible in this population, and that they can have healthful effects on both the physical and mental health and well-being of individuals with schizophrenia"*

X-Box Video Games are a way to Promote Physical Activity in Older Adults with Schizophrenia

Leutwyler, Heather, "Videogames to Promote Physical Activity in Older Adults with Schizophrenia." Games for Health Journal 1, no. 5 (October 2012): 381–83. doi:10.1089/g4h.2012.0051.

- *"Older adults with schizophrenia need physical activity programs that promote well-being, are accessible, and are easily incorporated into their treatment programs. Video-games that use the Kinect for X-Box 360 game system are an ideal way to promote physical activity in this population because it makes physical activity fun, accessible, and social. Preliminary acceptability results from an ongoing pilot physical activity program reveal that older adults with schizophrenia rate bowling as an enjoyable and fun way to be active. In order for participants to stay engaged, participants need to feel they have the necessary skills to play the games. Participants who frequently bowled gutter balls rated the game as less enjoyable, whereas participants who bowled strikes indicated greater*

satisfaction. Offering a practice session prior to playing the game may improve the overall acceptability."

Mindfulness and Meditation

Meditation

Loving-Kindness Meditation is Associated with Decreased Negative Symptoms, Increased Positive Emotions and Psychological Recovery

Johnson, David P., "A Pilot Study of Loving-Kindness Meditation for the Negative Symptoms of Schizophrenia." Schizophrenia Research 129, no. 2–3 (July 2011): 137–40. doi:10.1016/j.schres.2011.02.015.

- *"This pilot study examined loving-kindness meditation (LKM) with 18 participants with schizophrenia-spectrum disorders and significant negative symptoms. Findings indicate that the intervention was feasible and associated with decreased negative symptoms and increased positive emotions and psychological recovery."*

Loving-Kindness Meditation May Be an Important Intervention for Schizophrenic Patients with Negative Symptoms

Johnson, David P.,"Loving-Kindness Meditation to Enhance Recovery from Negative Symptoms of Schizophrenia." Journal of Clinical Psychology 65, no. 5 (May 2009): 499–509. doi:10.1002/jclp.20591.

- *"In this article, we describe the clinical applicability of loving-kindness meditation (LKM) to individuals suffering from schizophrenia-spectrum disorders with persistent negative symptoms. LKM may have potential for reducing negative symptoms such as anhedonia, avolition, and asociality while enhancing factors consistent with psychological recovery such as hope and purpose in life. Case studies will illustrate how to conduct this group treatment with clients with negative symptoms, the potential benefits to the client, and difficulties that may arise. Although LKM requires further empirical support, it promises to be an important intervention since there are few treatments for clients afflicted with negative symptoms."*

Mindfulness

The Use of Mindfulness on Anxiety in Schizophrenia

Davis, Louanne W.,"Mindfulness: An Intervention for Anxiety in Schizophrenia." Journal of Psychosocial Nursing and Mental Health Services 45, no. 11 (November 2007): 23–29.

- *"Despite evidence that individuals with schizophrenia spectrum disorders experience significant and persistent symptoms of anxiety, there are few reports of the use of empirically supported treatments for anxiety in this population. This article describes how we have tried to adapt mindfulness interventions to help individuals with schizophrenia who experience significant anxiety symptoms. Although mindfulness has been widely used to help individuals without psychosis, to our knowledge, this is the first study adapting it to help those with schizophrenia manage worry and stress. We provide an overview of the intervention and use an individual example to describe how our treatment development group responded. We also explore directions for future research of mindfulness interventions for schizophrenia."*

Mindfulness is effective for Distressing Thoughts and Images

Chadwick, Paul, "Mindfulness Groups for Distressing Voices and Paranoia: A Replication and Randomized Feasibility Trial." Behavioural and Cognitive Psychotherapy 37, no. 4 (July 2009): 403–12. doi:10.1017/S1352465809990166.

- *"There were no significant differences between intervention and waiting-list participants. Secondary analyses combining both groups and comparing scores before and after mindfulness training revealed significant improvement in clinical functioning ($p = .013$) and mindfulness of distressing thoughts and images ($p = .037$). Findings on feasibility are encouraging and secondary analyses replicated earlier clinical benefits and showed improved mindfulness of thoughts and images, but not voices."*

Mindfulness Provides Significant Improvement for Distressing Thoughts and Images in Patients with Schizophrenia

Chadwick P. Mindfulness groups for distressing voices and paranoia: a replication and randomized feasibility trial. Behav Cog Psychother 2009 Jul;37(4):403-12

- *"Secondary analysis combing both groups and comparing scores before and after mindfulness training revealed significant improvement in clinical functioning and mindfulness of distressing thoughts and images."*

Mindfulness Has Beneficial Impact on Cognition and Voices

Newman TK. Impact of mindfulness on cognition and effect in voice hearing: evidence from two case studies. Behav Cogn Psychother 2009 Jul;(4):397-402

- *"Findings show that mindfulness training has an impact on cognition and affect specifically associated with voices, and thereby beneficially alters relationship with voices."*

Mindfulness Can Impact Cognition and Paranoid Beliefs

Ellett L. Mindfulness for paranoid beliefs: evidence from two case studies .Behav Cogn Psychother 2013 Mar;41(2):238-42

- "*Findings suggest that mindfulness training can impact on cognition and affect specifically associated with paranoid beliefs, and is potentially relevant to both Poor Me and Bad Me paranoia.*"

Autogenic Training

Application of Autogenic Training to Schizophrenic Patients Proves Favorable

Shibata J. The application of autogenic training to a group of schizophrenic patients. The American Journal of Clinical Hypnosis, Volume X, Number 1, July 1967

- *"The progress of the Standard Exercises of the Autogenic Training program in 65 schizophrenic patients was favorable, being the same as for normal persons, the patients learning them in about two months and being able to proceed on to the Meditation Exercises. All patients progressed favorably during the Standard Exercises, but after proceeding on to the Meditation Exercises there were several patients whose symptoms aggravated."*

Shibata J. Clinical evaluation with psychological tests of schizophrenic patients treated with autogenic training. The American Journal of Clinical Hypnosis, Volume X, Number 1, July 1967

- *"What we can say from the results of the psychological tests alone, is that evidently we can obtain good results in some recuperating schizophrenic patients who take up AT as a medium for rehabilitation."*

Mind-Body Therapies

Basic Body Awareness Therapy

Schizophrenic Patients Report Positive Effects with Basic Body Awareness Therapy (BBAT) for Increasing Body Awareness and Self-Esteem

Hedlund, Lena, "The Experiences of Basic Body Awareness Therapy in Patients with Schizophrenia." Journal of Bodywork and Movement Therapies 14, no. 3 (July 2010): 245–54. doi:10.1016/j.jbmt.2009.03.002.

- *"Patients with schizophrenia report positive treatment effects of physiotherapy with BBAT. Four main categories were identified: affect regulation, body awareness and self-esteem, effects described in a social context and effects on the ability to think. These should be targeted in a future randomized and controlled study."*

Body-ego Technique

Body-ego Technique Focuses on Body Posture and Movement and Improves General Functioning of Schizophrenic Patients

Goertzel, V., "Body-Ego Technique: An Approach to the Schizophrenic Patient." The Journal of Nervous and Mental Disease 141, no. 1 (July 1965): 53–60.

- *"Body-ego technique (BET) is a predominantly nonverbal approach to the psychotic patient that has a theoretic basis in ego psychology. As described in detail in a previous communication by May, Wexler, Salkin and Schoop (22),this approach focuses attention on body posture and movement as they relate to body image; on the patients sense of time as experienced and expressed in different speeds of movement; on body-ego boundaries; and on reality contact and experience in movement. There is a deliberate attempt to recreate for the patient the physical experience of the posture and movements associated with a wide range of emotions and attitudes, and by this route to rebuild ego structure. Thus this approach is primarily concerned with the process of recathexis of ego function.*

- *In this first controlled clinical trial of its use with chronic regressed schizophrenic patients, the therapists felt that they could establish contact and elicit cooperation in a high proportion of cases. Those treated with BET did significantly better than the controls in terms of independent psychiatric ratings of overall improvement and affective contact and nursing ratings of motility and general functioning. On other ratings there were no significant differences between the groups. These results and the results that BET has some promise for further research study and clinical exploration. It is not proposed as a therapeutic cure-all for schizophrenic patients, but rather it is suggested that it may have value in making contact and establishing a relationship and as an adjunct to, or in preparing the way for, the more verbal forms of therapy such as psychotherapy and the social therapies."*

Body-oriented Psychotherapy

Body-oriented Psychotherapy Lowers Negative Symptom Scores of Schizophrenia

Rohricht F. Effect of body-oriented psychotherapy on negative symptoms in schizophrenia: a randomized controlled trial. Psychol Med 2006 May;36(5):669-78

- *" Patients receiving BPT attended more sessions and had significantly lower negative symptom scores after treatment (PANSS negative, blunted affect, motor retardation). The differences held true at 4 month follow-up. Other aspects of psychopathology and subjective quality of life did not change significantly in either group. Treatment satisfaction and ratings of the therapeutic relationship were similar in both groups. BPT may be an effective treatment for negative symptoms in patients with chronic schizophrenia."*

Body-Oriented Psychological Therapy Significantly Lowers Negative Symptoms after Treatment

Röhricht, Frank, "Effect of Body-Oriented Psychological Therapy on Negative Symptoms in Schizophrenia: A Randomized Controlled Trial." Psychological Medicine 36, no. 5 (May 2006): 669–78. doi:10.1017/S0033291706007161.

- *"Patients receiving BPT attended more sessions and had significantly lower negative symptom scores after treatment (PANSS negative, blunted affect, motor retardation). The differences held true at 4-month follow-up. Other aspects of psychopathology and subjective quality of life did not change significantly in either group. Treatment satisfaction and ratings of the therapeutic relationship were similar in both groups. BPT may be an effective treatment for negative symptoms in patients with chronic schizophrenia. The findings should merit further trials with larger sample sizes and detailed studies to explore the therapeutic mechanisms involved."*

Rohricht F. Ego-pathology, body experience, and body psychotherapy in chronic schizophrenia. Psychol Psychother 2009 Mar;82(Pt 1):19-30

- *"In patients with chronic schizophrenia, body oriented psychological interventions may be effective for both positive therapeutic changes in ego-pathology and negative symptoms…*

Andres K. Empirical study of a physically oriented therapy with schizophrenic patients. Z Klin Psychol Psychopathol Psychother 1993;41(2):159-69

- *"The study shows that this body-oriented therapy is a worthy consideration as a method for giving schizophrenic patients a greater awareness of their own body limits"*

Massage

Physically Oriented Massage Therapy Give Schizophrenic Patients an Increase in Awareness in Their Body Limits

Andres, K., "[Empirical study of a physically oriented therapy with schizophrenic patients]." Zeitschrift Für Klinische Psychologie, Psychopathologie Und Psychotherapie / Im Auftrag Der Görres-Gesellschaft 41, no. 2 (1993): 159–69.

- *"Ten predominantly chronic schizophrenics were given body therapy, including massage to the feet, back and neck. The aim of the therapy was to increase patients' awareness of their own bodily limits. This objective is based on the view that schizophrenia is a problem of delimitation, that psychic problems have their physical embodiment, and that problems of delimitation can therefore be tackled at the physical level by enhancing the patients' ability to experience their own bodily limits. The relaxing effect of the therapy is indicated in physiological measurements of skin conductance and heart rate, plus patients' self-perceptions. The close physical presence of the therapist did not trigger any anxiety conditions. The study shows that this body-oriented therapy is worthy of consideration as a method for giving schizophrenic patients a greater awareness of their own bodily limits."*

Progressive Muscle Relaxation

Progressive Muscle Relaxation May Be a Cost Effective Way to Treat Persecutory Ideation

Ben-Zeev, Dror, "A Possible Role for Progressive Muscle Relaxation in the Treatment of Persecutory Ideation." Medical Hypotheses 75, no. 6 (December 2010): 568–71. doi:10.1016/j.mehy.2010.07.033.

- *"We hypothesize that PMR could be used to help ameliorate anxiety in patients who are at risk or already experiencing persecutory ideation, subsequently reducing the frequency, level of conviction, and distress associated with persecutory thoughts. Our hypothesis could be tested through feasibility and randomized control trials of PMR for treatment of persecutory ideation in individuals with schizophrenia. We expect the relationship between PMR and persecutory ideation will be mediated by reduction in anxiety. Potential advantages of examining our hypothesis include identifying a viable, efficacious, cost-effective novel intervention for paranoia in patients with psychosis. In addition, PMR could be easily facilitated by practitioners with varying levels of training and integrated with other existing interventions for persecutory ideation."*

Progressive Muscle Relaxation Might Be a Useful Add-on Treatment to Reduce Anxiety in Schizophrenia

Vancampfort, Davy,"Progressive Muscle Relaxation in Persons with Schizophrenia: A Systematic Review of Randomized Controlled Trials." Clinical Rehabilitation 27, no. 4 (April 2013): 291–98. doi:10.1177/0269215512455531.

- *"Progressive muscle relaxation might be a useful add-on treatment to reduce state anxiety and psychological distress and improve subjective well-being in persons with schizophrenia."*

Progressive Muscle Relaxation Can Effectively Alleviate Anxiety in Schizophrenia

Chen WC . Efficiency of progressive muscle relaxation training in reducing anxiety in patients with acute schizophrenia. J Clin Nurs 2009 Aug;18(15):2187-96

- "*This study demonstrated that progressive muscle relaxation can effectively alleviate anxiety in patients with schizophrenia"*

Relaxation Exercises Reduce Anxiety Levels in Psychiatric Inpatients

Weber, S. "The Effects of Relaxation Exercises on Anxiety Levels in Psychiatric Inpatients." Journal of Holistic Nursing: Official Journal of the American Holistic Nurses' Association 14, no. 3 (September 1996): 196–205.

- *"The purpose of this study was to investigate the effects of relaxation exercises on anxiety levels in an inpatient general psychiatric unit. The conceptual framework used was holism. A convenience sample of 39 subjects was studied. Anxiety levels were measured prior to and post interventions with the state portion of the State-Trait Anxiety Inventory. Progressive muscle relaxation, meditative breathing, guided imagery, and soft music were employed to promote relaxation. A significant reduction in anxiety level was obtained on the post-test. The findings of this study can be incorporated by holistic nurses to help reduce anxiety levels of general psychiatric inpatients by using relaxation interventions."*

Qigong

Qigong is a Mindful Exercise that Assists with Recovery for the Mentally Ill

Lloyd C. Qigong as a mindful exercise intervention for people living with mental ill health. International Journal of Therapy and Rehabilitation, 16 (7), 393-399

- *"It is suggested that mindful exercise may be used as an intervention to assist people living with mental ill health to improve their community functioning and hence their recovery."*

Shiatsu Therapy

Shiatsu Therapy Provides Substantial Improvement for Schizophrenia

Lichtenberg P. Shiatsu as an adjunctive therapy for schizophrenia: an open-label pilot study. Altern Ther Health Med 2009 Sep-Oct;15(5):44-6

- *"On the scales of psychopathology and side effects, the subjects showed a statistically and clinically significant improvement by the end of treatment. This improvement was maintained at the 12 week follow-up."*

Tai-Chi

Tai-Chi is Beneficial for Movement Coordination and Interpersonal Functioning in Schizophrenia

Rainbow TH. Ho. Tai-Chi for residential patients with schizophrenia on movement coordination, negative symptoms, and functioning: A pilot randomized controlled trial. Evidence-Based Complementary and Alternative Medicine, Volume 2012

- *"Tai-Chi buffered from deteriorations in movement coordination and interpersonal functioning, the latter with sustained effectiveness 6 weeks after the class was ended. Controls showed marked deteriorations in those areas, The Tai-chi group also experienced fewer disruptions to life activities at the 6-week maintenance. There was no significant improvement in negative symptoms after Tai-chi. The study demonstrated encouraging benefits of Tai-chi in preventing deteriorations in movement coordination and interpersonal functioning for residential patients with schizophrenia. The ease of implementation facilitates promotion at institutional psychiatric services."*

Yoga

Yoga is a Feasible Add-on Intervention for the Treatment of Psychotic Disorder

Manjunath, R. B., "Efficacy of Yoga as an Add-on Treatment for in-Patients with Functional Psychotic Disorder." Indian Journal of Psychiatry 55, no. Suppl 3 (July 2013): S374–378. doi:10.4103/0019-5545.116314.

- *"Adding yoga intervention to standard pharmacological treatment is feasible and may be beneficial even in the early and acute stage of psychosis."*

Yoga Therapy Can Help Improve Basic Living Skills of Persons with Schizophrenia

Paikkatt, Babu, "Efficacy of Yoga Therapy on Subjective Well-Being and Basic Living Skills of Patients Having Chronic Schizophrenia." Industrial Psychiatry Journal 21, no. 2 (July 2012): 109–14. doi:10.4103/0972-6748.119598.

- *"Yoga could improve patients' subjective well-being, their daily basic living functioning, personal hygiene, self-care, interpersonal activities and communication, and prompted more involvement in routine work."*

Yoga Provides Better Clinical Outcome in Schizophrenia

Vancampfort D. State anxiety, psychological stress and positive well-being responses to yoga and aerobic exercise in people with schizophrenia: a pilot study. Disabil Rehabil 2011;33(8):684-9

- *"After single sessions of yoga and aerobic exercises individuals with schizophrenia or schizoaffective disorder showed significantly decreased state anxiety, decreased psychological stress and increased subjective well-being compared to no exercise control."*

Visceglla E. Yoga therapy as an adjunctive treatment for schizophrenia: a randomized, controlled pilot study. J Altern Complement Med 2011 Jul;17(7):601-7

- *"The YT group obtained significant improvements in positive and negative symptoms of schizophrenia symptoms compared to WL, including PANSS scores on positive syndrome, negative syndrome, general psychopathology. Activation, paranoia, and depression subscales. YT had improved perceived quality of life in physical and psychological domains."*

Duraiswarmy G. Yoga therapy as an add-on treatment in the management of patients with schizophrenia-a randomized controlled trial. Acta Psychiatr Scand 2007 Sep;116(3):226-32

- *"Subjects in the YT group had significantly less psychopathology than those in the PT group at the end of four months"*

Yoga Therapy Improves Cognitive Function in Schizophrenia

Bhatia, Triptish, "Adjunctive Cognitive Remediation for Schizophrenia Using Yoga: An Open, Non-Randomized Trial." Acta Neuropsychiatrica 24, no. 2 (April 1, 2012): 91–100. doi:10.1111/j.1601-5215.2011.00587.x.

- *"Compared with the SZ/TAU group, the SZ/YT group showed significantly greater improvement with regard to measures of attention following corrections for multiple comparisons; the changes were more prominent among the men. In the other diagnostic groups, differing patterns of improvements were noted with small to medium effect sizes. Our initial analyses suggest nominally significant improvement in cognitive function in schizophrenia with adjunctive therapies such as YT. The magnitude of the change varies by cognitive domain and may also vary by diagnostic group."*

Sensory Therapies

Hydrotherapy

Hydrotherapy Works as a Neuroleptic and Sedative Treatment

Nikolia S. Hydrotherapy as a possible neuroleptic and sedative treatment. Medical Hypotheses (2008) 70, 230-238

- *"As described previously, an adapted cold shower could work as a mild electroshock applied to the sensory and therefore, it might have an antipsychotic effect similar to that of electroconvulsive therapy. Additionally, a cold shower is a vivid example of stress-induced analgesia and would also be expected to "crowd out" or suppress psychosis related neurotransmission with-in the mesolimbic system."*

Harmon RB. Hydrotherapy in the state mental hospitals in the mid-twentieth century. Issues Ment Health Nurs 2009 Aug;30(8):491-4

- *"Student and graduate nurses were required to demonstrate competence in hydrotherapy treatments used to calm agitated or manic patients in the era before neuroleptics. The nurses interviewed for this study indicated that, although labor intensive, hydrotherapy worked, at least temporarily……."*

Light and Dark Therapy

Bright Light Therapy is Safe and Effective for Schizophrenia

Aichhorn W. Bright light therapy for negative symptoms in schizophrenia: a pilot study. J Clin Psychiatry 2007 Jul;68(7):1146

- *"Bright light therapy was safe in our patients and did not result in psychotic exacerbation, as seen in unchanged positive scores on the PANSS. The subjective improvement in drive was statistically significant after 4 weeks, but did not persist after discontinuation of bright light therapy."*

Heim M. Bright light therapy in schizophrenic diseases. Psychiatr Neuol Med Psychol (Leipz) 1990 Mar;42(3):146-50

- *"20 patients with schizophrenic disorders, displaying a depressive syndrome, were given bright-light therapy, and compared with 11 patients treated by means of partial deprivation of sleep. Against a figure of 27% in the case of sleep-deprivation, syndrome remittance was 55% in the case of bright-light therapy. As depressive syndromes improve under bright-light therapy, schizophrenic syndromes also recede, which suggests close syndromatologic links…."*

Bright Light Therapy Proves Superior to Previous Medications for Depression in Schizoaffective Patient

Oren D. Bright Light Therapy for Schizoaffective Disorder. Am J Psychiatry 158:12, December 2001

- *"Bright light therapy proved comparable or superior to treatment with previous medications for depression for this patient."*

Early Morning Sunlight Reduces Length of Hospitalization

Benedetti F. Morning sunlight reduces length of hospitalization in bipolar depression. J Affect Disord 2001 Feb;62(3):221-3

- *"Natural sunlight can be an underestimated and controlled light therapy for bipolar depression."*

Dark Therapy: The Use of Amber Tinted Safety Glasses for Creating Virtual Darkness in the Treatment of Schizoaffective Disorder

German Gomez-Bernal. Dark therapy for schizoaffective disorder: A case report. Med Hypotheses Volume 72, Issue 1, pp. 105-6, January 2009

- *"James Phelps describes how amber-tinted safety glasses, could be useful for patients with rapid cycling bipolar disorder. These lens could block more than 90% wavelengths around 450mm (blue to blue-green) of light spectrum creating "virtual darkness" which could has a physiologic effect equivalent to true darkness, at least at the level of melatonin synthesis. I report a case that could support Phelps hypotheses."*

Neurofeedback and Biofeedback

Neurofeedback has Been Found Effective for the Treatment of Schizophrenia

Surmeli T. Schizophrenia and efficacy of qEEG-guided neurofeedback treatment: clinical case series. Clin EEG Neurosci 2012 Apr;43(2):133-44

- *"Changes in PANSS, MMPI, and TOVA were analyzed to evaluate the effectiveness of NF treatment. The mean number of sessions completed by the participants was 58.5 sessions within 24 to 91 days. Three dropped out of treatment between 30 and 40 sessions on NF, and one did not show any response. Of the remaining 48 participating 47 showed clinical improvement after NF treatment, based on changes in their PANSS scores. The participants who were able to take the MMPI ant the TOVA showed significant improvements in these measures as well. Forty were followed up for more than 22 months, 2 for 1 year, 1 for 9 months, and 3 for between 1 and 3 months after completion of NF. Overall NF was shown to be effective."*

Bolea AS. Neurofeedback Treatment of Chronic Inpatient Schizophrenia. Journal of Neurotherapy: Investigations in Neuromodulation, Neurofeedback and Applied Neuroscience, Volume 14, Issue 1, 2010

- *" This is a study on the effect of neurofeedback on chronic inpatient complex paranoid schizophrenics. The purpose of this research was twofold: first, to determine the effects of the application of neurofeedback to very chronic cases of schizophrenia that had been resistant to years of inpatient medical and psychological treatment and second, to propose a connection paradigm of schizophrenia. The author obtained progress using affective neurofeedback with more than 70 hospitals in patients with chronic schizophrenia. Improvements were seen in the EEG patterns and in cognitive, affective and behavioral patterns that often resulted in successful release from the hospital to live in the community. A 2-year follow up found that positive changes were sustained. It is the author's impression that reinforcement of right parietal alpha and inhibiting frontal delta and fast beta activity obtained the best results."*

Neurofeedback Treatments Enhance Cognitive Performance in Schizophrenia

Rocha N. Neurofeedback treatment to enhance cognitive performance in Schizophrenia. Porto 17-18 June 2011

- *"Following treatment, patients showed evidence of improved performance in different cognitive measures. The most important and consistent increases were observed in attention/vigilance, working memory and processing speed. We also observed changes in EEG patterns during the treatment, suggesting a learning effect. Patients were very collaborative during the treatment sessions and showed increased interest in their performance. Results from this exploratory study support the feasibility of using neurofeedback to enhance cognition in schizophrenia, but this method should not be considered alone for this purpose."*

Biofeedback Improves Social Competence and Interest Factors for Schizophrenics

Pharr OM. The use and utility of EMG biofeedback with chronic schizophrenic patients. Biofeedback Self Regul 1989 Sept:14(3):229-45

- *"On the nurses observation scale for inpatient evaluation the biofeedback group significantly improved on the Social Competence and Social Interest factors"*

Biofeedback Induces Neuroleptic-like EEG Changes

Schneider SJ. Neuroleptic-like electroencephalographic changes in schizophrenics through biofeedback. Biofeedback Self Reg 1982 Dec;7(4):479-90

- *"The results suggest that the EEG of schizophrenics can be temporarily altered, using feedback techniques, in a way that mimics the EEG changes that have been shown to occur with neuroleptic induced clinical improvement*

Anxiety Reduction in Schizophrenia through Thermal Biofeedback and Relaxation Training

Hawkins RC 2nd. Anxiety reduction in hospitalized schizophrenics through thermal biofeedback and relaxation training. Percept Mot Skills 1980 Oct;51(2);475-82

- *"The present study investigated the efficacy of thermal biofeedback and relaxation as adjunctive treatments to antipsychotic medication for reduction of anxiety in 40 hospitalized schizophrenics who were randomly assigned to four groups: biofeedback, relaxation, biofeedback and relaxation, and minimal treatment control. Significant reduction in anxiety followed treatment, but there were no between-group differences. One year follow-up and post boc analyses indicated a subgroup of "anxious" schizophrenics who showed substantial reduction in anxiety following treatment with biofeedback and relaxation."*

Biofeedback is Effective for the Treatment of Polydipsia in Schizophrenia

Walter G. A "biofeedback" approach to the treatment of chronic polydipsia. J Behv Ther Exp Psychiatry 1993 Sep;24(3):225-9

- *"The patient showed substantially increased sodium concentration, which was maintained despite the withdrawal of feedback. This behavioral method appears promising in settings where restriction of fluid intake is not practical or ethical."*

Sound Therapy

Masking Techniques for Tinnitus Work Well for Auditory Hallucinations in Schizophrenia

Musiek, Frank, "Auditory Hallucinations: An Audiological Perspective." The Hearing Journal 60, no. 9 (September 2007): 32–52. doi:10.1097/01.HJ.0000295756.39258.41.

- *"Using one earplug and distracting oneself with external sounds or self- vocalization has been reported to help patients with Ahs. In one study of 20 patients with AHs, 14 reported that listening to an external acoustic stimulus was helpful, while 8 found the earplug useful. Collins et al., had mixed results when they used an earplug in one ear and had the subjects listen to music, the news, and discussions. It is difficult from an auditory stand- point to understand how an earplug in one ear influences the perception of AHs. It might allow the patient to hear his or her own voice better through the occlusion effect, but it is difficult to envision any other advantage in regard to AHs. Shergill et al. relates that acoustic stimuli serve primarily as a distraction, which pre-vents the patient from*

focusing on the hallucinations. Auditory distractions seem to work reasonably well. We would submit that, in addition to distraction, there is another phenomenon known as "auditory masking" that plays a role in helping these patients. Auditory masking is defined as one sound (the masker) interfering with or even obliterating the perception of another sound. In the first author's experience, use of a white noise masker and appropriate masking protocols easily masked AHs, much to the patient's surprise. Wearable maskers have been used for many years to treat patients with tinnitus.62 Masking techniques may also hold much promise for helping patients with auditory hallucinations."

White Noise Therapy Might Decrease Auditory Hallucinations, Behavioral and Psychological Symptoms of Dementia in Schizophrenic Patients

Kaneko, Yutaka, "Efficacy of White Noise Therapy for Dementia Patients with Schizophrenia." Geriatrics & Gerontology International 13, no. 3 (July 2013): 808–10. doi:10.1111/ggi.12028.

- *"We suggest that white noise therapy might decrease BPSD in dementia patients with schizophrenia. The mechanisms of white noise decreasing BPSD are not known. We note that BPSD in dementia patients without schizophrenia is often associated with confusion as to why they cannot live their lives as before; they might express anger if they perceive they are not being treated properly relative to their expectations, even when these might be unrealistic. However, patients with dementia coupled with schizophrenia often lash out without a reason and are difficult to comfort. These are completely different from those patients with BPSD, but without schizophrenia.12 White noise might mask these auditory hallucinations in patients with schizophrenia, and lead at least transiently to some level of relaxation for the patients. This is consistent with previous case reports, which also support the idea that white noise might soften or mitigate some aspects of auditory hallucination in patients with schizophrenia.8 The present study suggests that white noise therapy is a candidate of non-medical care to decrease BPSD in dementia patients with schizophrenia."*

Humming My Help Reduce Auditory Hallucinations

Green, M. F.,"Auditory Hallucinations in Schizophrenia: Does Humming Help?" Biological Psychiatry 25, no. 5 (March 1, 1989): 633–35.

- *"Though Falloon and Talbot (1981) did not list humming as a spontaneously used coping strategy, we found that it reduced reported hallucinations in our subjects. The present study demonstrates the value of using behavioral techniques (with a hypothesis-driven approach) to control auditory hallucinations."*

Ear Plug Reduces Auditory Hallucinations in Schizophrenic Patient

Done, D. J., "Reducing Persistent Auditory Hallucinations by Wearing an Ear-Plug." The British Journal of Clinical Psychology / the British Psychological Society 25 (Pt 2) (May 1986): 151–52.

- *"A case study is presented of the effects of wearing an ear-plug in a single patient with persistent auditory hallucinations. Beneficial effects were detected when the plug was in the dominant ear only."*

Personal Stereo to Treat Auditory Hallucinations Leads to Decrease in Psychopathology

Johnston, Olwyn, "The Efficacy of Using a Personal Stereo to Treat Auditory Hallucinations. Preliminary Findings." Behavior Modification 26, no. 4 (September 2002): 537–49.

- *"This article presents preliminary findings from the first participant to complete an experiment assessing the efficacy of the personal stereo in treating auditory hallucinations. O.C., a 50-year-old woman, took part in a controlled treatment trial in which 1-week baseline, personal stereo, and control treatment (nonfunctioning hearing aid) stages were alternated for 7 weeks. The Positive and Negative Syndrome Scale, Clinical Global Impression Scales, Beliefs About Voices Questionnaire, Rosenberg Self-Esteem Scale, and Topography of Voices Rating Scale were used. The personal stereo led to a decrease in the severity of O.C.'s auditory hallucinations. For example, she rated her voices as being fairly distressing during baseline and control treatment stages but neutral during personal stereo stages. A slight decrease in other psychopathology also occurred during personal stereo stages. Use of the personal stereo did not lead to a decrease in self-esteem, contradicting suggestions that counterstimulation treatments for auditory hallucinations may be disempowering."*

Reading Out Loud Reduces Levels of Auditory Hallucinations

Gallagher, A. G., "The Effects of Varying Auditory Input on Schizophrenic Hallucinations: A Replication." The British Journal of Medical Psychology 67 (Pt 1) (March 1994): 67–75.

- *"The aim of this study was to investigate the effects of different types of auditory stimulation on reports of auditory hallucinations at the time of the experiment. The results showed that self-reports by seven schizophrenic patients of auditory hallucinations were reduced by different types of auditory stimulation, particularly by listening to pop music. Requiring the subject to read a passage aloud also reduced the levels reported. This study was a replication of one by Margo, Hemsley & Slade (1981) who reported similar findings."*

Sound Therapy with a Tinnitus Sound Generators Successfully Treats Auditory Hallucinations in Treatment Resistant Schizophrenia

Kaneko Y. Two cases of intractable auditory hallucination successfully treated with sound therapy. International Tinnitus Journal 2010;16(1):29-31

- *"We report two cases of AVHs successfully treated with sound therapy safely using a tinnitus control instrument (sound generator). The present study showed that sound therapy induced a complete remission of AVHs safely in two patients 2 years 7 months and 1 year 6 months. These results imply that the neuromechanism of AVHs is sensitive to sound therapy."*

Audio Hallucinations Eliminated with Radio Headphones

Feder R. Auditory hallucinations treated by radio headphones. Am J Psychiatry 1982 Sep;139(9):1188-90

- *"Listening to a radio through stereo headphones in conditions of low auditory stimulation eliminated the patient's hallucinations."*

Auditory Hallucinations Decreased with Personal Stereo

Johnston O. The efficacy of using a personal stereo to treat auditory hallucinations. Behav Modif 2002 Sep;26(4):537-49

- *"The personal stereo led to a decrease in severity of O.C.'s auditory hallucinations. A slight decrease in other psychopathology also occurred during personal stereo stages."*

Sony Walkman Eliminates Auditory Hallucinations in Patient

Mallya AR. Radio in the treatment of auditory hallucinations. Am J Psychiatry 1983 Sep;140(9):1264-5

- *"From 1976 to 1981 he did well receiving 40mg/day of fluphenazine hydrochloride and 6 mg/day of trihexyphenityl. In 1981 his disability benefit was terminated and the financial stress increased his hallucinations, but the neurologist warned against the increase of neuroleptics for fear of worsening his parkinsonism. The patient was advised to buy a pair of headphones to control his hallucinations. The relief was so dramatic that the patient bought a Sony Walkman. However, when he takes off the headphones, auditory hallucinations recur immediately."*

Audiotape Therapy Decreased Persistent Auditory Hallucinations in Patient

Mclnnis M. Audiotape therapy for persistent auditory hallucinations. Br J Psychiatry 1990 Dec; 157:913-4

- *"We report a case of a man with recurrent depression and persistent second-person auditory hallucinations telling him to kill himself. Using and audiotape cassette and headphones the duration of the hallucinations decreased significantly. Helpfulness of the audiotape continued at 15 months follow-up."*

Vestibular Stimulation

Vestibular Stimulation for the Treatment of Schizophrenia

Baker G. Vestibular stimulation with autistic and schizophrenic children. 14(4) 1977 434-5

- *" Behavior changes such as increased awareness, increased eye contact and verbalization, and decrease of self-destructive behaviors were also observed in the experimental group. The hypothesis was supported that vestibular stimulation can lower the threshold for vestibular activation to improve system functioning."*

Psychosocial Therapies

Befriending

Befriending Patients with Medication Resistant Schizophrenia Can Predict a Good Response for those that are Delusional and Not for those Who Have Hallucinations

Samarasekera, N.,"Befriending Patients with Medication-Resistant Schizophrenia: Can Psychotic Symptoms Predict Treatment Response?" Psychology and Psychotherapy 80, no. Pt 1 (March 2007): 97–106. doi:10.1348/147608306X108998.

- *"Baseline delusions predicted a good response and auditory hallucinations predicted a poor response at 9 months."*

Bibliotherapy

Bibliotherapy is Important for Rehabilitation of Schizophrenics

Alexander RH. Bibliotherapy with chronic schizophrenics. J Rehabil 1967 Nov-Dec;33(6):26-7

- *'Bibliotherapy should continue to play an increasingly important function in the rehabilitation of chronic schizophrenics. Schizophrenic persons have shown ready response*

to the reality approach of bibliotherapy when it is presented in an interesting and challenging manner by a skilled therapist. With careful professional guidance bibliotherapy can provide a significant "first step" in the rehabilitation of mental patients to become interacting members of society. A significant finding of the study of which the above is a resume and one which the study was not aimed at, is that with the application of bibliotherapy, a group of chronic schizophrenic patients undergoing drug therapy can learn to consistently perform tasks heretofore considered beyond their ability."

Exposure Control

Exposure approach could help patients gain more control over persistent auditory hallucinations.

Persaud R. A pilot study of exposure control of chronic auditory hallucinations in schizophrenia. Br J Psychiatry 1995 Jul;167(1):45-50

- *"Many patients complain less of their auditory hallucinations per se than of lack of control of the experiences. There is reason to believe that a non-distraction (exposure) approach could help patients gain more control over persistent auditory hallucinations and teach them that their experience is a form of thinking and has no external source. This study is a pilot test of that idea. Five DSM-III-R schizophrenic outpatients with medication-resistant auditory hallucinations improved with a mean of 31 hour-long sessions over 3 months of therapist-guided exposure to their hallucinations and situations likely to evoke them. Improvement was the greatest in the patient's anxiety and sense of control over their hallucinations, less in social use of leisure and hallucinating time. These mildly encouraging pilot results warrant a controlled study of exposure for drug-resistant chronic auditory hallucinations and other psychotic experiences which are associated with anxious avoidance. "*

Hypnosis

Hypnosis Shows Positive Effects in Schizophrenic Patients

Scagnelli, J. "Hypnotherapy with Schizophrenic and Borderline Patients: Summary of Therapy with Eight Patients." The American Journal of Clinical Hypnosis 19, no. 1 (July 1976): 33–38.

- *"As a result of this program of traditional insight-oriented, dynamic therapy and hypnotherapy using the techniques described above, all eight patients discussed in this paper have shown progress. They were generally able to reduce their medication requirements and to achieve partial or full time status as functioning members of society as students or job holders. All the patients achieved varying levels of reintegration of personalities. Although the growth and development of two of the patients appear to be subject to some of the inevitable schizophrenic setbacks, the general overall results of hypnotherapy appear to be positive and progressive. "*

Hypnosis May Be a Highly Successful Technique for Schizophrenia

Izquierdo de S. Hypnosis for Schizophrenia. Cochrane Database Syst Rev. 2007 Oct;17(4):CD004160

- *"Hypnosis could be helpful for people with schizophrenia"*

Abrams S. Short-term hypnotherapy of a schizophrenic patient.

- *"The only generalization that can be made from this study is that hypnotherapy may be a highly successful technique with some schizophrenic patients; but whether this is a method that might be of value for schizophrenia in general remains inconclusive. "*

Abrams S. The use of hypnotic techniques with psychotics. American Journal of Psychotherapy

- *"The case histories of psychotics treated by hypnotic methods point up the value of this treatment modality. Some patients improved with hypnotherapy after other therapeutic techniques had failed, and other patients with long-term illness dramatically recovered when hypnosis was employed. This would strongly suggest that hypnotherapeutic methods may be valuable tool for the treatment of specific psychotic disorders.*

Language Therapy

Significant Reductions in Auditory Hallucinations from Language Therapy for Schizophrenic Patients

Hoffman, R. E., "Language Therapy for Schizophrenic Patients with Persistent 'Voices.'" The British Journal of Psychiatry: The Journal of Mental Science 162 (June 1993): 755–58.

- *"One of us has hypothesized that the 'voices' of schizophrenic patients reflect altered preconscious planning of discourse that can produce involuntary 'inner speech' as well as incoherent overt speech. Some schizophrenic patients reporting voices do not, however, have disorganized speech. We hypothesize that these 'counterexample' patients compensate for impairments of discourse planning by reducing language complexity and relying on highly rehearsed topics. A 'language therapy' designed to challenge and enhance novel discourse planning was administered to four such patients; three had significant albeit temporary reductions in the severity of their voices. These clinical findings provide further evidence that alterations of discourse planning may underlie hallucinated voices."*

Maudsley Review

The Maudsley Review Computerized Training Program Targets Reasoning Biases in Delusions

Waller, Helen, "Targeting Reasoning Biases in Delusions: A Pilot Study of the Maudsley Review Training Programme for Individuals with Persistent, High Conviction Delusions." Journal of Behavior Therapy and Experimental Psychiatry 42, no. 3 (September 2011): 414–21. doi:10.1016/j.jbtep.2011.03.001.

- *"The computerized programme was developed on Microsoft PowerPoint and then transferred to a Real BASIC programme to incorporate the interactive elements. It comprised a general introduction to JTC and five training tasks (see below). It was designed to be completed together with a therapist, who emphasized key messages and provided together with a therapist, who emphasized key messages and provided feedback on participants' comments, for example by reinforcing useful insights and normalizing JTC. This was summarized, with participants' permission, in a handout to be taken away at the end of the session. No explicit mention of psychosis or direct challenging of beliefs was included. However, in order to increase relevance to delusional experience, video clips and scenarios, with the potential for paranoid interpretation, were used. "*

- *"Overall, the results suggest that the programme holds promise in changing, over a single session, outcomes which are typically resistant to standard treatments. Additionally, the programme is relatively easy to administer and may hold potential to be delivered by 'non-expert' staff following brief training."*

Morita Therapy

Morita Therapy for Schizophrenia May Have Some Positive Effects

Li C. Morita therapy for schizophrenia. Schizophrenia Bulletin vol. 34, no. 6, pp1021-1023 ,2008

- *"Morita therapy may have some positive effects, but there are no data to assess whether this sustained. For schizophrenia, therefore, Morita therapy remains and experimental intervention."*

Nidotherapy

Nidotherapy is a Novel Therapy Distinctly Different form Standard Treatment

Chamberlain, Ian J., "Nidotherapy for People with Schizophrenia." The Cochrane Database of Systematic Reviews 3 (2013): CD009929. doi:10.1002/14651858.CD009929.pub2.

- *"Further research is needed into the possible benefits or harms of this newly-formulated therapy. Until such research is available, patients, clinicians, managers and policymakers should consider it an experimental approach."*

Personal Therapy

Personal Therapy A Disorder-Relevant Psychotherapy for Schizophrenia

Hogarty, G. E., "Personal Therapy: A Disorder-Relevant Psychotherapy for Schizophrenia." Schizophrenia Bulletin 21, no. 3 (1995): 379–93.

- *"While the long-term care of ambulatory schizophrenia patients requires highly effective interpersonal treatment skills among clinicians, there is little evidence to support an empirically validated individual psychotherapy of schizophrenia. Personal therapy (PT) attempts to address the apparent limitations of traditional psychotherapy by modifying the "model of the person" to accommodate an underlying pathophysiology, minimizing potential iatrogenic effects of maintenance antipsychotic medication, controlling sources of environmental provocation, and extending therapy to a time when crisis management has lessened and stabilization is better ensured. By means of graduated, internal coping strategies, PT attempts to provide a growing awareness of personal vulnerability, including the "internal cues" of affect dysregulation. The goals are to increase foresight through the accurate appraisal of emotional states, their appropriate expression, and assessment of the reciprocal response of others. The strategies are supplemented by phase-specific psychoeducation and behavior therapy techniques. Practical issues in the application of this new intervention are discussed. Preliminary observations from two samples of patients, one living with and the other living independent of family, suggest differential improvement over time among PT recipients."*

Creative Engagement Therapies

Animal Assisted Therapy

Therapeutic Riding Sessions Improve Negative Symptoms and Reduce Rate of Hospitalization

Cerino, Stefania, "Non-Conventional Psychiatric Rehabilitation in Schizophrenia Using Therapeutic Riding: The FISE Multicentre Pindar Project." Annali dell'Istituto Superiore Di Sanità 47, no. 4 (2011): 409–14. doi:DOI: 10.4415/ANN_11_04_13.

- *"The FISE (Federazione Italiana Sport Equestri) Pindar is a multicentre research project aimed at testing the potential effects of therapeutic riding on schizophrenic patients. Twenty-four subjects with a diagnosis of schizophrenia were enrolled for a 1 year-treatment involving therapeutic riding sessions. All subjects were tested at the beginning and at the end of treatment with a series of validated test batteries (BPRS and 8 items-PANSS). The results discussed in this paper point out an improvement in negative symptoms, a constant disease remission in both early onset and chronic disease subjects, as well as a reduced rate of hospitalization."*

Therapeutic Horseback Riding Benefits Individuals with Schizophrenia

Corring, Deborah, "Therapeutic Horseback Riding for ACT Patients with Schizophrenia." Community Mental Health Journal 49, no. 1 (February 2013): 121–26. doi:10.1007/s10597-011-9457-y.

- *"One form of psychiatric leisure rehabilitation which has only recently been explored for individuals with schizophrenia is Therapeutic Horseback Riding (THBR). This study is the first to examine THBR for Assertive Community Treatment (ACT) patients with schizophrenia. A sample of 6 ACT patients with schizophrenia or schizoaffective disorder who reside in the community and 6 mental health care staff participated in 10 weeks of weekly horseback riding sessions with an experienced THBR instructor. Participating patients, staff and the THBR instructor were qualitatively interviewed at the start, during and at the end of the THBR program and these semi-structured interviews were analyzed for recurrent themes. We found that THBR benefitted this group of patients. In spite of our study's limitations, such as its exploratory nature and the small sample size, it demonstrates that THBR has promise and should be further developed and studied for individuals with schizophrenia."*

Farm-based Interventions Can Alleviate Psychiatric Symptoms in Patients with Persistent Mental Disorders

Iancu, Sorana C.,"Farm-Based Interventions for People with Mental Disorders: A Systematic Review of Literature." Disability and Rehabilitation, June 25, 2014, 1–10. doi:10.3109/09638288.2014.932441.

- *"Our results suggest that the farm environment should be considered, especially for patients with mental disorders who do not achieve an adequate response with other treatment options. Further research is needed to clarify potential social and occupational benefits. Implications for Rehabilitation Despite the developments in mental healthcare, in many countries farms still play a role in the provision of psychiatric rehabilitation services. Farm-based interventions can alleviate psychiatric symptoms in patients with*

persistent mental disorders and can facilitate mental health recovery. The social and occupational aspects of the farm-based interventions are central to the experiences of mental health recovery."

Animal Assisted Therapy is Associated with Reduced Anxiety Levels for Hospitalized Patients

Barker, S. B., "The Effects of Animal-Assisted Therapy on Anxiety Ratings of Hospitalized Psychiatric Patients." Psychiatric Services (Washington, D.C.) 49, no. 6 (June 1998): 797–801.

- *"Animal-assisted therapy was associated with reduced state anxiety levels for hospitalized patients with a variety of psychiatric diagnoses, while a routine therapeutic recreation session was associated with reduced levels only for patients with mood disorders."*

Animal-assisted Therapy May Contribute to Psychosocial Rehabilitation for Schizophrenia Patients

Nathans-Barel I. Animal-assisted therapy ameliorates anhedonia in schizophrenia patients. A controlled pilot study. Psychother Psychosom 2005;74(1):31-5

- *"The AAT group showed a significant improvement in the hedonic tone compared to controls. They also showed an improvement in the use of leisure time and a trend towards improvement in motivation.. AAT may contribute to the psychosocial rehabilitation and quality of life of chronic schizophrenia patients."*

Animal-assisted Therapy Improves Non-verbal Communication in Schizophrenic Patients

Kovacs Z. An exploratory study of the effect of animal-assisted therapy on nonverbal communication in three schizophrenic patients. A Multidisciplinary Journal of the Interactions of People & Animals, 1 December 2006, vol.19, no.4, pp353-364(12)

- *"The therapy was oriented toward improving non-specific (i.e., general well-being) and specific (i.e., communication patterns) areas of the patient's daily activities. The outcome measure was the change in the patient's nonverbal communication, as measured by analysis of standardized, video-recorded scenarios registered at the beginning of the therapy, and six months later, and the end of it. Because two patients completed less than half of the sessions, we analyzed the data of only three parameters. All three patients improved in the usage of space during communication, while partial improvement in other domains of nonverbal communication (anatomy of movements, dynamics of*

gestures, regulator gestures) was also observed. Animal-assisted therapy can improve certain aspects of nonverbal communication in schizophrenic patients."

Animal-assisted Therapy Improves Socialization, ADL's and General Well-being in Elderly Schizophrenic Patients

Barak Y. Animal-assisted therapy for elderly schizophrenic patents: a one-year controlled trial. Am J Geriatr Psychiatry 2001 Fall;9(4):439-42

- *"The authors evaluated, in a blinded, controlled manner, the effects of AAT in a closed psychogeriatric ward over 12 months. Subjects were 10 elderly schizophrenic patients and 10 matched patients (mean age: 79.1 +/-6.7 years). The outcome measure was the Scale for Social Adaptive Functioning Evaluation (SAFE). AAT was conducted in weekly 4-hour sessions. Treatment encouraged mobility, interpersonal contact, and communication and reinforced activities of daily living (ADLs), including personal hygiene and independent self-care, through the use of cats and dogs as "modeling companions." The SAFE scores at termination showed significant improvement compared with baseline scores and on the Social Functions subscale. AAT proved a successful tool for enhancing socialization, ADLs, and general well-being."*

Animal-assisted Therapy with Farm Animals May Have Positive Influences on Self-Efficiency for Persons with Schizophrenia

Berget B. Animal-assisted therapy with farm animals for persons with psychiatric disorders: effects on self-efficiency, coping ability and quality of life, a randomized controlled trial. Clinical Practice and Epidemiology in Mental Health 2008, 4:9

- *"AAT with farm animals may have positive influences on self-efficiency and coping ability among psychiatric patients with long lasting psychiatric symptoms."*

Art Therapy

Art Therapy Can Help Alter Psychotic Projections and Aid in Psychotherapeutic Rehabilitation

Honig, Sylvia. "Art Therapy Used in Treatment of Schizophrenia." Art Psychotherapy 4, no. 2 (1977): 99–104. doi:10.1016/0090-9092(77)90007-2.

- *"I have found that art therapy, used in a positive, realistic, structured and supportive way, such as displayed in contour drawing sessions, can help alter psychotic projections and aid in overall psychotherapeutic rehabilitation of schizophrenia."*

Computer-based Art Therapy Helps Decrease Fear and Let Patients Transfer Feelings to Drawings

Hartwich, Peter, "Computer-Based Art Therapy with Inpatients: Acute and Chronic Schizophrenics and Borderline Cases." The Arts in Psychotherapy 24, no. 4 (1997): 367–73. doi:10.1016/S0197-4556(97)00042-7.

- *"Many people feel inhibited when they are asked to paint in a traditional way. They do not feel able to transfer their feelings and experiences onto paper. They argue that they are not artists. With computer based painting this threshold of fear is decreased. After a little training they are able to express at least some intrapsychic experiences. The stimulating nature of colors, shapes and tools is great and seems to be like a box of toys for the patients. The second important difference between traditional and computer-based painting is that one can save the painting in its various steps of development. The whole process of events in drawing a picture can be fixed and saved step by step. The painting can be brought back to the screen whenever wanted or any aspect of the painting can be accessed at will. Also, the whole process of the painting can be put on a videotape electronically without using a camera. One then has two different opportunities to mirror the patient's creative drawing process. The finished picture is the goal in the traditional way of painting. The process is over when the picture is completed. Painting by computer enables us to store the process and to recall it. The patient gets into an "interaction" with the computer and the painting process becomes a mirror of the relationship. The outer expression of an intrapsychic process can be recorded with the help of technology. The reproduction of the unfolding intrapsychic events becomes possible.* Our computer painting therapy is not to be regarded as exclusive psychotherapeutic method. We hope it becomes a helpful part in the concerted action of all our therapeutic efforts. Schizophrenic patients' treatment should always be a combination of different pharmacotherapeutic and psychotherapeutic methods adapted to individual needs."*

Art Therapies Improve Mental Health and Negative Symptoms of Schizophrenia

Crawford, Mike J.,"Arts Therapies for People with Schizophrenia: An Emerging Evidence Base." Evidence-Based Mental Health 10, no. 3 (August 2007): 69–70.

- *"An evidence base for the effectiveness of arts therapies in the treatment of people with schizophrenia is beginning to emerge. Arts therapies combine the use of art materials with psychotherapeutic techniques that aim to encourage self-expression and promote self-awareness. They appear to be popular with patients and may result in improved mental health, especially reductions in negative and general symptoms of schizophrenia, which are those least responsive to pharmacological interventions. Further research is needed to establish the effects and cost effectiveness of arts therapies for people with schizophrenia outside of specialist centres."*

Group Art Therapy for Psychosis may have a Positive Effect

Montag, Christiane, "A Pilot RCT of Psychodynamic Group Art Therapy for Patients in Acute Psychotic Episodes: Feasibility, Impact on Symptoms and Mentalising Capacity." PloS One 9, no. 11 (2014): e112348. doi:10.1371/journal.pone.0112348.

- *"Evidence on the efficacy and effectiveness of AT in patients with schizophrenia is far from being conclusive and benefits might be limited to a subgroup of patients. Results of this pilot study suggest that RCTs of AT can be implemented in routine hospital settings for patients experiencing acute psychotic states. With all due caution, findings from this first European pilot RCT of psychodynamic AT in acutely psychotic inpatients prove the feasibility of similar projects and point to a possible positive effect of the intervention on psychotic symptoms, psychosocial functioning and the ability to mentalise emotions. These preliminary results must be substantiated by further independent research."*

Art Therapy Strengthens the Sense of Self in Schizophrenic Patients

Teglbjaerg, Hanne Stubbe. "Art Therapy May Reduce Psychopathology in Schizophrenia by Strengthening the Patients' Sense of Self: A Qualitative Extended Case Report." Psychopathology 44, no. 5 (2011): 314–18. doi:10.1159/000325025.

- *"All patients reported a very good outcome, and the qualitative analysis showed that the positive effect of art therapy is mainly due to a strengthening of the patients' minimal sense of self."*

Art Therapy May Strengthen the Patients Sense of Self in Schizophrenia

Tegibaerg HS. Art therapy may reduce psychopathology in schizophrenia by strengthening the patients sense of self: a quantitative extended case report. Psychopathology 2011:44(5):314-8

- *"The most important benefit of the art therapy was a strengthening of the patients' sense of self. All patients reported a good outcome, and qualitative analysis showed that the positive effect of art therapy is mainly due to a strengthening of patients' minimal sense of self."*

Ruddy R. Art therapy for schizophrenia or schizophrenia-like illnesses. Cochrane Database Syst Rev 2005 Oct 19;(4):CD003728

- *"Data from one mental state measure (SANS) showed a small but significant difference favoring the art-therapy group. ….a measure of social functioning (SFS) showed no clear difference between groups in endpoint scores and in quality of life, as measured by PerQol, did not indicate the effects of art therapy."*

Art as a Therapeutic Tool Help Clients Communicate and Express Themselves

Noronha KJ. Working with Art in a Case of Schizophrenia. Indian J Pschol Med. 2013 Jan-Mar; 35(1):89-92

- *"This study used art as a therapeutic tool in therapy with a client diagnosed with schizophrenia, along with medical management. The purpose of using art was to enable the non-communicative client to communicate. The client's drawings were used as a process medium. Progress was seen in changes in social behaviors and communication evidenced by him speaking more, expressing feelings and gaining better insight.*

Games

The Card Game "Michael's Game" is Feasible for Treatment of Delusional Behaviors

Khazaal, Yasser, "A Card Game for the Treatment of Delusional Ideas: A Naturalistic Pilot Trial." BMC Psychiatry 6 (2006): 48. doi:10.1186/1471-244X-6-48.

- *"Michael's Game", a training module for hypothetical reasoning is a treatment inspired by CBTs of psychotic symptoms. It was conceived by the first two authors as a tool to promote the dissemination of CBTs in natural clinical settings. Principles of the game are founded on cognitive therapy of psychotic symptoms and use their techniques such as: developing a therapeutic alliance based on the patients perspective, normalizing psychotic symptoms, cognitive restructuring techniques aiming to develop alternative explanations to their delusions, reality testing and connecting belief to emotion and behavior. It could be used as a preliminary or complement of individual CBTs. "Michael's Game" is a program aiming at training hypothetical reasoning. Participants have to help Michael to find alternatives to the erroneous conclusions that Michael draws from situations described on each card. It was conceived as a group card game in order to allow patients to become partners of fictive character (Michael) interacting together with cards containing impersonal information which may however reflect their own problems.*

- *This pilot study supports the feasibility of this therapeutic approach and the ease of its diffusion in various clinical settings. "Michael's game" has been used easily after a short training, in different sites that were not specialized in CBTs."*

A Card Game Helps Those Preoccupied with Psychotic Symptoms

Khazaal, Yasser, "'Michael's Game,' a Card Game for the Treatment of Psychotic Symptoms." Patient Education and Counseling 83, no. 2 (May 2011): 210–16. doi:10.1016/j.pec.2010.05.017.

- *"Data about 107 patients were included in the entire analyses. Significant improvements were observed on BCIS subscales as well as a reduction of severity of conviction and preoccupation scores on the PDI-21. The intervention has a moderate effect on the PDI-*

21 preoccupation and conviction as well as the BCIS subscales. Patients who benefit the most from the program are patients who have a low degree of self-reflectiveness and patients who are concomitantly preoccupied by their symptoms. The present study supports the feasibility and effectiveness of "Michael's Game" in naturalistic settings. The game seems to be a useful tool for patients with psychotic disorders."

Playing Chess Can Easily Restore Executive Functions in Schizophrenics

Demily, Caroline, "The Game of Chess Enhances Cognitive Abilities in Schizophrenia." Schizophrenia Research 107, no. 1 (January 2009): 112–13. doi:10.1016/j.schres.2008.09.024.

- *"When considered together, our results suggest that playing chess for mere 10 h can restore (at least partially) executive functions of patients with schizophrenia. It may be interesting to note that chess can be proposed easily –at almost no cost—to all psychotic patients. Most of the patients kept playing chess on their own, after the completion of the study."*

Michael's Game is a Card Game of Hypothetical Reasoning in the Written Form Used to Treat Cognitive Symptoms in Psychotic Patients

Khazaal, Yasser, "'Michael's Game,' a Card Game for the Treatment of Psychotic Symptoms." Patient Education and Counseling 83, no. 2 (May 2011): 210–16. doi:10.1016/j.pec.2010.05.017.

- *"Data about 107 patients were included in the entire analyses. Significant improvements were observed on BCIS subscales as well as a reduction of severity of conviction and preoccupation scores on the PDI-21. The intervention has a moderate effect on the PDI-21 preoccupation and conviction as well as the BCIS subscales. Patients who benefit the most from the program are patients who have a low degree of self-reflectiveness and patients who are concomitantly preoccupied by their symptoms. The present study supports the feasibility and effectiveness of "Michael's Game" in naturalistic settings. The game seems to be a useful tool for patients with psychotic disorders."*

Cognitive Training via a Laptop Computer Games is a Promising Treatment for Schizophrenia

Fisher, Melissa, "Neuroplasticity-Based Auditory Training Via Laptop Computer Improves Cognition in Young Individuals With Recent Onset Schizophrenia." Schizophrenia Bulletin, January 20, 2014. doi:10.1093/schbul/sbt232.

- *"Neuroscience-informed cognitive training via laptop computer represents a promising treatment approach for cognitive dysfunction in early schizophrenia. An individual's*

baseline motivational system functioning (reward anticipation), and ability to engage in auditory processing speed improvement, may represent important predictors of treatment outcome. Future studies must investigate whether cognitive training improves functioning and how best to integrate it into critical psychosocial interventions."

Creative Writing

Evidence that Creative Writing Forms an Important Recovery Experience

King, Robert, "Creative Writing in Recovery from Severe Mental Illness." International Journal of Mental Health Nursing 22, no. 5 (October 2013): 444–52. doi:10.1111/j.1447-0349.2012.00891.x.

- *"There is evidence that creative writing forms an important part of the recovery experience of people affected by severe mental illness. In this paper, we consider theoretical models that explain how creative writing might contribute to recovery, and we discuss the potential for creative writing in psychosocial rehabilitation. We argue that the rehabilitation benefits of creative writing might be optimized through focus on process and technique in writing, rather than content, and that consequently, the involvement of professional writers might be important. We describe a pilot workshop that deployed these principles and was well-received by participants. Finally, we make recommendations regarding the role of creative writing in psychosocial rehabilitation for people recovering from severe mental illness and suggest that the development of an evidence base regarding the effectiveness of creative writing is a priority."*

Dance

Traditional Dancing Improves Functional Capacity and Quality of Life in Patients with Schizophrenia

Kaltsatou, A., "Effects of Exercise Training with Traditional Dancing on Functional Capacity and Quality of Life in Patients with Schizophrenia: A Randomized Controlled Study." Clinical Rehabilitation, December 18, 2014, 0269215514564085. doi:10.1177/0269215514564085.

- *"After the eight months, Group A increased walking distance in the 6-minute walk test (328.4 ± 35.9 vs. 238.0 ± 47.6 m), sit-to-stand test (19.1 ± 1.8 vs. 25.1 ± 1.4 seconds), Berg Balance Scale score (53.1 ± 2.1 vs. 43.2 ± 6.7), lower limbs maximal isometric force (77.7 ± 25.7 vs. 51.0 ± 29.8 lb.), Positive and Negative Syndrome Scale total score (77.0 ± 23.1 vs. 82.0 ± 24.4), Global Assessment of Functioning Scale total score (51.3 ± 15.5 vs. 47.7 ± 13.3) and Quality of Life total score (34.9 ± 5.2 vs. 28 ± 4.5), compared with Group B. Our results demonstrate that Greek traditional dances improve functional capacity and quality of life in patients with schizophrenia."*

Dance Group for Psychotic Patients is used as a Therapeutic Tool for Recovery

Tavormina, Romina, "The Advantages of 'Dance-Group' for Psychotic Patients." Psychiatria Danubina 26 Suppl 1 (November 2014): 162–66.

- *"Psychosocial rehabilitation and in particular group dances allow the recovery of lost or compromised ability of patients with mental illness, and they facilitate their reintegration into the social context. The dance group has enabled users of the Day Centre of the Unit of Mental Health Torre del Greco ASL NA 3 south to achieve the objectives of rehabilitation such as: taking care of themselves, of their bodies and their interests, improving self-esteem, the management of pathological emotions, socialization and integration, overcoming the psychotic closing and relational isolation. In particular, patients with schizophrenia, psychotic and mood disorders had a concrete benefit from such rehabilitation activities, facilitating interpersonal relationships, therapy compliance and significantly improved mood, quality of life, providing them with the rhythm and the security in their relationship with each other. The dance group and for some individuals, also psychotherapy and drug therapy, have facilitated social inclusion, improved the quality of life and cured their diseases. The work is carrying out in a group with patients, practitioners, family members, volunteers, social community workers, following the operating departmental protocols. Using the chorus group "Sing that you go" as an operational tool for psychosocial rehabilitation and therapeutic element we promote the psychological well-being and the enhancement of mood."*

Dance Therapy is a Non-verbal Variant of Psychotherapy that Explores the Unconscious Process in Schizophrenic Patients

Romero, Emilio F., "Dance Therapy on a Therapeutic Community for Schizophrenic Patients." The Arts in Psychotherapy 10, no. 2 (1983): 85–92. doi:10.1016/0197-4556(83)90034-5.

- *"We have discussed dance therapy as a nonverbal variant of psychotherapy. This experience allowed many patients to explore their own creativity and to experiment with new behaviors. After several weeks, some patients and staff became more and more creative, selecting new records, steps, movements, and themes. We have not found dance therapy to differ from or to oppose reconstructive psychotherapy; rather, it coadunates it. Dance is an additional way to explore unconscious processes in the schizophrenic patient."*

Dance Therapy is a Communication Activating Non-verbal Psychotherapy

Natalia Oganesian, "Dance therapy as form of communication activating psychotherapy for schizophrenic patients" Body, Movement and Dance in Psychotherapy Vol. 3, No. 2, September 2008, 97–106

- *"Before dance therapy, the patients were characterized by certain fencing off, instability in their mood, communication problems, and psycho-motoric inhibition. After dance therapy, their cooperation with the doctors improved, their stigmatization phenomena became less evident, their psycho-motoric inhibition decreased, and the patients became more accessible to contact and more active. As for medication therapy, in most cases it did not change. In conclusion, it may be said that dance therapy is a communication activating non-verbal psychotherapy. Introduction of dance therapy into the complex of clinical psychological interferences enables us to intensify the rehabilitation process for schizophrenic patients."*

Dance Movement Therapy for Schizophrenia

Xia J. Dance therapy for schizophrenia. Cochrane Database Syst Rev 2009 Jan 21;(1):CD006868

- "*At the end of treatment significantly more people in dance therapy group had a greater than 20% reduction in PANSS negative symptom score, and overall average endpoint scores were lower. There is no evidence to support-or refute-the use of dance therapy in this group of people"*

Application of the Primitive Expression Form of Dance Therapy in Psychotic Patients Leads to Increased Happiness and Positive Attitude

Margariti A. An application of the Primitive Expression form of dance therapy in a psychiatric population. The Arts in Psychotherapy 39 (2012) 95-101

- *"In this paper we present preliminary results of PE-based protocol with a small group of psychiatric patients (psychotic and depressive disorders). It is shown that a relatively short duration of PE treatment led to observable changes in psychological state, behavior, and brain physiology. It was found that the patients (1) experienced an increase in their happiness level, (2) expressed a positive attitude to the PE process by utilizing appropriate word associations, and (3) exhibited (a patient subset) an increase in EEG activity related to relaxed awake state. The study presents encouraging results related to the application of PE therapy with psychiatric patients. PE can be added to other dance therapy methodologies which have been shown to be promising therapeutic approaches in psychiatric populations."*

Social Partnered Dance May Benefit those with Serious and Persistent Mental Illness

Hackney, Madeleine E., "Social Partnered Dance for People with Serious and Persistent Mental Illness: A Pilot Study." The Journal of Nervous and Mental Disease 198, no. 1 (January 2010): 76–78. doi:10.1097/NMD.0b013e3181c81f7c.

- *"Individuals with serious mental illness (SMI) often experience isolation and poor health, but normalized social opportunities aid recovery. This study aimed to determine social dance's feasibility and effects on mood, functional mobility, and balance confidence in 12*

people with SMI. Participants danced once per week in 1-hour lessons for 10 weeks. Before and after lessons, participants were evaluated for gait velocity and with one-leg stance, Timed Up and Go, and 6-minute walk tests. Participants self-completed Beck Depression II and Beck Anxiety Inventories and the Activities-specific Balance Confidence Scale. Posttesting included an exit questionnaire assessing participant experiences. Participants significantly improved on the Timed Up and Go, (p = 0.012, effect size = 0.68), and demonstrated nonsignificant improvements in anxiety, depression, and balance confidence (effect sizes of 0.41, 0.54, and 0.64, respectively). Participants reported enjoying classes, and interest to continue. Social dance is feasible and may benefit mobility for those with SMI."

Drama

Improvisational Drama Groups are Beneficial for Psychiatric Inpatients

Sheppard, J., "Improvisational Drama Groups in an Inpatient Setting." Hospital & Community Psychiatry 41, no. 9 (September 1990): 1019–21.

- *"Many descriptive case studies have been written about psychodrama, drama therapy, and related therapies. However, few studies have used experimental techniques to demonstrate the positive effects of these therapies. This study found nearly a 100 percent increase in the frequency of appropriate verbalization for a group of ten inpatients in a psychiatric rehabilitation program. Quantitative procedures were useful for measuring changes in verbalization. Nineteen of the initial 29 participants chose not to continue in the drama groups. Many of these people were restless or incapable of concentrating. The drop-out group differed from those who completed in that they were slightly older, included a higher percentage of women, and included two people with a diagnosis of mental retardation. Subjects' creativity flourished in the improvisational drama sessions. Some presented soliloquies they had memorized. Others sang or read their own poetry. They were fascinated to watch themselves on videotape. Participants interacted in an increasingly cooperative manner. After scheduled drama group sessions, subjects began to use role playing, role reversal and charades in ward meetings, creating a relaxed atmosphere and breaking down role and communication barriers in the hospital environment. These effects continued for months after the sessions had ended."*

Drama Therapy May Be an Adjunctive Therapy for Schizophrenia

Ruddy, R. A., "Drama Therapy for Schizophrenia or Schizophrenia-like Illnesses." The Cochrane Database of Systematic Reviews, no. 1 (2007): CD005378. doi:10.1002/14651858.CD005378.pub2.

- *"Drama therapy is one of the creative therapies suggested to be of value as an adjunctive treatment for people with schizophrenia or schizophrenia-like illnesses. Randomised studies have been successfully conducted in this area but poor study reporting meant that*

no conclusions could be drawn from them. The benefits or harms of the use of drama therapy in schizophrenia are therefore unclear and further large, high quality studies are required to determine the true value of drama therapy for schizophrenia or schizophrenia-like illnesses."

Humor

Humor Skills Training Can Improve Rehabilitation Outcomes for Schizophrenic Patients

Cai, Chunfeng, "Effectiveness of Humor Intervention for Patients with Schizophrenia: A Randomized Controlled Trial." Journal of Psychiatric Research 59 (December 2014): 174–78. doi:10.1016/j.jpsychires.2014.09.010.

- *"The implementation of humor skill training in a mental health service can improve rehabilitative outcomes and sense of humor for schizophrenia patients who were in the rehabilitation stage."*

Humor has Positive Effect on Hospitalized Schizophrenic Patients

Gelkopf, M., "Laughter in a Psychiatric Ward. Somatic, Emotional, Social, and Clinical Influences on Schizophrenic Patients." The Journal of Nervous and Mental Disease 181, no. 5 (May 1993): 283–89.

- *"The study was designed to explore the potential therapeutic effects of humor on hospitalized schizophrenics. For this purpose, in the first stage, we conducted a review of findings in regard to physical health, emotions, psychiatric state, and social behavior. In the second stage, we carried out an experiment with 34 resident patients in two chronic schizophrenic wards who were exposed to 70 movies during 3 months. The experimental group was exposed to humorous movies only, and the control group to different kinds of movies. Before and after the exposure to films for 3 months, both groups were tested on different health, emotional, social, and clinical measures using the Cognitive Orientation of Health Questionnaire, the Shalvata Symptom Rating Scale, blood pressure, heart rate, Perceived Verbal and Motor Aggression (rated by nurses), the Multiple Affect Adjective Check List, the Social Support Questionnaire 6, and the Brief Psychiatric Rating Scale (BPRS; rated by psychiatrists). Covariance analyses yielded significant reductions in Perceived Verbal Hostility, BPRS scales (total score, anxiety/depression), and significant increases in BPRS (activation) and degree of staff support experienced by the patients. The results indicate that the effects of exposure to humor may be mediated by the effects on the staff of the incidental exposure to humorous films."*

Humorous Movies Reduce Levels of Psychopathology of Schizophrenics

Gelkopf M. The effect of humorous movies on inpatients with chronic schizophrenia. J Nerv Ment Dis 2006 Nov;194(11):880-3

- *"Reduced levels of psychopathology, anger, anxiety, and depression symptoms and improvement in social competence were reveled in the study group.*

Humorous Movies Create a Therapeutic Alliance between Staff and Patients

Gelkopf M. Therapeutic use of humor to improve social support in an institutionalized schizophrenic inpatient community. J Soc Psychol 1994 Apr;134(2):175-82

- *"We concluded that the positive atmosphere that humor creates affects the therapeutic alliance between staff and patients but does not affect other social networks because of the regressed nature of schizophrenic social relationships."*

The Use of Humor with Chronic Schizophrenic Patients Raises Patient Self-esteem

Witztum E. The use of humor with chronic schizophrenic patients. Journal of Contemporary Psychotherapy, Volume 29, Number 3, 1999, pp 223-234 (12)

- *"The use of humorous therapeutic approach combined with drug therapy in the treatment of chronic schizophrenia patients institutionalized for prorated periods of time led to positive changes in their symptoms. The majority of the patients responded well to humorous interpretations. The patients felt that they had the option of adopting the doctor's humorous manner. This approach appealed to them and raised self-esteem; they likewise gained confidence in their own ability to form judgments. They cooperated better with the doctor in issues pertaining to treatment. The fact that humor made an impact on the patient's cognition was evaluated according to the BPRS scale, before the treatment, on a monthly basis during the treatment, and three months upon the completion of the experiment. In the course of the experiment, pharmacological treatment remained unchanged. On average, a perceptible reduction in the BPRS value ($p<.05$) was detected as a result of humor therapy. Amusing representations of affective external stimuli were incorporated into the patient's cognition and, along with a newly gained awareness of the possibility of relating to them with humor, were retained long after the termination of the project."*

Vancampfort D. Effects of progressive muscle relaxation on state anxiety and subjective well-being in people with schizophrenia. Clin Rehabil 2011 Jun;25(6):587-75

- *"Progressive muscle relaxation is highly effective in reducing acute feelings of stress and anxiety in patients with schizophrenia."*

Music Therapy

Karaoke Therapy is Effective at Improving Social Interaction in Mental Patients

Leung, C. M., "Karaoke Therapy in the Rehabilitation of Mental Patients." Singapore Medical Journal 39, no. 4 (April 1998): 166–68.

- *"Karaoke therapy may be more effective than simple singing in improving social interaction. There is preliminary evidence that it may be anxiety-provoking for unstable schizophrenic patients. More research is required for further elucidation of the characteristics of favourable candidates, optimal schedule and active components of the therapy."*

Music Improvisation Improves Schizophrenics Self-assessment Scores

Pfeiffer, H., "Music improvisation with schizophrenic patients--a controlled study in the assessment of therapeutic effects]." Die Rehabilitation 26, no. 4 (November 1987): 184–92.

- *"The effects of a course of music therapy with free improvisation, consisting of 27 sessions over a period of 6 months, were examined in a controlled study of matched therapy and waiting group, each comprising 7 patients with a diagnosis of schizophrenia or schizoaffective psychosis. The psychopathologic picture having essentially remained unaltered on the measuring instrument used (Lorr scales), significant positive changes were found in the self-assessment questionnaires completed by the participants. Improvements in recreational and social behaviours could not be shown. The disease and reintegration processes took similarly positive courses in both groups, supported by the extensive range of psychiatric/psychotherapeutic services available in the Munich area. The improvising orientation of the music therapy course had mostly been approved of by the patients, it however also gave rise to a desire for more structuring and a more goal-directed therapeutic approach. A tendency towards the initial values, i.e. a deterioration, was stated in the therapy group at follow-up six months post-therapy."*

Music Therapy May Diminish Schizophrenic Symptoms

Na HJ. Effects of listening to music on auditory hallucinations and psychiatric symptoms in people with schizophrenia. J Korean Acad Nurs 2009 Feb;39(1):62-71

- *"….listening to music may be useful for managing auditory hallucinations in schizophrenic inpatients.*

Ulrich G. The additional effect of group music therapy for schizophrenic patients: a randomized study. Acta Psychiatr Scand 2007 Nov;116;116(5):362-70

- *"Musical activity diminishes negative symptoms and improves interpersonal contact."*

Tang W. Rehabilitative effect of music therapy for residual schizophrenia. A one-month randomized controlled trial in Shanghai. Br J Psychiatry Suppl 1994 Aug:24:38-44

- *"Music therapy significantly diminished patient's negative symptoms, increasing their ability to converse with one another."*

Gold C. Music therapy for schizophrenia-like illnesses. Cochrane Database Syst Rev 2005 Apr 18;(2):CD004925

- *"Music therapy as an addition to standard care helps people with schizophrenia to improve their global state and may also improve mental state and functioning if sufficient number of music sessions are provided."*

Music Therapy May Improve Social Functioning in Schizophrenia

Mössler, Karin, "Music Therapy for People with Schizophrenia and Schizophrenia-like Disorders." The Cochrane Database of Systematic Reviews, no. 12 (2011): CD004025. doi:10.1002/14651858.CD004025.pub3.

- *"Music therapy as an addition to standard care helps people with schizophrenia to improve their global state, mental state (including negative symptoms) and social functioning if a sufficient number of music therapy sessions are provided by qualified music therapists. Further research should especially address the long-term effects of music therapy, dose-response relationships, as well as the relevance of outcomes measures in relation to music therapy."*

Music Therapy Could Be a Useful Adjunct to Pharmacotherapy during In-Patient Hospital Stay

Morgan, K.,"A Controlled Trial Investigating the Effect of Music Therapy during an Acute Psychotic Episode." Acta Psychiatrica Scandinavica 124, no. 5 (November 2011): 363–71. doi:10.1111/j.1600-0447.2011.01739.x.

- *"Statistically significant changes in BPRS scores were seen in the treatment group (n = 25) compared with the control group (n = 24). No significant differences were seen in the results of the Calgary, NOSIE-30 or DASS21 scores. Despite the treatment group, having a 9.3% decrease in their length of stay in hospital as opposed to the control group, this did not reach statistical significance. No significant differences were found when comparing the two groups in their doses of antipsychotic, benzodiazepine, mood stabilising or antidepressant medication or at the 1-month follow-up assessment."*

Music Alleviates Cognitive Dysfunction in Schizophrenia

Glicksohn, J., "Can Music Alleviate Cognitive Dysfunction in Schizophrenia?" Psychopathology 33, no. 1 (February 2000): 43–47. doi:29118.

- *"It has recently been reported that students performed relatively better on cognitive tasks after listening to music. Conceivably, music might reduce the level of arousal in subjects who are tense, thereby improving their performance. A test case would be schizophrenic subjects, noted for poor performance on tasks demanding attention, who have been characterized as suffering from hyperarousal, which mediates these attentional deficits. We investigated whether cognitive task performance could be facilitated by music in schizophrenics and report a beneficial effect."*

Nature Therapy

Horticulture Therapy May Be an Effective Treatment for Schizophrenia

Kamioka, Hiroharu, "Effectiveness of Horticultural Therapy: A Systematic Review of Randomized Controlled Trials." Complementary Therapies in Medicine 22, no. 5 (October 2014): 930–43. doi:10.1016/j.ctim.2014.08.009.

- *"Although there was insufficient evidence in the studies of HT due to poor methodological and reporting quality and heterogeneity, HT may be an effective treatment for mental and behavioral disorders such as dementia, schizophrenia, depression, and terminal-care for cancer."*

Reliable Evidence Supports the Effectiveness of Nature-assisted Therapy for Psychiatric Illness

Annerstedt, Matilda, "Nature-Assisted Therapy: Systematic Review of Controlled and Observational Studies." Scandinavian Journal of Public Health 39, no. 4 (June 2011): 371–88. doi:10.1177/1403494810396400.

- *"This review gives at hand that a rather small but reliable evidence base supports the effectiveness and appropriateness of NAT as a relevant resource for public health. Significant improvements were found for varied outcomes in diverse diagnoses, spanning from obesity to schizophrenia. Recommendations for specific areas of future research of the subject are provided."*

Adventure and Recreation Based Group Intervention Promotes Well Being and Weight Loss in Schizophrenia

Voruganti, Lakshmi N. P., "Going beyond: An Adventure- and Recreation-Based Group Intervention Promotes Well-Being and Weight Loss in Schizophrenia." Canadian Journal of Psychiatry. Revue Canadienne De Psychiatrie 51, no. 9 (August 2006): 575–80.

- *"Treatment adherence was 97%, and there were no dropouts. Patients in the study group showed marginal improvement in perceived cognitive abilities and on domain-specific functioning measures but experienced a significant improvement in their self-esteem and global functioning ($P < 0.05$), as well as a weight loss of over 12 lb. Improvement was sustained over 1 year with further occupational and social gains. In the context of overcoming barriers to providing early intervention for youth and preventing metabolic problems among older adults with schizophrenia, adventure- and recreation-based interventions could play a useful complementary role."*

Outdoor Adventure Camp for People with Mental illness Demonstrates Significant Improvements in Mastery, Self-esteem, and Social Connectedness

Cotton, Sue, "Outdoor Adventure Camps for People with Mental Illness." Australasian Psychiatry: Bulletin of Royal Australian and New Zealand College of Psychiatrists 21, no. 4 (August 2013): 352–58. doi:10.1177/1039856213492351.

- *"Participants demonstrated significant improvements in mastery, self-esteem and social connectedness from baseline to end of the camp; however, these improvements were not sustained by the four-week follow-up."*

Gardening May Be a Therapeutic Form of Exercise for Schizophrenia

Sullivan, M. E. "Horticultural Therapy--the Role Gardening Plays in Healing." Journal - American Health Care Association 5, no. 3 (May 1979): 3, 5–6, 8.

- *"Horticultural therapy is an adjunct therapy--to be used in addition to occupational and physical therapies, and combining means used by both. It is meant to increase the motivation of the physically and/or mentally handicapped, while at the same time stimulating the five senses and furnishing a means of self-gratification and self-esteem. Now that neurologically orientated psychologists are identifying schizophrenia as being biologically based and capable of being reversed with exercise, it is time to study the many benefits of gardening as a therapy method."*

Community Coping Skills Enhanced by an Adventure Camp for Chronic Adult Psychiatric Patients

Banaka, W. H., "Community Coping Skills Enhanced by an Adventure Camp for Adult Chronic Psychiatric Patients." Hospital & Community Psychiatry 36, no. 7 (July 1985): 746–48.

- *"The effect of a two-week wilderness camp on ten skill areas related to community survival of the chronic mentally ill was assessed both by participants, who were adult*

chronic psychiatric patients from two Oregon state mental hospitals, and by camp and hospital staff. Compared with 30 controls, the 48 participants improved on seven of the ten areas by the end of camp and maintained their improvements in four of the seven areas for several weeks following their return to the hospital. Although discharge and recidivism rates for participants and controls did not differ at six-month follow-up, participants spent a greater proportion of time in the community than did controls. The authors discuss the specific skills improved by the program and those that contributed to duration of community survival, as well as the program's cost-effectiveness."

Sailing Can Improve Quality of Life of People with Severe Mental Disorders

Carta, Mauro Giovanni, "Sailing Can Improve Quality of Life of People with Severe Mental Disorders: Results of a Cross over Randomized Controlled Trial." Clinical Practice and Epidemiology in Mental Health: CP & EMH 10 (2014): 80–86. doi:10.2174/1745017901410010080.

- *"The aim of this study was to evaluate the impact of a sailing rehabilitation program on the quality of life (QoL) in a sample of patients with severe mental disorders. The study adopted a randomized, crossover, waiting-list controlled design. The participants enrolled in the study were outpatients diagnosed with severe chronic mental disorders. The participants (N=40) exposed to rehabilitation with sailing took part in a series of supervised cruises near the gulf of Cagliari, South Sardinia, and showed a statistically significant improvement of their quality of life compared to the control group. This improvement was comparable to the improvement in psychopathologic status and social functioning as shown in a previous report of the same research project. The improvement was maintained at follow-up only during the trial and for a few months later: after 12 months, patients returned to their baseline values and their quality of life showed a worsening trend. This is the first study to show that rehabilitation with sailing may improve the quality of life of people with severe chronic mental disorders. In all likelihood, a program grounded on learning how to manage a sailing vessel - during which patients perform cruises that emphasize the exploration of the marine environment by sailing - might be interesting enough and capture the attention of the patients so as to favour greater effectiveness of standard rehabilitation protocols, but this should be specifically tested."*

Play Therapy

Play Therapy can be used in Treatment of Hebephrenia Schizophrenia

Hudson, W. C. "Play Therapy in the Treatment of Hebephrenia." Psychotherapy and Psychosomatics 26, no. 5 (1975): 286–93.

- *"This paper has attempted to outline a multiple technique therapy designed for the treatment of hebephrenia. The first phase of the technique utilizes play therapy, followed by an interchange of therapist and patient's drawings, and finally, analytic psychotherapy. These three phases may be characterized, respectively, as expressive, expressive-communicative, and communicative."*

Electric Brain Stimulation Therapies

Cranial Electrotherapy

Cranial Electrotherapy Stimulation Reduces Aggression in Violent Schizophrenic Patient

Childs, Allen. "Cranial Electrotherapy Stimulation Reduces Aggression in a Violent Retarded Population: A Preliminary Report." The Journal of Neuropsychiatry and Clinical Neurosciences 17, no. 4 (2005): 548–51. doi:10.1176/appi.neuropsych.17.4.548.

- *"Nine aggressive, retarded patients refractory to conventional care at a maximum security hospital were given a 3-month course of cranial electrotherapy stimulation. Aggressive episodes declined 59% from baseline; seclusions were down 72%; restraints were down 58%; and use of prescribedas- needed sedative medications decreased 53%. The most dramatic change was that of a disorganized, schizophrenic patient whose aggressive episodes declined from 62 to 9, seclusions from 53 to 8, restraints from 9 to 1 and PRNs from 25 to 1. No patients discontinued cranial electrotherapy stimulation (CES) because of side effects. This preliminary report indicates that CES appears to be an efficacious, safe, and cost-effective addition to the treatment regimen in this patient population."*

Neuro-electric Therapy

Neuro-electric Therapy is an Effective Treatment for Schizophrenia and Affective Psychosis

Klimke, A., "[Effectiveness of neuro-electric therapy in drug resistant endogenous psychoses]." Fortschritte Der Neurologie-Psychiatrie 59, no. 2 (February 1991): 53–59. doi:10.1055/s-2007-1000679.

- *"A retrospective chart review of 50 pharmacotherapeutically resistant patients was performed after treatment with NET in 1986-1988. 28 patients suffered from schizophrenia and 22 from affective psychosis. In contrast to literature where NET as therapy of first choice has favourable results in depression in this study 60.7% of the treatment resistant acute schizophrenics responded well to NET. 3 months after discharge from hospital 9 schizophrenics (32.1%) but only 3 patients with affective psychosis (13.6%) presented a 'good' outcome (full remission). A longer duration of schizophrenia (more than 5 years since first manifestation) and a good response to neuroleptics in history*

was predictive for a good actual NET response (14 of 17 patients), whereas 7 of 11 patients suffering from schizophrenia less than 3 years without any period of full remission on neuroleptics were also non-responders to NET."

Transcranial Direct Current Stimulation

Transcranial Direct Current Stimulation May Be Effective for Treatment Catatonic Schizophrenia

Shiozawa, Pedro, "Transcranial Direct Current Stimulation (tDCS) for Catatonic Schizophrenia: A Case Study." Schizophrenia Research 146, no. 1–3 (May 2013): 374–75. doi:10.1016/j.schres.2013.01.030.

- *"The intervention protocol consisted in 10 consecutive daily tDCS sessions (including the weekend). The cathode was positioned over the right and the anode over the left dorsolateral prefrontal cortex. We used a direct current of 2.0 mA for 20 mn. The 35 cm_2-rubber electrodes were wrapped in cotton material, which was moistened with saline to reduce impedance. For, assessment of catatonic symptoms we used the Bush-Francis catatonic scale, a widely used assessment tool in clinical practice that account for the main symptoms of schizophrenia. As shown in Fig. 1, catatonic symptoms substantially improved during the treatment course. After one month of treatment, she progressively started to perform eye and verbal contact with the medical team and engaged in daily activities such as eating, walking and showering without help. After four months, the patients remain without catatonic symptoms."*

Transcranial Direct Current Stimulation May be a Promising Tool for the Treatment of Negative Symptoms in Schizophrenia

Palm, Ulrich, "Prefrontal Transcranial Direct Current Stimulation (tDCS) Changes Negative Symptoms and Functional Connectivity MRI (fcMRI) in a Single Case of Treatment-Resistant Schizophrenia." Schizophrenia Research 150, no. 2–3 (November 2013): 583–85. doi:10.1016/j.schres.2013.08.043.

- *"In conclusion, anodal tDCS of the left DLPFC seems to be a promising tool for the treatment of negative symptoms in schizophrenia and may even alter positive symptoms. However, randomized controlled trials are needed for investigating the specific action of tDCS on the symptom spectrum in schizophrenia, using different electrode placements and stimulation protocols."*

Once to Twice Daily Transcranial Direct Current Stimulation is Effective for Severe Clozapine Refractory Continuous Auditory Hallucinations in Schizophrenia

Andrade, Chittaranjan. "Once- to Twice-Daily, 3-Year Domiciliary Maintenance Transcranial Direct Current Stimulation for Severe, Disabling, Clozapine-Refractory Continuous Auditory Hallucinations in Schizophrenia." The Journal of ECT 29, no. 3 (September 2013): 239–42. doi:10.1097/YCT.0b013e3182843866.

- *"Once daily, 20-minute tDCS sessions at 1-mA intensity produced noticeable improvement within a week: cognitive and psychosocial functioning improved, followed by attenuation in the experience of hallucinations. There was greater than 90% self-reported improvement within 2 months. Benefits accelerated when the current was raised to 3 mA; treatment duration was increased to 30-minute sessions, and session frequency was increased to twice daily. The patient improved from a psychosocially vegetative state to near-normal functioning. Once- to twice-daily domiciliary tDCS was continued across nearly 3 years and is still ongoing. Benefits attenuated or were even lost when alternate day session spacing was attempted, or when electrode positioning was changed; benefits were regained when the original stimulation protocol was reintroduced. There was confirmation of benefit in 2 separate on-off-on situations, which occurred inadvertently and under blinded conditions. There were no adverse events attributable to tDCS."*

Add-on Transcranial Direct Current Stimulation is Effective for Rapid Amelioration of Auditory Hallucinations in Schizophrenics

Shivakumar, Venkataram, "Rapid Improvement of Auditory Verbal Hallucinations in Schizophrenia after Add-on Treatment with Transcranial Direct-Current Stimulation." The Journal of ECT 29, no. 3 (September 2013): e43–44. doi:10.1097/YCT.0b013e318290fa4d.

- *"Treatment of nonresponsive auditory hallucinations in schizophrenia have been reported to improve with transcranial direct-current stimulation. This case description illustrates the use of add-on transcranial direct-current stimulation for rapid amelioration of auditory hallucinations in schizophrenia during the acute phase. Because transcranial direct-current stimulation is safe, largely well tolerated, and relatively inexpensive, this add-on treatment option is worth exploring through further rigorous studies."*

Transcranial Direct Current Stimulation Improves Treatment-resistant Auditory Hallucinations in Schizophrenic Patient

Nawani, Hema, "Neural Basis of tDCS Effects on Auditory Verbal Hallucinations in Schizophrenia: A Case Report Evidence for Cortical Neuroplasticity Modulation." The Journal of ECT 30, no. 1 (March 2014): e2–4. doi:10.1097/YCT.0b013e3182a35492.

- *"Transcranial direct current stimulation (tDCS) has been reported to ameliorate auditory hallucinations that are nonresponsive/minimally responsive to antipsychotic treatment in schizophrenia. The neurobiological basis of the tDCS effects in ameliorating*

auditory hallucinations is yet to be explored. In this case report, for the first time, using the novel method for noninvasive assessment of cortical plasticity, we demonstrate potential neuroplasticity effect of tDCS in improving treatment-resistant auditory hallucinations in a schizophrenic patient."

Transcranial Random Noise Stimulation

Transcranial Random Noise Stimulation is a Sustainable Treatment in Drug-free Schizophrenic Patients

Haesebaert, Frederic, "Efficacy and Safety of Fronto-Temporal Transcranial Random Noise Stimulation (tRNS) in Drug-Free Patients with Schizophrenia: A Case Study." Schizophrenia Research 159, no. 1 (October 2014): 251–52. doi:10.1016/j.schres.2014.07.043.

- *"This case illustrates for the first time that fronto-temporal high frequency tRNS seems to be a sustainable treatment in drug-free patients with schizophrenia, alleviating delusions and enhancing insight of the illness."*

Modest Clinical Improvement was shown with Transcranial Random Noise Stimulation for the Treatment of Schizophrenia

Palm, Ulrich, "Transcranial Random Noise Stimulation for the Treatment of Negative Symptoms in Schizophrenia." Schizophrenia Research 146, no. 1–3 (May 2013): 372–73. doi:10.1016/j.schres.2013.03.003.

- *"At baseline, the patient presented with a Positive and Negative Symptom Scale (PANSS) score of 102 (subscales: positive 9, negative 34, cognition 32, excitement/hostility 4, depression/anxiety 23), a Scale for the Assessment of Negative Symptoms (SANS) score of 73, and a Calgary Depression Scale in Schizophrenia (CDSS) score of 6. For the Trail Making Test (TMT), he needed 19 s (TMT-A) and 55 s (TMT-B). After 20 stimulations he showed a modest clinical improvement in the domain of negative symptoms (i.e. emotional withdrawal, poor rapport, lack of spontaneity), cognition (i.e. disorganization, difficulties in abstract thinking, and disturbance of volition) and depression/anxiety: PANSS score 68 (subscales: positive 5, negative 21, cognition 25, excitement/hostility 4, depression/anxiety 13), SANS score 48, CDSS score 5, TMT-A 17 s, TMT-B 38 s. tRNS was well tolerated and there were no adverse effects. However, there are some limitations: clinical improvement could also be due to non-specific effects of the treatment or a delayed onset of medication effects. Furthermore, information processing (TMT-A) and executive functioning (TMT-B) were intact at baseline and the modest improvement could be due to learning effects. There also may be several factors limiting the efficacy of tRNS, e.g. chronicity of the disease, short duration of treatment and concomitant medication (Fertonani et al.,2011). For example, lamotrigine and pregabaline may potentially decrease the neuromodulatory effects of tRNS by blocking the opening of voltage-gated sodium channels (lamotrigine) or voltage-*

gated calcium channels (pregabaline) (Nitsche et al., 2012). However, this case report supports the findings of cognitive enhancement by excitatory noninvasive electrical brain stimulation (Kuo and Nitsche, 2012; Nitsche et al., 2012). Thus, therapeutic effects of tRNS in psychiatric disorders merit systematic investigation."

Alternative Reality

Avatar Therapy

Avatar Therapy is Effective for Persecutory Auditory Hallucinations

Leff, Julian, "Avatar Therapy for Persecutory Auditory Hallucinations: What Is It and How Does It Work?" Psychosis 6, no. 2 (June 2014): 166–76. doi:10.1080/17522439.2013.773457.

- *"We have developed a novel therapy based on a computer program, which enables the patient to create an avatar of the entity, human or non-human, which they believe is persecuting them. The therapist encourages the patient to enter into a dialogue with their avatar, and is able to use the program to change the avatar so that it comes under the patient's control over the course of six 30-min sessions and alters from being abusive to becoming friendly and supportive. The therapy was evaluated in a randomised controlled trial with a partial crossover design. One group went straight into the therapy arm: "immediate therapy". The other continued with standard clinical care for 7 weeks then crossed over into Avatar therapy: "delayed therapy". There was a significant reduction in the frequency and intensity of the voices and in their omnipotence and malevolence. Several individuals had a dramatic response, their voices ceasing completely after a few sessions of the therapy. The average effect size of the therapy was 0.8. We discuss the possible psychological mechanisms for the success of Avatar therapy and the implications for the origins of persecutory voices."*

Computer-assisted Therapy for Medication-resistant Auditory Hallucinations

Leff J. Computer-assisted therapy for medication-resistant auditory hallucinations: proof-of-concept study. Br J Psychiatry 2013 Jun;202:428-33

- *"Avatar therapy was evaluated by a randomized, single blind, partial crossover trial comparing the novel therapy with treatment as usual (TAU). We used three main outcome measures: (a) the Psychotic Symptom Rating Scale (PSYRATS), hallucination section; (b) the Omnipotence and Malevolence subscales of Revised Beliefs About Voices Questionnaire (BAVQ-R); and (c) the Calgary Depression Scale (CDS). The control group showed no change over time in their scores on three assessments, whereas the novel therapy group showed mean reductions in total PSYRATS score (auditory hallucinations) of 8.75 (P=0.003) and in the BAVQ-R combined score of omnipotence*

and malevolence of the voices of 5.88 (P=0.004). There was no significant reduction in the CDS total score for depression. For the crossover group, comparison of the period of the TAU with the period of avatar therapy confirmed the findings of the previous analysis. The effect size of therapy was 0.8. Avatar therapy represents a promising treatment for medication resistant auditory hallucinations."

Video Games

Videogames as Game Therapy are Attractive, Safe, and Easy to Monitor

Samoilovich, S., "Attitude of Schizophrenics to Computer Videogames." Psychopathology 25, no. 3 (1992): 117–19.

- *"Considered as labor or game therapy, the games are attractive, safe and easy to monitor, even in defected patients. The value of continued use of videogames in individual or group sessions merits to be investigated."*

Video Game Training could be Used to Counteract Risk Factors Such as Smaller Hippocampus and Prefrontal Cortex in Schizophrenia

Kühn, S., "Playing Super Mario Induces Structural Brain Plasticity: Gray Matter Changes Resulting from Training with a Commercial Video Game." Molecular Psychiatry 19, no. 2 (February 2014): 265–71. doi:10.1038/mp.2013.120.

- *"Video gaming is a highly pervasive activity, providing a multitude of complex cognitive and motor demands. Gaming can be seen as an intense training of several skills. Associated cerebral structural plasticity induced has not been investigated so far. Comparing a control with a video gaming training group that was trained for 2 months for at least 30 min per day with a platformer game, we found significant gray matter (GM) increase in right hippocampal formation (HC), right dorsolateral prefrontal cortex (DLPFC) and bilateral cerebellum in the training group. The HC increase correlated with changes from egocentric to allocentric navigation strategy. GM increases in HC and DLPFC correlated with participants' desire for video gaming, evidence suggesting a predictive role of desire in volume change. Video game training augments GM in brain areas crucial for spatial navigation, strategic planning, working memory and motor performance going along with evidence for behavioral changes of navigation strategy. The presented video game training could therefore be used to counteract known risk factors for mental disease such as smaller hippocampus and prefrontal cortex volume in, for example, post-traumatic stress disorder, schizophrenia and neurodegenerative disease."*

Video Games Used to Treat Mental Disorders Including Schizophrenia

Fernández-Aranda, "Video Games as a Complementary Therapy Tool in Mental Disorders: PlayMancer, a European Multicentre Study." Journal of Mental Health (Abingdon, England) 21, no. 4 (August 2012): 364–74. doi:10.3109/09638237.2012.664302.

- *"The video game was created and developed within the European research project PlayMancer. It aims to prove potential capacity to change underlying attitudinal, behavioural and emotional processes of patients with impulse-related disorders. New interaction modes were provided by newly developed components, such as emotion recognition from speech, face and physiological reactions, while specific impulsive reactions were elicited. The video game uses biofeedback for helping patients to learn relaxation skills, acquire better self-control strategies and develop new emotional regulation strategies. In this article, we present a description of the video game used, rationale, user requirements, usability and preliminary data, in several mental disorders."*

Internet Video Game Play was found to Have Clinical Improvement and Could Be an Adjunctive Treatment for Rehabilitation of Schizophrenic Patients

Han, Doug Hyun, "The Effect of Internet Video Game Play on Clinical and Extrapyramidal Symptoms in Patients with Schizophrenia." Schizophrenia Research 103, no. 1–3 (August 2008): 338–40. doi:10.1016/j.schres.2008.01.026.

- *"To the best of our knowledge, this is the first clinical study to assess psychiatric symptoms and EPS in schizophrenic patients who engage in internet videogame play. In addition, the current study also showed that EPS in IVP-SCZ was improved, as compared to nIVP-SCZ. Based on the current findings of improvement in clinical symptoms and EPS, we suggest that limited internet video game play could be considered as an adjunctive treatment and rehabilitation modality for patients with schizophrenia."*

Virtual Reality

Virtual Reality-Integrated Program May Be Effective for Improving Social Skills

Rus-Calafell, Mar, "A Virtual Reality-Integrated Program for Improving Social Skills in Patients with Schizophrenia: A Pilot Study." Journal of Behavior Therapy and Experimental Psychiatry 45, no. 1 (March 2014): 81–89. doi:10.1016/j.jbtep.2013.09.002.

- *"The results of a series of repeated measures ANOVA revealed significant improvement in negative symptoms, psychopathology, social anxiety and discomfort, avoidance and social functioning. Objective scores obtained through the use of the VR program showed a pattern of learning in emotion perception, assertive behaviours and time spent in a conversation. Most of these gains were maintained at four-month follow-up. The results showed that the intervention may be effective for improving social dysfunction. The use*

of the VR program contributed to the generalisation of new skills into the patient's everyday functioning."

Virtual Reality for Treatment of Schizophrenia

De Costa RM. The acceptance of virtual reality devices for cognitive rehabilitation: a report of positive results with schizophrenia. Comput Methods Programs Biomed 2004 Mar;73(3):173-82

- *"The subjects that participated in this experiment accepted to work with computers and immersive glasses and demonstrated a high level of interest in the proposed tasks. No problems of illness have been observed."*

Virtual Reality for Paranoia

Fornells-Ambrojo M. Virtual reality and persecutory delusions: safety and feasibility. Schizophr Res 2008 Sep; 104(1-3):228-36

- *"Exposure to social situations using VR has the potential to be incorporated into cognitive behavioral interventions for paranoia."*

Virtual Reality Cognitive Training Program Offers Potential for Significant Gains in Cognitive Function in Older Adults with Schizophrenia

Chan, Christopher L. F., "Effect of the Adapted Virtual Reality Cognitive Training Program among Chinese Older Adults with Chronic Schizophrenia: A Pilot Study." International Journal of Geriatric Psychiatry 25, no. 6 (June 2010): 643–49. doi:10.1002/gps.2403.

- *"After the 10-session intervention, older adults with chronic schizophrenia preformed significantly better than control in overall cognitive function (p .000), and in two cognitive subscales: repetition (p .001) and memory (p .040). These participants engaged in the VR activities volitionally. No problem of cybersickness was observed. The results of the current study indicate that engaging in the adapted virtual reality cognitive training program offers the potential for significant gains in cognitive function of the older adults with chronic schizophrenia."*

Energy & Spiritual Healing

Personal Belief System

Sound Spiritual, Religious or Personal Belief System is Associated with Adaptive Coping Skills in Schizophrenia

Shah, Ruchita,"Relationship between Spirituality/religiousness and Coping in Patients with Residual Schizophrenia." Quality of Life Research: An International Journal of Quality of Life Aspects of Treatment, Care and Rehabilitation 20, no. 7 (September 2011): 1053–60. doi:10.1007/s11136-010-9839-6.

- *"A sound spiritual, religious, or personal belief system is associated with active and adaptive coping skills in subjects with residual schizophrenia. Understanding and assessing the spirituality and religiousness of subjects with schizophrenia can help in better management of the disorder."*

Religion Has a Clinical Significance in the Care of Patients with Schizophrenia

Mohr, Sylvia, "Toward an Integration of Spirituality and Religiousness into the Psychosocial Dimension of Schizophrenia." The American Journal of Psychiatry 163, no. 11 (November 2006): 1952–59. doi:10.1176/appi.ajp.163.11.1952.

- *"Our results highlight the clinical significance of religion in the care of patients with schizophrenia. Religion is neither a strictly personal matter nor a strictly cultural one. Spirituality should be integrated into the psychosocial dimension of care. Our results suggest that the complexity of the relationship between religion and illness requires a highly sensitive approach to each unique story."*

Religious Support

Religious Support and Enduring with Faith Were Positively Associated with Recovery from Severe Mental Illness

Webb, Marcia, "Struggling and Enduring with God, Religious Support, and Recovery from Severe Mental Illness." Journal of Clinical Psychology 67, no. 12 (December 2011): 1161–76. doi:10.1002/jclp.20838.

- *"Religious support and enduring with faith were positively associated with recovery. Struggling was negatively associated with recovery, and that relationship was mediated by religious support."*

Spiritual Emotional Freedom Technique

Spiritual Emotional Freedom Technique (SEFT) is Effective in Schizophrenia

Puspitaningrum Ike. Effectiveness of spiritual emotional freedom technique (SEFT) intervention in schizophrenia with depression anxiety stress. Nursing Intervention, Complementary and Alternative Therapy, In JAVA International Nursing Conference 2012 October 6-7, Semarang

- *The results of statistical tests concluded that the variables had a significant result (0.017). It can be concluded that SEFT intervention was effective to reduce depression anxiety stress levels in patients with schizophrenia."*

Spiritually Oriented Group Therapy

Spiritually Oriented Group Therapy as a Tool for Healing Mental Illness

Sageman, Sharon. "Breaking through the Despair: Spiritually Oriented Group Therapy as a Means of Healing Women with Severe Mental Illness." The Journal of the American Academy of Psychoanalysis and Dynamic Psychiatry 32, no. 1 (2004): 125–41.

- *"Studies have shown that 96% of Americans believe in God and over 90% pray yet there is relatively little education available for clinicians on how to use spirituality as a tool for healing mental illness, particularly when treating very sick patients. This article illustrates how spiritually oriented group therapy with severely ill women can help to improve mood, affect, motivation, interpersonal bonding, and sense of self, and can succeed in reaching patients and promoting recovery in ways that traditional therapy cannot. Specific modalities including group prayer, yoga breathing, and spiritual readings are described. Breaking Through the Despair offers both a psychodynamic and a neurophysiologic perspective for understanding how this type of treatment helps patients transcend their mental illness and be able to grasp abstract spiritual concepts, develop a sense of belonging to a caring community, and integrate a new sense of themselves as productive and valued individuals."*

Reiki & Pranic Healing

Energy Healing Shows Promise as a Complementary Treatment for Paranoid Schizophrenia

Chhibber K. Energy healing as a complementary treatment for paranoid schizophrenia: A case report. 141st APHA Annual Meeting (November 2-November 6, 2013) APHA 2013

- *"Energy Healing Treatments: The subject received 4 energy healing treatments daily for a period of 16 weeks, consisting of both Pranic healing and Reiki. Additional treatments were administered as necessary, when hallucinations or abnormal behavior persisted. Results: Subject noted feelings of lightness, with sustained periods of calmness and coherence. The subjects mother/father also observed changes in mood and behavior, including increased responsiveness and social proclivity. Hallucinations and erratic behavior diminished in frequency and magnitude. Physician recommended lowering lowering dosage of main antipsychotic based on observations. The subject continues to exhibit improvement. These results indicate Energy healing to be a potent and effective method of complementary therapy for schizophrenia."*

Combination Therapies

Alpha Lipoic Acid and Niacinamide

Alpha Lipoic Acid and Niacinamide Help Preserve Mitrochondrial Integrity and Protect from Oxidative Stress which Contributes to the Pathophysiology of Schizophrenia

Seybolt, Sheila E. J. "Is It Time to Reassess Alpha Lipoic Acid and Niacinamide Therapy in Schizophrenia?" Medical Hypotheses 75, no. 6 (December 2010): 572–75. doi:10.1016/j.mehy.2010.07.034.

- *"As sulfur containing thiols, alpha lipoic acid (ALA) and its reduced form dihydrolipoic acid (DHLA) are powerful antioxidants and free radical scavengers capable of performing many of the same functions as glutathione (GSH). ALA supplementation may help protect mitochondria from oxidative stress, a possible mechanism contributing to certain forms of brain diseases called schizophrenia. Shortly before the advent of antipsychotic medications, two small studies found ALA relieved psychiatric symptoms in schizophrenia. More recently, animal studies have shown ALA augmentation improves mitochondrial function. At pharmaceutical levels, niacinamide helps preserve mitochondrial membrane integrity and acts as an antioxidant. ALA is a precursor for lipoamide, an essential mitochondrial coenzyme and niacinamide is a component of niacinamide adenine dinucleotide (NAD). NADH, the reduced form of NAD, is involved in the reduction of ALA to DHLA within the mitochondria. This is relevant to contemporary research because DHLA increases GSH and low GSH levels contribute to mitochondrial dysfunction and oxidative stress which have been implicated in the pathophysiology of schizophrenia."*

Antioxidants

Adjunctive Treatment with Antioxidants May Prevent Further Oxidative Injury and Deterioration Associated with Schizophrenia

Mahadik, S. P., "Oxidative Injury and Potential Use of Antioxidants in Schizophrenia." Prostaglandins, Leukotrienes, and Essential Fatty Acids 55, no. 1–2 (August 1996): 45–54.

- *"Adjunctive treatment with antioxidants (e.g. vitamins E and C, beta-carotene and quinones) at the initial stages of illness may prevent further oxidative injury and thereby ameliorate and prevent further possible deterioration of associated neurological and behavioral deficits in schizophrenia."*

Adjunctive Treatment with Antioxidants May Prevent Further Deterioration Associated with Schizophrenia

Mahadik SP. Oxidative injury and the potential use of antioxidants in schizophrenia. Prostaglandins Leukot Essent Fatty Acids 1996 Aug;55(1-2):45-54

- *"Adjunctive treatment with antioxidants (e.g. vitamins E and C, beta-carotene and quinones) at the initial stages of illness may prevent further oxidative injury and thereby ameliorate and prevent further possible deterioration of associated neurological and behavioral deficits in schizophrenia."*

Antioxidants and Omega-3 fatty acids

Prevention of Oxidative Stress Neuropathology in Schizophrenia

Mahadik S. P. Prevention of oxidative stress-meditated neuropathology and improved clinical outcome by adjunctive use of a combination of antioxidants and omega-3 fatty acids in schizophrenia. International Review of Psychiatry, April 2006: 18(2):119-131

- *"In summary, oxidative stress and cell damage likely exist at very early stages of schizophrenia and if not treated early, it can trigger progressive deterioration of neuropathology and thereby symptomology; dietary antioxidants and omega-3 fatty acids are found to effectively prevent and restore the oxidative neuropathology and improve the outcome under a variety of situations. Moreover, these supplements are also found to prevent and cure important medical morbidities such as obesity, hypertension, diabetes, and cardiovascular abnormalities that are often associated with illness and treatment."*

Bodywork and Psychotherapy

Combination of Bodywork and Psychotherapy can Enhance, Accelerate and Improve Therapy

Ventegodt, Søren, "Clinical Holistic Medicine (mindful Short-Term Psychodynamic Psychotherapy Complimented with Bodywork) in the Treatment of Schizophrenia (ICD10-F20/DSM-IV Code 295) and Other Psychotic Mental Diseases." TheScientificWorldJournal 7 (2007): 1987–2008. doi:10.1100/tsw.2007.298.

- *"Clinical holistic medicine (CHM) has developed into a system that can also be helpful with mentally ill patients. CHM therapy supports the patient through a series of emotionally challenging, existential, and healing crises. The patient's sense of coherence and mental health can be recovered through the process of feeling old repressed emotions, understanding life and self, and finally letting go of negative beliefs and delusions. The Bleuler's triple condition of autism, disturbed thoughts, and disturbed emotions that characterizes the schizophrenic patient can be understood as arising from the early defense of splitting, caused by negative learning from painful childhood traumas that made the patient lose sense of coherence and withdraw from social contact. Self-insight*

gained through the therapy can allow the patients to take their bodily, mental, and spiritual talents into use. At the end of therapy, the patients are once again living a life of quality centered on their life mission and they relate to other people in a way that systematically creates value. There are a number of challenges meeting the therapist who works with schizophrenic and psychotic patients, from the potential risk of experiencing a patient's violence, to the obligation to contain the most difficult and embarrassing of feelings when the emotional and often also sexual content of the patient's unconsciousness becomes explicit. There is a long, well-established tradition for treating schizophrenia with psychodynamic therapy, and we have found that the combination of bodywork and psychotherapy can enhance and accelerate the therapy and might improve the treatment rate further."

Exercise and Glucose

Exercise and Glucose Supplement My Effectively Treat Cognitive Impairment in Schizophrenia

Li, Yuet-Keung, "Coupling Physical Exercise with Dietary Glucose Supplement for Treating Cognitive Impairment in Schizophrenia: A Theoretical Model and Future Directions." Early Intervention in Psychiatry 8, no. 3 (August 2014): 209–20. doi:10.1111/eip.12109.

- *"The paper represents a first step in providing a theoretical model of how coupling of exercise with glucose supplement may help to alleviate cognitive impairment in schizophrenia patients. Exercise and glucose supplement work in concert to enhance glucose transport and insulin into the brain, and at the same time augment IGF-1 and BNDF output. Indeed, most research on cognitive benefits of glucose supplement and exercise and their underlying mechanisms is conducted in the general population. Research should first confirm the benefits and their mechanisms of action in schizophrenia patients, and then to elucidate the right dose of physical exercise and glucose to effectively treat cognitive impairment in schizophrenia"*

Insulin and D-ribose

High Doses of Insulin and D-ribose for the Treatment of Frontal Lobe Dysfunction in Schizophrenia

Lichtigfeld, F., "New Vistas in Chronic Schizophrenia." The International Journal of Neuroscience 38, no. 3–4 (February 1988): 355–67.

- *"In view of the distinct possibility that the disturbed glucose regulation in the frontal area and basal ganglia of chronic schizophrenia is very germane to the successful treatment of this condition, a survey is given of the many factors that have to be*

considered in developing a therapy that takes into account this new information. The suggestion is made that the balance between cAMP and cGMP in the cells affected are dysregulated so that there is an excessive activity of the cAMP generating system which eventually leads to the pathological picture found in this condition. To restore the normal metabolic balance, use will have to be made of the various substances that are known to enhance the cGMP generating system in the cell, thereby restoring a more normal metabolic integrity. In this connection, the use of high doses of insulin under cover of hyperglycaemia and also the addition of D-ribose could become the cornerstone of a series of treatments to enhance the action of currently used medications in this often intractable illness."

Leucine and Genistein

Leucine and Genistein Combined Have Potential Antipsychotic Activity

Suresh, Palle, "Antidopaminergic Effects of Leucine and Genistein on Schizophrenic Rat Models." Neurosciences (Riyadh, Saudi Arabia) 18, no. 3 (July 2013): 235–41.

- *"The individual administration of leucine and genistein had less anti dopaminergic activity when compared with their combined administration. These results suggest that leucine and genistein may have a potential clinical application in the management of psychiatric disorders."*

Vitamins and Fatty Acids

Omega-3 Fatty Acids, Vitamin C and E Supplementation have a Beneficial Effect on Positive and Negative Symptoms in Schizophrenia

Sivrioglu, E. Y., "The Impact of Omega-3 Fatty Acids, Vitamins E and C Supplementation on Treatment Outcome and Side Effects in Schizophrenia Patients Treated with Haloperidol: An Open-Label Pilot Study." Progress in Neuro-Psychopharmacology & Biological Psychiatry 31, no. 7 (October 1, 2007): 1493–99. doi:10.1016/j.pnpbp.2007.07.004.

- *"Our results support the beneficial effect of the supplementation on positive and negative symptoms of schizophrenia as well as the severity of side effects induced by haloperidol. The effect of supplementation on akathisia is especially noteworthy and it has not been investigated in previous studies."*

Supplementation with Omega-3 Fatty Acids and Vitamin E and C Significantly Reduces Psychopathology in Schizophrenia

Arvindakshan M. Supplementation with a combination of w-3 fatty acids and antioxidants (vitamin E and C) improves the outcome of schizophrenia. Schizophrenia Res 62 (2003) 195-204

- *"Concomitantly, there was significant reduction in psychopathology based on reduction in individual total scores for brief psychiatric rating scale (BPRS) and positive and negative syndrome scale (PANSS), general psychopathology-PANSS and increase in Henrich's Quality of Life (QOL) scale."*

Vitamin E and Polyunsaturated Fatty Acids Supplementation Improves Antioxidant Defense in Schizophrenic Patients

Bošković, Marija, "Vitamin E and Essential Polyunsaturated Fatty Acids Supplementation in Schizophrenia Patients Treated with Haloperidol." Nutritional Neuroscience, July 24, 2014. doi:10.1179/1476830514Y.0000000139.

- *"Discussion Our study indicates that supplementation with vitamin E and EPUFAs may improve the antioxidative defense, especially glutathione system, while there is no major effect on symptoms severity. Supplemental treatment with EPUFAs and vitamin E in schizophrenia patients treated with haloperidol is potentially beneficial and a larger independent study appears warranted."*

Vitamins and Beta-carotene

Vitamin E, Vitamin C, and Beta Carotene May Prevent Oxidative Injury and Deterioration Associated with Schizophrenia

D'Souza, Benedicta, "Oxidative Injury and Antioxidant Vitamins E and C in Schizophrenia." Indian Journal of Clinical Biochemistry: IJCB 18, no. 1 (January 2003): 87–90. doi:10.1007/BF02867671.

- *"Impaired antioxidant defense and increased lipid peroxidation suggests that treatment with antioxidants (Vitamin E, Vitamin C, beta carotene) at the initial stages of illness may prevent further oxidative injury and deterioration of associated neurological deficits in Schizophrenia."*

Citicoline and Galantamine

Citicoline and Galantamine Combined Showed a Reduction in Positive and Negative Symptoms

Deutsch, Stephen I., "First Administration of Cytidine Diphosphocholine and Galantamine in Schizophrenia: A Sustained alpha7 Nicotinic Agonist Strategy." Clinical Neuropharmacology 31, no. 1 (February 2008): 34–39. doi:10.1097/wnf.0b013e31806462ba.

- *"The combination of CDP-choline and galantamine was administered to 6 schizophrenic patients with residual symptoms in a 12-week, open-label trial. Patients were maintained*

on stable dose regimens of antipsychotic medications for 4 weeks before study entry and for the trial duration. All reached target doses of both agents and completed the trial. Transient side effects resolved without slowing of dose titration. Gastrointestinal adverse effects were most common. Of the 6 patients, 5 showed reduction in Clinical Global Impressions severity scores and Positive and Negative Syndrome Scale total scores. Three patients requested continuation of the adjunctive combination at the end of the trial. These results suggest further investigation of the combination of CDP-choline and galantamine as an alpha7 nAChR agonist intervention."

Enterosorption and Antioxidants

Entersorption and Antioxidants Has a Significant Effect on a Majority of Schizophrenics Tested

Rachkauskas, G. S. "[The efficacy of enterosorption and a combination of antioxidants in schizophrenics]." Likars'ka Sprava / Ministerstvo Okhorony Zdorov'ia Ukraïny, no. 4 (June 1998): 122–24.

- *"A total of 143 patients with schizophrenia, who ranged from 28 to 42 years old, were studied. Of these, 68 patients were running a continuously progredient course, 75 were in the phase of exacerbation of the attack-like progredient course of schizophrenia. Group I (n = 76) of patients received the enterosorbent polysorb and a complex of antioxidants (tocoferolum acetatum, ascorbic acid, quercetin) as a supplement to the conventional therapy, group II (n = 67) was placed on the conventional therapy only. A complex of the antioxidants as well as the enterosorbent had a positive effect on the clinical course of the condition in 63.2% of group I patients who managed, among other therapeutic benefits, to achieve a stable remission. They have also demonstrated a concomitant improvement or normalization of indices for lipid peroxidation."*

Blood Detoxification Treatments

Dialysis

Dialysis Treatment is Effective for Schizophrenia

Splendiani, G., "Dialysis Treatment in Schizophrenia: Two Years Experience." Artificial Organs 5, no. 2 (May 1981): 175–77.

- *"The authors summarize two years trial of dialysis treatment of schizophrenia. Twenty-five schizophrenic patients were treated with hemodialysis using PAN membranes. The dialysis schedule was: dialyzer; RP 610; blood flow: 250 ml/min; dialysate flow: 500 ml/min; time: 3 hr; vascular access: arteriovenous fistula, femoral vein, antebrachial veins. Dialysis was first performed for three days, repeated after one week, two weeks,*

three weeks, and one month, and then performed once a month. The drug regimen was never modified or interrupted. The results were evaluated with the Overall and Lorr scale. Nine patients interrupted the treatment early and were not considered; nine patients showed disappearance of psychiatric symptomatology (Overall and Lorr index decreased to 21.8 at 2); non-significant modifications of the main schizophrenic symptoms were observed in seven patients. According to our trial, dialysis with polyacrylonitrile membranes can modify the psychotic attitude in a group of schizophrenic "dialysis responders".

Dialysis is Effective for Treatment of Schizophrenia

Splendiani, G., "Five-Year Trial of Dialytic Treatment for Schizophrenia." Artificial Organs 7, no. 3 (August 1983): 322–25.

- *"Thirty schizophrenic patients were treated with hemodialysis for 4-36 months. The clinical results were evaluated using two psychiatric scales: the Brief Psychiatric Rating Scale and the Inpatient Multidimensional Psychiatric Scale. In 13 schizophrenic patients psychiatric symptoms disappeared completely, and complete social reintegration followed. Eight patients showed no significant modification of schizophrenic disease after more than 30 dialysis sessions. Nine patients were not considered because their treatment was interrupted during the first month. Dialysis improved the psychotic attitude in one group of schizophrenic patients. The best results were obtained using polyacrylonitrile membranes."*

Hemodialysis Puts Auditory Hallucinations in Remission

Malek-Ahmadi, P., "Effect of Hemodialysis on Hallucinations." Southern Medical Journal 73, no. 4 (April 1980): 520–21.

- *"A patient with chronic schizophrenia had two hemodialyses and two sham dialyses in a single-blind design. There was no change in the patient's affect after either procedure, but her auditory hallucinations disappeared after both hemodialysis and sham dialysis, with hemodialysis inducing a much longer partial remission."*

Dialysis May Be Effective for Treatment of Schizophrenia

Fogelson, D. L., "Dialysis for Schizophrenia: Review of Clinical Trials and Implications for Further Research." The American Journal of Psychiatry 137, no. 5 (May 1980): 605–7.

- *"At least 67 schizophrenic patients have undergone dialysis for renal failure, without improvement in schizophrenic symptoms. Ninety-two nonuremic schizophrenic patients*

have received dialysis in nonblind studies; 22 improved, 21 improved partially, 47 showed no change, and 2 became worse. The authors point out factors other than dialysis that may affect outcome, including family respones and reduction in drug dose. They believe that until the results of current double-blind, sham-controlled trials are known, dialysis should not be prescribed as a treatment for schizophrenia."

Hemodialysis Improves Schizophrenic Symptoms

Malek-Ahmadi, P., "Hemodialysis and Schizophrenia: A Double-Blind Study." Southern Medical Journal 73, no. 7 (July 1980): 873–74.

- *"Partial or total remission of schizophrenic symptoms after exchange transfusion or hemodialysis have been reported in the literature. Although the results of these reports are encouraging, they have not been confirmed by controlled studies. We have conducted a double-blind placebo-controlled study to evaluate the effect of hemodialysis on chronic schizophrenia. Our data seem to indicate that some schizophrenic symptoms improve after hemodialyses."*

Dialysis Pretreatment Improved Depression and Anxiety in Schizophrenic Patients

Scheiber, S. C., "Dialysis for Schizophrenia: An Uncontrolled Study of 11 Patients." The American Journal of Psychiatry 138, no. 5 (May 1981): 662–65.

- *"The authors evaluated hemodialysis as a treatment for schizophrenia in an uncontrolled study of 11 patients. Eight men and two women with chronic schizophrenia who had responded poorly to conventional treatments or who had sought alternate treatments received three dialyses weekly for 3 weeks; 1 additional subject dropped out after eight treatments. MMPI, Psychiatric Status Scale, and Inpatient Multidimensional Psychiatric Scale scores were obtained before, immediately following, and at intervals after the nine treatments. Preliminary results, including 1-month follow-up, suggest that subjects with pretreatment anxiety and depression improved. No endorphins were discovered in the dialysate."*

Haemodialysis Removes Some Endogenous Dialysable Substance in the Pathogenesis of Mood Disturbances in Schizophrenia

Vanherweghem, J. L., . "Haemodialysis in Schizophrenia: A Double Blind Study - Preliminary Report." Proceedings of the European Dialysis and Transplant Association. European Dialysis and Transplant Association 16 (1979): 148–54.

- *"Nine of the 12 patients were improved by both extracorporeal procedures with or without active dialysis. No significant difference appeared however between both groups in the rate and degree of improvement of nuclear symptoms of schizophrenia.*

Nevertheless, AD was significantly more efficient in relieving affective symptomatology, suggesting the potential involvement of some endogenous dialysable substance (s) in the pathogenesis of mood disturbances in schizophrenia."

Blood Detoxification

Blood Detoxification Treatment in Schizophrenia Proves to Be Therapeutic

Nedopil, N., "Detoxification Treatment for Chronic Schizophrenic Patients: Experimental Results and Data from a Survey." Artificial Organs 7, no. 3 (August 1983): 304–9.

- *"Blood detoxification as a treatment of schizophrenia has been studied intensively since 1977 by a number of research centers. Results of an open study on 10 chronic schizophrenic patients--two showing improvement--were less favorable than those reported in the initial publications. In order to possibly identify a subgroup of responders to this treatment, a survey was undertaken in which 95 centers were invited to participate. Of the 95 centers which originally treated schizophrenic patients with detoxification and which were asked to send data on these patients to the Registry of the European Dialysis and Transplant Association, 39 centers replied (35 from Europe and four from the United States). From the 100 patients reported on in Europe, 17 were reported to be very much improved and 22 to be improved. Of the patients from the United States, 86% were reported as improved. No subgroup of responders could be identified, and differences between centers concerning nosological subgroups, treatment methods, and results were so great that no real comparison was possible. Although data from this survey are not totally conclusive, in connection with the updated literature they do not encourage further research in this treatment of schizophrenia."*

Hallucination Reduction Treatments

Continuous Positive Air Pressure (CPAP)

CPAP led to Complete Remission of Hallucinations in Schizophrenic Patient

Karanti, Alina, "Treatment Refractory Psychosis Remitted upon Treatment with Continuous Positive Airway Pressure: A Case Report." Psychopharmacology Bulletin 40, no. 1 (2007): 113–17.

- *"A 63-year-old women previously diagnosed with hebephrenic schizophrenia developed treatment resistant auditory hallucinations along with extreme daytime fatigue and obesity. She was eventually diagnosed with Pickwickian syndrome or OHS and received treatment with continuous positive airway pressure (CPAP). Restoring the patient's*

alveolar hypoventilation with nocturnal CPAP led to the complete remission of hallucinations."

CPAP Treatment of Obstructive Sleep Apnea Should Be More Highly Acknowledged in Clinical Psychiatry

Hiraoka, Toshiaki, "[Treatment of psychiatric symptoms in schizophrenia spectrum disorders with comorbid sleep apnea syndrome: a case report]." Seishin Shinkeigaku Zasshi = Psychiatria Et Neurologia Japonica 115, no. 2 (2013): 139–46.

- *"Sleep apnea syndrome (SAS) is characterized by apnea and hypopnea during sleep. SAS manifests various symptoms, and can become a risk factor for a variety of diseases. Typical psychiatric presentations of SAS are depressive symptoms, and those resembling negative symptoms in schizophrenia. We report two patients with schizophrenia spectrum disorders. Both patients showed the partial improvement of psychiatric symptoms with pharmacotherapy. After diagnosing comorbid SAS and subsequent treatment with continuous positive airway pressure (CPAP), the psychiatric symptoms improved. The first case was a 54-year-old woman, who presented with auditory hallucinations and delusions and was diagnosed with schizophrenia at 32 years of age. Her positive symptoms responded immediately to medication; however, her negative symptoms persisted despite switching to atypical antipsychotics. We diagnosed her with SAS using pulse oximetry and portable polysomnography (PSG), and, after treatment with CPAP, her fatigue and shallow sleep improved, as well as her quality of life (QOL). The second case was is a 61-year-old man, who presented with delusions of persecution and was diagnosed with delusional disorder at 49 years of age. His delusional symptoms fluctuated under medication, and repeatedly worsened under stressful situations. We suspected SAS as a Complicating factor, and diagnosed him with severe SAS using PSG. After treatment with CPAP, his hypertension and delusions of persecution improved. Screening for SAS is available in psychiatric hospitals and outpatient clinics. We believe that the possibility of comorbid SAS in psychiatric patients should be more widely acknowledged in clinical psychiatry."*

CPAP can be Effective for Negative Symptoms and Remission of Auditory Hallucination in Schizophrenia

Sugishita K. Continuous positive airway pressure for obstructive sleep apnea improved negative symptoms in patient with schizophrenia. Psychiatry and Clinical Neurosciences 2010;64:663-667

- *"The present case report is in line with previous reports, including a patient with delusional schizophrenia showing improvement of negative symptoms and a case of hebephrenic schizophrenia showing complete remission of auditory hallucinations after successful treatments of OSA with CPAP."*

Oxygen Treatment of Behavioral Problems

Hypobaric Oxygen Inhalation Reduces All Symptoms Relative to Mood and Attitude Significantly

Fraiberg, P. L. "Oxygen Inhalation in the Control of Psychogeriatric Symptoms in Patients with Long-Term Illness." Journal of the American Geriatrics Society 21, no. 7 (July 1973): 321–24.

- *"In general, the results of our study on the use of hypobaric oxygen inhalation upheld our impression of its usefulness in the treatment of behaviorally disturbed elderly patients. All of the psychogeriatric symptoms relative to mood and attitude were improved to a statistically significant degree. Usually the symptoms which were both severe and predominant showed the most improvement. These included nervous tension, withdrawal-apathy, restlessness, and confused states. There was a steady improvement throughout the treatment period. When treatment was discontinued, regression followed rapidly. In some instances the improvement in cognition was marked enough to arouse comment from the staff. No complications arising from the treatment were observed. Hypobaric oxygen therapy, although no panacea, is a useful procedure in the management of difficult geriatric behavioral problems."*

Oxygen-enriched Air Inhalation has a Significant Improvement on Schizophrenia Patients Symptoms

Bloch, Yehudit, "Normobaric Hyperoxia Treatment of Schizophrenia." Journal of Clinical Psychopharmacology 32, no. 4 (August 2012): 525–30. doi:10.1097/JCP.0b013e31825d70b8.

- *"There was significant improvement in total Positive and Negative Symptoms Scale score of patients who received oxygen compared with the control group. There were positive effects of oxygen on memory and attention in neuropsychological performance tests. The effect size is small despite the statistical significance, but the patient group was extremely chronic and severely impaired. These results are a proof of concept, and normobaric hyperoxia should be studied in patients with milder forms of the illness and earlier in the course of illness."*

Hyperbaric Oxygen is Effective in Schizophrenic Patients Resistant to Pharmacotherapy Treatment

Kutko II. The use of hyperbaric oxygenation in treating mental patients resistant to psychopharmacotherapy. Zh Nervol Psikhaitr Im S S Korsakova 1996;96(5):47-51

- *"A positive clinical effect was marked in 72.5% of cases (in 67.4% of schizophrenic patients and in 77.4% of patients with vascular disease)."*

Isakov IuV. Clinical effectiveness of hyperbaric oxygenation in the combined treatment of patients with schizophrenia. Zh Nevropatol Psikhiatr Im S S Korsakova 1987;87(12):1832-5

- *"The maximum therapeutic effect was observed after 10-12 sessions"*

Stellate Ganglion Block Technique

Stellate Ganglion Block Technique Reduced the Severity and Frequency of Hallucinations in Schizophrenic Patient

Takano, Manami, "Unexpected Beneficial Effect of Stellate Ganglion Block in a Schizophrenic Patient." Canadian Journal of Anaesthesia = Journal Canadien D'anesthésie 49, no. 7 (September 2002): 758–59. doi:10.1007/BF03017464.

- *"Stellate ganglion block (SGB) is a technique widely used for treating chronic pain in the upper extremities, head, face and neck. Here we report a schizophrenic patient who presented with neck-shoulder pain in whom repeated SGB reduced the severity and frequency of hallucination as well as pain. The patient was a right-handed 37-yr-old man. At the age of 36 yr, he fell from a horse and developed intractable pain around the neck and left shoulder. After unsuccessful conventional therapies, a course of weekly left SGB was commenced. Before beginning SGB, the patient often felt that a third person was watching his work and criticizing him. After the first SGB, the third person in his mind became puzzled and less confident. One month later, he felt less noise, and auditory hallucinations changed from mandatory to recommendatory. With discontinuation of SGB, hallucinations worsened. During this period, no anti-psychotic medications were administered. The psychiatrist confirmed the diagnosis of schizophrenia, DSM-IV code 295.3. The Brief Psychiatric Rating Scale (BRPS), which assesses 18 objective and subjective symptoms through interview by a psychiatrist, was evaluated ten days after the last SGB. The BPRS score (min 18 - max 196) was 19, indicating the patient's mental state at this time was close to normal. Telaranta1 showed that pathognomonic symptoms of social phobia are alleviated by endoscopic thoracic sympathectomy. Comparable effects would be expected from SGB which blocks sympathetic efferents originating from the thoracic spinal cord. SGB is known to increase cerebral blood flow on the injected side.2 Modified blood flow to the cerebrum may have affected schizophrenia-related symptoms.3 The relaxing effect of SGB may have been additive. We were impressed with this unexpected, beneficial effect of SGB on psychiatric symptoms and suggest that more research in this direction may be warranted."*

Insomnia Treatments

Salt of Gamma Hydroxbutyric Acid (GHB)

Sodium Salt of Gamma Hydroxbutyric Acid (GHB) Has Demonstrated Improvement in Objective Sleep Measures

Kantrowitz, Joshua T., "The Importance of a Good Night's Sleep: An Open-Label Trial of the Sodium Salt of Gamma-Hydroxybutyric Acid in Insomnia Associated with Schizophrenia." Schizophrenia Research 120, no. 1–3 (July 2010): 225–26. doi:10.1016/j.schres.2010.03.035.

- *"Although limited by an open-label design and small sample size, we demonstrate convergent improvement in subjective sleep, daytime sleepiness and objective sleep measures. More broadly, we found an interrelationship between negative symptoms and measures of sleep. We are only aware of two previous trials specifically evaluating sleep in schizophrenia (Luthringer et al., 2007; Muller et al., 2004), neither of which reported an interrelationship with negative symptoms. Present findings suggest that SBX may improve objective sleep architecture and moreover, improvement in sleep may lead to downstream improvement in symptoms and function. Future double blind studies incorporating both symptoms and sleep-related cognitive measures appear warranted."*

Acupuncture

Acupuncture is Effective on Insomnia and Psychopathology in Schizophrenia

Reshef, Alon, "The Effects of Acupuncture Treatment on Sleep Quality and on Emotional Measures among Individuals Living with Schizophrenia: A Pilot Study." Sleep Disorders 2013 (2013): 327820. doi:10.1155/2013/327820.

- *"Overall, the findings of this pilot study suggest that acupuncture has beneficial effects as a treatment for insomnia and psychopathology symptoms among patients with schizophrenia."*

Melatonin

Melatonin is a Useful Short-term Hypnotic for Schizophrenic Patients

Suresh Kumar, P. N., "Melatonin in Schizophrenic Outpatients with Insomnia: A Double-Blind, Placebo-Controlled Study." The Journal of Clinical Psychiatry 68, no. 2 (February 2007): 237–41.

- *"Melatonin may be a useful short-term hypnotic for schizophrenic patients with insomnia. Melatonin could be considered for patients in whom conventional hypnotic drug therapy or higher sedative antipsychotic drug doses may be problematic."*

Melatonin Improves Sleep Efficiency in Patients with Schizophrenia

Shamir, E., "Melatonin Improves Sleep Quality of Patients with Chronic Schizophrenia." The Journal of Clinical Psychiatry 61, no. 5 (May 2000): 373–77.

- *"Melatonin improves sleep efficiency in patients with schizophrenia whose sleep quality is low."*

Melatonin Significantly Improves Nighttime Sleep in Schizophrenia

Suresh Kumar PN. Melatonin in schizophrenic outpatients with insomnia: a double-blind, placebo-controlled study. J Clin Psychiatry 2007 Feb;88(2):237-41

- *"The modal stable dose of melatonin was 3mg. Relative to placebo, melatonin significantly improved the quality and depth of sleep of nighttime sleep, reduced the number of nighttime awaking's, and increased the duration of sleep without producing a morning hangover. Subjectively, melatonin also reduced sleep-onset latency, heightened freshness on awaking, improved mood, and improved daytime functioning."*

Music Relaxation

Music Relaxation is Beneficial for Insomnia and Anxiety in People with Schizophrenia

Bloch, Boaz, "The Effects of Music Relaxation on Sleep Quality and Emotional Measures in People Living with Schizophrenia." Journal of Music Therapy 47, no. 1 (2010): 27–52.

- *"Results showed an improvement in sleep latency and sleep efficiency after the music relaxation was played. Likewise, music relaxation was shown to improve participants' total psychopathology score (PANSS) as well as their level of depression. Moreover, a significant correlation was found between reduction in level of situational anxiety and improvement in sleep efficiency. The findings suggest the beneficial effect of music relaxation as a treatment both for insomnia and for emotional measures in people living with schizophrenia."*

Mismatch Negativity Treatments

N-acetylcysteine

N-acetylcysteine Improves Mismatch Negativity

Lavoie S. Glutathione precursor, N-Acetyl-Cysteine, Improves mismatch negativity in schizophrenic patients. Neuropsychopharmacology, 2008, 33, 2187-2199

- *"MMN improvement was observed in the absence of robust changes in assessments of clinical severity, thought the latter was observed in larger and more prolonged clinical study"*

Glycine

High-dose Glycine Attenuates Mismatch Negativity

Leung, Sumie, "Acute High-Dose Glycine Attenuates Mismatch Negativity (MMN) in Healthy Human Controls." Psychopharmacology 196, no. 3 (February 2008): 451–60. doi:10.1007/s00213-007-0976-8.

- *"These findings suggest that an acute high dosage of glycine attenuates MMN in healthy controls, raising the possibility that optimal effects of glycine and other glycine agonists may depend on the integrity of the NMDA receptor system."*

PrePulse Inhibition Treatments

Leptin

Leptin Significantly Increases Prepulse Inhibition and Has Antipsychotic Properties

Dashti, Somayeh, "The Effect of Leptin on Prepulse Inhibition in a Developmental Model of Schizophrenia." Neuroscience Letters 555 (October 25, 2013): 57–61. doi:10.1016/j.neulet.2013.09.027.

- *"In conclusion, our results reveal that leptin significantly increases PPI in socially-isolated rats. The findings of this study suggest possible antipsychotic properties for leptin. We suggest further studies on the possible disruption of leptin signaling in schizophrenia, and also the possible interaction of leptin with therapeutic effects of second generation antipsychotics."*

Kami-ondam-tang

Kami-ondam-tang Attenuates MK-801-induced Pre Pulse Inhibition Disruption

Oh, Hee Kyong, "Kami-Ondam-Tang, a Traditional Herbal Prescription, Attenuates the Prepulse Inhibition Deficits and Cognitive Impairments Induced by MK-801 in Mice." Journal of Ethnopharmacology 146, no. 2 (March 27, 2013): 600–607. doi:10.1016/j.jep.2013.01.032.

- *"These findings suggest that KODT attenuates MK-801-induced PPI disruption, social interaction deficits, and cognitive impairments, possibly, by regulating of cortical Akt and ERK signaling."*

Sulforaphane

Sulforaphane Has Antipsychotic Activity in Animal Model of Schizophrenia

Shirai, Yumi, "Effects of the Antioxidant Sulforaphane on Hyperlocomotion and Prepulse Inhibition Deficits in Mice after Phencyclidine Administration." Clinical Psychopharmacology and Neuroscience: The Official Scientific Journal of the Korean College of Neuropsychopharmacology 10, no. 2 (August 2012): 94–98. doi:10.9758/cpn.2012.10.2.94.

- *"These results suggest that SFN has antipsychotic activity in an animal model of schizophrenia. Therefore, it is likely that SFN may be a potential therapeutic drug for schizophrenia."*

CDP-Choline

CDP-Choline Attenuates Scopolamine Induced Disruption of Prepulse Inhibition

Uslu, Gulsah, "CDP-Choline Attenuates Scopolamine Induced Disruption of Prepulse Inhibition in Rats: Involvement of Central Nicotinic Mechanism." Neuroscience Letters 569 (May 21, 2014): 153–57. doi:10.1016/j.neulet.2014.03.070.

- *"These results demonstrate that exogenous administration of CDP-choline attenuates scopolamine induced PPI disruption and show that the activation of central α7-nAChR may play a critical role in this effect."*

Substance Abuse Treatments

Oxytocin

Oxytocin May Be a Treatment for Alcoholism in Schizophrenia

Pedersen, Cort A. "Schizophrenia and Alcohol Dependence: Diverse Clinical Effects of Oxytocin and Their Evolutionary Origins." Brain Research 1580 (September 11, 2014): 102–23. doi:10.1016/j.brainres.2014.01.050.

- *"In the ways discussed above, recent discoveries of clinical efficacy of OT in schizophrenia and alcohol withdrawal may provide new insights into OT mechanisms which may have been selected for during the evolution of placental mammals to facilitate maternal-infant and other social attachments."*

D-serine, Sarcosine, and Glycine

D-serine, Sarcosine, and Glycine May Work to Treat Substance Abuse in Schizophrenic Patients

Coyle, Joseph T. "Substance Use Disorders and Schizophrenia: A Question of Shared Glutamatergic Mechanisms." Neurotoxicity Research 10, no. 3–4 (December 2006): 221–33.

- *"Schizophrenia is noted for the remarkably high prevalence of substance use disorders (SUDs) including nicotine (>85%), alcohol and stimulants. Mounting evidence supports the hypothesis that the endophenotype of schizophrenia involves hypofunction of a subpopulation of cortico-limbic NMDA receptors. Low doses of NMDA receptor antagonists such as ketamine replicate in normal volunteers positive, negative and cognitive symptoms of schizophrenia as well as associated physiologic abnormalities such as eye tracking and abnormal event related potentials. Genetic studies have identified putative risk genes that directly or indirectly affect NMDA receptors including D-amino acid oxidase, its modulator G72, proline oxidase, mGluR3 and neuregulin. Clinical trials have shown that agents that directly or indirectly enhance the function of the NMDA receptor at its glycine modulatory site (GMS) reduce negative symptoms and in the case of D-serine and sarcosine improve cognition and reduce positive symptoms in schizophrenic subjects receiving concurrent anti-psychotic medications. Notably, the GMS partial agonist D-cycloserine exacerbates negative symptoms in clozapine responders whereas full agonists, glycine and D-serine have no effects, suggesting clozapine may act indirectly as a full agonist at the GMS of the NMDA receptor. Clozapine treatment is uniquely associated with decreased substance use in patients with schizophrenia, even without psychologic intervention. Given the role of NMDA receptors in the reward circuitry and in substance dependence, it is reasonable to speculate that NMDA receptor dysfunction is a shared pathologic process in schizophrenia and co-morbid SUDs"*

Preventive Treatments

Antioxidants

Use of Antioxidants Before Psychosis Onset May Dramatically Improve Outcome of Illness

Mahadik, S. P., "Oxidative Stress and Role of Antioxidant and Omega-3 Essential Fatty Acid Supplementation in Schizophrenia." Progress in Neuro-Psychopharmacology & Biological Psychiatry 25, no. 3 (April 2001): 463–93.

- *"Since the oxidative stress exists at or before the onset of psychosis the use of antioxidants from the very onset of psychosis may reduce the oxidative injury and dramatically improve the outcome of illness."*

Breast Feeding

Breast Feeding May Postpone the Onset of Schizophrenic Illness

Amore, M., "Can Breast-Feeding Protect against Schizophrenia? Case-Control Study." Biology of the Neonate 83, no. 2 (2003): 97–101. doi:67960.

- *"Breast-feeding is no less common in those who develop schizophrenia in later life. However, breast milk might postpone the onset of the illness in schizophrenic patients."*

D-serine

D-serine May Prevent the Onset of Psychosis in Adults

Hagiwara, Hiroko, "Neonatal Disruption of Serine Racemase Causes Schizophrenia-like Behavioral Abnormalities in Adulthood: Clinical Rescue by D-serine." PloS One 8, no. 4 (2013): e62438. doi:10.1371/journal.pone.0062438.

- *"This study shows that disruption of D-serine synthesis during developmental stages leads to behavioral abnormalities relevant to prodromal symptoms and schizophrenia, in later life. Furthermore, early pharmacological intervention with D-serine may prevent the onset of psychosis in adult."*

Glycine

Glycine Treatment of Prodromal Symptoms No Patients Converted to Psychosis

Woods S.W.. Glycine treatment of prodromal symptoms. Schizophrenia Res Vol. 86 Suppl 2006 pp S7

- *"Of seven completers, three met early remission criteria during the 8 weeks on glycine. No patients converted to psychosis. In MMRM analyses, patients improved significantly from baseline on SOPS total (-18.2+-9.9, p<0.001) and on positive symptom, disorganization, and general symptom subscales. Negative symptoms improved only at the trend level."*

Long-Chain Polyunsaturated Fatty Acid

Perinatal Long-Chain Polyunsaturated Fatty Acid Supplementation May Prevent Schizophrenia in Adulthood

Das, Undurti N. "Can Perinatal Supplementation of Long-Chain Polyunsaturated Fatty Acids Prevents Schizophrenia in Adult Life?" Medical Science Monitor: International Medical Journal of Experimental and Clinical Research 10, no. 12 (December 2004): HY33–37.

- *"It is suggested that perinatal supplementation of long-chain polyunsaturated fatty acids (LCPUFAs) especially; eicosapentaenoic and docosahexaenoic acids prevent schizophrenia in the adult. I propose that schizophrenia could be a low-grade systemic inflammatory disease with its origins in the perinatal period, probably triggered by maternal infection in a genetically susceptible individual that leads to excess production of pro-inflammatory cytokines both in the mother and the fetus. These cytokines, in turn, induce damage to the fetal neurons leading to the adult onset of schizophrenia. I suggest that maternal infection perse interferes with the metabolism of essential fatty acids (EFAs) resulting in deficiency of LCPUFAs that are known to have neuroprotective action. Alternatively, decreased formation of LCPUFAs as a result of decreased activity of D6 and D5 desaturases (due to prematurity) can result in neuronal damage due to the absence/decrease in the neuroprotective LCPUFAs. This is supported by the observation that LCPUFAs suppress the production of pro-inflammatory cytokines, have anti-inflammatory and neuroprotective actions. Furthermore, LCPUFAs are essential for brain growth and development. If this hypothesis is true, it implies that perinatal supplementation of appropriate amounts of LCPUFAs in the right combination is helpful in the prevention of schizophrenia in adult life."*

N-acetylcysteine

N-acetylcysteine May Prevent Oxidative Damage from Early Life Environmental Insults

Cabungcal, Jan-Harry, "Early-Life Insults Impair Parvalbumin Interneurons via Oxidative Stress: Reversal by N-Acetylcysteine." Biological Psychiatry 73, no. 6 (March 15, 2013): 574–82. doi:10.1016/j.biopsych.2012.09.020.

- *"In Gclm KO mice, early-life insults inducing oxidative stress are detrimental to immature parvalbumin interneurons and have long-term consequences. In analogy, individuals carrying genetic risks to redox dysregulation would be potentially vulnerable to early-life environmental insults, during the maturation of parvalbumin interneurons. Our data support the need to develop novel therapeutic approaches based on antioxidant and redox regulator compounds such as N-acetylcysteine, which could be used preventively in young at-risk subjects."*

N-acetylcysteine is a useful Medication to Prevent Conversion to Schizophrenia in at Risk Individuals

Asevedo E. N-acetylcsteine as a potentially useful medication to prevent conversion to schizophrenia in at-risk individuals. Rev Neurosci 2012;23(4):353-62

- *"In this article, we purpose that NAC could be a useful medication to prevent evolution of schizophrenia in individuals at risk for psychosis."*

Omega-3 Fatty Acids

Omega-3 Fatty Acids May Help Prevent Most Psychotic Episodes

Saugstad, Letten F. "Are Neurodegenerative Disorder and Psychotic Manifestations Avoidable Brain Dysfunctions with Adequate Dietary Omega-3?" Nutrition and Health 18, no. 2 (2006): 89–101.

- *The olfactory agnosia observed in schizophrenia supports an N-3 deficit as does a reduction of key ologodendrocyte- and myelin-related genes in this disorder and affective disorder, where a rise in dementia accords with a deficit of N-3 also in this disorder. N-3 normalizes cerebral excitability at all levels. That the two disorders are localized at the extremes of excitability is supported by their opposing treatments: convulsant neuroleptics and anti-epileptic anti-depressants. An adequate N-3 diet will probably prevent most psychotic episodes and prove that neurodegenerative disorder with dementia is also to a large extent not only preventable but avoidable.*

Omega-3 Fatty Acids May Be Used in the Prevention of Psychotic Episodes

Mossaheb, Nilufar, "Polyunsaturated Fatty Acids in Emerging Psychosis." Current Pharmaceutical Design 18, no. 4 (2012): 576–91.

- *"Furthermore, we examine the available evidence in indicated prevention in emerging psychosis, monotherapy, add-on therapy and tolerability. The neuroprotective potential of n-3 LC-PUFAs for indicated prevention, i.e. delaying transition to psychosis in high-risk populations needs to be further explored."*

Omega-3's May Reduce the Risk of Progression to Psychotic Disorder and May Prevent Subthreshold Psychotic States

Amminger, G. Paul, "Long-Chain Omega-3 Fatty Acids for Indicated Prevention of Psychotic Disorders: A Randomized, Placebo-Controlled Trial." Archives of General Psychiatry 67, no. 2 (February 2010): 146–54. doi:10.1001/archgenpsychiatry.2009.192.

- *"Long-chain omega-3 PUFAs reduce the risk of progression to psychotic disorder and may offer a safe and efficacious strategy for indicated prevention in young people with subthreshold psychotic states."*

Omega-3 Fatty Acids Reduce the Risk of Progression to Psychosis

Amminger GP. Long-chain Omega-3 Fatty Acids for indicated prevention of psychotic disorders: A randomized, placebo-controlled trial. Arch Gen Psychiatry Vol 67 (No. 2) Feb 2010

- "*Long-chain Omega-3 PUFAs reduce the risk of progression to psychotic disorder and may offer a safe and efficacious strategy for indicated prevention in young people with subthreshshold psychotic states."*

Prenatal Vitamin D, Folic Acid and Iron

Adequate Prenatal Vitamin D, Folic Acid and Iron May Prevent Schizophrenia in Adulthood

McGrath, John,"Prevention and Schizophrenia--the Role of Dietary Factors." Schizophrenia Bulletin 37, no. 2 (March 2011): 272–83. doi:10.1093/schbul/sbq121.

- *"Adequate prenatal nutrition is essential for optimal brain development. There is a growing body of evidence from epidemiology linking exposure to nutritional deprivation and increased risk of schizophrenia. Based on studies from the Netherlands and China, those exposed to macronutrient deficiencies during famine have an increased risk of schizophrenia. With respect to micronutrients, we focus on 3 candidates where there is biological plausibility for a role in this disorder and at least 1 study of an association with schizophrenia. These nutrients include vitamin D, folic acid, and iron. While the current evidence is incomplete, we discuss the potential implications of these findings for the prevention of schizophrenia. We argue that schizophrenia can draw inspiration from public health interventions related to prenatal nutrition and other outcomes and speculate on relevant factors that bear on the nature, risks, impact, and logistics of various nutritional strategies that may be employed to prevent this disorder."*

Bipolar Disorder Treatments

Dietary Changes

Dietary Tryptophan

Dietary Tryptophan Depletion as Treatment for Acute Mania

Applebaum J. Rapid tryptophan depletion as a treatment for acute mania: a double blind, pilot-controlled study. Bipolar Disord 2007 Dec;9(8):884-7

- *"Rapid tryptophan depletion may have an antimanic effect."*

Fasting

Fasting during Ramadan has a Significant Decrease on Depression and Mania Rating Scales in Bipolar Patients on Lithium

Farooq, Saeed, "Effect of Fasting during Ramadan on Serum Lithium Level and Mental State in Bipolar Affective Disorder." International Clinical Psychopharmacology 25, no. 6 (November 2010): 323–27. doi:10.1097/YIC.0b013e32833d18b2.

- *"The scores on HDRS and YMRS showed significant decrease during Ramadan (F=34.12, P=0.00, for HDRS and F=15.6, P=0.000 for YMRS). The side effects and toxicity also did not differ significantly at three points. In conclusion, the patients who have stable mental state and lithium levels before Ramadan can be maintained on lithium during Ramadan. Fasting in an average temperature of 28°C for up to 12 h per day did not result in elevated serum lithium levels or more side effects and did not have adverse effects on mental state of patients suffering from bipolar affective disorder."*

Inositol Deficiency Diet

Inositol Deficiency Diet had Major Effect on Reducing the Effect of Affective Disorder in Bipolar Patients

Shaldubina, Alona, "Inositol Deficiency Diet and Lithium Effects." Bipolar Disorders 8, no. 2 (April 2006): 152–59. doi:10.1111/j.1399-5618.2006.00290.x.

- *"Dietary inositol restriction significantly augmented the inositol-reducing effect of Li in rat frontal cortex. Li reduced inositol levels by 4.7%, inositol-deficient diet by 5.1%, and Li plus inositol-deficient diet by 10.8%. However, feeding with the inositol-deficient diet did not enhance the behavioral effect of Li in the Li-pilocarpine seizure model. Fifteen patients participated in an open clinical study of the inositol-deficient diet: six rapid cycling bipolar patients responding inadequately to Li or valproate in different phases of illness; two Li-treated bipolar outpatients with residual symptomatology, and seven inpatient Li-treated bipolar patients in non-responding acute mania. The diet had a major effect in reducing the severity of affective disorder in 10 of the patients within the first 7-14 days of treatment. These results suggest that dietary inositol restriction may be useful in some bipolar patients, but controlled replication is necessary."*

Ketogenic Diet

Ketogenic Diet May Have Mood Stabilizing Properties

Phelps JR. The ketogenic diet for type II bipolar disorder. Neurocase 2012 Oct 3

- *"Two woman with type II bipolar disorder were able to maintain ketosis for prolonged periods of time (2 and 3 years, respectively). Both experienced mood stabilization that exceeded that achieved with medication; experienced a significant subjective improvement that was directly related to ketosis and tolerated diet well. There was no significant adverse effects in either case. These cases demonstrate that the ketogenic diet is potentially sustainable option for mood stabilization in type II bipolar illness."*

Ketogenic Diet has Antidepressant Properties

Murphy P. The antidepressant properties of the ketogenic diet. Biol Psychiatry 2004 Dec 15:56(12):981-3

- *"The rats on the ketogenic diet spent less time immobile, suggesting that the rats on a ketogenic diet, like rats treated with antidepressants are less likely to exhibit "behavioral despair". It is concluded that the ketogenic diet has antidepressant properties."*

The Ketogenic Diet May Have Mood Stabilizing Properties in Mood Disorders

El-Mallakh, R. S., "The Ketogenic Diet May Have Mood-Stabilizing Properties." Medical Hypotheses 57, no. 6 (December 2001): 724–26. doi:10.1054/mehy.2001.1446.

- *"The ketogenic diet, originally introduced in the 1920s, has been undergoing a recent resurgence as an adjunctive treatment for refractory epilepsy, particularly in children. In this difficult-to-treat population, the diet exhibits remarkable efficacy with two-thirds showing significant reduction in seizure frequency and one-third becoming nearly seizure-free. There are several reasons to suspect that the ketogenic diet may also have utility as a mood stabilizer in bipolar illness. These include the observation that several anticonvulsant interventions may improve outcome in mood disorders. Furthermore, beneficial changes in brain-energy profile are noted in subjects on the ketogenic diet. This is important since global cerebral hypometabolism is a characteristic of the brains of depressed or manic individuals. Finally, the extracellular changes that occur in ketosis would be expected to decrease intracellular sodium concentrations, a common property of all effective mood stabilizers. Trials of the ketogenic diet in relapse prevention of bipolar mood episodes are warranted."*

Micronutrients

Successful Treatment of Bipolar Disorder with Micronutrient Formula

Ruckidge JJ. Successful treatment of bipolar disorder II and ADHD with a micronutrient formula: a case study. CNS Specs 2010 May;15(5):289-95

- *"After 8 weeks on the formula she showed significant improvements in mood, anxiety, and hyperactivity/impulsivity. Shen then choose to come off the formula; after 8 weeks her depression scores returned to baseline, and anxiety and ADHD symptoms worsened."*

Empower Plus Microsupplement Resulted in Outcome Superior to Conventional Treatment

Frazier EA. Micronutrient supplement as treatment: literature review and case report of a 12-year-old boy with bipolar disorder. J Child Adolesc Psychopharmacol 2009 Aug;19(4):453-60

- *" EMP+ [Empower Plus] resulted in outcome superior to conventional treatment."*

Frazier EA. Nutritional and safety outcomes from an open-label micronutrient intervention for pediatric bipolar spectrum disorders. J Clin Adolesc Psychopharmacol 2013 Oct;23(8):558-67

- *"In this open prospective study. Short-term use of EMP+ in children with BPSD appeared safe and well-tolerated, with a side effect profile preferable to fist line psychotropic drugs for pediatric bipolar spectrum disorders."*

Over Half the Adults with Bipolar Disorder Experienced Improvement Consuming a Micronutrient Supplement Formula at 6 Months

Dermot G. Database analysis of adults with bipolar disorder consuming a micronutrient formula. Clinical Medicine Psychiatry 2009:4 3-16

- *"Mean symptom severity was 41% lower tan baseline after 3 months (effect size =0.78), and 45% lower after 6 months (effect size= 0.76) (both paired t-tests significant. P< 0.001) In terms of responder status, 53% experienced >50% improvement at 6 months ."*

Nutritional Supplements

Some Cases of Bipolar Disorder May Be Ameliorated by Nutritional Supplementation

Bonnie K. Effective mood stabilization with chelated mineral supplement: An open-label trial in bipolar disorder. J Clin Psychiatry 2001;62:936-944

- *"Some cases of bipolar illness may be ameliorated by nutritional supplementation.*

Vitamin Therapy

Vitamin B_9 (Folate, Folic Acid)

Adjunctive Folic Acid is Effective for Treatment of Mania in Bipolar Disorder

Behzadi AH. Folic acid efficacy as an alternative drug added to sodium valproate in treatment of acute phase of mania in bipolar disorder: a double-blind randomized controlled trial. Acta Psychiatric Scand 2009 Dec;120(6):441-5

- *"Based on our findings, folic acid seems to be an effective adjunctive to sodium valproate in the treatment of the acute phase of mania in patients with bipolar disorder."*

Folic Acid Enhances Lithium Prophylaxis

Coppen A. Folic acid enhances lithium prophylaxis. J Affect Disord 1986 Jan-Feb;10(1):9-13

- *"A double-blind trial was carried out to investigate the effect the effect on affective morbidity of a daily supplement of 200 micrograms folic acid or a matched placebo in a group of 75 patients on lithium therapy. During the trial the patients with the highest plasma folate concentrations showed a significant reduction in their affective morbidity. Patients who had their plasma folate increased to 13 ng/ml or above had a 40% reduction in their affective morbidity. It is suggested that a daily supplement of 300-400 micrograms folic acid would be useful in long term lithium prophylaxis."*

Vitamin B Complex

Choline is Effective in the Treatment of Rapid-Cycling Bipolar Disorder

Stoll AL. Choline in the treatment of rapid-cycling bipolar disorder: clinical and neurochemical findings in lithium-treated patients. Biol Psychiatry 1996 Sep 1;40(5):382-8

- "*The study examined choline augmentation of lithium for rapid cycling bipolar disorder. Choline bitartrate was given openly to 6 consecutive lithium-treated outpatients with rapid-cycling bipolar disorder. Five patients also underwent brain proton magnetic*

resonance spectroscopy. Five of 6 rapid-cycling patients had a substantial reduction in manic symptoms, and 4 patients had marked reduction in all mood symptoms during choline therapy."…"Choline, in the presence of lithium, was a safe and effective treatment for 4 of the 6 rapid-cycling patients in our series."

Vitamin C

Vitamin C Produced Statically Significant Improvement in Depressive, Manic and Paranoid symptom Complexes in Chronic Psychiatric Patients

Milner G. Ascorbic Acid in Chronic Psychiatric Patients—A Controlled Trial. Brit J Psychiat (1963), 109, 294-299

- *"Statistically significant improvement in depressive, manic and paranoid symptom complexes, together with an improvement in overall personality functioning, was obtained following saturation with ascorbic acid."*

Fatty Acids

Omega-3

Omega-3's May Be Effective for the Treatment of Bipolar Disorder Depression

Sarris J. Omega-3 for bipolar disorder: meta-analyses of use in mania and bipolar depression. J Clin Psychiatry 2012 Jan;73(1):81-6

- *"The meta-analytic findings provide strong evidence that bipolar depressive symptoms may be improved by adjunctive use of omega-3. The evidence, however, does not support its adjunctive use in attenuating mania."*

Omega-3 Fatty Acids Decrease Irritability in Bipolar Disorder

Sagduyu K. Omega-3 fatty acids decreased irritability of patients with bipolar disorder in add-on, open lablel study. Nutrition Journal 2005 4:6

- *"Omega-3 Fatty Acid intake helped with irritability component of patients suffering from bipolar disorder with significant presenting sign of irritability. Low dose (to 2 grams per day), add-on O-3FA may also help with the irritability component of different clinical conditions, such as schizophrenia, borderline personality disorder and other psychiatric conditions with a common presenting sign of irritability. "*

Omega-3 Fatty Acid Supplementation May Be Helpful Adjunct in Selected Patients with Bipolar Disorder

Turnbull, Teresa, "Efficacy of Omega-3 Fatty Acid Supplementation on Improvement of Bipolar Symptoms: A Systematic Review." Archives of Psychiatric Nursing 22, no. 5 (October 2008): 305–11. doi:10.1016/j.apnu.2008.02.011.

- *"Those using an omega-3 combination of eicosapentaenoic acid and docosahexanoic acid demonstrated a statistically significant improvement in bipolar symptoms, whereas those using a single constituent did not. Dosage variations did not demonstrate statistically significant differences. Due to its benign side effect profile and some evidence supporting its usefulness in bipolar illness, omega-3 may be a helpful adjunct in treatment of selected patients. Future studies are needed to conclusively confirm the efficacy of omega-3s in bipolar disorder, uncovering a new well-tolerated treatment option."*

Adjunctive Use of Omega-3 Fatty Acids are Effective for Depressive Symptoms in Bipolar Disorder

Sarris, Jerome, "Omega-3 for Bipolar Disorder: Meta-Analyses of Use in Mania and Bipolar Depression." The Journal of Clinical Psychiatry 73, no. 1 (January 2012): 81–86. doi:10.4088/JCP.10r06710.

- *"The meta-analytic findings provide strong evidence that bipolar depressive symptoms may be improved by adjunctive use of omega-3. The evidence, however, does not support its adjunctive use in attenuating mania."*

Adjunctive Omega-3 Fatty Acids are Effective for Depressive Symptoms in Bipolar Disorder

Montgomery, P., "Omega-3 Fatty Acids for Bipolar Disorder." The Cochrane Database of Systematic Reviews, no. 2 (2008): CD005169. doi:10.1002/14651858.CD005169.pub2.

- *"Results from one study showed positive effects of omega-3 as an adjunctive treatment for depressive but not manic symptoms in bipolar disorder. These findings must be regarded with caution owing to the limited data available. There is an acute need for well-designed and executed randomised controlled trials in this field."*

Flax Oil

Flax Oil May Decrease the Severity of Illness in Children with Bipolar Disorder

Barbra GL. Randomized, placebo-controlled trial of flax oil in pediatric bipolar disorder. Bipolar Disord 2010 March; 12(2):142-154

- *"Although flax oil may decrease severity of illness in children and adolescents with bipolar disorder who have meaningful increases in serum EPA percent levels and/or decreased AA and DPA-n6 levels, individual variations in conversion of a-LNA to EPA and DHA as well as dosing burden favor the use of fish oil both for clinical trials and clinical practice."*

Amino Acids

5-HTP

Antidepressant Potentiation by 5-HTP Showed Greater Clinical Improvement

Mendlewicz J. Antidepressant potentiation of 5-hydroxytryptophan by L-deprenil in affective illness. J affect Disord 1980 Jun;2(2):137-46

- *"In an open label study, L-Deprenil, an irreversible selective MAO-B inhibitor without 'cheese effect' was given to 14 patents with unipolar and bipolar depression receiving L-5-Hydroxytryptophan (L-5-HTP) and benzerazide. Ten out of 14 patients showed a good response to the combination of drugs and correlation was found between the degree of platelet MAO inhibition and clinical response. In a double-blind controlled study, 18 affectively ill patients were randomly allocated to L-Deprenil plus L-5-HTP and benzerazide, 21 patients were treated with L-5-HTP and benzerazide and 19 patients placebo only. Patients treated with combination of L-Deprenil and L-5-HTP showed a significantly greater clinical improvement than placebo patients but this was not the case with 5-HTP alone. "*

Branched Amino Acids

Branched Amino Acid Drink Ameliorate Manic Symptoms

Scarna A. Effects of branched-chain amino acid drink in mania. Br J Psychiatry 2003 Mar;182:210-3

- *"A nutritional intervention that decreases tyrosine availability to the brain acutely ameliorating's manic symptoms."*

L-tryptophan

Tryptophan Combined with Lithium Results in Significantly Greater Improvement in Bipolar and Schizoaffective Disorders

Brewerton, T. D."Lithium Carbonate and L-Tryptophan in the Treatment of Bipolar and Schizoaffective Disorders." The American Journal of Psychiatry 140, no. 6 (June 1983): 757–60.

- *"The authors review theoretical and clinical data supporting the hypothesis that L-tryptophan may potentiate the effects of lithium carbonate and report on a double-blind clinical comparison of lithium plus L-tryptophan and lithium plus placebo in 9 bipolar and 7 schizoaffective patients. Overall the combination of lithium and L-tryptophan resulted in significantly greater improvement. However, the results may have been confounded by the greater, although nonsignificant, doses of neuroleptics administered to the group receiving L-tryptophan. The authors discuss the interactions of lithium and L-trypotophan with the serotonin system."*

L-tryptophan Has Some Therapeutic Effect for Treatment of Acute Mania

Chouinard G. A controlled trial of L-tryptophan in acute mania. Biol Psychiatry 1985 May;20(5):546-57

- "*In a 2 week study, 24 newly admitted manic patients were treated for 1 week with L-tryptophan (12g/day); during the second week, half the patients, chosen at random, continued to receive tryptophan, while placebo was substituted in the other half under double-blind conditions. In the open phase of the study, there was a clinically and statistically (p less than 0.001) significant reduction in manic symptom scores, with little need for haloperidol prn. Patients who continued to be treated with tryptophan showed no significant change in mean scores during the second week, but those who were switched to placebo tended (p less than 0.10) to show an increase in mean scores for manic symptoms."…"These results suggest that increasing the synthesis of 5-hydroxytyptamine has some therapeutic effect in mania."*

L-Tryptophan is a Safe Alternative for Maintenance Treatment of Bipolar II Disorder

Beitman BD. L-typtophan in the maintenance treatment of bipolar II manic-depressive illness. Am J Psychiatry 139:11, November 1982

- *"Although tryptophan is quite expensive and may require concomitant ascorbic acid and/or nicotinamide, it appears safe and may be considered an alternative maintenance treatment in bipolar patients who are unresponsive to or unable to take lithium. The*

effective dose range appears to be quite wide (2-12 g/day), which may indicate the absence of a therapeutic window."

Tryptophan for Treatment of Rapid-Cycling Bipolar Disorder Comorbid with Fibromyalgia in Middle-aged Woman

Sharma V. Tryptophan for the treatment of rapid-cycling bipolar disorder comorbid with fibromyalgia. Can J Psychiatry 2001 Jun;46(5):452-3

- *"Ms. A is a 40-year-old lady who has presented with a history of recurrent episodes of depression since her mid-teens. She questioned the effectiveness of various treatment interventions and became increasingly frustrated with her ongoing mood instability, chronic pain condition, and poor psychosocial functioning. At this time, it was decided to prescribe a trial of tryptophan. The dosage was gradually increased over a couple of weeks to 4 g daily. She remained on lorazepam 1mg and oxazepam 25mg daily, which she had taken for years. Within 2 weeks of reaching the 4 g dosage, she developed a mixed state characterized by symptoms of feeling "revved up, "irritable, agitated, with racing thoughts, preoccupation with thoughts of suicide, and dysphroia. The tryptophan dosage was gradually lowered to 2 g, and her mood has been quite stable for a least 18 months. She continues to experience symptoms of fibromyalgia, but these are not as intense or disabling as before. She has been gainfully employed for more than 1 year and remains on the drug regimen of tryptophan 2g, lorazepam 1mg, and oxazepam 25mg daily."*

Tryptophan for Refractory Bipolar Disorder and Sleep Phase Delay

Cooke RG. Tryptophan for refractory bipolar spectrum disorder and sleep phase delay. J Psychiatry Neurosci 2010;35(2)

- *"A trial of L-tryptophan, starting at a dose of 1 g in the evening was begun in June 2007, and within 3 weeks she began to report an improvement in her ability to get to sleep and wake in time on the morning. Over a few more weeks, the dosage was increased to 3.5g daily combined with over –the-counter pyridoxine to limit the toxic metabolites of tryptophan. After about 10 weeks of treatment, she began to consistently arrive at work at 9 am, and her depressive symptoms cleared. Two years after L-tryptophan was initiated, she continued to show a normal sleep-wake pattern and remained free of depressive and hypomanic symptoms. She was taking no prescribed medications except L-tryptophan and pyridoxine."*

L-tryptophan and Niacin

Potentiation of Lithium by L-Tryptophan/Niacin Combination Results in Complete Remission in Patient with Bipolar Disorder

Chouinard G. Potentiation of Lithium by tryptophan in patient with bipolar illness. Am J Psychiatry 136:5, May 1979

- *"It was decided to add L-tryptophan, 3 g p.o. b.i.d., and nicotinamide, 750mg p.o. b.i.d., to her treatment regimen…*
- *"In this case described here, the patient had been treated with tryciclics, lithium alone, and subsequently with lithium in combination with a neuroleptic. These treatment regimens had not adequately controlled her manic or depressive symptoms or altered her cycles length. However, the addition of tryptophan-nicotinamide to lithium resulted in an almost complete remission of symptoms. The first effect was seen 7 weeks after addition of tryptophan-nicotinamide, with a reduction in the severity of the depressed phase. After 10 weeks the patient entered her first extended period of normality since the illness began 4 years ago."*

Schrauwen E. Galantamine treatment of cognitive impairment in bipolar disorder: four cases. Bipolar Disord 2006 Apr:8(2):196-9

- *"This pilot case series suggests that galantamine may have some utility in improving chronic cognitive impairment in bipolar disorder. "*

Tyrosine

Dietary Tyrosine Depletion Attenuates Symptoms of Mania

McTavish SFB. Antidoperminergic effects of dietary tyrosine depletion in healthy subjects and patients with manic illness. Br J Psychiatry 2001, 179:356-360

- *"We also obtained preliminary evidence that the TYR-free mixture is capable of attenuating the symptoms of acute mania. As is common in the in-patient treatment of manic illness, our subjects were receiving treatment with antipsychotic drugs at doses likely to produce a high degree of dopamine D2 receptor occupancy. Despite this, they continued to experience clinically significant manic symptomology that was diminished by tyrosine depletion."*

Hormones

Estrogen and Progesterone

Estrogen-Progesterone Combination May Be Effective As Mood Stabilizers for Bipolar Disorder

Chouinard, G., "Estrogen-Progesterone Combination: Another Mood Stabilizer?" The American Journal of Psychiatry 144, no. 6 (June 1987): 826.

- *"The mechanism of mood stabilization is unknown but may involve noradrenergic, dopaminergic, and/or serotonergic systems. Estrogen, administered chronically, increases dopaminergic receptor density (1) and decreases dopaminergic concentration in the limbic structures (2), while progesterone inhibits reuptake of serotonin and decreases its metabolism, resulting in enhanced serotonergic activity in the CNS. Chronic estrogen treatment also increases progesterone receptors in target organs, possibly augmenting the activity of progesterone in the CNS. Thus, the modulation of mood appears to be mediated through progesterone. These cases suggest that hormones may be effective as mood stabilizers in bipolar patients resistant to standard treatments."*

Estrogen-Progesterone Combination is Effective in Treatment of Post-partum Mania

Huang, Ming-Chyi, "Estrogen-Progesterone Combination for Treatment-Refractory Post-Partum Mania." Psychiatry and Clinical Neurosciences 62, no. 1 (February 2008): 126. doi:10.1111/j.1440-1819.2007.01782.x.

- *"Estrogen modulates various systems of neurotransmission, especially dopaminergic transmission. A low rate of relapse is reported under prophylaxis of estrogen in patients with histories of post-partum affective disorder.2 The beneficial effect of estradiol treatment in post-partum psychosis could be related to low serum estradiol level.3 Combined estrogen and progesterone appeared effective as adjuvant treatment for mood stabilization.4 A recent pilot study also suggested that medroxyprogesterone may have benefits in the management of manic symptoms.5 In the present patient the prolonged post-partum manic episode might have been due to rapid decrease of both estrogen and progesterone levels, and which then subsided following HRT. To our knowledge this is the first report regarding the role of HRT in the treatment of post-partum mood swings."*

Insulin

Intranasal Insulin Significantly Improved a Single Measure of Executive Function in Bipolar Disorder

McIntyre, Roger S., "A Randomized, Double-Blind, Controlled Trial Evaluating the Effect of Intranasal Insulin on Neurocognitive Function in Euthymic Patients with Bipolar Disorder." Bipolar Disorders 14, no. 7 (November 2012): 697–706. doi:10.1111/bdi.12006.

- *"Adjunctive intranasal insulin administration significantly improved a single measure of executive function in bipolar disorder. We were unable to detect between-group differences on other neurocognitive measures, with improvement noted in both groups. Subject phenotyping on the basis of pre-existing neurocognitive deficits and/or genotype [e.g., apolipoprotein E (ApoE)] may possibly identify a more responsive subgroup."*

Melatonin

Melatonin Treatment Leads to Rapid Relief of Insomnia and Aborts Manic Episode in Boy with Bipolar Disorder

Robertson JM. Case study: the use of melatonin in a boy with refractory bipolar disorder. J Am Acad Child Adolesc Psychiatry 1997 Jun;36(6):822-5

- *"A trial of melatonin led to rapid relief of insomnia and aborted a manic episode. He continued to take melatonin and adjunctive alprazolam for 15 months without reoccurrence of insomnia or mania."*

Pregnenolone

Pregnenolone May Improve Depressive Symptoms in Patients with Bipolar Disorder

Brown, E. Sherwood, "A Randomized, Double-Blind, Placebo-Controlled Trial of Pregnenolone for Bipolar Depression." Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology 39, no. 12 (November 2014): 2867–73. doi:10.1038/npp.2014.138.

- *"Depression remission rates were greater in the pregnenolone group (61%) compared with the placebo group (37%), as assessed by the IDS-SR ($\chi(2)(1)=3.99$, $p=0.046$), but not the HRSD. Large baseline-to-exit changes in neurosteroid levels were observed in the pregnenolone group but not in the placebo group. In the pregnenolone group, baseline-to-exit change in the HRSA correlated negatively with changes in allopregnanolone ($r(22)=-0.43$, $p=0.036$) and pregNANolone ($r(22)=-0.48$, $p=0.019$) levels. Pregnenolone was well tolerated. The results suggest that pregnenolone may improve depressive symptoms in patients with BPD and can be safely administered."*

Traditional Ayurvedic/Asian/Chinese/Kampo Medicine

Ashwagandha (Indian Ginseng)

Ashwagandha Appears to Improve Auditory Verbal Working Memory in Bipolar Disorder

Chengappa, K. N. Roy, "Randomized Placebo-Controlled Adjunctive Study of an Extract of Withania Somnifera for Cognitive Dysfunction in Bipolar Disorder." The Journal of Clinical Psychiatry 74, no. 11 (November 2013): 1076–83. doi:10.4088/JCP.13m08413.

- *"Although results are preliminary, WSE appears to improve auditory-verbal working memory (digit span backward), a measure of reaction time, and a measure of social cognition in bipolar disorder. Given the paucity of data for improving cognitive capacity in bipolar disorder, WSE offers promise, appears to have a benign side-effects profile, and merits further study."*

Free and Easy Wanderer Plus

Adjunctive Free and Easy Wanderer Plus Results in Significant Improvement of Depression for the Treatment of Bipolar Disorder

Zhang ZJ. Adjunctive herbal medicine with carbamazepine for bipolar disorders: A double-blind, randomized, placebo-controlled study. J Psychiatr Res 2007 Apr-Jun;41(3-4):360-9

- *"Compared to CBZ momotherapy, adjunctive FEWP with CBZ resulted in significantly greater improvement on depressed subjects (84.8% vs. 63.8%, p=.032), but failed to produce significantly greater improvement on manic measures and the response rate in manic subjects."*

Zhang ZJ. The beneficial effects of the herbal medicine Free and Easy Wanderer Plus (FEWP) for mood disorders: double-blind, placebo-controlled studies. J Psychiatry Res 2007 Nov;41(10):826-36

- *"Both unipolar and bipolar patients assigned to FEWP displayed significantly greater improvement on the three efficiency indices and significantly higher clinical response rate (74%) than those treated with placebo (42%) at endpoint.*

Siberian Ginseng

Siberian Ginseng as Adjunctive Therapy for Lithium in Pediatric Bipolar Disorder is as effective as Prozac

Shenhong W. Comparison of the addition of Siberian Ginseng (acanthopanax senticosus) versus Fluoxetine to Lithium for the treatment of bipolar disorder in adolescents: A randomized, double-blind trial. Current Therapeutic Research, Vol. 68 No. 4, July/August 2007

- *Our study found no significant differences in these adolescents with BD treated with lithium plus adjunctive A senticous or fluoxetine. All treatments were generally well tolerated.*

Xiao Yao San Jia Wei

Xiao Yao San Jia Wei for Marked Improvement of Bipolar Disorder

Zhang LD. Traditional Chinese medicine typing of affective disorders and treatment. Am J Chin Med 1994;22(3-4):321-7

- *"The results are 26 patients with marked improvement, 17 patients with improvement, 7 patients with no improvement."*

Other Natural Compounds

Cannabis

Cannabis as a Mood Stabilizer in Bipolar Disorder

Grinspoon, L., "The Use of Cannabis as a Mood Stabilizer in Bipolar Disorder: Anecdotal Evidence and the Need for Clinical Research." Journal of Psychoactive Drugs 30, no. 2 (June 1998): 171–77. doi:10.1080/02791072.1998.10399687.

- *"The authors present case histories indicating that a number of patients find cannabis (marihuana) useful in the treatment of their bipolar disorder. Some used it to treat mania, depression, or both. They stated that it was more effective than conventional drugs, or helped relieve the side effects of those drugs. One woman found that cannabis curbed her manic rages; she and her husband have worked to make it legally available as a medicine. Others described the use of cannabis as a supplement to lithium (allowing reduced consumption) or for relief of lithium's side effects. Another case illustrates the fact that medical cannabis users are in danger of arrest, especially when children are encouraged to inform on parents by some drug prevention programs. An analogy is drawn between the status of cannabis today and that of lithium in the early 1950s, when its effect on mania had been discovered but there were no controlled studies. In the case of cannabis, the law has made such studies almost impossible, and the only available evidence is anecdotal. The potential for cannabis as a treatment for bipolar disorder unfortunately can not be fully explored in the present social circumstances."*

Cannabinoids

Cannabinoids have Pharmacological Properties that Could Be Therapeutic in Patients with Bipolar Disorder

Ashton, C. H., "Cannabinoids in Bipolar Affective Disorder: A Review and Discussion of Their Therapeutic Potential." Journal of Psychopharmacology (Oxford, England) 19, no. 3 (May 2005): 293–300. doi:10.1177/0269881105051541.

- *"Despite the sparse anecdotal data in humans and the absence of controlled clinical trials, the evidence discussed above shows that both THC and CBD have pharmacological properties that could be therapeutic in patients with BAD."*

Chelation

Control of Mania in Wilson 's disease by Chelation Only

Mitra, Saikat, "Control of Mania with Chelation-Only in a Case of Wilson's Disease." The Journal of Neuropsychiatry and Clinical Neurosciences 26, no. 1 (2014): E6. doi:10.1176/appi.neuropsych.12110271.

- *"In this case, psychiatric manifestations appeared in the course of WD without any worsening of motor manifestations, which is quite rare.1 Emergence of manic symptoms on omission of penicillamine and remission after reinstitution confirms it to be a primary neuropsychiatric manifestation of WD. This case also signifies that only optimization of primary management with chelating agents may suffice for controlling psychiatric manifestations in WD. This agrees well with the concept of organic psychosis.4 This is important to reduce unnecessary health costs and the burden of side effects of psychotropics5 in these cases."*

Chelerythrine

PKC Inhibitor Chelerythrine May Have Antimanic Effects

Einat, Haim. "Partial Effects of the Protein Kinase C Inhibitor Chelerythrine in a Battery of Tests for Manic-like Behavior in Black Swiss Mice." Pharmacological Reports: PR 66, no. 4 (August 2014): 722–25. doi:10.1016/j.pharep.2014.03.013.

- *"The partial effects in the battery are not unique as previous studies showed that lithium, valproate and risperidone, all used in the treatment of bipolar disorder, have distinct profiles in the battery. It is therefore concluded that chelerythrine may have antimanic effects and additional dose and time response studies are warranted to further evaluate its range of activity."*

Chromium

Chromium is Well Tolerated for Treatment Resistant Rapid-Cycling Bipolar Disorder

Amann BL. A 2-year, open-label pilot study of adjunctive chromium in patients with treatment-resistant rapid-cycling bipolar disorder. Journal of Clinical Psychopharmacology Volume 27, Number 1 February 2007

- *"Six of 7 patients showed a reduction in the numbers of affective episodes within 1 year. The mean number of affective episodes in 7 patients before entry decreased from 6 (SD, 4.0; range , 4]5) to 2.6 (SD, 2.0; range, 0]6) after 1 year having received add-on CC. This reduction in 6 of 7 patients was also evident in the analysis of the CGI-BP. The mean overall CGI changed from 3.9 (SD, 1.4; range. 1]6) to 3.2 (SD, 1.8; range 1]6)…In general , chromium in doses up to 800 Ag/d was very well tolerated by all patients. However, some patients reported side effects, which were in general mild and did not lead to any dropout during the study."*

Citicoline

Citicoline Add-on Therapy was Associated with Improvement in Declarative Memory and Cocaine Use in Bipolar Disorder

Brown ES. A randomized, placebo-controlled trial of citicoline add-on therapy in outpateints with bipolar disorder and cocaine dependence. J Clin Psychopharmacol 2007 Oct;27(5):498-502

- *"The use of citicoline was associated with improvement relative to placebo in some aspects of declarative memory and cocaine use, but not for mood. The findings are promising and suggest that larger trials of citicoline are warranted. "*

Citicoline Add-on Therapy May Have Antidepressant Properties in Bipolar Methamphetamine Users

Brown, E. Sherwood, "A Randomized, Double-Blind, Placebo-Controlled Trial of Citicoline for Bipolar and Unipolar Depression and Methamphetamine Dependence." Journal of Affective Disorders 143, no. 1–3 (December 20, 2012): 257–60. doi:10.1016/j.jad.2012.05.006.

- *"To our knowledge this is the first placebo-controlled trial in a dual diagnosis sample with methamphetamine use disorders. Findings suggest that citicoline may have antidepressant properties in this population. Greater treatment retention with citicoline is also noteworthy in a patient population with substance dependence. Larger trials targeting depressive symptoms and treatment retention seem warranted."*

Curcumin

Curcumin Has Anti-inflammatory and Antioxidant Properties in the Treatment of Bipolar Disorder

Brietzke E. Is there a role for curcumin in the treatment of bipolar disorder? Medical Hypotheses 80 (2013) 606-612

- *"Curcumin putative targets, known based on studies of diverse central nervous system disorders other than bipolar disorders (BD) include several proteins currently implicated in the pathophysiology of BD. These targets include, but are not limited to, transcription factors activated by environmental stressors and pro-inflammatory cytokines, protein kinases (PKA, PKC), enzymes, growth factors, inflammatory mediators, and anti-apoptotic proteins (Bcl-XL). Herein, we review previous studies on the anti-inflammatory and antioxidant properties of curcumin and discuss its therapeutic potential in BD."*

Dopamine Beta-Hydroxylase Inhibition

Fusaric Acid Dopamine Beta-Hydroxylase Inhibition Decreased a Patient's Manic Symptoms

Pandey, R. S., "Dopamine Beta-Hydroxylase Inhibition in a Patient with Wilson's Disease and Manic Symptoms." The American Journal of Psychiatry 138, no. 12 (December 1981): 1628–29.

- *The authors studied the effect of dopamine beta-hydroxylase inhibition on the manic symptoms of a 34-year-old man. They found that fusaric acid decreased the patient's manic symptoms and that his symptoms approximately reverted to their previous state when a placebo was reinstituted."*

Herbal Medicines

Herbal Medicines Have Potential to Alleviate Symptoms of Anxiety and Insomnia in Bipolar Disorder

Baek, Ji Hyun, "Clinical Applications of Herbal Medicines for Anxiety and Insomnia; Targeting Patients with Bipolar Disorder." The Australian and New Zealand Journal of Psychiatry 48, no. 8 (June 19, 2014): 705–15. doi:10.1177/0004867414539198.

- *"Adjunctive herbal medicines may have the potential to alleviate these symptoms and improve the outcomes of standard treatment, despite limited evidence. Physicians need to have a more in-depth understanding of the evidence of benefits, risks, and drug interactions of alternative treatments."*

Inositol

Inositol is Effective for Treatment of Bipolar Depression

Chengappa KN. Inositol as add-on treatment for bipolar depression. Bipolar Disorder 2000 Mar;2(1):47-55

- *"Among 22 subjects who completed the trial, six (50%) of the inositol-treated subjects responded with a 50% of greater decrease in baseline Hamilton Depression Rating Scale (HAM-D) score and a Clinical Global Improvement (CGI) scale score change of much or very much improved, as compared to three subjects assigned to placebo, a statistically non-significant difference."*

Lecithin

Attenuation of Mania with Lecithin

Cohen BM. Lecithin in mania: A preliminary report. Am J Psychiatry 137:2 February 1980

- *"The design of this preliminary study does not permit definite conclusions as to the efficiency of lecithin in mania. However, the results are consistent with a beneficial effect. All subjects who received Phosophilipon 100 improved rapidly, and three of four showed some worsening following withdrawal of lecithin."*

Magnesium oxide

Magnesium Augmentation in Mania May Increase Antimanic Efficacy of Verapamil

Giannini AJ. Magnesium oxide augmentation of verapamil maintenance therapy in mania. Psychiatry Res 2000 Feb 14;93(1):83-7

- "*The authors compared the antimanic effects of verapamil-magnesium (V-M) combination with verapamil-placebo combination (V-P) in patients pretreated with verapamil. BPRS scores and serum magnesium levels were compared. The V-M combination was found to be significantly more effective the V-P in reducing manic symptoms (P=0,015). Serum magnesium levels were significantly higher in V-M group (P<0.04). These data suggest that magnesium may increase antimanic efficacy of verapamil by mechanisms which may operate at the intercellar level."*

Magnesiocard

Magnesiocard as a Mood Stabilizer for Rapid Cycling Bipolar Disorder Has Found to Have Clinical Results Equivalent to Those of Lithium

Chouninard G. Apilot study of magnesium asparatate hydrochloride (Magnesiocard) as a mood stabilizer for rapid cycling bipolar affective disorder patients. Prog Neuropsychopharmacol Biol Psychiarty 1990;14(2):171-80

- *"Nine severe rapid cycling manic-depressive patients were treated with magnesium preparation, Magnesiocard 40mEq/day in an open label study for a period up to 32 weeks.. Magnesiocard was found to have clinical results at least equivalent to those of lithium in about 50% of these patients. These results were obtained in an exploratory study and should be interpreted with caution."*

Magnesium Sulphate

Intravenous Magnesium Sulphate (Epsom Salt) May Be Used for Clinical Management of Severe Manic Agitation

Heiden A. Treatment of severe mania with intravenous magnesium sulphate as supplemental therapy. Psychiatry Res 1999 Dec 27;89(3):239-46

- *"Ten patients with severe, therapy-resistant manic agitation received magnesium sulphate infusions with continuous magnesium (Mg) flow of approximately 200mg/h (4353+/-836mg/day;daily monitored Mg plasma level: 2.44+/-0.34 mmol/l) for periods ranging from 7 to 23 days." "Seven patients showed a marked improvement in the Clinical Global Impression Scale. In case of bradycardia detected by the ECG monitor (n=5), mg flow was reduced and bradycardia disappeared promptly. Mg i.v. may be a useful supplemental therapy for the clinical management of severe manic agitation."*

N-acetylcysteine

N-acetyl cysteine Add-on Treatment for Bipolar Disorder Achieves Full Remission of Both Depressive and Manic Symptoms

Magalhaes PV. N-acetyl cysteine add-on treatment for bipolar II disorder: a subgroup analysis of randomized placebo-controlled trial.

- "*Fourteen individuals were available for this report, seven in each group. Six people achieved full remission of both depressive and manic symptoms in the NAC group; this was true for only two people in the placebo group."*

N-acetylcysteine as Adjunctive Treatment Demonstrates a Robust Decrease in Bipolar Depression

Berk M. The efficacy of N-acetycysteine as and adjunctive treatment in bipolar depression: an open label trial. J Affect Disord 2011 Dec;135(1-3):389-94

- *"In this trial, the estimated mean baseline Bipolar Depression Rating Scale (BDRS) score was 19.7 (SE=0.8), and the mean BDRS score at the end of the 8 week open label treatment phase was 11.1 (SE=0.8). This reduction was statistically significant*

(p<0.001). Improvements in functioning and quality of life were similarly evident. These open label data demonstrate a robust decrement in depression scores with NAC treatment."

Berk M. N-Acetyl Cysteine for Depressive Symptoms in Bipolar Disorder—A Double-Blind Randomized Placebo-Controlled Trial. Biol Psychiatry 2008;64:468-475

- *"NAC appears a safe and effective augmentation strategy for depressive symptoms in bipolar disorder."*

Prolyl Oligopeptidase Inhibitors

Tarrango T. The natural product berberine is a human prolyl oligopeptidas inhibitor. ChenMedChem 2007 Mar;2(3):354-9

- *"As berberine is a natural compound that has been safely administered to humans, it opens up new perspectives for the treatment of neuropsychiatric diseases.*

Tarrago T. Identification by 19F NMR of traditional Chinese medicinal plants possessing prolyl oligopeptidase inhibitory activity. Chembiochem 2006 May;7(5):827-33

- *"This peptidase has been associated with schizophrenia, bipolar affective disorder, and related neuropsychiatric disorders and might therefore have important clinical implications."*

Sodium Butyrate

Sodium Butyrate May Be a Potential Mood Stabilizer for Bipolar Disorder

Resende, Wilson R., "Effects of Sodium Butyrate in Animal Models of Mania and Depression: Implications as a New Mood Stabilizer." Behavioural Pharmacology, August 29, 2013. doi:10.1097/FBP.0b013e32836546fc.

- *"Bipolar disorder is a severe mood disorder with high morbidity and mortality. Despite adequate treatment, patients continue to have recurrent mood episodes, residual symptoms, and functional impairment. Some preclinical studies have shown that histone deacetylase inhibitors may act on depressive-like and manic-like behaviors. Therefore, the aim of the present study was to evaluate the effects of sodium butyrate (SB) on behavioral changes in animal models of depression and mania. The animals were submitted to protocols of chronic mild stress or maternal deprivation for induction of depressive-like behaviors and subjected to amphetamine, or ouabain administration for induction of manic-like behaviors. SB reversed the depressive-like and manic-like behaviors evaluated*

in the animal models. From these results we can suggest that SB may be a potential mood stabilizer."

Sodium Butyrate May Be New Medication for the Treatment of Mania

Moretti, Morgana, "Behavioral and Neurochemical Effects of Sodium Butyrate in an Animal Model of Mania." Behavioural Pharmacology 22, no. 8 (December 2011): 766–72. doi:10.1097/FBP.0b013e32834d0f1b.

- *"The present study investigated the effect of the histone deacetylase inhibitor, sodium butyrate (SB), on locomotor behavior and on mitochondrial respiratory-chain complexes activity in the brain of rats subjected to an animal model of mania induced by d-amphetamine (d-AMPH). In the reversal treatment, Wistar rats were first treated with d-AMPH or saline (Sal) for 14 days. Thereafter, between days 8 and 14, rats were administered SB or Sal. In the prevention treatment, rats were treated with SB or Sal for 14 days and received d-AMPH or Sal between days 8 and 14. The d-AMPH treatment increased locomotor behavior in Sal-treated rats under reversion and prevention treatment, and SB reversed and prevented d-AMPH-related hyperactivity. Moreover, d-AMPH decreased the activity of mitochondrial respiratory-chain complexes in Sal-treated rats in the prefrontal cortex, hippocampus, striatum, and amygdala in both experiments, and SB was able to reverse and prevent this impairment. The present study suggests that the mechanism of action of SB involves induction of mitochondrial function in parallel with behavioral changes, reinforcing the need for more studies on histone deacetylase inhibitors as a possible target for new medications for bipolar disorder treatment."*

Sodium Butyrate Reversed Ouabain-Induced Manic Behavior and Increased Neurotrophins in Animal Model of Bipolar Disorder

Varela, Roger B., "Sodium Butyrate and Mood Stabilizers Block Ouabain-Induced Hyperlocomotion and Increase BDNF, NGF and GDNF Levels in Brain of Wistar Rats." Journal of Psychiatric Research, November 21, 2014. doi:10.1016/j.jpsychires.2014.11.003.

- *"Bipolar Disorder (BD) is one of the most severe psychiatric disorders. Despite adequate treatment, patients continue to have recurrent mood episodes, residual symptoms, and functional impairment. Some preclinical studies have shown that histone deacetylase inhibitors may act on manic-like behaviors. Neurotrophins have been considered important mediators in the pathophysiology of BD. The present study aims to investigate the effects of lithium (Li), valproate (VPA), and sodium butyrate (SB), an HDAC inhibitor, on BDNF, NGF and GDNF in the brain of rats subjected to an animal model of mania induced by ouabain. Wistar rats received a single ICV injection of ouabain or artificial cerebrospinal fluid. From the day following ICV injection, the rats were treated*

for 6 days with intraperitoneal injections of saline, Li, VPA or SB twice a day. In the 7th day after ouabain injection, locomotor activity was measured using the open-field test. The BDNF, NGF and GDNF levels were measured in the hippocampus and frontal cortex by sandwich-ELISA. Li, VPA or SB treatments reversed ouabain-related manic-like behavior. Ouabain decreased BDNF, NGF and GDNF levels in hippocampus and frontal cortex of rats. The treatment with Li, VPA or SB reversed these impairment induced by ouabain. In addition, Li, VPA and SB per se increased NGF and GDNF levels in hippocampus of rats. Our data support the notion that neurotrophic factors play a role in BD and in the mechanisms of the action of Li, VPA and SB."

Vitis Labrusca

Grape Extract Exhibits Protective Properties against Oxidative Stress in Bipolar Disorder

Scola, Gustavo, "Vitis Labrusca Extract Effects on Cellular Dynamics and Redox Modulations in a SH-SY5Y Neuronal Cell Model: A Similar Role to Lithium." Neurochemistry International 79 (December 2014): 12–19. doi:10.1016/j.neuint.2014.10.002.

- *"The findings of this study suggest that VLE exhibits protective properties against oxidative stress-induced alterations similar to that of lithium. These findings suggest that VLE may be an attractive potential candidate as a novel therapeutic agent for BD."*

Zinc

Zinc is Beneficial in Altering the Cognitive Function and Short-term Memory of Animals Treated with Lithium

Bhalla, Punita, "Effectiveness of Zinc in Modulating Lithium Induced Biochemical and Behavioral Changes in Rat Brain." Cellular and Molecular Neurobiology 27, no. 5 (August 2007): 595–607. doi:10.1007/s10571-007-9146-0.

- *"Further, lithium-treated rats showed an increase in depression time as compared to normal controls both after 1 and 4 months of treatment. Short-term memory significantly improved in lithium-treated rats in all treatment groups. However, no change in the cognitive behavior of the animals was reported after lithium treatment. Zinc co-administration with lithium significantly improved the short-term memory and cognitive functions of the animals. From the above results it can be concluded that zinc proved beneficial in altering the status of neurotransmitters as well as the behavior patterns of the animals treated with both short and long-term lithium therapy."*

Sensory Therapies

Ambient Air Anionization

Treatment with Ambient Air Anionization Produces Significant Antimanic Effect

Giannini AJ. Treatment of acute mania with ambient air anionization: variants of climatic heat stress and serotonin syndrome. Psychol Rep 2007 Feb;100(1):157-63

- *"High concentrations of ambient anions (O2-) were used to augment treatment for 20 acutely manic male patients. Anions were produced by anion generator in sealed room. A double-blind crossover design was used and responses were evaluated with Brief Psychiatric Rating Scale by 2 blinded raters. This produced significant antimanic effect: total rating scores declined with anion treatment. Presham and postsham total scores for these 5 were 31.3 and 31.6, respectively. Pretreatment and posttreatemnt total scores were 31.6 and 26.3, respectively."*

Chronotherapy

Chronotherapy Accelerates the Antidepressant Response in Bipolar Disorder

Wu, Joseph C., "Rapid and Sustained Antidepressant Response with Sleep Deprivation and Chronotherapy in Bipolar Disorder." Biological Psychiatry 66, no. 3 (August 1, 2009): 298–301. doi:10.1016/j.biopsych.2009.02.018.

- *"Significant decreases in depression in the CAT versus MED patients were seen within 48 hours of SD and were sustained over a 7-week period. This is the first study to demonstrate the benefit of adding three noninvasive circadian-related interventions to SD in medicated patients to accelerate and sustain antidepressant responses and provides a strategy for the safe, fast-acting, and sustainable treatment of BPD."*

Chronobiological Treatment is enhanced by Lithium in Bipolar Depression

Benedetti, F., "Sleep Phase Advance and Lithium to Sustain the Antidepressant Effect of Total Sleep Deprivation in Bipolar Depression: New Findings Supporting the Internal Coincidence Model?" Journal of Psychiatric Research 35, no. 6 (December 2001): 323–29.

- *"Recent European studies suggested that sleep phase advance (SPA) could sustain the effects of total sleep deprivation (TSD) both with or without a combined antidepressant drug treatment. Previous studies by our group showed that an ongoing lithium treatment could enhance and sustain the effect of repeated TSD. In the present study we studied the effect of a single TSD followed by 3 days SPA (beginning with sleep allowed from 17:00 until 24:00, with daily shiftbacks of 2 h) in consecutively admitted bipolar*

depressed inpatients who were taking a chronic lithium salts treatment (n=16) or who were devoid of psychotropic medications (n=14). Changes in mood during treatment were recorded with self administered visual analogue scales and with Hamilton rating scale for depression. Results showed that SPA could sustain the acute antidepressant effect of TSD, and that lithium enhanced the effect of the chronobiological treatment. According to the internal coincidence model, the better clinical effects observed in lithium-treated patients could be due to the phase delaying effect of lithium on biological rhythms, leading to a better synchronization of biological rhythms with the sleep-wake cycle."

Light and Dark Therapy

Blue Light Blockade is Effective for Mania and Sleep in Patient with Bipolar Disorder

Henriksen, Tone Eg, "Blocking Blue Light during Mania - Markedly Increased Regularity of Sleep and Rapid Improvement of Symptoms: A Case Report." Bipolar Disorders 16, no. 8 (December 2014): 894–98. doi:10.1111/bdi.12265.

- *"Manic symptoms were unaltered during the first seven days. The transition to the blue-blocking regime was followed by a rapid and sustained decline in manic symptoms accompanied by a reduction in total sleep, a reduction in motor activity during sleep intervals, and markedly increased regularity of sleep intervals. The patient's total length of hospital stay was 20 days shorter than the average time during his previous manic episodes."*

Morning Sunlight Reduces Length of Hospital Stay in Bipolar Depression

Benedetti, F., "Morning Sunlight Reduces Length of Hospitalization in Bipolar Depression." Journal of Affective Disorders 62, no. 3 (February 2001): 221–23.

- *"Bipolar inpatients in E rooms (exposed to direct sunlight in the morning) had a mean 3.67-day shorter hospital stay than patients in W rooms. No effect was found in unipolar inpatients. Natural sunlight can be an underestimated and uncontrolled light therapy for bipolar depression."*

Phototherapy is Effective in Bipolar Disorder at 3 Month Follow-up

Deltito, J. A., "Effects of Phototherapy on Non-Seasonal Unipolar and Bipolar Depressive Spectrum Disorders." Journal of Affective Disorders 23, no. 4 (December 1991): 231–37.

- *"In a group of 17 patients with non-SAD depressive disorders we compared the response of bipolar spectrum versus unipolar patients to treatment with light therapy. The main hypothesis was that bipolar spectrum depressed patients would preferentially respond to bright light therapy as compared to unipolar depressed patients. All patients were treated*

with either 400 or 2500 lux phototherapy for 2 h on seven consecutive days. All outcome measures, which included the SIGH-SAD, CGI, and the Anxiety and Depressive Factors of the SCL-90, showed significant improvement in the bipolar vs. the unipolar spectrum patients. Unexpected this occurred regardless of the intensity of the light. These changes were judged to be quite clinically significant. All patients showing response were noted to have maintained their response at a 3-month follow-up."

Phototherapy Treatment Decreases Depression and Anxiety and Normalizes Sleep Behavior in Affective Psychosis

Peter, K., "[Initial results with bright light (phototherapy) in affective psychoses]." Psychiatrie, Neurologie, Und Medizinische Psychologie 38, no. 7 (July 1986): 384–90.

- *"The biological foundations of light-treatment and their relation to neurophysiological and biochemical mechanisms were discussed. We developed an apparatus for treatment and report of first experiences in affective psychosis. In addition to a decrease of depressivity and anxiety we found an unequivocal tendency to normalization of sleep-behaviour. The farther clinical and paraclinical investigations has to show the position of this method of treatment in the total conception of a biological therapy."*

Bright Light Therapy for Bipolar Disorder Treats Depressive Symptoms

Papatheodorou G. The effect of adjunctive light therapy on ameliorating breakthrough depressive symptoms in adolescent-onset bipolar disorder.

- *"These preliminary results indicate that some bipolar adolescents with breakthrough depressive symptoms could benefit from light therapy as an adjunct to their continued thymoleptic treatment."*

Dark Therapy for Mania Results in a Significant Decrease in YMRS Scores

Barbini B. Dark Therapy for mania: a pilot study. Bipolar Disord 2005 Feb;7(1):98-101

- *"Adding DT to TAU [therapy as usual] resulted in a significantly faster decrease of YMRS scores when patients were treated within 2 weeks from onset of the current manic episode."*

Dark Therapy May Work for Rapid Cycling Bipolar Disorder

Phelps J. Dark therapy for bipolar disorder using amber lenses for blue light blockade. Med Hypotheses 2008;70(2):224-9

- *"If amber lenses can effectively simulate darkness, a broad range of conditions might respond to this inexpensive therapeutic tool: common forms of insomnia; sleep deprivation in nursing mothers; circadian rhythm disruption in shift workers; and*

perhaps even rapid cycling bipolar disorder, a difficult-to-treat variation of common illness."

Negative Air Ions

There May Be a Calming Effect of Negative Air Ions on Manic Patients

Misiaszek J. The calming effects of negative air ions on manic patients: a pilot study. Biol Psychiatry 1987 Jan;22(1):107-10

- *"The unexpected finding in this two-phase study is that seven of eight manic patients fell asleep during negative ion exposure and that six of them had to be awakened after the session was over. The short-lived calm behavior and sense of well-being following awakening may have been as much a function of sleep as of any direct effect benefit of negative ions. It is unlikely that medications accounted for the decrease in agitation."*

Sleep

Forced Bed Rest for Treatment of Rapid Cycling Bipolar Disorder May Help Prevent Mania and Rapid Cycling

Wehr TA. Treatment of rapidly cycling bipolar patient by using extended bed rest and darkness to stabilize the timing and duration of sleep.

- *"Fostering sleep and stabilizing its timing by scheduling regular nightly periods of enforced bed rest in the dark may help prevent mania and rapid cycling in bipolar patients."*

Sleep Deprivation

Sleep Restriction and Stimulus Control are Efficacious Procedures for treating insomnia in Bipolar Disorder

Kaplan, Katherine A., "Behavioral Treatment of Insomnia in Bipolar Disorder." The American Journal of Psychiatry 170, no. 7 (July 1, 2013): 716–20. doi:10.1176/appi.ajp.2013.12050708.

- *"Sleep restriction and stimulus control appear to be safe and efficacious procedures for treating insomnia in patients with bipolar disorder. Practitioners should encourage regularity in bedtimes and rise times as a first step in treatment, and carefully monitor changes in mood and daytime sleepiness throughout the intervention."*

Sleep Deprivation Provides a Positive Antidepressant Response in Rapid Cycling Bipolar Disorder

Gill, D. S., "Antidepressant Response to Sleep Deprivation as a Function of Time into Depressive Episode in Rapidly Cycling Bipolar Patients." Acta Psychiatrica Scandinavica 87, no. 2 (February 1993): 102–9.

- *"Three patients with treatment-resistant rapidly cycling bipolar disorder were studied with multiple sleep deprivations (SD) during several depressive episodes to assess the effect of phase or duration of a depressive episode on SD response. There was little response to SD early in a depressive episode, but responses were often robust late in an episode, sometimes triggering its termination. In 2 subjects, the duration of antidepressant response to SD increased linearly as time into episode increased. Neither the number of SD given in an episode nor the medication status of the patients appeared to account for the observed increases in antidepressant response. These results suggest that the neurobiological substrates underlying depression may change over the course of an episode, resulting in an increased responsivity to sleep deprivation later compared with earlier in the course of an episode in rapidly cycling patients. The generalizability of these findings to unipolar patients remains to be explored."*

Sleep Deprivation Shortened Mood Cycle of Manic Depressive Female Patient

Lovett Doust, J. W., "Repeated Sleep Deprivation as a Therapeutic Zeitgeber for Circular Type Manic Depressive Disturbance." Chronobiologia 7, no. 4 (December 1980): 505–11.

- *"A post-menopausal woman suffering from a circular type manic depressive psychosis who had been treated by drugs was followed for 8 months on a self-reporting mood rating scale. The drug regimen was continued over a further 8 months but with the addition of 5 nights of sleep deprivation at the depth of her recurrent depressed moods. Time series analyses of the subject's longitudinal mood scores revealed a persistent cycle of 32 days. After 5 sleep deprivation treatments this cycle shortened to 28 days which endured at least for the ensuing 8 months. After sleep deprivation and decrease of the amplitude, an improvement of mood was obtained. It is suggested that the increased LD ratio obtained in sleep deprivation may be as therapeutic as the actual loss of sleep itself."*

Combined Total Sleep Deprivation and Light Therapy is Useful in Triggering an Acute Response in Drug-resistant Bipolar Depressed Patients

Benedetti, Francesco, "Combined Total Sleep Deprivation and Light Therapy in the Treatment of Drug-Resistant Bipolar Depression: Acute Response and Long-Term Remission Rates." The Journal of Clinical Psychiatry 66, no. 12 (December 2005): 1535–40.

- *"The combination of repeated TSD and LT in drug-resistant patients was useful in triggering an acute response. Further clinical research is needed to optimize this treatment option for drug-resistant patients in the long term."*

Combined Sensory Therapies

Combination of Sleep Deprivation, Sleep Phase Advance, and Bright Light Therapy use in Bipolar Disorder

Gottlieb, John F., "Outpatient Triple Chronotherapy for Bipolar Depression: Case Report." Journal of Psychiatric Practice 18, no. 5 (September 2012): 373–80. doi:10.1097/01.pra.0000419822.69914.8e.

- *"There is an urgent need for rapid, effective, and safe treatments for bipolar depression. Triple chronotherapy is a combination of sleep deprivation, sleep phase advance, and bright light therapy that has been shown to induce accelerated and sustained remissions in bipolar depression. This case report describes the first outpatient program designed to administer triple chronotherapy and reviews the organizational and clinical requirements for providing such care."*

Total Sleep Deprivation and Light Therapy is Useful in Triggering a Response in Drug-Resistant Bipolar Depressed Patients

Benedetti, Francesco, "Combined Total Sleep Deprivation and Light Therapy in the Treatment of Drug-Resistant Bipolar Depression: Acute Response and Long-Term Remission Rates." The Journal of Clinical Psychiatry 66, no. 12 (December 2005): 1535–40.

- *"The combination of repeated TSD and LT in drug-resistant patients was useful in triggering an acute response. Further clinical research is needed to optimize this treatment option for drug-resistant patients in the long term."*

Total Sleep Deprivation Combined with Lithium and Light Therapy Obtains a Sustained Antidepressant Response in Bipolar Patients

Colombo, C., "Total Sleep Deprivation Combined with Lithium and Light Therapy in the Treatment of Bipolar Depression: Replication of Main Effects and Interaction." Psychiatry Research 95, no. 1 (July 24, 2000): 43–53.

- *"The results showed that both light therapy and ongoing lithium treatment significantly enhanced the effects of TSD on the perceived mood, with no additional benefit when the two treatments were combined. Subjective sleepiness during TSD, as rated by the self-administered Stanford Sleepiness Scale, was significantly reduced by light exposure, and*

was correlated with the outcome. This study confirms the possibility of obtaining a sustained antidepressant response to TSD in bipolar patients."

Long Nights, Bedrest, Light Therapy for Rapid Cycling Bipolar Disorder

Wirz-Justice A. A rapid-cycling bipolar patient treated with long nights, bedrest, and light. Biol Psychiatry 1999;45: 1075-1077

- *A previous study using morning light therapy in rapid-cycling bipolar patients worsened clinical state (Leibenluft et al 1995), but was not, as here, administered in combination with long nights and extended sleep. Our independent replication of dark/rest treatment strategy (Wehr et al 1998) indicates that chronobiologic protocols may be used as valuable adjunctive treatments to psychopharmacology, in particular, to interrupt rapid cycling."*

Chronotherapeutics Rapidly Decreases Depressive Suicidality in Drug-resistant Bipolar Disorder

Benedetti, Francesco, "Rapid Treatment Response of Suicidal Symptoms to Lithium, Sleep Deprivation, and Light Therapy (chronotherapeutics) in Drug-Resistant Bipolar Depression." The Journal of Clinical Psychiatry 75, no. 2 (February 2014): 133–40. doi:10.4088/JCP.13m08455.

- *"The combination of total sleep deprivation, light therapy, and lithium is able to rapidly decrease depressive suicidality and prompt antidepressant response in drug-resistant major depression in the course of bipolar disorder."*

Exercise and Movement

Aerobic Exercise

Aerobic Exercise is a Possible Treatment for Cognitive Dysfunction in Bipolar Disorder

Kucyi, Aaron, "Aerobic Physical Exercise as a Possible Treatment for Neurocognitive Dysfunction in Bipolar Disorder." Postgraduate Medicine 122, no. 6 (November 2010): 107–16. doi:10.3810/pgm.2010.11.2228.

- *"Available studies have documented an array of persisting neurocognitive deficits across disparate bipolar populations. Abnormalities in verbal working memory are highly replicated; deficits in executive function, learning, attention, and processing speed are also a consistent abnormality. The effect sizes of neurocognitive deficits in BD are intermediate between those reported in schizophrenia and major depressive disorder. Several original reports and reviews have documented the neurocognitive-enhancing*

effects of aerobic exercise in the general population as well as across diverse medical populations and ages. Proposed mechanisms involve nonexclusive effects on neurogenesis, neurotrophism, immunoinflammatory systems, insulin sensitivity, and neurotransmitter systems. Each of these effector systems are implicated in both normal and abnormal neurocognitive processes in BD."

Aerobic Physical Exercise May Be a Possible Treatment for Neurocognitive Dysfunction in Bipolar Disorder

Kucyi, Aaron, "Aerobic Physical Exercise as a Possible Treatment for Neurocognitive Dysfunction in Bipolar Disorder." Postgraduate Medicine 122, no. 6 (November 2010): 107–16. doi:10.3810/pgm.2010.11.2228.

- *"Available evidence provides a rationale for empirically evaluating the neurocognitive benefits of aerobic exercise in BD."*

Chiropractic Care

Chiropractic Care Reduces Symptoms in Bipolar Patient

Elster, Erin L. "Treatment of Bipolar, Seizure, and Sleep Disorders and Migraine Headaches Utilizing a Chiropractic Technique." Journal of Manipulative and Physiological Therapeutics 27, no. 3 (April 2004): E5. doi:10.1016/j.jmpt.2003.12.027.

- *"At initial examination, evidence of a subluxation stemming from the upper cervical spine was found through thermography and radiography. Chiropractic care using an upper cervical technique was administered to correct and stabilize the patient's upper neck injury. Assessments at baseline, 2 months, and 4 months were conducted by the patient's neurologist. After 1 month of care, the patient reported an absence of seizures and manic episodes and improved sleep patterns. After 4 months of care, seizures and manic episodes remained absent and migraine headaches were reduced from 3 per week to 2 per month. After 7 months of care, the patient reported the complete absence of symptoms. Eighteen months later, the patient remains asymptomatic."*

Physical Activity

Physical Activity has A Therapeutic Role in Bipolar Disorder

Ng, Felicity, "The Effects of Physical Activity in the Acute Treatment of Bipolar Disorder: A Pilot Study." Journal of Affective Disorders 101, no. 1–3 (August 2007): 259–62. doi:10.1016/j.jad.2006.11.014.

- *"The results of this trial provide preliminary support for a therapeutic role of physical activity in bipolar disorder, and warrant further investigation with randomised controlled trials."*

Yoga

Yoga Exercises Improved Positive State and Lowered Negative Emotion in Bipolar Disorder

Upmesh K. Talwar*, "Role of Yogic Exercises in Bipolar Affective Disorder and Schizophrenia" APRIL 2010 DELHI PSYCHIATRY JOURNAL Vol. 13 No.1

- *"In personal interview, the patients with Bipolar Disorders revealed enhancement in their positive emotional state and lowering of negative emotion. They subjectively reported improvement and control over their physical energy. Marked improvement was noticed in psychopathology among the patients of the study group in specific areas like anxiety, hostility, and excitement. In a pre-conclusive way, it can be said that yogic exercise therapy proved efficacious in the improvement and psychological wellbeing of the patients in the present study."*

Mindfulness, Hypnosis and Meditation

Hypnosis

Hypnosis in Regulating Bipolar Affective Disorders

Feinstein, A. D., "Hypnosis in Regulating Bipolar Affective Disorders." The American Journal of Clinical Hypnosis 29, no. 1 (July 1986): 29–38.

- *"A hypnotic procedure is presented for treating bipolar patients in instances where problems encountered in maintaining the patient on pharmacotherapy. Recent studies revealing electrochemical hemispheric asymmetry in manic-depressive illness, in the action of lithium, and in the effects of hypnosis led to speculation of hemispheric electrochemical activity. Advances allowing increased specificity in the regulation of physiological conditions through the use of hypnosis, biofeedback, meditation, and guided imagery provide a plausible rationale for this experimental technique. The procedure includes 1) determining relevant medical and psychosocial parameters, 2) establishing rapport and a positive response set for the therapy, 3) formulating suggestions for electrochemical regulation during heterohypnosis, 4) introducing self-hypnosis, and 5) addressing self-concept issues regarding the role of the illness in the patient's identity. The course of treatment of five bipolar patients is described."*

Meditation

Meditation Practice Lowers Depression and Anxiety Symptoms in those with Bipolar Disorder

Perich, Tania, "The Association between Meditation Practice and Treatment Outcome in Mindfulness-Based Cognitive Therapy for Bipolar Disorder." Behaviour Research and Therapy 51, no. 7 (July 2013): 338–43. doi:10.1016/j.brat.2013.03.006.

- *"There were significant differences found between those who meditated for 3 days a week or more and those who meditated less often on trait anxiety post-treatment and clinician-rated depression at 12-month follow-up whilst trends were noted for self-reported depression. A greater number of days meditated during the 8-week MBCT program was related to lower depression scores at 12-month follow-up, and there was evidence to suggest that mindfulness meditation practice was associated with improvements in depression and anxiety symptoms if a certain minimum amount (3 times a week or more) was practiced weekly throughout the 8-week MBCT program."*

Mindfulness

Mindfulness for Bipolar Disorder is Associated with Changes in Depressive Symptoms

Weber B. Mindfulness-based cognitive therapy for bipolar disorder: a feasibility trial. Eur Psychiatry 2010)ct;25(6):334-7

- *"Most participants reported having durably, moderately to very much benefited from the program, although mindfulness practice decreased over time. ….change of mindfulness skills was significantly associated with change in depressive symptoms between pre- and post-MBCT assessments."*

Deckersbach T. Mindfulness-based cognitive therapy for nonremitted patients with bipolar disorder. CNS Neurosci Ther 29=012 Feb;18(2):133-41

- *"These findings suggest that treating residual mood symptoms with MBCT may be another avenue to improving mood, emotion regulation, well being, and functioning in individuals with bipolar disorder."*

Electric Stimulation

Transcranial Direct Current Stimulation

Transcranial Direct Current Stimulation is Effective in Bipolar Depressive Disorder

Brunoni, A. R., "Transcranial Direct Current Stimulation (tDCS) in Unipolar vs. Bipolar Depressive Disorder." Progress in Neuro-Psychopharmacology & Biological Psychiatry 35, no. 1 (January 15, 2011): 96–101. doi:10.1016/j.pnpbp.2010.09.010.

- *"Transcranial direct current stimulation (tDCS) is a non-invasive method for brain stimulation. Although pilot trials have shown that tDCS yields promising results for major depressive disorder (MDD), its efficacy for bipolar depressive disorder (BDD), a condition with high prevalence and poor treatment outcomes, is unknown. In a previous study we explored the effectiveness of tDCS for MDD. Here, we expanded our research, recruiting patients with MDD and BDD. We enrolled 31 hospitalized patients (24 women) aged 30-70 years 17 with MDD and 14 with BDD (n = 14). All patients received stable drug regimens for at least two weeks before enrollment and drug dosages remained unchanged throughout the study. We applied tDCS over the dorsolateral prefrontal cortex (anodal electrode on the left and cathodal on the right) using a 2 mA-current for 20 min, twice-daily, for 5 consecutive days. Depression was measured at baseline, after 5 tDCS sessions, one week later, and one month after treatment onset. We used the scales of Beck (BDI) and Hamilton-21 items (HDRS). All patients tolerated treatment well without adverse effects. After the fifth tDCS session, depressive symptoms in both study groups diminished, and the beneficial effect persisted at one week and one month. In conclusion, our preliminary study suggests that tDCS is a promising treatment for patients with MDD and BDD.2."*

Cranial Electrotherapy Stimulation

Cranial Electrotherapy Stimulation Has Modest Improvement of Patients with Bipolar Disorder

Amr, Mostafa, "Cranial Electrotherapy Stimulation for the Treatment of Chronically Symptomatic Bipolar Patients." The Journal of ECT 29, no. 2 (June 2013): e31–32. doi:10.1097/YCT.0b013e31828a344d.

- *"The Clinical Global Impression improved significantly [mean (SD), 2.7 (0.6) at baseline vs 2.0 (0.0), t = 0, P < 0.001], but mood symptoms change minimally. There were very few adverse effects of CES. Patients with CSBP continue to experience symptoms with CES but also are modestly improved."*

Radioelectric Asymmetric Conveyor

Treatment with a Radioelectric Asymmetric Conveyor Shows Good Efficacy in Treating Both Manic and Depressive Phases in Bipolar Disorder

Mannu P. Long-term treatment of bipolar disorder with a radioelectric asymmetric conveyor. Neuropsychiatric Disease and Treatment 2011:7 373-379

- *"REAC showed good efficacy in treating both the manic and depressive phases of bipolar disorder, and the prevention of recurrences/relapses."*

Vestibular Stimulation

Caloric Vestibular Stimulation Has a Modulating Effect on Mood and Affective Control

Preuss, Nora, "Caloric Vestibular Stimulation Modulates Affective Control and Mood." Brain Stimulation 7, no. 1 (February 2014): 133–40. doi:10.1016/j.brs.2013.09.003.

- *"The sensitivity index d' (hits - false alarms) was used to measure affective control. Affective control improved during right ear CVS when viewing positive stimuli (P = .005), but decreased during left ear CVS when compared to sham stimulation (P = .009). CVS had a similar effect on positive mood ratings (Positive and Negative Affect Schedule). Positive mood ratings decreased during left ear CVS when compared to sham stimulation, but there was no effect after right ear CVS. The results suggest that CVS, depending on side of stimulation, has a modulating effect on mood and affective control. The results complement previous findings in manic patients and provide new evidence for the clinical potential of CVS."*

Left Ear Caloric Vestibular Stimulation is Effective for Short Term Reduction of Manic Delusions

Levine, Joseph, "Beneficial Effects of Caloric Vestibular Stimulation on Denial of Illness and Manic Delusions in Schizoaffective Disorder: A Case Report." Brain Stimulation 5, no. 3 (July 2012): 267–73. doi:10.1016/j.brs.2011.03.004.

- *"All three patients showed a difference favoring left versus right ear CVS that was maintained for 20 minutes, and diminished over a 60 minute period. EEG analyses showed a numerically non-significant increase in bilateral frontal and central alpha EEG band activation (more pronounced in the right hemisphere) with left but not right ear CVS 5 minutes after the CVS, and that diminished after 20 minutes. The results suggest that left versus right CVS may have a short lived beneficial effect on manic delusions and insight of illness that seem to appear in other types of psychoses (i.e., schizophrenia). These preliminary results suggest that single session CVS may have short lived beneficial effects in mania and perhaps in other types of psychoses. Further research is mandatory."*

Caloric Vestibular Stimulation is a Novel Approach for Treatment of Mania

Dodson MJ. Vestibular stimulation in mania: a case report. J Neurol Neurosurg Psychiarty 2004:75:163-171

- *"This case describes an impressive and relatively sustained improvement in manic symptoms following left caloric vestibular stimulation. Caloric vestibular stimulation represents a novel approach to the treatment of mania."*

Drugs

Aspirin

Aspirin Reduces Clinical Deterioration in Subjects on Lithium

Stolk P. Is aspirin useful in patients on lithium? A pharmacoepidemilogical study related to bipolar disorder. Prostagladins Leukot Essent Fatty Acids 2010 Jan;82(1):9-14

- **"***Low dose aspirin produced a statistically significant duration-independent reduction in relative risk of clinical deterioration in subjects on lithium, whereas other NSAIDs and glucocorticoids did not."*

Aspirin for Treatment of Lithium-associated Sexual Dysfunction in Men

Saroukhani S. Aspirin for the treatment of lithium-associated sexual dysfunction in men: randomized double-blind placebo-controlled study. Bipolar Disord 2013 Sep;15(6):650-6

- *"By week 6, patients in the aspirin group showed significantly greater improvement in the total (63.9% improvement from baseline) and erectile function domain (85.4% improvement from baseline) scores than the placebo group (14.4% and 19.7% improvement from baseline, p-values=0.002 and 0.001, respectively). By week 6, 12 (80%) patients in aspirin group and three (20%) patients in placebo group met the criteria of minimal clinically important change [x(2) (1)=10.800, p=0.001]. Other IIEF domains also showed significant improvement at end of trial."*

Medroxyprogesterone

Medroxyprogesterone May Improve Manic Symptoms in Women with Bipolar Disorder

Kulkarni, Jayashri, "A Pilot Study of Hormone Modulation as a New Treatment for Mania in Women with Bipolar Affective Disorder." Psychoneuroendocrinology 31, no. 4 (May 2006): 543–47. doi:10.1016/j.psyneuen.2005.11.001.

- *"We tested and compared the use of two adjunctive hormonal agents, tamoxifen and medroxyprogesterone acetate (MPA), for the treatment of acute mania or hypomania. A*

total of 13 women with acute Bipolar Affective Disorder in the manic or hypomanic phase were recruited from a clinical population to participate in this 28-day, three-arm, double blind, placebo-controlled study. The women who received tamoxifen exhibited significant improvement in symptoms of mania from baseline to final assessment compared with the placebo group. The MPA group improved more than the placebo group. Further exploration of tamoxifen as a useful adjunct in the treatment of acute manic symptoms in women with Bipolar Affective Disorder is warranted."

Medroxyprogesterone Provided Rapid Treatment of Manic Symptoms in Women with Mania

Kulkarni, Jayashri, "A Four Week Randomised Control Trial of Adjunctive Medroxyprogesterone and Tamoxifen in Women with Mania." Psychoneuroendocrinology 43 (May 2014): 52–61. doi:10.1016/j.psyneuen.2014.02.004.

- *"Emerging research has suggested that hormone treatments such as selective oestrogen receptor modulators (SERMs) or progestins may be useful in the treatment of mania. The current pilot study compared the use of the SERM tamoxifen and the progestin medroxyprogesterone acetate (MPA), as an adjunct to mood stabiliser medications, for the treatment of mania symptoms in 51 women in a 28-day double blind, placebo controlled study. The primary outcome was the change between baseline and day 28 mania scores as measured by the Clinician Administered Rating Scale for Mania (CARS-M). Adjunctive MPA treatment provided greater and more rapid improvement in mania symptoms compared with adjunctive placebo and tamoxifen treatment. Adjunctive therapy with MPA may be a potentially useful new treatment for persistent mania, leading to a greater and more rapid resolution of symptoms compared with mood stabiliser treatment alone."*

Medication-Induced Side Effect Treatments

Neuroprotection from Neuroleptics

Alpha Lipoic Acid

Alpha Lipoic Acid Down Regulates Antipsychotic-induced DRD2 Upregulation

Deslauriers, Jessica, "Antipsychotic-Induced DRD2 Upregulation and Its Prevention by A-Lipoic Acid in SH-SY5Y Neuroblastoma Cells." Synapse (New York, N.Y.) 65, no. 4 (April 2011): 321–31. doi:10.1002/syn.20851.

- *"Our results suggest that haloperidol-induced DRD2 upregulation is linked to oxidative stress and provide potential mechanisms by which (±)-α-lipoic acid can be considered as a*

therapeutic agent to prevent and treat side effects related to the use of first-generation APs."

Alpha Lipoic Acid Significantly Reduces Haldol-induced Neuronal Damage

Perera, Joachim, "Neuroprotective Effects of Alpha Lipoic Acid on Haloperidol-Induced Oxidative Stress in the Rat Brain." Cell & Bioscience 1, no. 1 (2011): 12. doi:10.1186/2045-3701-1-12.

- *"In the present study, we evaluate the protective effect of alpha lipoic acid against haloperidol-induced oxidative stress in the rat brain. Sprague Dawley rats were divided into control, alpha lipoic acid alone (100 mg/kg p.o for 21 days), haloperidol alone (2 mg/kg i.p for 21 days), and haloperidol with alpha lipoic acid groups (for 21 days). Haloperidol treatment significantly decreased levels of the brain antioxidant enzymes super oxide dismutase and glutathione peroxidase and concurrent treatment with alpha lipoic acid significantly reversed the oxidative effects of haloperidol. Histopathological changes revealed significant haloperidol-induced damage in the cerebral cortex, internal capsule, and substantia nigra. Alpha lipoic acid significantly reduced this damage and there were very little neuronal atrophy. Areas of angiogenesis were also seen in the alpha lipoic acid-treated group. In conclusion, the study proves that alpha lipoic acid treatment significantly reduces haloperidol-induced neuronal damage."*

Antioxidants

Antioxidants as Potential Therapeutics in Neuropsychiatric Disorders

Pandya, Chirayu D., "Antioxidants as Potential Therapeutics for Neuropsychiatric Disorders." Progress in Neuro-Psychopharmacology & Biological Psychiatry 46 (October 1, 2013): 214–23. doi:10.1016/j.pnpbp.2012.10.017.

- *"The present article will give an overview of the potential strategies and outcomes of using antioxidants as therapeutics in psychiatric disorders."*

Beta-glucan

Beta-glucan has Protective Effects against Lipid Peroxidation Induced by Haldol

Dietrich-Muszalska A. Beta-glucan from Saccharomyces cerevisiae reduces plasma lipid peroxidation induced by haloperidol. Int J Biol Macromol 2011 Jul 1;49(1): 113-6

- *"The presented results indicate that beta-glucan seems to have distinctly protective effects against the impairment of plasma lipid molecules induced by haloperidol."*

Choke Berries

Polyphenols from Choke Berries Reduce Lipid Peroxidation Caused by Geodon

Dietrich-Muszalska, Anna, "Polyphenols from Berries of Aronia Melanocarpa Reduce the Plasma Lipid Peroxidation Induced by Ziprasidone." Schizophrenia Research and Treatment 2014 (2014): 602390. doi:10.1155/2014/602390.

- *"Conclusion. Aronox causes a distinct reduction of lipid peroxidation induced by ziprasidone."*

Curcumin

Curcumin Has a Protective Effect against the Neurochemical Changes Associated with Haldol Administration

Bishnoi M. Protective effect of curcumin and its combination with piperine (bioavailability enhancer) against haloperidol-associated neurotoxicity: cellular and neurochemical evidence. Neurotox Res 2011 Oct;20(3):215-25

- *"Interestingly, co-administration of curcumin (25 and 50mg/kg, i.p., 21 days) dose dependently prevented all behavioral, cellular, and neurochemical changes associated with administration of haloperidol."*

Green Tea Epicatechin

Green Tea Epicatechin Significantly Reduces the Lipid Peroxidation of Haldol

Dietrich-Muszalska A. Epicatechin inhibits human plasma lipid peroxidation caused by haloperidol in vitro. Neurochem Res 2012 Mar;37(3):557-62

- *'In conclusion, the presented results indicate that epicatechin-the major polyphenolic component of green tea reduced significantly human plasma lipid peroxidation caused by haloperidol. Moreover, epicatechin was found to be more effective antioxidant, than the solution of pure resveratrol or quercetin."*

Nutrition

Dietitians Can Play a Supportive Role in Psychiatric Treatment

Gray, G. E., "Nutritional Aspects of Psychiatric Disorders." Journal of the American Dietetic Association 89, no. 10 (October 1989): 1492–98.

- *"As most diet therapy texts provide little information about psychiatric illnesses and their treatment, this article is intended as a brief introduction for dietitians. Several*

psychiatric illnesses, including schizophrenia, mood disorders, eating disorders, and substance abuse, may adversely affect food intake and nutritional status. The drugs used to treat those disorders similarly have effects on appetite and gastrointestinal function and interact with food and nutrients. Antipsychotics, antidepressants, and monoamine oxidase inhibitors (MAOIs) cause dry mouth, constipation, and weight gain. Lithium may cause nausea, vomiting, diarrhea, polydipsia, and weight gain. MAOIs have well-known interactions with foods containing tyramine. Lithium interacts with dietary sodium and caffeine; decreasing dietary intakes of those substances may produce lithium toxicity. Despite claims to the contrary, major psychiatric illnesses cannot be cured by nutritional therapies alone. Dietitians can, however, play an important role as part of a multidisciplinary team in the treatment of patients with psychiatric illness. Such a role includes nutrition assessment and monitoring, nutrition interventions, patient and staff education, and some forms of psychotherapy, including supportive and behavioral therapies for patients with eating disorders."

Early Nutrition is Important on Cognitive Neurodevelopment

Dauncey, M. J.,"Nutrition and Neurodevelopment: Mechanisms of Developmental Dysfunction and Disease in Later Life." Nutrition Research Reviews 12, no. 2 (December 1999): 231–53. doi:10.1079/095442299108728947.

- *"Randomized intervention studies have revealed important effects of early nutrition on later cognitive development, and recent epidemiological findings show that both genetics and environment are risk factors for schizophrenia. Particularly important is the effect of early nutrition on development of the hippocampus, a brain structure important in establishing learning and memory, and hence for cognitive performance. A major aim of future research should be to elucidate the molecular mechanisms underlying nutritionally-induced impairment of neurodevelopment and specifically to determine the mechanisms by which early nutritional experience affects later cognitive performance. Key research objectives should include: (1) increased understanding of mechanisms underlying the normal processes of ageing and neurodegenerative disorders; (2) assessment of the role of susceptibility genes in modulating the effects of early nutrition on neurodevelopment; and (3) development of nutritional and pharmaceutical strategies for preventing and/or ameliorating the adverse effects of early malnutrition on long-term programming."*

Phytochemicals

Phytochemicals Have Neuroprotective Effects in Neuropsychiatric Diseases

Kumar, G. Phani, "Neuroprotective Potential of Phytochemicals." Pharmacognosy Reviews 6, no. 12 (July 2012): 81–90. doi:10.4103/0973-7847.99898.

- *"In this review, we briefly deal with some medicinal herbs focusing on their neuroprotective active phytochemical substances like fatty acids, phenols, alkaloids, flavonoids, saponins, terpenes etc. The resistance of neurons to various stressors by activating specific signal transduction pathways and transcription factors are also discussed. It was observed in the review that a number of herbal medicines used in Ayurvedic practices as well Chinese medicines contain multiple compounds and phytochemicals that may have a neuroprotective effect which may prove beneficial in different neuropsychiatric and neurodegenerative disorders. Though the presence of receptors or transporters for polyphenols or other phytochemicals of the herbal preparations, in brain tissues remains to be ascertained, compounds with multiple targets appear as a potential and promising class of therapeutics for the treatment of diseases with a multifactorial etiology."*

Resveratrol and Quercetin

Resveratrol and Quercetin Decrease Lipid Peroxidation Caused by Antipsychotics

Dietrich-Muszalska A. Inhibitory effects of polyphenol compounds on lipid peroxidation caused by antipsychotics (haloperidol and amisulpride) in human plasma in vitro. The World Journal of Biological Psychiatry, 2009, 1-6

- *"We showed that in the presence of polyphenols: resveratrol and quercetin, lipid peroxidation in plasma samples treated with tested drugs was significantly decreased."*

Sulforaphane

Broccoli Sprouts Exract Sulforaphane Protects Against Antipsychotic Drug-induced Oxidative Stress

Mas, Sergi, "Sulforaphane Protects SK-N-SH Cells against Antipsychotic-Induced Oxidative Stress." Fundamental & Clinical Pharmacology 26, no. 6 (December 2012): 712–21. doi:10.1111/j.1472-8206.2011.00988.x.

- *"Our results indicate that SF increases GSH levels and induces NQO1 activity and the removal of electrophilic quinones and radical oxygen species. Furthermore, SF could provide protective effects against AP-induced toxicity in dopaminergic cells."*

Vitamin C

Vitamin C Reduces the Production of Reactive Oxygen Species from Antipsychotics

Heiser P. Effects of antipsychotics and vitamin C on the formation of reactive oxygen species. Journal of Psychopharmacology, (2009) 1-6

- *"Vitamin C reduced the ROS production of all drugs tested and for haloperidol and clozapine the level of significance was reached. Our study demonstrated that induce the formation of ROS in whole blood of rats, which can be reduced by application of vitamin C."*

Vitamin E

Vitamin E Has Plasma Membrane Stabalazation Properties that are compromised by Antipsychotics

Maruoka, Nobuyuki, "Effects of Vitamin E Supplementation on Plasma Membrane Permeabilization and Fluidization Induced by Chlorpromazine in the Rat Brain." Journal of Psychopharmacology (Oxford, England) 22, no. 2 (March 2008): 119–27. doi:10.1177/0269881107078487.

- *"CPZ can reduce plasma membrane integrity in the brain, and this reduction can be prevented by vitamin E via its membrane-stabilizing properties, not via its antioxidant activity."*

Vitamin E May Be Protective form Haldol-associated Neurotoxicity

Post A. Mechanisms underlying the protective potential of a-Tocopherol (Vitamin E) against Haloperidol-associated neurotoxicity. Neuropsychopharmacology. 2002, Vol. 26, No. 3

- *"…the present study shows that pre- and co-treatment with vitamin E interferes with the stimulation of apoptotic cascades by haloperidol and, in addition, attenuates some of the undesirable behavioral side-effects of the neuroleptic."*

Reversal of Cerebral Atrophy

Exercise

Cardiorespiratory Fitness Increases Brain Volume in Schizophrenic Patients

Scheewe, Thomas W., "Exercise Therapy, Cardiorespiratory Fitness and Their Effect on Brain Volumes: A Randomised Controlled Trial in Patients with Schizophrenia and Healthy Controls." European Neuropsychopharmacology: The Journal of the European College of Neuropsychopharmacology 23, no. 7 (July 2013): 675–85. doi:10.1016/j.euroneuro.2012.08.008.

- *"The objective of this study was to examine exercise effects on global brain volume, hippocampal volume, and cortical thickness in schizophrenia patients and healthy controls. Irrespective of diagnosis and intervention, associations between brain changes and cardiorespiratory fitness improvement were examined. Sixty-three schizophrenia patients and fifty-five healthy controls participated in this randomised controlled trial. Global brain volumes, hippocampal volume, and cortical thickness were estimated from 3-Tesla MRI scans. Cardiorespiratory fitness was assessed with a cardiopulmonary ergometer test. Subjects were assigned exercise therapy or occupational therapy (patients) and exercise therapy or life-as-usual (healthy controls) for six months 2h weekly. Exercise therapy effects were analysed for subjects who were compliant at least 50% of sessions offered. Significantly smaller baseline cerebral (grey) matter, and larger third ventricle volumes, and thinner cortex in most areas of the brain were found in patients versus controls. Exercise therapy did not affect global brain and hippocampal volume or cortical thickness in patients and controls. Cardiorespiratory fitness improvement was related to increased cerebral matter volume and lateral and third ventricle volume decrease in patients and to thickening in the left hemisphere in large areas of the frontal, temporal and cingulate cortex irrespective of diagnosis. One to 2h of exercise therapy did not elicit significant brain volume changes in patients or controls. However, cardiorespiratory fitness improvement attenuated brain volume changes in schizophrenia patients and increased thickness in large areas of the left cortex in both schizophrenia patients and healthy controls."*

Omega-3 Fatty Acid EPA

Omega-3 Fatty Acid EPA can Reverse Both Phospholipid Abnormalities and Cerebral Atrophy

Puri BK. Eicosapentaenoic acid treatment in schizophrenia associated with symptom remission, normalization of blood fatty acids, reduced neuronal membrane phosopholipid turnover and brain structure changes. Int J Clin Pract 2000; 54(1):57-63

- *"These results demonstrate that EPA can reverse both the phospholipid abnormalities previously described in schizophrenia and cerebral atrophy."*

Omega-3 Fatty Acid EPA Reveresed Cerebral Atrophy in Schizophrenic Patient

Puri, Basant K. "High-Resolution Magnetic Resonance Imaging Sinc-Interpolation-Based Subvoxel Registration and Semi-Automated Quantitative Lateral Ventricular Morphology Employing Threshold Computation and Binary Image Creation in the Study of Fatty Acid Interventions in Schizophrenia, Depression, Chronic Fatigue Syndrome and Huntington's Disease." International Review of Psychiatry (Abingdon, England) 18, no. 2 (April 2006): 149–54. doi:10.1080/09540260600583015.

- *"The first patient with schizophrenia to be treated solely with the n-3 long-chain polyunsaturated fatty acid eicosapentaenoic acid (EPA) showed a remark- able and sustained remission of positive and negative symptoms starting within a month of this intervention (Puri & Richardson, 1998). His brain was scanned with high-resolution MRI both at one year and six months before starting the EPA, while he remained antipsychotic drug-free. He underwent MRI brain scanning again at baseline (on starting the EPA), and then after taking the fatty acid daily for six months. Using the two techniques described in the previous section, it was found that cerebral atrophy had been taking place during the year before taking the EPA, with an increase in lateral ventricular volume occur- ring from 18,750mm3 (at minus one year with respect to EPA treatment), through 19,440mm3 (at minus six months) to 19,800mm3 at baseline. Normalizing these volumes to the total brain volume at each scan gave corresponding values of the ventricle-to-brain ratios (VBRs) of 0.0147, 0.0153 and 0.0155 (Puri et al., 2000; Puri & Richardson, 2003). After six months of taking EPA (and no other medication), there was a reversal of this cerebral atrophy, with the lateral ventricular volume being 18,850mm3 and the corresponding VBR falling back to 0.0148. These results were the first to indicate that EPA might be able to reverse cerebral atrophy, at least in schizo- phrenia, as well as to treat positive and negative symptoms in this disorder."*

Vitamin A

Vitamin A Supplementation May Reverse Loss of Hippocampal Long Term Synaptic Plasticity

Misner, D. L., "Vitamin A Deprivation Results in Reversible Loss of Hippocampal Long-Term Synaptic Plasticity." Proceedings of the National Academy of Sciences of the United States of America 98, no. 20 (September 25, 2001): 11714–19. doi:10.1073/pnas.191369798.

- *"Despite its long history, the central effects of progressive depletion of vitamin A in adult mice has not been previously described. An examination of vitamin-deprived animals revealed a progressive and ultimately profound impairment of hippocampal CA1 long-term potentiation and a virtual abolishment of long-term depression. Importantly, these losses are fully reversible by dietary vitamin A replenishment in vivo or direct application of all trans-retinoic acid to acute hippocampal slices. We find retinoid responsive transgenes to be highly active in the hippocampus, and by using dissected explants, we show the hippocampus to be a site of robust synthesis of bioactive retinoids. In aggregate, these results demonstrate that vitamin A and its active derivatives function as essential competence factors for long-term synaptic plasticity within the adult brain, and suggest that key genes required for long-term potentiation and long-term depression*

are retinoid dependent. These data suggest a major mental consequence for the hundreds of millions of adults and children who are vitamin A deficient."

Weight Gain Side Effect Treatments

Alpha Lipoic Acid

Alpha Lipoic Acid is Effective for Weight loss in Patients with Schizophrenia without Diabetes

Ratliff, Joseph C., "An Open-Label Pilot Trial of Alpha-Lipoic Acid for Weight Loss in Patients with Schizophrenia without Diabetes." Clinical Schizophrenia & Related Psychoses, March 7, 2013, 1–13. doi:10.3371/CSRP.RAPA.030113.

- *"A possible mechanism of antipsychotic-induced weight gain is activation of hypothalamic monophosphate-dependent kinase (AMPK) mediated by histamine 1 receptors. Alpha-lipoic acid (ALA), a potent antioxidant, counteracts this effect and may be helpful in reducing weight for patients taking antipsychotics. The objective of this open label study was to assess the efficacy of ALA (1200mg) on 12 non-diabetic schizophrenia patients over ten weeks. Participants lost significant weight during the intervention (-2.2 kg ± 2.5 kg). ALA was well tolerated and was particularly effective for individuals taking strongly antihistaminic antipsychotics (-2.9 kg ± 2.6 kg vs. -0.5 kg ± 1.0 kg)."*

Alpha Lipoic Acid is effective Treatment of Antipsychotic-induced Weight Gain and Improves Metabolic Abnormalities

Kim, Eosu, "A Preliminary Investigation of Alpha-Lipoic Acid Treatment of Antipsychotic Drug-Induced Weight Gain in Patients with Schizophrenia." Journal of Clinical Psychopharmacology 28, no. 2 (April 2008): 138–46. doi:10.1097/JCP.0b013e31816777f7.

- *"The mean (SD) weight loss was 3.16 (3.20) kg (P = 0.043, last observation carried forward; median, 3.03 kg; range, 0-8.85 kg). On average, body mass index showed a significant reduction (P = 0.028) over the 12 weeks. During the same period, a statistically significant reduction was also observed in total cholesterol levels (P = 0.042), and there was a weak trend toward the reduction in insulin resistance (homeostasis model assessment of insulin resistance) (P = 0.080). Three subjects reported increased energy subjectively. The total scores on the Brief Psychiatric Rating Scale and the Montgomery-Asberg Depression Rating Scale did not vary significantly during the study. These preliminary data suggest the possibility that ALA can ameliorate the adverse metabolic effects induced by AAPDs. To confirm the benefits of ALA, more extended study is warranted."*

Alpha Lipoic Acid Prevented Olanzapine-induced Weight Gain in Mice

Kim, Hyunjeong, "Phosphorylation of Hypothalamic AMPK on serine(485/491) Related to Sustained Weight Loss by Alpha-Lipoic Acid in Mice Treated with Olanzapine." Psychopharmacology, April 15, 2014. doi:10.1007/s00213-014-3540-3.

- *"Body weights were increased by olanzapine in parallel with increased levels of Thr172 phosphorylation of hypothalamic AMPK. Initially increased rate of weight gain was diminished as Thr172 phosphorylation levels were decreased to control levels after 10 days of olanzapine treatment. ALA successfully not only prevented olanzapine-induced weight gain but also induced additional weight loss even relative to control levels throughout the treatment period. During the initial stage, ALA's action was indicated by both suppression of olanzapine-induced Thr172 phosphorylation and an increase in Ser485/491 phosphorylation levels. However, in the later stage when no more increases in Thr172 phosphorylation and weight gain by olanzapine were observed, ALA's action was only indicated by increased levels of Ser485/491 phosphorylation. Our data suggest that anti-obesity effects of ALA may be related to modulation of both Ser485/491 phosphorylation and Thr172 phosphorylation of hypothalamic AMPK, while olanzapine-induced weight gain may be only associated with increase in Thr172 phosphorylation. This might be an important mechanistic clue for the future development of anti-obesity drugs beyond control of AAPD-induced weight gain."*

Behavioral Intervention

A Behavioral Weight Loss Intervention Significantly Reduced Weight Over a Period of 18 Months

Daumit, Gail L., "A Behavioral Weight-Loss Intervention in Persons with Serious Mental Illness." The New England Journal of Medicine 368, no. 17 (April 25, 2013): 1594–1602. doi:10.1056/NEJMoa1214530.

- *"A behavioral weight-loss intervention significantly reduced weight over a period of 18 months in overweight and obese adults with serious mental illness. Given the epidemic of obesity and weight-related disease among persons with serious mental illness, our findings support implementation of targeted behavioral weight-loss interventions in this high-risk population."*

Dietian Assisted Nutritional Intervention Reduces Weight Gain in Patients on Atypical Antipsychotics

Evans, Sherryn, "Nutritional Intervention to Prevent Weight Gain in Patients Commenced on Olanzapine: A Randomized Controlled Trial." The Australian and New

Zealand Journal of Psychiatry 39, no. 6 (June 2005): 479–86. doi:10.1111/j.1440-1614.2005.01607.x.

- *"After 3 months, the control group had gained significantly more weight than the treatment group (6.0 kg vs 2.0 kg, p < or = 0.002). Weight gain of more than 7% of initial weight occurred in 64% of the control group compared to 13% of the treatment group. The control group's BMI increased significantly more than the treatment group's (2 kg/m(2)vs 0.7 kg/m(2), p < or = 0.03). The treatment group reported significantly greater improvements in moderate exercise levels, quality of life, health and body image compared to the controls. At 6 months, the control group continued to show significantly more weight gain since baseline than the treatment group (9.9 kg vs 2.0 kg, p < or = 0.013) and consequently had significantly greater increases in BMI (3.2 kg/m(2)vs 0.8 kg/m(2), p < or = 0.017). Individual nutritional intervention provided by a dietitian is highly successful at preventing olanzapine-induced weight gain."*

Berberine

Berberine Prevents Zyprexa-induced Weight Gain in Rats

Hu, Yueshan, "Metformin and Berberine Prevent Olanzapine-Induced Weight Gain in Rats." PloS One 9, no. 3 (2014): e93310. doi:10.1371/journal.pone.0093310.

- *"Olanzapine is a first line medication for the treatment of schizophrenia, but it is also one of the atypical antipsychotics carrying the highest risk of weight gain. Metformin was reported to produce significant attenuation of antipsychotic-induced weight gain in patients, while the study of preventing olanzapine-induced weight gain in an animal model is absent. Berberine, an herbal alkaloid, was shown in our previous studies to prevent fat accumulation in vitro and in vivo. Utilizing a well-replicated rat model of olanzapine-induced weight gain, here we demonstrated that two weeks of metformin or berberine treatment significantly prevented the olanzapine-induced weight gain and white fat accumulation. Neither metformin nor berberine treatment demonstrated a significant inhibition of olanzapine-increased food intake. But interestingly, a significant loss of brown adipose tissue caused by olanzapine treatment was prevented by the addition of metformin or berberine. Our gene expression analysis also demonstrated that the weight gain prevention efficacy of metformin or berberine treatment was associated with changes in the expression of multiple key genes controlling energy expenditure. This study not only demonstrates a significant preventive efficacy of metformin and berberine treatment on olanzapine-induced weight gain in rats, but also suggests a potential mechanism of action for preventing olanzapine-reduced energy expenditure."*

Berberine May Prevent Weight Gain during Use of Second Generation Antipsychotic Medication

Hu, Yueshan, "Berberine Inhibits SREBP-1-Related Clozapine and Risperidone Induced Adipogenesis in 3T3-L1 Cells." Phytotherapy Research: PTR 24, no. 12 (December 2010): 1831–38. doi:10.1002/ptr.3204.

- *"The results showed that neither clozapine nor risperidone, alone or in combination with berberine had significant effects on cell viability. Eight days treatment with 15 μM clozapine increased adipogenesis by 37.4% and 50 μM risperidone increased adipogenesis by 26.5% during 3T3-L1 cell differentiation accompanied by increased SREBP-1, PPARγ, C/EBPα, LDLR and Adiponectin gene expression. More importantly, the addition of 8 μM berberine diminished the induction of adipogenesis almost completely accompanied by down-regulated mRNA and protein expression levels of SREBP-1-related proteins. These encouraging results may lead to the use of berberine as an adjuvant to prevent weight gain during second generation antipsychotic medication."*

Bofu-tsusho-san

Bofu-tsusho-san Effectively Attenuates Weight Gain in Woman on Zyprexa

Yamamoto N. Bofu-tsusho-san effectively attenuates the weight gain observed after receiving olanzapine. Psychiatry Clin Neurosci 2008 Dec;62(6):747

- *A 20 year old woman with schizophrenia on medication, experiencing weight gain, lost 2.7kg of weight in 6 months with additional use of Bofu-tsusho-san with no changes of food intake . "In study of obese mice, bofu-tsusho-san produced a significant decrease in fat mass and weight compared with placebo, with-out effecting amount of food ingested"*

Green Tea and CLA

Green Tea and CLA Decrease Body Fat in Patients Taking Seroquel Antipsychotic

Katzman M. Weight gain and psychiatric treatment: is there as role for green tea and conjugayed linoleic acid? Lipids in Health and Disease 2007, 6:14

- *"In these four adults who were taking quietiapine, the concurrent self-administration of green tea and conjugated linoleic acid appeared to be protective against gains in body fat. The results were fairly consistent; each had a decrease in body fat percentage and increase in lean body mass."*

Ling Gui Zhu Gan Tang

Ling Gui Zhu Gan Tang Mixture is Effective for Psychotropic Drug-Induced Obesity

Ding, Guo'an, "The Therapeutic Effects of Ling Gui Zhu Gan Tang Mixture in 50 Psychotic Patients with Obesity Induced by the Psychoactive Drugs." Journal of

Traditional Chinese Medicine = Chung I Tsa Chih Ying Wen Pan / Sponsored by All-China Association of Traditional Chinese Medicine, Academy of Traditional Chinese Medicine 25, no. 1 (March 2005): 25–28.

- *"In order to observe the therapeutic effects of Ling Gui Zhu Gan Tang Mixture (苓桂术甘汤) on obesity induced by psychoactive drugs, 100 psychotics with obesity induced by psychoactive drugs were randomly divided into a treatment group (50 cases) and acontrolgroup (50 cases) for a 8-week treatment. The changes were determined by means of the Brief Psychiatric Rating Scale (BPRS) and the Treatment Emergent Symptom Scale (TESS) with the body weight recorded before and after treatment. The results showed that the total effective rate was 72%in the treatment group, and 14% in the control group, with the former obviously superior to the latter (P <0.01). The BPRS scores were 33.02±7.34 in the treatment group and 32.39±3.51 in the control group before treatment; and 20.38±5.10 in the treatment group and 20.82± 1.75 in the control group after treatment. The BPRS scores were obviously reduced after treatment in the two groups (both P <0.01), but with no significant difference between the two groups (P >0.05). This indicates that the Ling Gui Zhu Gan Tang Mixture does not influence the curative effect of the psychoactive drugs while showing the body weight-reducing effect. Therefore, the Ling Gui Zhu Gan Tang Mixture can be used for those psychotic patients with obesity induced by the psychoactive drugs (the incidence is 10-25%) in their continuous course of treatment with the latter drugs."*

Melatonin

Melatonin Attenuates Weight Gain, Abdominal Obesity and Hypertriglycerdemia in Schizophrenic Patients on Zyprexa

Modabbernia, Amirhossein, "Melatonin for Prevention of Metabolic Side-Effects of Olanzapine in Patients with First-Episode Schizophrenia: Randomized Double-Blind Placebo-Controlled Study." Journal of Psychiatric Research 53 (June 2014): 133–40. doi:10.1016/j.jpsychires.2014.02.013.

- *"To summarize, in patients treated with olanzapine, short-term melatonin treatment attenuates weight gain, abdominal obesity, and hypertriglyceridemia. It might also provide additional benefit for treatment of psychosis."*

Zyprexa-induced Weight Gain is blocked by Melatonin Replacement Therapy in Rats

Raskind, Murray A., "Olanzapine-Induced Weight Gain and Increased Visceral Adiposity Is Blocked by Melatonin Replacement Therapy in Rats." Neuropsychopharmacology: Official Publication of the American College of

Neuropsychopharmacology 32, no. 2 (February 2007): 284–88. doi:10.1038/sj.npp.1301093.

- *"Olanzapine treatment reduced nocturnal plasma melatonin by 55% ($p<0.001$), which was restored to control levels by olanzapine+melatonin. Body weight increased 18% in rats treated with olanzapine alone, but only 10% with olanzapine+melatonin, 5% with melatonin alone, and 7% with vehicle control. Body weight and visceral fat pad weight increases in rats treated with olanzapine alone were greater than in each of the other three groups (all $p<0.01$), which were not significantly different. These results suggest that olanzapine-induced increases in body weight and visceral adiposity may be at least in part secondary to olanzapine-induced reduction of plasma melatonin levels, and that melatonin may be useful for the management of olanzapine-induced weight gain in humans."*

Tamarindus Indica

Tamarindus Indica Fruit Pulp Showed Significant Weight Reducing and Hypolipidemic Acitivity in Antipsychotic-induced Obese Rats

Jindal, Vaneeta, "Hypolipidemic and Weight Reducing Activity of the Ethanolic Extract of Tamarindus Indica Fruit Pulp in Cafeteria Diet- and Sulpiride-Induced Obese Rats." Journal of Pharmacology & Pharmacotherapeutics 2, no. 2 (2011): 80–84. doi:10.4103/0976-500X.81896.

- *"Thus, the ethanolic extract of Tamarindus indica fruit pulp showed a significant weight-reducing and hypolipidemic activity in cafeteria diet- and sulpiride-induced obese rats."*

Vitamin D

Vitamin D May Be a Possible Candidate for Weight Loss from Second Generation Antipsychotics

Nwosu, Benjamin U., "A Potential Role for Adjunctive Vitamin D Therapy in the Management of Weight Gain and Metabolic Side Effects of Second-Generation Antipsychotics." Journal of Pediatric Endocrinology & Metabolism: JPEM 24, no. 9–10 (2011): 619–26.

- *"In summary, SGA medications are increasingly being prescribed to treat psychiatric illnesses in children and adolescents. However, the use of these agents is limited by their severe metabolic side effects. The mechanism(s) of these adverse events are unknown, and there is a lack of consensus on the best approach to address these problems. In conclusion, adjunctive vitamin D therapy may play a role in counteracting the adipogenic effects of SGA agents."*

Polydipsia-Hyponatremia Side Effect Treatments

Behavioral Intervention

Behavioral Intervention for Polydipsia in Schizophrenia Incorporates Self-monintoring, Stimulus Control, Coping Skills Training and Reinforement Components

Costanzo, Erin S., "Behavioral and Medical Treatment of Chronic Polydipsia in a Patient with Schizophrenia and Diabetes Insipidus." Psychosomatic Medicine 66, no. 2 (April 2004): 283–86.

- *"The 12-session individual behavioral intervention incorporated self-monitoring, stimulus control, coping skills training, and reinforcement components. The patient engaged fully in the treatment program, and she successfully restricted her fluid intake. Her diabetes insipidus could therefore be treated with desmopressin, a medication that requires fluid restriction, and she experienced a concomitant reduction in polyuria and urinary incontinence. The outpatient behavioral intervention demonstrated promising outcomes in a chronically mentally ill patient whose polydipsia had underlying psychogenic and physiological components. This case highlights the efficacy of combining behavioral and medical interventions."*

Behavioral Treatment of Polydipsia is Effecive in After Hospital Discharge

Bowen, L., "Successful Behavioral Treatment of Polydipsia in a Schizophrenic Patient." Journal of Behavior Therapy and Experimental Psychiatry 21, no. 1 (March 1990): 53–61.

- *"Behavioral treatment of a 35 year old female with chronic schizophrenia and water intoxication with seizures was conducted on an inpatient psychiatric unit. Treatment included frequent daily weights, restricted fluid intake, positive reinforcement for program compliance, and time-out from reinforcement following significant weight gain or other specified program violations. The final 6 months of the 30 month treatment program were a maintenance phase during which most contingencies were faded and all fluid restrictions were removed. There was no reported recurrence of polydipsia after 18 months of community placement."*

Behavioral Intervention to Reduce Water Intake Reduces Hyponatremia in Schizophrenic Patient

Pavalonis, D. "Behavioral Intervention to Reduce Water Intake in the Syndrome of Psychosis, Intermittent Hyponatremia, and Polydipsia." Journal of Behavior Therapy and Experimental Psychiatry 23, no. 1 (March 1992): 51–57.

- *"We describe a non-intensive behavioral intervention using an A-B design with extended follow-up on an open psychiatric unit to reduce water intake in a 52-year-old man with the syndrome of psychosis, intermittent hyponatremia, and polydipsia. A reinforcement schedule contingent upon weight gain secondary to water intake was employed. Mean diurnal weight gain was 7.1 pounds during a 23-week baseline which dropped to 4.1 pounds following 23 weeks of treatment and at a 1-year follow-up. Estimated fluid consumption dropped from 10 liters to 4 liters daily and incidents of hyponatremia decreased by 62%."*

Salt

Salt in the Management of Self-induced Water Intoxication of Schizophrenic Patients

Vieweg, W. V., "Oral Sodium Chloride in the Management of Schizophrenic Patients with Self-Induced Water Intoxication." The Journal of Clinical Psychiatry 46, no. 1 (January 1985): 16–19.

- *"Hyponatremia is always present in patients with water intoxication and accounts for many of the life-threatening symptoms and signs found in this population. In schizophrenic patients, water restriction, a cornerstone in the treatment of water intoxication, may be impossible to implement over the course of long-term management. The use of oral sodium chloride administration in such patients and its short-term efficacy in preventing major motor seizures are described."*

Sports Drink

Electrolyte-Balanced Sports Drink is Effective for Polydipsia-Hyponatremia in Schizophrenia

QUITKIN, FREDERIC M., "Electrolyte-Balanced Sports Drink for Polydipsia-Hyponatremia in Schizophrenia." American Journal of Psychiatry 160, no. 2 (February 1, 2003): 385–a. doi:10.1176/appi.ajp.160.2.385-a.

- *"One month after discharge, Mr. A's sodium levels were still below normal (127 mmol/liter) and appeared to be life threatening. He did not understand the importance of limiting fluid intake. His elderly mother was unable to monitor his drinking. Mr. A's fluid intake was limited to an electrolyte-balanced sports drink. He took one 19-mg salt pill with each meal. In the past year, his sodium levels have been normal, there have been no seizures, and his mental status has improved. At the time this treatment was initiated, hyponatremia, coma, and death appeared possible. Use of previously recommended behavioral and pharmacological treatments were unsuccessful (1–4). While water restriction of a delusional polydipsic patient outside a hospital may not be feasible, an electrolyte-balanced solution may be lifesaving. This anecdotal observation requires*

replication. Of note is that this patient's mental status improved, as evidenced by enhanced orientation, with stabilized sodium levels."

Urea

Oral Urea Treatment is Partialy Effective for Polydipsia-Hyponatermia Syndrome in Schizophrenic Patients

Kawai, Nobutoshi, "Oral Urea Treatment for Polydipsia-Hyponatremia Syndrome in Patients with Schizophrenia." *Journal of Clinical Psychopharmacology* 29, no. 5 (October 2009): 499–501. doi:10.1097/JCP.0b013e3181b3b38c.

- *"This study has some limitations. The study was designed as an open naturalistic trial without a control group. The sample sizewas small. The mean sodium concentration with the highest dosage used (67.5 g/d) was still below reference range, suggesting that oral urea treatment would not be an entire solution for PHS. We could not find significant difference between mean serum sodium concentrations with 45- and 67.5-g doses. The optimal urea dosage should be determined in future studies. Neverless, increased serum sodium levels not only in the morning but also in the afternoon in schizophrenic patients with PHS support the notion that the oral urea treatment possibly reduces the risk of severe hyponatremia. Further studies with larger sample sizes and longer-term protocols are required to evaluate benifical effects and safety of oral urea treatment for schizophrenic patients with PHS."*

Urea Appears to Be an Effective Therapuetic Appraoch for Polydisia-Hyponatermia Syndrome

Verhoeven, Anne, "Treatment of the Polydipsia-Hyponatremia Syndrome with Urea." The Journal of Clinical Psychiatry 66, no. 11 (November 2005): 1372–75.

- *"These preliminary data show that urea appears to be an effective therapeutic approach for the polydipsiahyponatremia syndrome."*

Group Psychotherapy

Group Psychotherapy for Polydipsia Reduces Self-Induced Water Intoxication in Schizophrenic Patients

Millson, R. C., "Self-Induced Water Intoxication Treated with Group Psychotherapy." The American Journal of Psychiatry 150, no. 5 (May 1993): 825–26.

- *"The authors conducted a controlled, prospective 4-month study of 10 male inpatients with chronic schizophrenia and polydipsia. The five men who were treated with group*

psychotherapy drank significantly less fluid than the five men not given this therapy. The effect of group psychotherapy quickly dissipated in the follow-up period, indicating the need for ongoing treatment."

Cardiac and Blood Disorder Side Effect Treatments

Aspirin

Aspirin appears to be the Molecule of Choice for Cardiovascular Disease Prevention in Bipolar Disorders

Fond, Guillaume, "Aspirin for Prevention of Cardiovascular Events in Bipolar Disorders." Psychiatry Research 219, no. 1 (September 30, 2014): 238–39. doi:10.1016/j.psychres.2014.05.011.

- *"The burden of CVD among patients with bipolar disorders is thus substantial. Aspirin appears as a molecule of choice to be tested in CVD prevention in bipolar disorders."*

Aspirin is Doubly Helpful in Bipolar Disorder

Fond, Guillaume, "Recently Discovered Properties of Aspirin May Be Doubly Helpful in Bipolar Disorders." Medical Hypotheses 82, no. 5 (May 2014): 640–41. doi:10.1016/j.mehy.2014.02.028.

- *"Aspirin may be doubly helpful in bipolar disorders, for prevention of cardiovascular events as well as an anti-inflammatory drug that may influence and protest the central nervous system."*

B Vitamin and Omega 3

Correction of Omega-3 EFA Deficiency and B Vitamin Status Reduces the Risk of Cardiovascular Disease

Kemperman, R. F. J., "Low Essential Fatty Acid and B-Vitamin Status in a Subgroup of Patients with Schizophrenia and Its Response to Dietary Supplementation." Prostaglandins, Leukotrienes, and Essential Fatty Acids 74, no. 2 (February 2006): 75–85. doi:10.1016/j.plefa.2005.11.004.

- *"We conclude that a subgroup of patients with schizophrenia has biochemical EFA deficiency, omega3/DHA marginality, moderate hyperhomocysteinemia, or combinations. Correction seems indicated in view of the possible relation of poor EFA and B-vitamin status with some of their psychiatric symptoms, but notably to reduce their high risk of cardiovascular disease."*

Coenzyme Q10

Coenzyme Q10 is Protective for Neuroleptic-induced Cell Damage in Rat Myocardial Cells

Chiba M. A protective action of coenzyme Q10 on chlorpromazine-induced cell damage in cultured rat myocardial cells. Jpn Heart J 1984 Jan;25(1):127-37

- *"These findings suggest that CoQ may protect myocardial cells from CPZ-induced injury, and that prostaglandins may play an important role in the action of CoQ."*

Omega-3

Omega-3 Fatty Acids Have a Significant Reduction on Triglyceride Levels in Patients Using Clozapine

Caniato, Riccardo N., "Effect of Omega-3 Fatty Acids on the Lipid Profile of Patients Taking Clozapine." The Australian and New Zealand Journal of Psychiatry 40, no. 8 (August 2006): 691–97. doi:10.1111/j.1440-1614.2006.01869.x.

- *"This study demonstrated high rates of lipid abnormalities in the participants. Participants taking omega-3 fatty acids demonstrated a statistically significant reduction in mean serum triglyceride levels of 22%. There was an associated increase in total cholesterol (6.6%) and low-density lipoprotein cholesterol (22%). Common side-effects included fishy burps or breath, but no serious side-effects or interactions where observed. Omega-3 fatty acids may be of value in patients taking clozapine and who have elevated serum triglyceride levels. Limitations of the study, practical implications and directions for future research are discussed."*

Omega-3 Fatty Acids Decrease Fasting Insulin Levels in Patients on Zyprexa, Depakote or Lithuim Combination

Toktam, Faghihi, "Effect of Early Intervention with Omega-3 on Insulin Resistance in Patients Initiated on Olanzapine with Either Sodium Valproate or Lithium: A Randomized, Double-Blind, Placebo-Controlled Trial." Iranian Journal of Psychiatry 5, no. 1 (2010): 18–22.

- *"At the end of the study, no significant difference was observed between the two arms in terms of FBS, fasting insulin, HbA(1c) and HOMA-IR. However, trends toward decreasing both fasting insulin levels (p=0.06) and HOMA-IR (p=0.07) were noted in the group receiving omega-3. No significant changes in the outcome variables were observed from the baseline to the final measurements in both groups. This study noted that adding omega-3 fatty acids at the commencement of olanzapine combination therapy with*

valproate or lithium could not favorably influence glucose-insulin homeostasis. However, trends toward a decrease in insulin levels (p=0.06) and HOMA-IR (p=0.07) observed in patients receiving omega-3 suggest a possible beneficial role of this supplement."

Omega-3 Fatty Acids are Promising Treaments for Antipsychotic-induced Dyslipidemia

Pisano, Simone, "Antipsychotic-Induced Dyslipidemia Treated with Omega 3 Fatty Acid Supplement in an 11-Year-Old Psychotic Child: A 1-Year Follow-Up." Journal of Child and Adolescent Psychopharmacology 23, no. 2 (March 2013): 139–41. doi:10.1089/cap.2012.0060.

- *"This case report represents the first example of treatment strategy of antipsychotic-induced dyslipidemia in children, on the basis of evidence that omega 3 is effective in the treatment of dyslipidemia in general medicine (Balk et al. 2006). Although considering all limitations of a single case report, the degree of reduction of TC, LDL, and TG, as well as the increase of HDL, the long period of follow-up and the stopping–reintroducing strategy provide some evidence of the direct effect of omega 3 supplement on metabolic changes. We have to highlight that non-significant changes of lifestyle or diet were reported by parents during the treatment. The data on weight need clarifi- cation. Weight seems to be independent of omega 3 supplement but we report a slight stabilization effect at beginning of treat- ment. On the basis of this report, a possible role of omega 3 fatty acid supplement in the treatment of antipsychotic-induced dyslipidemia could be hypothesized. We suggest that omega 3 supplement treatment, associated with physical exercise and balanced diet, could be a good strategy to moderate antipsy- chotic-induced dyslipidemia, and a short trial of this strategy can avoid sudden switches of antipsychotic drug. Our group is planning a trial to test the possible preventive role of omega 3 fatty acid supplement in antipsychotic-induced metabolic syn- drome in children and adolescents."*

Omega-3 Fatty Acids Are Associated With Improvements in Triglyceride and HDL Cholesterol Levels in Patients Taking Atyptical Antipsychotics

Fetter, Jeffrey Charles, "N-3 Fatty Acids for Hypertriglyceridemia in Patients Taking Second-Generation Antipsychotics." Clinical Schizophrenia & Related Psychoses 7, no. 2 (2013): 73–77A. doi:10.3371/CSRP.FEBR.012513.

- *"In this pilot study, treatment with N-3 FA was associated with improvements in triglyceride and HDL levels. Further study is warranted to assess more completely whether this prescription dietary supplement can reduce triglycerides in patients taking second-generation antipsychotics."*

Omega-3 Consumption and Supplementation May Protect Against Sudden Cardiac Death in Schizophrenia

Scorza, Fulvio A.,"Omega-3 Consumption and Sudden Cardiac Death in Schizophrenia." Prostaglandins, Leukotrienes, and Essential Fatty Acids 81, no. 4 (October 2009): 241–45. doi:10.1016/j.plefa.2009.06.008.

- *"As omega-3 fatty acids have been considered a cardioprotector agent, reducing cardiac arrhythmias and hence sudden cardiac deaths and given their relative safety and general health benefits, our update article summarizes the knowledge by the possible positive effects of omega-3 supplementation and fish consumption against sudden cardiac death in patients with schizophrenia. However, fish species should be selected with caution due to contamination with toxic methylmercury."*

Omega-3 Fatty Acids for Hypertriglycerdemia in Patients Taking Second Generation Antipsychotics

Fetter JC. N-3 fatty acids for hypertriglyceridemia in patients taking second-generation antipsychotics. Clin Schizophr Relat Psychoses 2013 Summer;7(2):73-77A

- *"Mean triglyceride levels decreased by 70.4+-50.4 mg/dL (p=0.001). Among secondary endpoints, mean HDL increased by 2.6+-3.5(p=0.03). However, LDL and total cholesterol, blood pressure, HOMA-IR and CPR did not significantly change."*

Caniato RN. Effect of omega-3 fatty acids on the lipid profile of patients taking clozapine. Aust N Z J Psychiatry 2006 Aug; 40 (8):691-7

- *Participants taking omega-3 fatty acids demonstrated a statistically significant reduction in mean serum triglyceride levels of 22%. There was an associated increase in total cholesterol (6'6%) and low-density lipoprotein cholesterol (22%). Common side-effects included fishy burps or breath, but no serious side effects or interactions were observed.Omega-3 fatty acids may be of value in patients taking clozapine and who have elevated serum triglyceride levels."*

Withania somnifera

Hypolipidemic and Hypoglycemic Actions of Withania somnifera for Treatment in Schizophrenia

Agnihotri AP. Effects of Withania somnifera in patients of schizophrenia: A randomized, double blind, placebo controlled pilot trial study. Indian Journal of Pharmacology 45. 4 (2013): 417

- *"No change in all three biochemical parameters was found after 1 month of treatment in the placebo group. However, a statistically significant (p<0.05) reduction in serum*

triglycerides and FBG was observed after 1 month of WS treatment compared to the placebo group."

Vitamin B

B Vitamin Therapy Causes a Decline in Symptoms of Schizophrenia and Homocysteine Levels to Decline

Levine, Joseph, "Homocysteine-Reducing Strategies Improve Symptoms in Chronic Schizophrenic Patients with Hyperhomocysteinemia." Biological Psychiatry 60, no. 3 (August 1, 2006): 265–69. doi:10.1016/j.biopsych.2005.10.009.

- *"Homocysteine levels declined with vitamin therapy compared with placebo in all patients except for one noncompliant subject. Clinical symptoms of schizophrenia as measured by the Positive and Negative Syndrome Scale declined significantly with active treatment compared with placebo. Neuropsychological test results overall, and Wisconsin Card Sort (Categories Completed) test results in particular, were significantly better after vitamin treatment than after placebo. A subgroup of schizophrenic patients with hyperhomocysteinemia might benefit from the simple addition of B vitamins."*

High-dose Vitamin B6 Decreases Homocysteine Levels in Patients with Schizophrenia

Miodownik, Chanoch, "High-Dose Vitamin B6 Decreases Homocysteine Serum Levels in Patients with Schizophrenia and Schizoaffective Disorders: A Preliminary Study." Clinical Neuropharmacology 30, no. 1 (February 2007): 13–17. doi:10.1097/01.WNF.0000236770.38903.AF.

- *"Age was significantly positively correlated with Hcy levels at baseline (r = 0.392, P = 0.004). All other parameters, including diagnosis, disease duration, and pyridoxal-5-phosphate serum level, were not correlated with Hcy serum levels at baseline. After vitamin B6 treatment, Hcy serum levels significantly decreased (14.2 +/- 3.4 vs. 11.8 +/- 2.0 micromol/L, respectively, t = 2.679, P = 0.023); this decrease being statistically significant in men but not in women. High doses of vitamin B6 lead to a decrease in Hcy serum level in male patients with schizophrenia or schizoaffective disorder."*

Vitamin D

Patients with Greater Vitamin D Levels have Significant Decrease in Total Cholesterol Levels

Thakurathi, Neelam, "Open-Label Pilot Study on Vitamin D_3 Supplementation for Antipsychotic-Associated Metabolic Anomalies." International Clinical

Psychopharmacology 28, no. 5 (September 2013): 275–82. doi:10.1097/YIC.0b013e3283628f98.

- *"Previous studies have linked vitamin D deficiency to hypertension, dyslipidemia, diabetes mellitus, and cardiovascular disease. The aim of this study was to investigate the short-term effects of vitamin D_3 supplementation on weight and glucose and lipid metabolism in antipsychotic-treated patients. A total of 19 schizophrenic or schizoaffective patients (BMI>27 kg/m²) taking atypical antipsychotics were recruited and dispensed a 2000 IU daily dose of vitamin D_3. On comparing baseline with week 8 (study end) results, we found a statistically significant increase in vitamin D_3 and total vitamin D levels but no statistically significant changes in weight, glucose, or lipids measurements. Patients whose vitamin D_3 level at week 8 was 30 ng/ml or more achieved a significantly greater decrease in total cholesterol levels compared with those whose week 8 vitamin D_3 measurement was less than 30 ng/ml. These results suggest that a randomized trial with a longer follow-up period would be helpful in further evaluating the effects of vitamin D_3 on weight, lipid metabolism, and on components of metabolic syndrome in antipsychotic-treated patients."*

Drug-induced Sexual Dysfunction Treatments

Acupuncture

Acupuncture is Effective Treatment for Sexual Dysfunction Secondary to Antidepressants

Khamba B. Efficacy of Acupuncture Treatment of Sexual Dysfunction Secondary to Antidepressants. J Altern Complemt Med 2013 Jun 21

- *"This study suggests a potential role for acupuncture in the treatment of sexual side effects of SSRIs and SNRIs as well for a potential benefit of integrating medical and complementary and alternative practitioners."*

Ginkgo Biloba

Prozac-Induced Genital Anesthesia Relieved by Ginkgo Biloba Extract

Ellison, J. M., "Fluoxetine-Induced Genital Anesthesia Relieved by Ginkgo Biloba Extract." The Journal of Clinical Psychiatry 59, no. 4 (April 1998): 199–200.

- *The improvement in this patient's genital anesthesia appears temporally associated with use of EGb, but this uncontrolled case report cannot refute with certainty the possibility that she improved spontaneously. Because antidepressant-induced sexual dysfunctions impair patients' quality of life and reduce compliance with treatment, more rigorously*

controlled double- blind investigation of EGb and other potential remedies for anti-depressant-induced sexual dysfunctions is desired.

Maca Root

Maca Root May Alleviate SSRI-induced Sexual Dysfunction

Dording, Christina M., "A Double-Blind, Randomized, Pilot Dose-Finding Study of Maca Root (L. Meyenii) for the Management of SSRI-Induced Sexual Dysfunction." CNS Neuroscience & Therapeutics 14, no. 3 (2008): 182–91. doi:10.1111/j.1755-5949.2008.00052.x.

- *"Maca was well tolerated. Maca root may alleviate SSRI-induced sexual dysfunction, and there may be a dose-related effect. Maca may also have a beneficial effect on libido."*

Saffron

Saffron is Efficacious Treatment for Prozac Related Erectile Dysfunction

Modabbernia, Amirhossein, "Effect of Saffron on Fluoxetine-Induced Sexual Impairment in Men: Randomized Double-Blind Placebo-Controlled Trial." Psychopharmacology 223, no. 4 (October 2012): 381–88. doi:10.1007/s00213-012-2729-6.

- *"Nine patients (60%) in the saffron group and one patient (7%) in the placebo group achieved normal erectile function (score > 25 on erectile function domain) at the end of the study (P value of Fisher's exact test = 0.005). Frequency of side effects were similar between the two groups. Saffron is a tolerable and efficacious treatment for fluoxetine-related erectile dysfunction."*

Saikokaryukotsuboreito

Saikokaryukotsuboreito Herbal Medicine is Effective for Antipsychotic Induced Sexual Dysfunction in Men

Takashi, Tsuboi,"Effectiveness of Saikokaryukotsuboreito (herbal Medicine) for Antipsychotic-Induced Sexual Dysfunction in Male Patients with Schizophrenia: A Description of Two Cases." Case Reports in Psychiatry 2014 (2014): 784671. doi:10.1155/2014/784671.

- *"Antipsychotics sometimes cause sexual dysfunction in people with schizophrenia. The authors report the effectiveness of Saikokaryukotsuboreito (Japanese traditional herbal medicine, Chai-Hu-Jia-Long-Gu-Mu-Li-Tang in Chinese) for antipsychotic-induced sexual dysfunction in two male patients with schizophrenia. The first patient was a 28-year-old man with schizophrenia who suffered erectile dysfunction induced by olanzapine*

10 mg/day; the erectile dysfunction significantly improved following the treatment of Saikokaryukotsuboreito 7.5 g/day. The other case was a 43-year-old man with schizophrenia who was receiving fluphenazine decanoate at 50 mg/month and had difficulties in ejaculation; add-on of Saikokaryukotsuboreito 7.5 g/day recovered his ejaculatory function. There has been no report on the effectiveness of Japanese herbal medicine formulations for antipsychotic-induced sexual dysfunction. Although the effectiveness of Saikokaryukotsuboreito needs to be tested in systematic clinical trials, this herbal medicine may be a treatment option to consider for this annoying side effect."

Hypersalvation Side Effect Treatments

Suoquan Pill

Suoquan Pill May Be Effective for Reducing Clozapine-induced Salvation

Kang B. Effect of suo quan pill for reducing clozapine induced salivation. Zhongguo Zhong Xi Yi Jie He Za Zhi 1993 Jun; 13(6) 347-8

- *"There was a significant difference in effect on salvation between the therapeutic group (21 cases) and the controlled group (19 cases), P<0.01."*

Wuling Powder

Suoquan Pill and Wuling Powder May Be Natural Treatments for Hypersalivation in Schizophrenia

Hung CC. Treatment effects of traditional Chinese medicines Suoquan Pill and Wuling Powder on clozapine-induced hypersalivation in patients with schizophrenia: study protocol of randomized, placebo-controlled trial. Zhong Xi Yi JIe He Xue Bao 2011 May;9(5):495-502

- *"It is hypothesized that SQP and WLP will have a beneficial effect in controlling clonzapine-induced hypersalivation symptoms."*

Metabolic Syndrome Side Effect Treatments

Diet and Exercise

Healthy Diet and Exercise are Interventions for Metabolic Syndrome in Bipolar Disorder Treated with Atypical Antipsychotics

Bell, Paul F., "Treatment of Bipolar Disorders and Metabolic Syndrome: Implications for Primary Care." Postgraduate Medicine 121, no. 5 (September 2009): 140–44. doi:10.3810/pgm.2009.09.2060.

- *"Recognition of the prevalence of mood disorders and increased availability of medication options have led to calls for treating bipolar disorders in the primary care setting. Second-generation antipsychotic medications (SGAs) were initially lauded for treating bipolar disorders because of their efficacy and perceived safety relative to first-generation antipsychotic medications. Metabolic syndrome is a constellation of risk factors for cardiovascular disease and type 2 diabetes mellitus, which may emerge when treating bipolar disorders with SGAs. We conducted a search of the research literature examining the association between different SGAs and metabolic syndrome. Based on our review, we offer guidelines for monitoring patient status regarding metabolic syndrome and for providing interventions to promote healthy diet and exercise."*

Healthy Eating and Physical Activity Communicated in Writing and Verbally with Social Support and Lifestyle Changes May Prevent the Development of Metabolic Syndrome in Psychotic Disorders

Bergqvist, Anette, "Preventing the Development of Metabolic Syndrome in People with Psychotic Disorders--Difficult, but Possible: Experiences of Staff Working in Psychosis Outpatient Care in Sweden." Issues in Mental Health Nursing 34, no. 5 (May 2013): 350–58. doi:10.3109/01612840.2013.771234.

- *"Nursing interventions focusing on organising daily routines before conducting a more active prevention of metabolic syndrome, including information and practical support, were experienced as necessary. The importance of healthy eating and physical activity needs to be communicated in such a way that it is adjusted to the person's cognitive ability, and should be repeated over time, both verbally and in writing. Such efforts, in combination with empathic and seriously committed community-based social support, were experienced as having the best effect over time. Permanent lifestyle changes were experienced as having to be carried out on the patient's terms and in his or her home environment."*

Melatonin

Melatonin Decreases Rise in Cholesterol and Systolic Blood Pressure in Bipolar Children

Mostafavi, Ali, "Melatonin Decreases Olanzapine Induced Metabolic Side-Effects in Adolescents with Bipolar Disorder: A Randomized Double-Blind Placebo-Controlled Trial." Acta Medica Iranica 52, no. 10 (October 2014): 734–39.

- *"Administration of melatonin along with olanzapine and lithium carbonate could significantly inhibit the rise in cholesterol level and SBP compared to placebo. The effect of melatonin on TG was more obvious in boys. Melatonin was more effective in prevention of SBP rise."*

Melatonin is Effective and Attenuates Antipsychotics Adverse Metabolic Effects in Bipolar Disorder

Romo-Nava, Francisco, "Melatonin Attenuates Antipsychotic Metabolic Effects: An Eight-Week Randomized, Double-Blind, Parallel-Group, Placebo-Controlled Clinical Trial." Bipolar Disorders 16, no. 4 (June 2014): 410–21. doi:10.1111/bdi.12196.

- *"Our results show that melatonin is effective in attenuating SGAs' adverse metabolic effects, particularly in bipolar disorder. The clinical findings allow us to propose that SGAs may disturb a centrally mediated metabolic balance that causes adverse metabolic effects and that nightly administration of melatonin helps to restore. Melatonin could become a safe and cost-effective therapeutic option to attenuate or prevent SGA metabolic effects."*

Saffron

Saffron Extract Prevents Metabolic Syndrome in Patients with Schizophrenia

Fadai, F., "Saffron Aqueous Extract Prevents Metabolic Syndrome in Patients with Schizophrenia on Olanzapine Treatment: A Randomized Triple Blind Placebo Controlled Study." Pharmacopsychiatry 47, no. 4–5 (July 2014): 156–61. doi:10.1055/s-0034-1382001.

- *"SAE could prevent metabolic syndrome compared to crocin and placebo. Furthermore, both SAE and crocin prevented increases in blood glucose during the study."*

Hyperprolactinemia and Amenorrhea Side Effect Treatments

Herbal Treatment

Herbal Treatment for Antipsychotic-induced Hyperprolactinemia

Yuan HN. A randomized, crossover comparison of herbal medicine and bromocriptine against risperidone-induced hyperprolactinemia in patients with schizophrenia. J Clin Psychopharmacol 2008 Jun;28(3):264-370

- *"These results suggest that herbal therapy can yield additional benefits while having comparable efficacy in treating antipsychotic-induced hyperprolactinemia in individuals with schizophrenia."*

Milk Thistle

Milk Thistle is Effective in Preventing Psychotropic Drug-Induced Hepatic Damage

Palasciano G. The effect of silymarin on plasma levels of malon-dialdehyde in patients receiving long-term treatment with psychotropic drugs. Current Therapeutic Research, Vol 55(5), May 1994, 537-545

- *"The data show that silymarin, when used at submaximal doses, reduces the lipoperoxidative hepatic damage that occurs during treatment with butyrophenones or phenothiazines. Results suggest that increased lipoperoxidation may contribute to PD-induced hepatotoxicity.*

Peony-Glycyrrhiza

Peony-Glycyrrhiza Decoction May Be a Natural Treatment for Hyperprolactinemia in Schizophrenia

Yuan HN. A randomized, crossover comparison of herbal medicine and brocriptine against risperidone-induced hyperprolactinemia in patients with schizophrenia. J Clin Psychopharmacol 2008 Jun;28(3):264-370

- *"Peony-Glycyrrhiza Decoction treatment produced a significant baseline-endpoint decrease in serum PRL levels, without exacerbating psychosis and changing other hormones, and decreased the amplitudes were similar to those of BMT (24% vs 21%-38%)."*

Shakuyaku-kanzo-to

Shakuyaku-kanzo-to is Effective for Treatment of Neuroleptic-induced Hyperprolactinemia

Yamanda K. Effectiveness of Herbal Medicine (Shakuyaku-kanzo-to) for Neuroleptic_Induced Hyperprolactinemia. J Clin Psychopharmacol Vol 17/No 3 June 1997

- *"There were statistically significant changes in p-PRL levels from 26.6 (SD 10.8) ng/mL at baseline to 20.8 (SD 11.2) mg/mL at 4 weeks and 24.0 (SD 11.4) ng/mL at 8 weeks ($F=8.408$, $df=2,38$, $p= 0.0009$). Post hoc analysis demonstrated statistically significant differences between p-PRL levels at 4 and 8 weeks ($p< 0.01$) and between p-PRL levels at 4*

and 8 weeks ($p<0.05$). Plasma PRL levels at 8 weeks were not significantly different from those at baseline. In five patients, the p-PRL levels decreased by more than 50% with TJ-68 treatment. Three of 10 patients, who had complained of reduced sexual desire, experienced subjective improvement. Potassium levels and other laboratory data showed no significant changes with TJ-68 administration. Neither exacerbation of psychosis nor other adverse effects occurred."

Hori H. Herbal medicine (Shakuyaku-kanzo-to) improves Olanzapine-associated hyperprolactinemia: A case report. Letters to the Editor, Journal of Clinical Psychopharmacology, Volume 33, Number 1, February 2013

- *"In conclusion, shakuyaku-kanzo-to might be useful for treating amenorrhea without worsening psychotic symptoms in patients with schizophrenia."*

Shakuyaku-kanzo-to is Effective in Correcting Neuroleptic-induced Amenorrhea

Yamanda K. Herbal medicine (Shakuyaku-kanzo-to) in the treatment of risperidone-induced amenorrhea. J Clin Psychopharmacol, Vol. 19/No.1 August 1999

- *"This report demonstrates TJ-68 to be effective in correcting neuroleptic-induced amenorrhea and hyperprolactinemia. Addition of TJ-68 lowered the p-PRL level from 22 to 9.5ng/mL, and menstruation recovered after 3 weeks of administration. Discontinuation of this compound resulted in the return of irregularity of menstruation and hyperprolactinemia."*

Tongdatang

Tongdatang Serial Recipe May Be an Effective Natural Treatment of Antipsychotic-induced Glactorrhea-Amenorrhea Syndrome

Ding Y. Effect of Tongdatang Serial Recipe on antipsychotic drug-induced glactorrhea-amenorrhea syndrome. Zhongguo Zhong Xi Yi Jie He Za Zhi 2008 Mar;28(3):263-5

- *Therapeutic efficacy on the 49 patients of the treatment group was cured in 31 (63.3%), markedly effective in 11 (22.4%), effective in 4 (8.2%) and ineffective in 3 (6.1%), with a total effective rate of 93.9%, while in 47 patients of the control group, the corresponding cases (%) was 0, 3(6.4%), 7(14.9%) and 37 (78.7%), respectively, with the total effective rate of 21.3%. "*

Vitamin C

Vitamin C May Obviate the Negative Effects of Neuroleptics Have on Menstruation

Kanofsky JD. Ascorbic Acid action in neuroleptic-associated amenorrhea. J Clin Psychopharmacol, Vol 9/No. 5 Oct. 1989

- *"The above cases suggest that ascorbic acid at the dose of 2 g orally three times a day may obviate the negative effect neuroleptics can have on menstruation. Given, the wide array of suggestive evidence, we believe that ascorbic acid supplementation should be systematically studied in women who are amenorrheic secondary to neuroleptic use."*

Antipsychotic Drugs May Be Enhanced with Concurrent Administration of Vitamin C

De Angelis, L. "Ascorbic Acid and Atypical Antipsychotic Drugs: Modulation of Amineptine-Induced Behavior in Mice." Brain Research 670, no. 2 (January 30, 1995): 303–7.

- *"In conclusion, these data provide further in vivo support for the effect of ascorbic acid on dopaminergic system and demonstrate that the antidopaminergic effects of both typical and atypical antipsychotic drugs may be enhanced with concurrent administration of ascorbic acid."*

Yi-gan san

Yi-gan san Add-on Treatment Improved Neuroleptic-induced Nocturnal Eating/Drinking Syndrome with Restless Legs Syndrome

Kawabe K. Nocturnal eating/drinking syndrome with restless legs syndrome caused by neuroleptics improved by Yi-gan san add-on treatment: a case report Clin Neuropharmacol 2012 Nov-Dec;35(6):290-1

- *We report a middle-aged male patient with schizophrenia who had nocturnal eating/drinking syndrome with restless leg syndrome whose condition improved with the administration of the herbal medicine Yi-gan san (Yokukan-San in Japanese).*

Gastrointestinal Disorder Side Effect Treatments

Acidophilus

Acidophilus is Effective for Zoloft-induced Diarrhea

Kline, M. D., and S. Koppes. "Acidophilus for Sertraline-Induced Diarrhea." The American Journal of Psychiatry 151, no. 10 (October 1994): 1521–22.

- *"The mechanism by which selective serotonin reuptake inhibitor antidepressants cause gastrointestinal side effects, including· diarrhea, is unknown. OraIIy adminisitered Lactobacillus acidophilus has· been reported to he helpful for maldigestion secondary to lactose intolerance and also helpful for symptoms of irritable bowel syndrome (2). OraIIy*

administered acidophilus can ·apparently survive gastric acidity and alter intestinal flora and has been reported to inhibit same enteropathogens (3). Live acidophilus is available in capsule and tablet form in health food stores; both patients reported here took acidophil us capsules labeled to contain 500 million ·organisms per capsule. An open trial is planned to confirm the potential benefits of acidophilus for diarrhea iduced by selective serotonin reuptake inhibitors."

Dai-kenchu-to

Herbal Dai-kenchu-to Treatment Improves Antipsychotic –induced Hypoperistalsis

Satoh K. Effect of Dai-kenchu-to (Da-Jian-Zhong-Tang) on the delayed intestinal propulsion induced by chlorpromazine in mice. J Ethnopharmacol 2003 May;86(1):37-44

- *"These results demonstrated that Dai-kenchu-to improves chlorpromazine-induced hypoperistalsis via cholinergic systems and that Zanthoxylum Fruit is the main contributor to this action of Dai-kenchu-to."*

Gorei-san

Gorei-san Herbal Treatment May Be Effective for SSRI-induced Nausea and Dyspepsia

Yamada K. Herbal medicine in the treatment of fluvoxamine-induced nausea and dyspepsia. Psychiatry and Clinical Neurosciences (1999), 53, 681

- *In summary, our results suggest that a herbal medicine, Gorei-san, may be effective for fluvoxamine-induced nausea and dyspepsia, without severe adverse events. Further studies are needed to confirm our results."*

Yamada K. Effectiveness of Gorei-san (TJ-17) for the treatment of SSRI-induced nausea and dyspepsia: preliminary observations. Clin Neuropharmacol 2003 May-Jun;26(3):112-4

- *"Gorei-san (TJ-17), which is composed of five herbs (Alismatis rhizome, Atractylodis lanceae rhizome, Polyporus, Hoelen, and Cinnamomi cortex), is a Japenses herbal medicine that has been used to treat nausea, dry mouth, edema, headache, and dizziness. The authors investigated the effecincy of TJ-17 for patients who experienced nausea or dyspepsia induced by SSRIs. Twenty outpatients who experienced nausea or dyspepsia induced by SSRIs were recruited for the study. Seventeen patients were female, three were male, and patient age ranged from 21 to 74 years (49.8 +/- 17.0 years). TJ-17 was added to the previous regimen. Nausea and dyspepsia disappeared completely in nine patients, decreased in four patients, decreased slightly in two, and did not change in five patients. No adverse events were associated with the addition of TJ-17 in any patient."*

Probiotics

Probiotic Supplementation May Prevent Somatic Symptoms Associated with Schizophrenia

Dickerson, Faith B., "Effect of Probiotic Supplementation on Schizophrenia Symptoms and Association with Gastrointestinal Functioning: A Randomized, Placebo-Controlled Trial." The Primary Care Companion to CNS Disorders 16, no. 1 (2014). doi:10.4088/PCC.13m01579.

- *"Repeated-measures analysis of variance showed no significant differences in the PANSS total score between probiotic and placebo supplementation (F = 1.28, P = .25). However, patients in the probiotic group were less likely to develop severe bowel difficulty over the course of the trial (hazard ratio = 0.23; 95% CI, 0.09-0.61, P = .003). Conclusions: Probiotic supplementation may help prevent a common somatic symptom associated with schizophrenia."*

Rikkunshi

Herbal Rikkunshi Treatment Reduces Nausea and Vomiting Associated with SSRIs

Oka T. Rikkunshi-to attenuates adverse gastrointestinal symptoms induced by fluvoxamine. Biopsychosoc Med 2007 Nov 15;1:21

- *"This study suggests that Rikkunshi-to reduces FLV-induced adverse events, especially nausea, and improves QOL related to GI symptoms without affecting the antidepressant effect of FLV."*

Valproic Acid–induced Toxicity Side Effect Treatments

Carnitine

Carnitine is an Effective Treatment for Valproic Acid-induced Toxicity

Lheureux, Philippe E. R., "Science Review: Carnitine in the Treatment of Valproic Acid-Induced Toxicity - What Is the Evidence?" Critical Care (London, England) 9, no. 5 (October 5, 2005): 431–40. doi:10.1186/cc3742.

- *"Valproic acid (VPA) is a broad-spectrum antiepileptic drug and is usually well tolerated, but rare serious complications may occur in some patients receiving VPA chronically, including haemorrhagic pancreatitis, bone marrow suppression, VPA-induced hepatotoxicity (VHT) and VPA-induced hyperammonaemic encephalopathy (VHE). Some data suggest that VHT and VHE may be promoted by carnitine deficiency.*

Acute VPA intoxication also occurs as a consequence of intentional or accidental overdose and its incidence is increasing, because of use of VPA in psychiatric disorders. Although it usually results in mild central nervous system depression, serious toxicity and even fatal cases have been reported. Several studies or isolated clinical observations have suggested the potential value of oral L-carnitine in reversing carnitine deficiency or preventing its development as well as some adverse effects due to VPA. Carnitine supplementation during VPA therapy in high-risk patients is now recommended by some scientific committees and textbooks, especially paediatricians. L-carnitine therapy could also be valuable in those patients who develop VHT or VHE. A few isolated observations also suggest that L-carnitine may be useful in patients with coma or in preventing hepatic dysfunction after acute VPA overdose. However, these issues deserve further investigation in controlled, randomized and probably multicentre trials to evaluate the clinical value and the appropriate dosage of L-carnitine in each of these conditions."

Carnitine-pantothenic Acid Has Protective Effect on Valproic Acid-induced Hepatotoxicity

Felker, Dana, "Evidence for a Potential Protective Effect of Carnitine-Pantothenic Acid Co-Treatment on Valproic Acid-Induced Hepatotoxicity." Expert Review of Clinical Pharmacology 7, no. 2 (March 2014): 211–18. doi:10.1586/17512433.2014.871202.

- *"Valproic acid is approved for treatment of seizures and manic episodes of bipolar disorder, and continues to be one of the most commonly prescribed antiepileptic drugs in the world. Hepatotoxicity is a rare but serious side effect resulting from its use, particularly in young patients. This adverse effect does not display normal dose-response curves and can be lethal in children. A review of the purported mechanisms of action suggest hepatotoxicity results from increased oxidative stress, caused by a reduction in beta-oxidation and an increase in activation of certain metabolizing enzymes. There is also evidence that both carnitine and pantothenic acid are involved in the regulation of valproic acid-induced hepatotoxic processes, and clinical evidence has shown that treatment with either compound shows protective effects against hepatotoxicity. These results suggest a potential increase in protective effects with cotreatment of carnitine and pantothenic acid."*

Levocarnitine

Levocarnitine Supplementation May Enhance Recovery from Hypocarnitinemia in Psychiatric Patients

Cuturic, Miroslav, "Clinical Outcomes and Low-Dose Levocarnitine Supplementation in Psychiatric Inpatients with Documented Hypocarnitinemia: A Retrospective Chart Review." Journal of Psychiatric Practice 16, no. 1 (January 2010): 5–14. doi:10.1097/01.pra.0000367773.03636.d1.

- *"We hypothesize that correction of carnitine depletion, either by levocarnitine supplementation or by valproate dose reduction, may enhance recovery from hypocarnitinemia-associated encephalopathy in psychiatric patients. Our findings also suggest that ethnic traits may affect carnitine bioavailability as well as cognitive outcomes in this clinical context. Further studies of carnitine metabolism and supplementation in psychiatric patients are warranted."*

Tardive Dyskinesia Side Effect Treatments

Alpha Lipoic Acid

Alpha Lipoic Acid Improves Tardive Dyskinesia

Thaakur S. Effect of alpha lipoic acid on the tardive dyskinesia and oxidative stress induced by haloperidol in rats. J Neural Transm (2009) 116;807-814

- *"In conclusion, ALA improves TD and catalepsy by scavenging hydroxyl radicals, singlet oxygen hypochlorous acid, and regenerating other antioxidants such as glutathione, vitamin C, ubiquinol (coenzyme Q 10) an indirectly vitamin E…."*

Amino Acids

Branched Chained Amino Acids Decrease Tardive Dyskinesia Symptoms

Richardson MA. Branched chain amino acids decrease tardive dyskinesia symptoms. Psychopharmacology (Berl). 1999 Apr;143(4):358-64

- *"The BCAA show promise as a treatment for TD. The decrease in TD symptoms seen in the trial may have been modulated by the BCAA treatment-induced increased availability of the BCAA and decreased availability of Phe to the brain."*

Richardson MA. Efficacy of the branched-chain amino acids in the treatment of tardive dyskinesia in men. Am J Psychiatry 2003 Jun;160(6):1117-24

- *"Branched-chain amino acids constitute a novel, safe treatment for tardive dyskinesia, with a strong potential for providing significant improvement in the diseased physiognomy of the afflicted person."*

Richardson MA. Branched chain amino acid treatment of tardive dyskinesia in children and adolescents. J Clin Psychiatry 2004 Jan;65(1):92-6

- *"The substantial symptom decrease and tolerability observed suggest the use of the BCAA formulation for the treatment of TD in children and adolescents and warrant further large-scale studies."*

Ashwagandha

Ashwagandha Prevents Haldol –induced Tardive Dyskinesia

Bhattacharya SK. Effect of Withania sominfera glycowithanolides on rat model of tatdive dyskinesia. Phytomedicine 2002 Mar;9(2):167-70

- *"The results indicate the reported antioxidant effect of WSG rather than it's GABA-mimetic action , may be responsible for the prevention of haloperidol-induced TD."*

Biofeedback

Biofeedback May Be an Effective Treatment for Tardive Dyskinesia

Albanese, H.,"Biofeedback Treatment of Tardive Dyskinesia: Two Case Reports." The American Journal of Psychiatry 134, no. 10 (October 1977): 1149–50.

- *"The two patients described were both intelligent people who experienced social embarrassment because of severe mouth movements. The first patient had the movements for 5 months before biofeedback training; the second had the movements for only 1 month. Both had been off medication for 1 month for with out change in movements and improved markedly by the 3rd session of biofeedback training. A characteristic of tardive dyskinesia is that voluntary queting of movement in one part of the body often results in shifting the movement to another part of the body. This did not occur in either patient, despite the already existing foot and finger movements in the first patient described. A general reduction of tension was experienced by both patients, and both gave reports of increased well-being. Since spontaneous remission occurs in tardive dyskinesia, it cannot be proven that the biofeedback treatment was responsible for the marked improvement of these two patients. However, the improvement was first noted within the training sessions and increased progressively with training, later extending to periods out-side the training sessions. Also, in each instance there had been no noticeable improvement before treatment began. We believe this observation warrents further investigation of the treatment approach, and we hope that this report will stimulate others to try similar methods."*

Chaihu Taoren

Chaihu Taoren Capsules May Effectively Releive Symptoms of Tardive Dyskinesia

Su, Jian-min, "[Relationship between tardive dyskinesia and the polymorphism of superoxide dismutase val9Ala and efficacy of Chaihu Taoren Capsules on it]." Zhongguo Zhong Xi Yi Jie He Za Zhi Zhongguo Zhongxiyi Jiehe Zazhi = Chinese Journal of Integrated Traditional and Western Medicine / Zhongguo Zhong Xi Yi Jie He Xue Hui, Zhongguo Zhong Yi Yan Jiu Yuan Zhu Ban 27, no. 8 (August 2007): 700–703.

- *"The CTD could effectively relieve the symptoms of TD, its efficacy might be related with the genotype of SOD, and 9Ala is considered to be a protective factor for the susceptibility to TD."*

Chiropractic Manipulation

Chiropractic Management of Musculoskeletal Pain Secondary to Tardive Dyskinesia

Schoonderwoerd K. Chiropractic management of musculoskeletal pain secondary to tardive dyskinesia. J Can Chiropr Assoc 2005; 49(2)

- *"A case report is presented of a patient affected by TD who suffered mechanical musculoskeletal pain secondary to its effects, and was managed by chiropractic care."*

Ceruletide

Ceruletide is a Novel and Practical Treatment for Tardive Dyskinesia

Kojima, T., "Treatment of Tardive Dyskinesia with Ceruletide: A Double-Blind, Placebo-Controlled Study." Psychiatry Research 43, no. 2 (August 1992): 129–36.

- *"The effectiveness of a once-weekly i.m. injection of ceruletide (0.8 microgram/kg) in suppressing the symptoms of neuroleptic-induced tardive dyskinesia (TD) was evaluated in a double-blind, placebo-controlled, matched-pairs study. Global evaluation of the severity of TD symptoms over the 8-week study period revealed a significant improvement with ceruletide as compared with placebo. Analysis of the therapeutic response to ceruletide over the course of treatment revealed a slow, but long-lasting improvement of TD symptoms. Side effects, which were mild and transient, consisted mainly of nausea and epigastric discomfort. The incidence of side effects did not differ between the ceruletide- and placebo-treated groups. Ceruletide appears to be a novel and practical treatment that can substantially alleviate the symptoms of dyskinesia."*

Nishikawa, T., "Treatment of Tardive Dyskinesia with Ceruletide." Progress in Neuro-Psychopharmacology & Biological Psychiatry 12, no. 5 (1988): 803–12.

- *"Seven patients with TD were treated with a single dose of ceruletide 0.8 microgram/kg i.m. 2. EMG and MV were recorded, and the average power spectrum was computed. 3. Effect of ceruletide on TD within 2 hr after injection was varied (3 cases: inhibitory, 2*

cases: facilitatory, 2 cases: no effect). 4. Two patients with severe TD, who showed improvement after a single administration, received repeated administration of ceruletide (0.6 microgram/kg i.m.) and their TD symptoms were recorded on videotape for blind consensus ratings. In both patients ceruletide caused a marked decrease in severity of TD, and the effects lasted for several weeks. 5. The present findings might contribute to further understanding of the role of CCK in the brain and to the treatment of TD."

Choline

Oral Choline is Effective in the Treatment of Tardive Dyskinesia

Growdon JH. Oral choline administration to patients with tardive dyskinesia. New England Journal of Medicine , Vol 297, No.10, pp524-527, September 1977

- *"Twenty patients with stable buccal-lingual-masticatory movements took oral doses of choline for two weeks according to a double-blind crossover protocol. Plasma choline levels rose from 12.4 +-1.0 to 33.5+-2.5 nmol per milliliter (mean +- S.E.M.; P<0.001) during this period. Choreic movements decreased in nine patients, worsened in one and were unchanged in 10. Thus, oral doses of choline can be useful in neurologic diseases in which an increase in acetylcholine release is desired. "*

EMG Feedback

EMG Feedback from the Masseter Muscle was Effective in Controling Tardive Dsykinesia

Sherman, R. A. "Successful Treatment of One Case of Tardive Dyskinesia with Electromyographic Feedback from the Masseter Muscle." Biofeedback and Self-Regulation 4, no. 4 (December 1979): 367–70.

- *"Evidence from one case with a 15-month follow-up is presented to support the conclusion that electromyographic (EMG) feedback from the masseter was effective in controlling tardive dyskinesia, while a combination of EMG feedback from the frontalis and verbal muscle relaxation training were not."*

Fatty Acids

Fish oil Decreased Motor Disorders, Memory Dysfunction and Neuroleptic-Induced Oxidative Damage

Barcelos R. Effects of w-3 essential fatty acids (w-3 EFAs) on motor disorders and memory dysfunction typical neuroleptic-induced: Behavioral and biochemical parameter. Neurotox Res, 2009

- "*The FO (fish oil) decreased the motor disorders, memory dysfunction, and oxidative damage typical neuroleptic-induced"*

Essential Fatty Acids LA and GLA Supplementation Delays the Onset of Dyskinesia in Huntington's Disease

Krishna Vaddadi, Dyskinesia's and their treatment with essential fatty acids: a review. Prostaglandins, Leukotrienes and Essential Fatty Acids (1996) 55(1&2), 89-94

- *"Clinical improvement in HD (Huntington's Disease) with LA and GLA supplementation is a novel finding…." It has been suggested that in individuals at early stages of HD, or in individuals at risk of developing HD, if given EFA's probably of both n-6 and n-3 series on long term basis might delay the onset of HD."*

EPA Supplementation Produces Significant Improvement in Memory in Patients with Tardive Dyskinesia

Vaddadi KS. A double-blind trial of essential fatty acid supplementation in patients with tardive dyskinesia. Psychiatry Res 1989 Mar;27(3): 313-23

- *"The antidyskinetic effect of EPA supplementation was marginally significant but not clinically important. However, active treatment produced significant improvements in total psychopathology scores and schizophrenia subscales scores, and significant improvement in memory."*

Gingko Biloba

Gingko Biloba is an Effective Treatment for Tardive Dyskinesia

Zhang WF. Extract of gingko biloba treatment for tardive dyskinesia in schizophrenia: a randomized, double-blind, placebo-controlled trial. J Clin Psychiatry 2011 May;72(5):615-21

- *"EGb-761 appears to be an effective treatment for reducing the symptoms of TD in schizophrenia patient*

Indian Gooseberry

Indian Gooseberry Exerts a Prophylactive Effect Against Neuroleptic-induced Tardive Dyskinesia

Bhattacharya S. Effect of Embilica offcinallis tannoids on a rat model of tardive dyskinesia. Indian J of Experimental Biology, Vol. 38, September 2000, pp. 945-947

- *"The results suggest that EOT exerts a prophylactive effect against neuroleptic-induced TD….."*

Insulin

Insulin May Decrease the Intesnsity of Symptoms in Tardive Dykinesia

Mouret, J., "Low Doses of Insulin as a Treatment of Tardive Dyskinesia: Conjuncture or Conjecture?" European Neurology 31, no. 4 (1991): 199–203.

- *"Twenty chronic schizophrenic outpatients (13 males, 7 females), aged 20-67 (mean: 38.3), accepted to participate in this double-blind, placebo-controlled study. They were randomly assigned to either the insulin treatment group (10 patients) or to the insulin-placebo group (10 patients). They received a subcutaneous injection of 10 units of standard insulin or placebo at 10 a.m. From day 1 to day 15, injections were performed daily and, thereafter, every other week for 5 weeks totalizing 20 injections in 90 days. At day 7, the insulin treatment group showed a sharp decrease in the intensity of TD symptoms which persisted throughout the duration of the study. By contrast, no change in TD symptomatology was observed in the insulin-placebo-treated group. Although a direct effect on DA neurones, or at least the participation of such an effect, cannot be excluded, our data favor a role of decreased glucose availability in reversing receptor hypersensitivity."*

Kamisoyosan

Kampo Medicine Kamisoyosan Provides a Meaningful Reduction in Involuntary Movements in Tardive Dyskinesia

Lee JG. Clinical effectiveness of the Kampo medicine kamisoyosan for adjunctive treatment of tardive dyskinesia in patients with schizophrenia: a 16 week open trial. Pyschiatry Clin Neurosci 2007 Oct;61(5):509-14

- *"A meaningful reduction in total abnormal involuntary movement scale scores was observed in the tardive dyskinesia group"*

Lecithin

Lecithin Can Suppress Tardive Dyskinesia

Growdon JH. Lecithin can suppress tardive dyskinesia. New England Journal of Medicine, Vol 298, No. 18 pp1029, May 1978

- *"The mean number of movements decreased in all patients during lecithin ingestion (Table 1), and serum choline levels rose from a mean +-S.D. of 10.0 +- 2.2 to 22.8+-5.1*

nmol per milliliter (P<0.01). Lecithin was as effective as choline chloride: the number of buccal-lingual-masticatory movements decreased as they had during choline administration. In addition, lecithin may be more acceptable to patients, since it does not have a bitter taste of fishy body oder as associated with choline ingestion. These data suggest that lecithin may constitute an effective mode of neurotransmitter precursor therapy for conditions in which physicians wish to increase cholinergic tone."

Melatonin

Melatonin is Beneficial for The Treatment of Antipsychotic –induced Tardive Dyskinesia

Shamir E, Melatonin treatment for tardive dyskinesia. Arch Gen Psychiatry. 2001;58:1049-1052

- *"In conclusion, the results of the present study demonstrate that melatonin treatment is beneficial for antipsychotic-induced TD."*

Morin

Morin (Flavonol) Has Neuroprotective Potential in Haloperidol-induced Tardive Dyskinesia

Selvakumar GP. Morin attenuates Haloperidol induced tardive dyskinesia and oxidative stress in mice. Journal of Natural Sciences Research Vol.2, No.8, 2012

- *" These results indicate that morin have beneficial role in mitigating HP-induced damage of dopaminergic neurons, possibly via its neuroprotective and its antioxidant potential."*

Muscimol

GABA Agonist Muscimol was found to Provide Relief from Tardive Dyskinesia

Tamminga, C. A., "Improvement in Tardive Dyskinesia after Muscimol Therapy." Archives of General Psychiatry 36, no. 5 (May 1979): 595–98.

- *"Muscimol, thought to be a agonist of gamma-aminobutyric acid (GABA), was administered to eight neuroleptic-free subjects with tardive dyskinesia. At oral dose levels from 5 to 9 mg, involuntary movements were consistently attenuated, usually in the absence of sedation. These results support the view that pharmacologic attempts to stimulate GABA-mediated synaptic transmission may afford symptomatic relief to patients with tardive dyskinesia."*

Osteopathic Manipulation

Osteopathic Management of Tardive Dyskinesia is Beneficial

Reifsnyder, Jeremy W.,"Conservative Approach to Tardive Dyskinesia-Induced Neck and Upper Back Pain." The Journal of the American Osteopathic Association 113, no. 8 (August 2013): 636–39. doi:10.7556/jaoa.2013.025.

- *Although it is unlikely that spinal manipulation would result in a reversal of tardive dyskinesia, osteopathic physicians should consider the use of OMT to address pain associated with tardive dyskinesia. With relief of pain, patients can have an improved quality of life, with positive changes to their overall mental and physical health. A controlled clinical trial assessing the safety and effectiveness of spinal manipulation over a longer time frame would be helpful to establish further use of OMT in the management of tardive dyskinesia–induced neck and back pain."*

Quercetin

Quercetin Could Be a Potential Therapeutic Agent for the Treatment of Tardive Dyskinesia

Naidu P. Reversal of reserpine-induced orofacial dyskinesia and cognitive dysfunction by quercetin. Pharmacology 2004;70:59-67

- *"In conclusion, the results of the present study clearly indicated that quercetin has a protective role against reserpine-induced orofacial dyskinesia and associated cognitive dysfunction. Consequently, quercetin could be considered as a potential therapeutic agent for the treatment of TD."*

Spirulina

Spirulina Decreases Haldol-induced Oxidative Stress and Tardive Dyskinesia

Thaakur SR. Effects of spirulina maxima on haloperidol induced tardive dyskinesia and oxidative stress in rats. J Neural Transm 2007 Sep;114(9):1217-25

- *"Spirulina supplenation at a dose of 180mg/kg significantly improved enzymatic and nonenzymatic antioxidants and decreased tardive dyskinesia induced by haloperidol. In conclusion the results of the present investigation suggest that spirulina decreases haloperidol induced oxidative stress and TD by many mechanisms as it is a cocktail of antioxidants."*

Triiodothyronine

Triiodthyronine May Be Associated with Better Cognitive Function and Less EPS in Schizophrenia

Ichioka, Shugo, "Triiodothyronine May Be Possibly Associated with Better Cognitive Function and Less Extrapyramidal Symptoms in Chronic Schizophrenia." Progress in

Neuro-Psychopharmacology & Biological Psychiatry 39, no. 1 (October 1, 2012): 170–74. doi:10.1016/j.pnpbp.2012.06.008.

- *"These findings suggest that BDNF, free T_3, and prolactin may be associated with cognitive function and/or extrapyramidal symptoms in patients with chronic schizophrenia. Notably, free T_3 may be possibly associated with better cognitive function and less extrapyramidal symptoms, although our cross-sectional study could not reveal a causal relationship."*

Tryptophan

Tryptophan Supplementation May Ameliorate Neuroleptic-induced Tardive Dyskinesia

Ali O. Effects of tryptophan and valine administration on behavioral pharmacology of haloperidol. Pak J Pharm Sci 2005 Apr;18(2):23-8

- *"These findings suggest a possible serotonergic involvement in neuroleptic induced tardive dyskinesia and amelioration of the disorder through TRP supplementation."*

Vitamin B_6

Vitamin B6 is Effective in the Treatment of Tardive Dyskinesia

Lerner V. Vitamin B6 treatment for tardive dyskinesia: a randomized, double-blind, placebo-controlled, crossover study. J Clin Psychiatry 2007 Nov;68(11):1648-54

- *"Vitamin B6 appears to be effective in reducing symptoms of TD."*

Vitamin E and Vitamin C

Vitamin E and C is Efficacious Treatment for Tardive Dyskinesia

Nikolaus M, Severe tardive dyskinesia in affective disorders: Treatment with Vitamin E and C. Neuropsychobiology 2002;46(suppl 1):28-30

- *"…Combining vitamin E with C was a safe and efficacious in the treatment of tardive dyskinesia in affective disorder."*

Yi-gan-san

Yi-gan-san resulted in Significant Improvement of Tardive Dyskinesia and Psychotic Symptoms

Miyaoka T. Yi-gan san for the treatment of neuroleptic-induced tardive dyskinesia: an open-label study. Prog Neuropsychopharmacol Biol Psychiatry 2008 Apr 1; 32(3):781-4

- *"Administration of YGS resulted in a statistically significant improvement in tardive dyskinesia and psychotic symptoms"*

Orofacial Dyskinesia Side Effect Treatments

Ashwagandha

Ashwagandha is Effective at Preventing Haldol-induced Orofacial Dyskinesia

Naidu P. Effect of Withania somnifera root extract on Haloperidol-induced orofacial dyskinesia: Possible mechanism of action.
Journal of Medicinal Food, Vol. 6, No. 2, 2003

- *"These findings strongly suggest that oxidative stress plays a significant role in HP-induced orofacial dyskinesia and that Ws could be effective in preventing neuroleptic-induced extrapyramidal side effects."*

Brazilian Orchid

Brazilian Orchid Tree Prevents Vacuous Chewing Movements Induced By Haldol

Peroza LR. Bauhinia forficata prevents vacuous chewing movements induced by haloperidol in rats and has antioxidant potential in vitro. Neurochem Res 2013 Apr;38(4):789-96

- *"Haloperidol treatment induced VCMs, and co-treatment with B.forficata partially prevented this effect. Haloperidol reduced the locomotor and exploratory activities of animals in the open fields test, which was not modified by B. foficata treatment. Our present data showed that B. forficta has antioxidant potential and partially protects against VCMs induced by haloperidol in rats. Taken together, our data suggest the protection by natural compounds against VCMs induced by Haloperidol in rats."*

Ceruletide

Ceruletide is Effective on Severe Orofacical Dyskinesia

Nishikawa, T., "Biphasic and Long-Lasting Effect of Ceruletide on Tardive Dyskinesia." Psychopharmacology 86, no. 1–2 (1985): 43–44.

- *"A 55-year-old schizophrenic inpatient with buccolingual dyskinesia was treated with a single dose of ceruletide 0.8 micrograms/kg IM. Time-course effects of the drug were then*

followed for up to 6 weeks after injection. To assess changes in severity of bucco-lingual dyskinesia objectively, electromyogram (EMG) and microvibration (MV) were recorded. Simultaneously, bucco-lingual dyskinesias were also evaluated by using a five-point rating scale. Before injection of ceruletide, severity of dyskinesia was "moderate" and 3-4 Hz of dyskinetic oral movements were dominant. "Extremely severe" and repetitious gross oral movements (around 1 Hz) were observed within a few minutes after injection and continued for up to 1 h. Thereafter, oral movements tended to decrease, and they disappeared completely 3 weeks after injection. This biphasic and long-lasting effect of ceruletide on tardive dyskinesia might contribute to further understanding of the physio-pathophysiological role of cholecystokinin-like peptides in the brain, and provide a basis for practical treatment of tardive dyskinesia."

Curcumin

Curcumin is Able to Reverse Changes Caused by Exposure to Haldol in Orofacial Dyskinesia

Bishnoi M. Protective effect of Curcumin, the active principle of turmeric (Curcuma longa) in haloperidol-induced orofacial dyskinesia and associated behavioral, biochemical and neurochemical changes in rat brain. Pharmacol Biochem Behav. 2008 Feb;88(4):511-22

- *"In present study, curcumin was able to reverse the behavioral, biochemical and neurochemical changes caused by exposure to haloperidol possibly by virtue of its antioxidant effect…."*

Curcumin Prevents Haldol-induced Orofacial Dyskinesia

Sookram C. Curcumin prevents haloperidol-induced development of abnormal orofacial movements: possible implications of Bcl-XL in its mechanism of action. Synapse 2011 Aug;65(8):788-94

- *"These results suggest that curcumin may be a promising treatment to prevent the development of AOFMs and further suggest some therapeutic value in the treatment of movement disorders."*

Curry Tree Leaves

Curry Tree Leaves Could be a Potential Drug Candidate for the Prevention of Neuroleptic-induced Orofacial Dyskinesia

Patil R. Reversal of haloperidol-induced orofacial dyskinesia by Murraya koenigii leaves in experimental animals. Pharm Biol 2012 Jun;50(6):691-7

- *"The study concludes the M. koenigii could be screened as a potential drug for the prevention or treatment of neuroleptic-induced OD."*

Ginkgo Biloba

Ginkgo Biloba is Equivalent to Vitamin E in Attenuating and Preventing Vacuous Chewing Movements

An HM. Extract of Ginkgo biloba is equivalent to vitamin E in attenuating and preventing vacuous chewing movements in rat model of tardive dyskinesia. Behav Pharmacol 2013 Aug 29

- *" In study one, EGb761 and vitamin E, administered by an oral gavage for 5 weeks during withdrawal from chronic haloperidol treatment, decreased VCMs significantly, showing 83.8 and 91.0% reduction, respectively, compared with the haloperidol-alone group. In study two, the concomitant administration of EGb761 and vitamin E led to significantly fewer VCMs, by 64.4 and 73.9%, respectively, compared with the haloperidol-alone group. There was no significant difference in either study between EGb761 and vitamin E treatment."*

Glycine and D-Cycloserine

Glycine and D-Cycloserine Attenuate Vacuous Chewing Movements in Rats

Shoham, Shai, "Glycine and D-Cycloserine Attenuate Vacuous Chewing Movements in a Rat Model of Tardive Dyskinesia." Brain Research 1004, no. 1–2 (April 9, 2004): 142–47. doi:10.1016/j.brainres.2004.01.022.

- *"High dose DCS significantly reduced VCM without affecting other motor parameters. GLY treatment resulted in significantly less VCM but also reduced rearing, grooming and mobility. In contrast, low dose DCS and placebo did not significantly affect any of these parameters. These findings indicate that the use of GLY and DCS results in attenuation of VCM in rats and may have an effect on TD in humans. Clinical trials with this type of compounds for patients suffering from TD are warranted."*

Ginseng (Korean)

Korean Ginseng Could be Useful in the Treatment of Drug-induced Orofacial Dyskinesia

Sanghavi CR. Korean ginseng extract attenuates reserpine-induced orofacial dyskinesia and improves cognitive dysfunction in rats. Nat Prod Res 2011 Apr;25(7):704-15

- *"The present study concludes that oxidative stress might play an important role in reserpine-induced abnormal oral movements and Korean ginseng extract could be useful in the treatment of drug-induced dyskinesia and amnesia."*

Hibiscus

Hibiscus has a Protective Effect Against Resperpine-induced Orofacial Dyskinesia

Nade V. S. Effect of Hibiscus rosa sinesis on resperpine-induced neurobehavioral and biochemical alterations in rats. Indian Journal of Experimental Biology, Vol. 47, July 2009, pp. 559-563

- *"The results from the presents study suggested Hibiscus rosa sinensis had a protective role against resperpine-induced orofacial dyskinesia and oxidative stress."*

Melatonin

Melatonin Could Be a Potential Drug for the Prevention of Neuroleptic-induced Orofacial Dyskinesia

Naidu P. Possible mechanism of action in melatonin attenuation of haloperidol-induced orofacial dyskinesia. Pharmacology, Biochemistry and Behavior 74(2003) 641-648

- *"In conclusion, melatonin could be screened as a potential drug candidate for the prevention or treatment of neuroleptic-induced orofacial dyskinesia"*

Nicotine

Nicotine Reduces Antipsychotic-induced Orofacial Dyskinesia

Bordia T. Nicotine reduces antipsychotic-induced orofacial dyskinesia in rats. J Pharmacol Exp Ther 2012 Mar;340(3):612-9

- *"The present results are the first to suggest that nicotine may be useful for improving the tardive dyskinesia associated with antipsychotic use."*

Nitric Oxide

NO Donors L-arginine May Be a Possible Therapeutic Option for Orofacial Dyskensia

Bishnoi, Mahendra, "Co-Administration of Nitric Oxide (NO) Donors Prevents Haloperidol-Induced Orofacial Dyskinesia, Oxidative Damage and Change in Striatal

Dopamine Levels." Pharmacology, Biochemistry, and Behavior 91, no. 3 (January 2009): 423–29. doi:10.1016/j.pbb.2008.08.021.

- *"Besides, haloperidol also increased striatal superoxide anion levels and decreased striatal NO and citrulline levels which were prevented by molsidomine and l-arginine. On chronic administration of haloperidol, there was a decrease in the striatal levels of dopamine, which was again reversed by treatment with NO donors. The findings of the present study suggested for the involvement of NO in the development of neuroleptic-induced TD and indicated the potential of NO donors as a possible therapeutic option. Furthermore, a sub-study on a possible schizophrenic phenotype, i.e. a possible clinical worsening in the animals receiving NO donors and neuroleptics will substantiate the clinical utility of the study."*

Pecan Shell

Pecan Shell Extract is Able to Prevent and Reverse Orofacial Dyskinesia

Trevizol F. Comparative study between two animal models of extrapyramidal movement disorders: prevention and reversion by pecan nut shell aqueous extract. Behav Brain Res 2011 Aug 1;221(1):13-8

- *"Comparatively, the pecan shell AE was able to both prevent and reverse OD but only prevent catalepsy."*

Reveratrol

Reveratrol is a Neuroprotective Agent Reducing Motor Disorders Induced by Antipsychotic Treatment

Busanello A. Reveratrol reduces vacuous chewing movements induced by acute treatment with fluphenazine. Pharmacol Biochem Behav 2012 Apr; 101(2):307-10

- *"Fluphenazine treatment produced VCM in 70% of rats and concomitant treatment with resveratrol decreased the prevalence to 30%, but did not modify the intensity of the VCM's. Furthermore, the fluphenazine administration reduced the locomotor and exploratory activity of animals in the open field test. Resveratrol treatment was able to protect the reduction of both parameters. Taken together, our data suggest that resveratrol could be considered a potential neuroprotective agent by reducing motor disorders induced by fluphenzine treatment."*

Rubiaceae

Rubiaceae Significantly Inhibits Haldol-induced Orofacial Dyskinesia

Maxia A. Ethanolic extract of Rubia pergrina L. (Rubiaceae) inhibits haloperidol-induced catalepsy and resperpine-induced orofacial dyskinesia. Nat Prod Res 2012;26(5):438-45

- *"The extract of R. peregrine intraperitoneally significantly inhibited haloperidol-induced catalepsy in mice. In rats, the extract significantly inhibited orofacial dyskinesia induced by reserpine."*

Rubia cordifolia

Indian Madder Has a Protective Effect in Drug-induced Orofacial Dyskinesia

Patil RA. Protective effect of Rubia cordifolia on reserpine-induced orofacial dyskinesia. Nat Prod Res 2011 Nov 18

- *"It is concluded that oxidative stress might play an important role in reserpine-induced abnormal oral movements and MERC significantly protected animals against reserpine-induced orofacial dyskinesia and has great potential in the treatment of neuroleptic induced orofacial dyskinesia."*

Rutin

Rutin is a Possible Therapeutic Option to Treat Orofacial Dyskinesia

Bishnoi M. Protective effect of rutin, a polyphenolic flavonoid against haloperidol-induced orofacial dyskinesia and associated behavioral, biochemical and neurochemical changes. Fundamental and Clinical Pharmacology 21(2007) 521-529

- *"The findings of the present study suggested the involvement of free radicals in the development of neuroleptic-induced orofacial dyskinesia, a putative model of TD, and rutin as a possible therapeutic option to treat this hyperkinetic movement disorder."*

Sea Buckhorn

Sea Buckhorn Extract Has a Protective Role Against Haldol-induced Orofacial Dyskinesia

Batool F. Protective effects of aqueous fruit extract from Sea Buckthorn (Hippophae rhamnoides L. Spp. Turkestanica) on haloperidol-induced orofacial dyskinesia and neuronal alterations in the striatum. Med Sci Monit 2010 Aug;16(8);BR285-92

- *"Hippophae rhamnoides fruit extract has a protective role against haloperidol-induced orofacial dyskinesia. Consequently, use of Hippophae rhamnoides as a possible therapeutic agent for the treatment of tardive dyskinesia should be considered."*

Spikenard

Spikenard Offers Significant Protection Against Drug-induced Orofacial Dyskinesia

Patil RA. Reversal of reserpine-induced orofacial dyskinesia and catalepsy by Nardostchys jatamansi. Indian J Pharmacol 2012 May;44(3): 340-4

- *"The study concludes that ANJ and TNJ significantly protected animals against reserpine-induced orofacial dyskinesia as well as catalepsy suggesting its potential value in the treatment of neuroleptic-induced orofacial dyskinesia and Parkinson's disease."*

Velvet Bean

Velvet Bean Attenuates Haldol-induced Orofacial Dyskinesia

Pathan AA. Mucuna pruriens attenuates haloperidol-induced orofacial dyskinesia in rats. Nat Prod Res 2011 Apr;25(8):764-71

- *"The results of the present study suggest thst MEMP by virtue of its free radical scavenging activity prevents neuroleptic-induced TD."*

Visual Feedback

TV Monitor Visual Feedback Treatment, Self-Control and DD Promting Behavioral Treatments May Decrease Orofacial Dyskinesia's

Jackson, G. M., "A Comparison of Two Behavioral Treatments in Decreasing the Orofacial Movement of Tardive Dyskinesia." *Biofeedback and Self-Regulation* 8, no. 4 (December 1983): 547–53.

- *"In a study with an elderly female subject, two behavioral treatments were evaluated in terms of their effectiveness in decreasing orofacial movement associated with tardive dyskinesia. Video feedback and discreet-discrete prompting, a self-control procedure using a portable audio signal generator, were compared by means of an alternating treatments experimental design. Video and instructional controls were included in the study. Results indicated that both procedures were effective in decreasing orofacial movement. In addition, during the the concluding phase of the study, a promting card was carried by the subject at all times as a reminder to control mouth movements on an ongoing basis. The concluding phase resulted in generalization of treatment effect to the nontreatment environment. Follow-up sessions indicated maintenance of treatment effects."*

Vitamin B

B-vitamins Help Attenuate Haldol-induced Orofacial Dyskinesia

Macedo DS. B vitamins attenuate haloperidol-induced orofacial dyskinesia in rats: possible involvement of antioxidant mechanisms. Behav Pharmacol 2011 Oct;(7):674-80

- *"All groups treated with B vitamins presented a decrease in lipid peroxide formation. The data suggest a promising role for B vitamins in the prevention of OD."*

Vitamin C and E

Vitamin C and E have Beneficial Effects against the Development of Orofacial Dyskinesia

Faria RR. Beneficial effects of vitamin C and vitamin E on reserpine-induced oral dyskinesia in rats: critical role of striatal catalase activity. Neuropharmacology 2005 Jun;48(7):993-1001

- *"These results indicate a beneficial effect of these vitamins and reinforce the critical role of striatal catalase against the development of oral dyskinesia's."*

White Mulberry

White Mulberry Leaves Extract Has a Protective Effect Against Haldol-induced Orofacial Dyskinesia

Nade VS. Protective effect of Morbus alba leaves on haloperidol-induced orofacial dyskinesia and oxidative stress. Pharm Biol 2010 Jan;48(1): 17-22

- *"The results suggest a protective effect of Morbus alba extract against haloperidol-induced orofacial dyskinesia and oxidative stress."*

Yerba Mate

Yerba Mate Prevents Haldol-induced Orofacial Dyskinesia

Colpo G. Ilex paraguariensis has antioxidant potential and attenuates Haloperidol-induced orofacial dyskinesia and memory dysfunction in rats. Neurotoxicity Research, 2007, Vol. 12(3), pp.171-180

- *"Rats treated with "mate" did not exhibit an increase in vacuous chewing movements observed in rats treated with haloperidol." The "mate" prevented the effects of haloperidol in this behavioral paradigm."*

Yokukansan

Yokukansan is Effective in Reducing Vacuous Chewing Movements in Haldol Treated Rats

Sekiguchi K. Ameliorative effect of yokukansan on vacuous chewing movement in haloperidol-induced rat tardive dyskinesia model and involvement of the glutamatergic system. Brain Res Bull 2012 Dec 1;89(5-6):151-8

- *"Oral administration of YKS (0.1 and 0.5g/kg) once a day for three weeks (21 days) from the 12th week to 15th week ameliorated the haloperidol decanoate-induced increase in VCM in a dose-dependent manner."*

Tardive Dystonia Side Effect Treatments

Acupuncture

Acupuncture Has a Positive Effect on Tardive Dystonia

Tani M. Effect of acupuncture treatment for a patient with severe axial dystonia appearing during treatment for schizophrenia. Selshin Shinkeigaku Zasshi 2005;107(8):802-10

- "*It is suggested that acupuncture treatment has had a positive effect on tardive dystonia including axial dystonia. The patient also achieved improved stability with regards to symptoms of schizophrenia."*

Ceruletide

Ceruletide Showed Rapid Amelioration of Tardive Dystonia

Sugawara, M., "Tardive Dystonia and Ceruletide Effects: Case Report." Progress in Neuro-Psychopharmacology & Biological Psychiatry 16, no. 1 (January 1992): 127–34.

- *"One schizophrenic patient with drug-induced tardive dystonia was treated with ceruletide. 2. After the injection, dystonia showed a tendency toward rapid amelioration in 3 days; meanwhile, however, mental manifestations became exacerbated within 3 weeks. 3. We discuss some aspects of the effects of ceruletide."*

Orengedoku-to

Orengedoku-to Augmentation to Yokukan-san Treatment Results in Reduction of Tardive Dystonia

Okamoto H. Orengedoku-to augmentation in cases showing partial response to yokukan-san treatment: a case report and literature review of evidence for the use of Kampo herbal formulae. Neuropsychiatric Disease and Treatment 2013:9 151-155

- *"A 44-year-old male had started to use methamphetamine at the age of 20. When he he was 32 years old, he began to exhibit signs of methamphetamine-induced psychotic disorder accompanied by perceptional delusions and auditory hallucinations and started to take antipsychotic medication irregularly. After twice serving prison time, the patient stopped using methamphetamine and began taking 6mg of risperidone regularly at the age of 42, which caused severe tardive dystonia affecting his whole body. His tardive dystonia was refractory to conventional medications such as the maximum doses of tizanidine—a centrally acting skeletal muscle relaxant—benzodiazepines, and anticholinerigic drugs, as well as other atypical antipsychotics like 10mg of olanzapine or 30mg of aripiprazole. When he arrived at our hospital he was unable to sit still in the waiting room. In addition, he had been irritable and aggressive toward his mother, who lived with him, which often resulted in destruction of property at the home. When yokukan-san (7.5g/day) was added to his conventional medication, his involuntary movements were reduced by 30% after 2 weeks. Then, when orengedoku-to (7.5g/day) augmentation was started after 4 weeks, the tardive dystonia was reduced by 80% after 6 weeks. He was able to sit on the same bench with other patients in the waiting room for the first time in 2 years and property destruction became much less common occurrence, although the attitude toward his mother remained abrupt."*

Vitamin E

Vitamin E Substantially Improves Tardive Dystonia

Dannon P. Vitamin E treatment in tardive dystonia. Clinical Neuropharmacology. Vol. 20, No.5, pp. 434-437

- *"We present a case of one young man with tardive dystonia secondary to neuroleptic treatment, whose condition substantially improved with treatment by 1200mg/d(IU) of vitamin E."*

Parkinsonian Side Effect Treatments

DHEA

DHEA Supplementation is Effective for Parkinsonian Symptoms in Schizophrenics Treated with Antipsychotics

Nachshoni, Tali, "Improvement of Extrapyramidal Symptoms Following Dehydroepiandrosterone (DHEA) Administration in Antipsychotic Treated Schizophrenia Patients: A Randomized, Double-Blind Placebo Controlled Trial." Schizophrenia Research 79, no. 2–3 (November 15, 2005): 251–56. doi:10.1016/j.schres.2005.07.029.

- *"Recent investigation in schizophrenia indicated dehydroepiandrosterone (DHEA) levels to be inversely correlated with extrapyramidal symptomatology (EPS). This study thus investigates the effect of DHEA administration on medication-induced EPS. Inpatients*

with schizophrenia or schizoaffective disorder were randomized in double-blind fashion to receive either 100 mg DHEA or placebo in addition to a constant dosage of antipsychotic medication. Parkinsonism showed a favorable effect of DHEA with a significant time effect ($p < 0.0001$), as well as a significant group by time interaction ($p < 0.05$) and with no change noted on akathisia. Change of DHEA blood levels was negatively associated with change of Parkinsonism ($p < 0.05$) as well as with change of total EPS ratings ($p < 0.05$). DHEA appears to demonstrate a significant effect on EPS, with improvement observed particularly in Parkinsonian symptoms."

Kami-shoyo-san

Kampo Kami-shoyo-san is Effective for Antipsychotic-induced Parkinsonism

Ishikawa T. Effectiveness of the kampo kami-shoyo-san (TJ-24) for tremor of antipsychotic-induced parkinsonism. Psychiatry Clin Neurosci 2000)ct;54(5):579-82

- *"The results showed a statistical significant reduction in tremor after administration of kami-shoyo-san, with 62.5% patients showing improvements of one point or more."*

Kava Kava

Kava Kava Extract Attenuates Extrapyramidal Side Effects of Neuroleptic Drugs

Boerner RJ. Attenuation of neuroleptic-induced extrapyramidal side effects by Kava special extract WS 1490. Wien Med Wochenschr 2004 Nov;154(21-22):508-10

- *"We studied at 42 patients (17 female, 25 male) with different psychiatric diagnoses, who were pretreated by neuroleptics, the efficacy and tolerability of Kava special extract WS 1490 on extrapyramidal side effects. In both patient and physician questionnaires as well as in the physicians global ratings, significant improvements were found for all extrapyramidal signs and symptoms recorded. The concomitant intake of WS 1490 was well tolerated by the patients. The findings of this observational study suggest that extrapyramidal side effects of neuroleptic drugs may be attenuated by Kava special extract WS 1490."*

Magnesium-B6

Magnesium-B6 Treatment Results in a Marked Reduction of Extrapyramidal Disorders

Panteleeva, G. P., "[Cerebrolysin and magnesium-B6 in the treatment of side effects of psychotropic drugs]." Zhurnal Nevrologii I Psikhiatrii Imeni S.S. Korsakova / Ministerstvo Zdravookhraneniia I Meditsinskoĭ Promyshlennosti Rossiĭskoĭ Federatsii,

Vserossiĭskoe Obshchestvo Nevrologov [i] Vserossiĭskoe Obshchestvo Psikhiatrov 99, no. 1 (1999): 37–41.

- *"51 patients were observed. Schizophrenia was diagnosed in 31 patients and endogenous depression in 20 cases. All the patients had extrapyramidal and somato-vegetative side effects of neuroleptics and antidepressive drugs, and were resistant to conventional corrective therapy for at least a period of 3 weeks. In addition to current treatment of both basic disease and adverse effects, cerebrolysin was administered (5-10 ml i.v./dr, during 28 days) and magme B6 (20-30 ml per os during 21 days). By the treatment end-point either moderate or marked reduction of extrapyramidal disorders (according to ESRS) was observed in 74.4% of patients treated by cerebrolysin and in 72.2% treated by magne B6; somato-vegetative adverse effects reduced (by SARS) in 85.8% and in 83.8% respectively. Both drugs showed equally high efficacy against hyperkinetic and cardiovascular side effects (symptoms relief was in 59-62% and 65-69%, respectively). Cerebrolysin is more preferable in cases of side vegetative events, dysomnia and dysuria; magne B6 was more effective in correction of akineto-hypertonic and hyperkinetic-hypertonic syndromes as well as in cholinolytic side effects."*

Vitamin B6

Vitamin B6 May Be Efficient as a Treatment for Tardive Dyskinesia and Parkinsonism

Miodownik C. Vitamin B6 add-on therapy in treatment of schizophrenic patients with psychotic symptoms and movement disorders. Harefuah 2003 Sep;142(8-9):592-6, 647

- *The authors suggest that vitamin B6 may be efficient as a treatment for tardive dyskinesia and parkinsonism induced by neuroleptic agents."*

Vitamin B6 Improves Drug-induced Parkinsonism and Psychosis

Sandyk R. Pyridoxine improves drug-induced parkinsonism and psychosis in a schizophrenia patient. Int J Neurosci 1990 Jun;52(3-4):225-32

- *"A schizophrenia patient with severe neuroleptic-induced Parkinsonism and Tardive Dyskinesia is presented in whom administration of pyridoxine (vitamin B6) (100mg/d) resulted in a dramatic and persistant attenuation of the movement disorder as well as a reduction of psychoatic behavior."*

Miodownik C. Vitamin B6 add-on therapy in the treatment of schizophrenic patients with psychotic symptoms and movement disorders. Harefuah 2003 Sep;142 (8-9):592-6 647

- *"The authors suggest that vitamin B6 may be efficient as the treatment for tardive dyskinesia and parkinsonism induced by neuroleptic agents."*

Vitamin B12

Acute Onset of Extrapyramidal Symptom Can Be a Manifestation of Vitamin B 12 Deficiency

Joy, M. A. "Vitamin B12 Deficiency Presenting with an Acute Reversible Extrapyramidal Syndrome." Neurology India 53, no. 1 (March 2005): 120.

- *"In conclusion, acute onset extrapyramidal syndrome can be a rare manifestation of vitamin B12 deficiency, which is reversible with therapy. Serum B12 levels should be checked in patients who do not have an obvious cause for an acute extrapyramidal syndrome."*

Vitamin B12 Deficiency Presenting With an Acute Reversible Extrapyramidal Syndrome

Kumar S. Vitamin B12 deficiency presenting with an acute reversible extrapyramidal syndrome. Neurol India 2004 Dec;52(4):507-9

- *"Vitamin B12 deficiency usually presents with pernicious anemia or various neuropsychiatric manifestations. Commonly seen neuropsychiatric manifestations include large fiber neuropathy, myelopathy, (subacute combined degeneration of the spinal cord), dementia, cerebellar ataxia, optic atrophy, psychosis, and mood disorders. The present report highlights an unusual presentation of vitamin B12 deficiency-acute onset extrapyramidal syndrome in a 55-year-old man. The patient presented with a 10 day history of slowness of all activities including a slow gait, mild tremors of hands and low volume speech. On examination, he had features of mask0like facies, reduced blink rate and cogwheel rigidity. He was investigated for possible causes and was found to have features of vitamin B12 deficiency. Other causes for acute onset parkinsonism were excluded by appropriate investigations. He showed a dramatic improvement following treatment with intramuscular vitamin B12 injections. At five-year follow-up, he was found to be functionally independent with no neurological deficits.*

Vitamin B12 and Folate

Vitamin B12 and Folate Deficiency Cause Psychotic Disorder and Extrapyramidal Symptoms in a 12 year-old Boy

Dogan, Murat, "Psychotic Disorder and Extrapyramidal Symptoms Associated with Vitamin B12 and Folate Deficiency." Journal of Tropical Pediatrics 55, no. 3 (June 2009): 205–7. doi:10.1093/tropej/fmn112.

- *"Vitamin B12 and folate deficiency causing neuropsychiatric and thrombotic manifestations, such as peripheral neuropathy, subacute combined degeneration of cord, dementia, ataxia, optic atrophy, catatonia, psychosis, mood disturbances, myocardial infarction and portal vein thrombosis are well known. This present report highlights an unusual presentation of vitamin B12 deficiency-psychotic disorder, extrapyramidal symptoms in a 12-year-old boy. His symptoms responded to parenteral vitamin B12 therapy. So with this report we emphasized that serum vitamin B12 and folate levels should be measured, especially in those patients who present with other known neuropsychiatric features of vitamin B12 and folate deficiency."*

Vitamin E

Vitamin E Reduces Neuroleptic-induced Parkinsonism

Dorfman-Etrog P. The effect of vitamin E addition to acute neuroleptic treatment on the emergence of extrapyramidal side effects in schizophrenic patients: An open label study. European Neuropsychopharmacology 9 (1999) 475-477

- *"Addition of vitamin E to neuroleptics may reduce the severity of acute neuroleptic-induced Parkinsonism (NIP) in schizophrenic patients."*

Tardive Oculogric Spasm Side Effect Treatments

Vitamin E

Vitamin E is a Successful Treatment of Tardive Oculogric Spasms

Coupland N. Successful treatment of tardive oculogric spasms with vitamin E. Journal of Clinical Psychopharmacology, Vol. 15(4), August 1995, pp 285-286

- *"The baseline frequencies of episodes accorded with his history and their number fell substantially within a month on vitamin E, 1200 IU daily." "A trial of vitamin E seems merited in oculogric spasms that have not responded to standard approaches…."*

Neuroleptic Malignant Syndrome Side Effect Treatment

Vitamin E and Vitamin B6

Vitamin E Plus Vitamin B6 for Supportive Management of Neuroleptic Malignant Syndrome

Dursun SM. High-dose vitamin E plus vitamin B6 treatment of risperidone-related neuroleptic malignant syndrome. J Psychopharmacol 1998;12(2):220-1
PMID# 9694035

- *" This patient responded satisfactorily to the supportive management and vit E plus vit B6.*

Catalepsy Side Effect Treatments

Cannabidiol

Cannabidiol (CBD) Can Attenuate Catalepsy Induced by Pharmacological Mechanisms

Gomes FV. Cannabidiol attenuates catalepsy induced by distinct pharmacological mechanisms via 5-HT1A receptor activation in mice. Prog Neuropsychopharmacol Biol Psychiatry 2013 Oct;1;43-7

- *"These findings indicate that CBD can attenuate catalepsy caused by different mechanisms (D2 blockade, NOS inhibition and CB1 agonism) via 5-HT1A receptor activation, suggesting that it could be useful in the treatment of striatal disorders."*

NR-ANX-C

Polyherbal Formula NR-ANX-C has a Significant Reduction on Catalepsy

Nair V. Effect ofNR-ANX-C (a polyherbal formulation) on haloperidol induced catalepsy in albino mice. Indian J Med Res 2007 Nov;126(5):480-4

- *"In our study, maximum reduction in cataleptic score was observed in NR-ANX-C (25mg/kg) treated group. The maximum reduction in SOD activity was also observed in the same group. These findings suggest a possible involvement of the antioxidant potential of NRANX-C in alleviating haloperidol induced catalepsy."*

Quercetin

Quercetin is a Potential Drug Candidate for the Treatment of Neuroleptic-induced Extrapyramidal Side Effects

Naidu P.S. Quercetin, a bioflavonoid, reverses Haloperidol-induced catalepsy. Methods Find Exp Clin Pharmacol 2004, 26(5):323-326

- *"In conclusion, the findings of the present study strongly suggest that quercetin can be screened as a potential drug candidate or as an adjuvant for the treatment of neuroleptic-induced extrapyramidal side effects."*

Spikenard

Spikenard Has Potential in Reversing Haldol-induced Catalepsy

Rasheed AS. Evaluation of toxicological and antioxidant potential of Nardostachys jatamansi in reversng haloperidol-induced catalepsy in rats. International Journal of General Medicine 2010:3 127-136

- *"Our findings of behavioral studies and biochemical estimations show that Nardostachys jatamansi reversed the haloperidol-induced catalepsy in rats."*

Tic Side Effect Treatments

Magnesium and Vitamin B6

Magnesium and Vitamin B6 are Effective in Reducing the Tic Score in Children with Tourette syndrome

Garcia-Lopez R. An open study evaluating the efficiency and security of magnesium and vitamin B6 as a treatment of Tourette syndrome in children. Med Clin (Barc) 2008 Nov 22;131(18):689-91

- *The total tic score decreased from 26.7 (t0) to 12.9 (t4) and the total effect on the YGTSS was a reduction from 58.1 to 18.8."*

Glorybower Leaf

Glorybower Leaf Extract Dramatically Reduces Chronic Motor Tics

Fan, Pi-Chuan, "Intractable Chronic Motor Tics Dramatically Respond to Clerodendrum Inerme (L) Gaertn." Journal of Child Neurology 24, no. 7 (July 2009): 887–90. doi:10.1177/0883073808331088.

- *"Tics are characterized by involuntary, sudden, rapid, repetitive, nonrhythmic, stereotyped movements or phonic productions. Those who suffer from either motor or phonic tics, but not both, for more than 1 year are diagnosed with chronic tic disorder. Several pharmacological interventions have been proposed for the treatment of tic disorder. Dopamine D2 receptor blockers and dopamine depletors are thought to be the most effective ones clinically. However, such treatments are suboptimal in terms of effectiveness*

and side effects, such as body weight gain and extrapyramidal symptoms. We report on a 13-year-old girl, with chronic motor tic disorder refractory to multiple anti-tic therapies, who showed dramatic improvement and remission after taking the crude leaf extract of Clerodendrum inerme (L) Gaertn. No side effects were observed during a follow-up of more than 2 years. To the best of our knowledge, this is the first report on the anti-tic effect of Clerodendrum inerme."

Akathisia Side Effect Treatments

Gluten-free Diet

Gluten-free Diet in People with Schizophrenia Leads to Improvement in Extrapyramidal Side Effects and Akathisia

Jackson, Jessica, "A Gluten-Free Diet in People with Schizophrenia and Anti-Tissue Transglutaminase or Anti-Gliadin Antibodies." Schizophrenia Research 140, no. 1–3 (September 2012): 262–63. doi:10.1016/j.schres.2012.06.011.

- *"Our results suggest that a GFD in people with antibodies to anti-tTG or AGA may lead to symptom improvements in schizophrenia as well as robust improvements in extrapyramidal side effects (EPS). Both participants saw notable improvements on the BPRS and SANS. Both participants also had improvements in akathisia and EPS with participant B having notable changes in both at the end of the trial. The data shows that a GFD can be maintained in individuals with schizophrenia with no negative effects on behavior or attitude and no need for medication changes. Overall the diet was easily maintained, however it is recognized that much education would be needed to help patients understand the importance of a GFD and the gluten content of food and snacks."*

Iron

Minor Evidence that Iron Supplementation May aid in the Treatment of Akathisia

Gold R. Is there a rationale for iron supplementation in the treatment of akathisia? A review of the evidence. J Clin Psychiatry 1995 Oct;56(10):476-83

- *The rationale for iron supplementation in the treatment of akathisia is relatively weak, and there are potentially adverse long-term consequences as outlined in our review. More research is required to directly measure the level of iron in the brains of patients with akathisia…..before such therapeutic intervention can be recommended."*

Improvement of Akathisia with Intravenous Iron in Iron Deficient Patient

Cotter PE. Improvement in neuroleptic-induced akathisia with intravenous iron treatment in a patient with iron deficiency. J Neurol Neurosurg Psychiatry 2007 May:78(5):548

- *"The close temporal relationship between administration of intravenous iron deficiency can contribute to the development or persistence of akathisia in some patients. Iron repletion may be valuable in such cases, although this requires further evaluation."*

Neuroleptic Drugs May Chelate Iron and Cause Akathisia—Replenishment May Reverse This Mechanism

Chengappa, K. N., "Iron for Chronic and Persistent Akathisia?" The Journal of Clinical Psychiatry 54, no. 8 (August 1993): 320–21.

- *"Thus, neuroleptic drugs, which are known to chealate iron, may strip iron from the D2 receptor, causing akathisia in humans. Oral replenishment of iron may reverse this mechanism, thereafter allowing homeostatic mechanisms to take over. There is evidence that serum iron and transferrin decrease significantly in patients receiving neuroleptic drugs who experience akathisia but not in nonakathisic patients."*

L-tryptophan and Niacin

L-Tryptophan and Niacin May Reduce Akathisia

Kramer MS. L-tryptophan in neuroleptic-induced akathisia. Biol Psychiatry 1990 Mar 15;27(6):671-2

- *"Akathisia scores decreased an average of 39% of base line. Some patients and referring physicians felt that L-tryptophan was quite helpful and requested its continuation.. L-tryptophan, along with nicotinic acid appeared to reduce both objective and subjective components of akathisia in most patients."*

N-acetylcysteine

N-Acetylcysteine has a Moderate Benefit in the Treatment of Akathisia

Berk M. N-Acetyl Cysteine as glutathione precursor for Schizophrenia-A double-blind, randomized, placebo-controlled trial. Biol Psychiatry 2008;64:361-368

- "*A moderate benefit of NAC at end point for akathisia was also evident on the BAS, which approached significance."*

Relaxation

Structured Relaxation May Be a Promising Alternative to Traditional Treatment for Akathisia

Hansen LK. Structured relaxation in the treatment of akathisia. Neuropsychiatr Dis Treat 2010 May 25;6:269-71

- *"….the relaxation program appears to be a promising alternative to traditional treatment of akathisia. The patients appreciated the relaxation sessions but none of them managed to carry it out on their own without professional encouragement."*

Vitamin B6

High Dose Vitamin B6 is an Available Treatment for Neuroleptic-induced Akathisia

Lerner V. Vitamin B6 treatment in acute neuroleptic-induced akathisia: a randomized, double-blind, placebo-controlled study. J Clin Psychiatry 2004 Nov;65(11):1550-4

- *"The vitamin B6-treated patients in comparison with the placebo group showed a significant on the subjective-awareness of restlessness, subjective distress, and global subscales of BAS. Our preliminary results indicate that high doses of vitamin B6 may be useful additions to the available treatments for NIA….."*

Miodownik C. Vitamin B6 verses mianserin and placebo in acute neuroleptic-induced akathisia: a randomized, double blind, controlled study.

- *"Our results indicate that high doses of B6 and low dose of mianserin may be a useful addition to current treatments of NIA."*

Lithium-induced Tremor Side Effect Treatments

Vitamin B6

Vitamin B6 Shows Impressive Improvement for Lithium-induced Tremor

Miodownik C. Lithium-induced tremor treated with vitamin B6: a preliminary case series. Int J Psychiatry Med 2002; 32(1):103-8

- *"After the addition of vitamin B6 to their treatment, according to their SAS scores four patients showed impressive improvement until total disappearance of their tremor. The subjective scale, on which the patients scored their impression of clinical improvement, showed similar results."*

Dopaminergic Supersensitivity Side Effect Treatments

Estradiol

Estradiol caused a 2.8-fold Reduction of Dopamine Receptor Affinity for a Typical Antipsychotic

Gattaz, W. F., "[Estradiol inhibits dopamine mediated behavior in rats--an animal model of sex-specific differences in schizophrenia]." Fortschritte Der Neurologie-Psychiatrie 60, no. 1 (January 1992): 8–16. doi:10.1055/s-2007-999120.

- *"Since oestradiol caused a 2.8-fold reduction of dopamine receptor affinity for sulpiride, we assumed that the behavioural changes caused by oestradiol were accounted for by a down-regulation of the dopaminergic system."*

Estradiol can Suppress Haldol-induced Supersensitivity

Bedard PJ. Estradiol can suppress haloperidol-induced supersensitivity in dyskinetic monkeys. Neurosci Lett. 1986 Feb 28;64(2):206-10

- *"We have studied a monkey model of lingual dyskinesia, due to midbrain lesion, which is markedly increased by apomorphine. In such animals a single large intramuscular dose of haloperidol (HAL), 1mg/kg, almost completely abolishes the apomorphine potentiation after 24 h, but 15 days later there is is a 5-fold increase in the response to aporphine which we attribute to supersenitivity. Estradiol benzoate (0.15mg/kg, subcutaneously) on days 3, 6, 9, and 12 after HAL completely suppresses the expected rebound supersensitivity to apomorphine. However, the suppression is not seen if the animals have received HAL and estradiol together in the initial treatment."^*

Estrogen

Estrogen May Down Regulate Brain Dopamine Receptors

Fields, J. Z.,"Estrogen Inhibits the Dopaminergic Supersensitivity Induced by Neuroleptics." Life Sciences 30, no. 3 (January 18, 1982): 229–34.

- *"Administration of estrogen to rats during the period of withdrawal from chronic haloperidol attenuated the characteristic increase in apomorphine-induced stereotypy and the increase in (3H) spiroperidol binding. This apparent ability of estrogen to "down-regulate" brain dopamine receptors could lead to useful pharmacological treatments of tardive dyskinesia and possibly of other hyperdopaminergic states."*

Estrogen May Attenuate the Development of Dopaminergic Supersensitivity

Gordon JH. Antagonism of dopamine supersensitivity by estrogen: neurochemical studies in animal model of tardive dyskinesia. Biol Psychiatry 1981 Apr;16(4):365-71

- *"The administration of EB during the withdrawal from chronic haloperidol treatment or the continuous administration of EB decreases or prevents the proliferation of dopamine binding sites in the striatum that normally occur upon withdrawal of these two substances. These results indicate that exogenous estrogens may modulate the number of dopamine receptors in the central nervous system and, as such, may decrease the incidence and/or relieve the symptoms of tardive dyskinesia."*

Gordon JH. Modulation of dopamine receptor sensitivity by estrogen. Biol Psychiatry 1980 Jun;15(3):389-96

- *"Rats treated chronically with Haldol, and treated daily with EB following the Haldol treatment, showed an attenuation of drug-induced sterotypy. These preliminary data indicate that estrogen can attenuate the development or mask the display of the supersensitive dopamine receptor."*

Fields JZ. Estrogen inhibits the dopaminergic supersenitivity induced by neuroleptics. Life Sci 1982 Jan 18;30(3):229-34

- *"Administration of estrogen to rats during theperiod of withdrawal from chronic haloperidol attenuated the characteristic increase in apomorphine-induced sterotypy and increase in (3H) spiroperidol binding. This apparent ability of estrogen to "down regulate" brain dopamine receptors could lead to useful pharmacological treatments of tardive dyskinesia and possibly of other hyperdopaminergic states."*

Insulin

Insulin May Attenuate Dopamine Receptor Supersensitivity

Lozovsky, D. B., "Modulation of Dopamine Receptor Supersensitivity by Chronic Insulin: Implication in Schizophrenia." Brain Research 343, no. 1 (September 16, 1985): 190–93.

- *"Haloperidol-induced increases in the number of dopamine receptors, as measured by [3H]spiperone binding to striatal membranes, do not occur in rats repeatedly treated with insulin in doses eliciting pronounced hypoglycemia. Given alone, however, insulin has no effect on [3H]spiperone binding in normal rats. These findings demonstrate a modulating effect of insulin on brain dopamine receptor sensitization. This effect might be relevant to the mechanism of insulin coma therapy in schizophrenia and is consistent with and supports the dopaminergic hypothesis of this disorder."*

Light

Continuous Exposure to Light Leads to Lower Dopaminergic Supersensitivity Function

Vanessa C. Effects of continuous exposure to light on behavioral dopaminergic supersensitvity. Biol Psychiatry 1999;45:1622-1629

- *"The supersensitivity ratios were always lower for the animals kept under the LL cycle than those kept under the LD cycle regardless of the behavioral parameter used, suggesting that the development of the doperminergic supersensitvity was lower in animals continuously exposed to light. This effect could also be explained by increased endogenous dopamine avalibility, which would attenuate the postsynaptic dopaminergic blockade induced by haloperidol and, consequently, the compensatory dopaminergic supersensitivity."*

L-Prolyl-L-Leucyl-Glycinamide

L-Prolyl-L-Leucyl-Glycinamide (PLG) Inhibits Haldol Dopamine Receptor Supersensitivity

Chiu, P., "Mesolimbic and Striatal Dopamine Receptor Supersensitivity: Prophylactic and Reversal Effects of L-Prolyl-L-Leucyl-Glycinamide (PLG)." Peptides 6, no. 2 (April 1985): 179–83.

- *"Functional supersensitivity of mesolimbic and striatal dopamine receptors has been suggested to contribute to the pathogenesis of schizophrenia and tardive dyskinesia. Using the rodent model of chronic administration of the neuroleptic haloperidol, we investigated the possible desensitizing effects of a tripeptide structurally unrelated to dopamine agonists, L-prolyl-L-leucyl-glycinamide (PLG) on mesolimbic and striatal dopaminergic receptor supersensitivity. Administration of PLG either prior to or after chronic haloperidol, inhibited the supersensitivity of dopamine receptors. The results have implications for pharmacological intervention in preventing tardive dyskinesia and relapse psychosis of schizophrenia."*

Melatonin

Melatonin May Revert the Enhancement of Haldol-induced Dopaminergic Supersensitivity

Abilio VC. Effects of melatonin on behavioral dopaminergic supersensitivity. Life Sci 2003 May 16;72(26):3003-15

- *"Acute treatment with melatonin reverted the enhancement of the haloperidol-induced doperminergic supersensitvity produced by concomitant long-term treatment with melatonin, as well as melatonin-induced dopaminergic supersensitvity per se. Our results support previous evidence of antidopaminergic effects of melatonin and demonstrate that repeated administration of this hormone modifies the plasticity of behaviors mediated by central dopaminergic systems."*

Nicotine

Chronic Nicotine use Blocks Haldol-induced Increase in D2 Dopamine Receptor Density

Prasad C. Chronic nicotine use blocks haloperidol-induced increase in striatal D2-dopamine receptor density. Biochem Biophys Res Commun 1989 Feb 28;159(1):48-52

- *"Epidemiologic studies have suggested a positive association in man between nicotine use and the incidence of tardive dyskinesia, a disease characterized by dopaminergic supersensitivity after chronic neuroleptic therapy. In rats, repeated administration of neuroleptics results into dopaminerigic supersensitivity and increased density of striatal D2-dopamine receptors. We investigated the effects of 6-week continuous nicotine intake on the neuroleptic (haloperidol)-induced increase in murine striatal D2-dopamine receptor density. Contrary to expectations, our data show that nicotine blocked the increase in D2-dopamine receptor density after neuroleptic administration."*

Vitamin E

Attenuation of Dopaminergic Supersensitivity with Vitamin E

Gattaz W. F. Vitamin E attenuates the development of haloperidol-induced dopaminergic hypersensitivity in rats: possible implications for tardive dyskinesia. J Neural Transm (1993) 92: 197-201

- *"Within the context of the present experiment vitamin E attenuated the development of behavioral DA-supersensitvity after haloperidol treatment."*

Elecroconvulsive Therapy Side-Effect Treatments

Brahmi and Mandookaparni

Brahmi and Mandookaparni Attenuate Effects of Electroconvulsive Shock

Andrade, Chittaranjan, "Anti-Amnestic Properties of Brahmi and Mandookaparni in a Rat Model." Indian Journal of Psychiatry 48, no. 4 (October 2006): 232–37. doi:10.4103/0019-5545.31554.

- *"Brahmi and Mandookparni do not in themselves improve learning; however, each attenuates the amnestic effects of ECS without showing synergism in this beneficial action. Exercises in research and development are indicated to further investigate the anti-amnestic properties of these herbs, and to identify the specific chemical constituents which have procognitive effects."*

BR-16A

BR-16A is an Herbal Medication that Extends Protection against Electroconvulsive Shock Induced Anterograde Amnesia

Joseph, J., "BR-16A Protects against ECS-Induced Anterograde Amnesia." Biological Psychiatry 36, no. 7 (October 1, 1994): 478–81.

- *"BR-16A is an herbal (non allopathic) medication used in India to enhance cognition. In experiment 1, 28 Wistar rats received either BR-16A (200 mg/kg/day) or vehicle alone for 3 weeks. During the third week, the rats were tested for learning in the Hebb Williams complex maze. BR-16A-treated rats showed significantly better learning than did controls. Experiment 2 was conducted identically except that during the second week all of 32 rats additionally received six once-daily electroconvulsive shocks (ECS). An advantage for learning was again demonstrated for the BR-16A group. It is concluded that BR-16A facilitates learning, and that this effect extends to a protection against ECS-induced anterograde amnesia. Cognitive deficits induced by electroconvulsive therapy are a major disadvantage of the treatment and, to-date, no drug has been found to offer satisfactory protection against such deficits. It is suggested that BR-16A may hold promise in the containment of electroconvulsive therapy (ECT)-induced cognitive compromise."*

Caffeine

Caffeine Pretreatment Enhances Clinical Efficacy and Reduces Cognitive Effects of ECT

Calev, Avraham, "Caffeine Pretreatment Enhances Clinical Efficacy and Reduces Cognitive Effects of Electroconvulsive Therapy." Convulsive Therapy 9, no. 2 (1993): 95–100.

- *"In an open clinical trial, depressed patients received age-dosed, brief-pulse electroconvulsive therapy (ECT) either with or without 500 mg i.v. caffeine sodium benzoate before each treatment. Caffeine-pretreated patients required fewer ECT treatments, and after three to four treatments, their Hamilton Depression Scale (HDS) scores were significantly lower. At the end of the ECT course, both groups reached the same reduction in HDS scores. Of five memory tests, one showed better performance at the end of the ECT course for the caffeine-pretreated compared with the non-caffeine-*

pretreated patients. The results argue that caffeine-modified ECT differs from unmodified ECT in speed of response and the effects on cognitive tests."

Caffeine before ECT leads to Clinical Improvement in Patient who was Non-responsive to Treatment

Shapira, Baruch, "Potentiation of Seizure Length and Clinical Response to Electroconvulsive Therapy by Caffeine Pretreatment: A Case Report." Convulsive Therapy 1, no. 1 (1985): 58–60.

- *"A patient with a history of nonresponse to electroconvulsive therapy (ECT) was treated with ECT modified by i.v. caffeine before electrical stimulation for some of the seizures. Seizures preceded by i.v. caffeine were longer, and led to marked clinical improvement. Caffeine pretreatment may be a method to enhance seizure length and efficacy in resistant patients."*

Pretreatment with Caffeine Citrate Increases Seizure Duration during ECT

Pinkhasov, Aaron, "Pretreatment With Caffeine Citrate to Increase Seizure Duration During Electroconvulsive Therapy A Case Series." Journal of Pharmacy Practice, November 5, 2014, 0897190014549838. doi:10.1177/0897190014549838.

- *"Of the 12 ECT treatments utilizing caffeine citrate, 9 achieved at least 1 session lasting >30 seconds with an average seizure duration of 35 seconds. Increase in seizure duration ranged from −41% to 276% with an average increase of 48%. Only 3 treatment sessions utilizing caffeine citrate showed no increase in seizure duration. Doses ranged from 120 to 600 mg of both oral and parenteral caffeine citrate. Although increase in seizure duration was achieved for the majority of the ECT sessions, no dose–response correlation could be made. No significant adverse reactions were noted with the use of caffeine citrate during ECT."*

Electric Acupuncture

Electric Acupuncture Convulsive Therapy is more efficient than Electroconvulsive Therapy

Chongcheng, Xue, "Electric Acupuncture Convulsive Therapy." Convulsive Therapy 1, no. 4 (1985): 242–51.

- *"In 150 schizophrenic patients, a comparative investigation between electric acupuncture convulsive therapy (EACT) and electroconvulsive therapy (ECT) showed that the current used for eliciting a convulsion in EACT was only 3.6% of that for ECT when the electrodes were placed at acupoints Baihui and Renzhong. EACT is a modification of*

ECT in which stimulating currents are passed through acupuncture needle electrodes inserted in midline positions. In this study, the efficacy of EACT was better, the somatic and visceral reactions milder, and the incidence of spine fracture and changes in EEG and in memory were less than in ECT. The clinical efficacy of electroconvulsive therapy is seen to depend on changes in midline brain structures."

Galantamine

Galantamine May Be Protective Against Memory Impairment from ECT

Matthews, John D., "A Double-Blind, Placebo-Controlled Study of the Impact of Galantamine on Anterograde Memory Impairment during Electroconvulsive Therapy." The Journal of ECT 29, no. 3 (September 2013): 170–78. doi:10.1097/YCT.0b013e31828b3523.

- *"Galantamine may be protective against impairment in retention of new learning. Galantamine exhibited minimal adverse effects and was safe when administered during ECT. The present findings require replication by future researchers using larger samples before broad conclusions can be drawn."*

Galantamine May Reduce Cognitive Impairment during ECT

Matthews, John D., "The Impact of Galantamine on Cognition and Mood during Electroconvulsive Therapy: A Pilot Study." Journal of Psychiatric Research 42, no. 7 (June 2008): 526–31. doi:10.1016/j.jpsychires.2007.06.002.

- *"Our data support the hypothesis that galantamine may reduce cognitive impairment during ECT, especially with regards to new learning. In addition, galantamine may also enhance the antidepressant action of ECT. Galantamine was both safe and well tolerated during ECT."*

Herbal Treatments

Herbal Treatments for Electroconvulsive-Induced Memory Deficits

Andrade, C., "Herbal Treatments for ECS-Induced Memory Deficits: A Review of Research and a Discussion on Animal Models." The Journal of ECT 16, no. 2 (June 2000): 144–56.

- *"During the last decade the use of herbal medicinal substances in the attenuation of anterograde and retrograde amnesia induced by electroconvulsive shock (ECS) has been studied using animal research. We will discuss the background of herbal medicine in India, review the research findings on herbal medicines for ECS-induced amnestic deficits, and examine the applications and limitations of animal models in this context.*

We will focus on our own research and insights, with particular emphasis on practical issues."

Herbal Medicine for Electroconvulsive Therapy

Andrade, C., "Herbal Treatments for ECS-Induced Memory Deficits: A Review of Research and a Discussion on Animal Models." The Journal of ECT 16, no. 2 (June 2000): 144–56.

- *"In this article, we have briefly introduced the practice of herbal medicine in India, summarized the studies that have examined the herbal attenuation of amnestic deficits induced by ECS, and discussed the application and limitations of animal models in the context of such research. We have primarily focused on our own work and insights, and have also examined practical issues that are involved in studies of this nature. For a comprehensive review of the effects of ECS on memory and cognition, the effects of pharmacological agents on ECS-induced memory deficits, and the effect of coadministered drugs on ECS seizure properties, the reader is referred to Krueger et al. (1992) and Fochtmann (1994)."*

Herbal Treatments May Attenuate Amnestic Deficits Induced by Electroconvulsive Shock

Andrade, C., "Herbal Treatments for ECS-Induced Memory Deficits: A Review of Research and a Discussion on Animal Models." The Journal of ECT 16, no. 2 (June 2000): 144–56.

- *"In this article, we have briefly introduced the practice of herbal medicine in India, summarized the studies that have examined the herbal attenuation of amnestic deficits induced by ECS, and discussed the application and limitations of animal models in the context of such research. We have primarily focused on our own work and insights, and have also examined practical issues that are involved in studies of this nature. For a comprehensive review of the effects of ECS on memory and cognition, the effects of pharmacological agents on ECS-induced memory deficits, and the effect of coadministered drugs on ECS seizure properties, the reader is referred to Krueger et al. (1992) and Fochtmann (1994)."*

Ice Pack Therapy

Ice Pack Therapy May Be Useful for the Treatment of ECT-Induced Headache

Drew, Brian I., "Cryotherapy for Treatment of ECT-Induced Headache." Journal of Psychosocial Nursing and Mental Health Services 43, no. 4 (April 2005): 32–39.

- *"Because headache is a common side effect of electroconvulsive therapy (ECT), this study sought to determine the effectiveness of cryotherapy (i.e., a frozen gel band) in relieving*

pain in patients with post-ECT headaches, and whether headache intensity and physiological measurements could predict use of an alternative analgesic (rescue medication). We used a quasi-experimental, crossover design to collect data from 31 patients ages 24 to 85 who had been referred for ECT at two medical facilities in San Diego, California. Measurements of patients' pain intensity were made at three intervals: upon perceiving headache, and at 30 and 60 minutes following the cryotherapy or acetaminophen interventions, based on the order of the crossover design. Data were analyzed using Hotelling's T2 and logistic regression. No significant difference was found between cryotherapy and acetaminophen in relieving ECT-induced headaches (p = .420). There was no influence due to the crossover design (p = .313), nor where there significant changes in physiological measures from treatment (p = .420). Logistic regression showed that 50% of patients required rescue medication after 60 minutes for both treatments (R2 = .498, p = .001), and 66% required rescue medication based on pain level and physiological measures (R2 = .662, p < .008). Based on these results, cryotherapy is an alternative treatment that may be helpful to some patients with ECT-induced headaches."

Memoral Herbal

Memoral Herbal Showed Effective Prevention of ECT induced Cognitive Impairment

Mousavi, Seyed Ghafur, "Efficacy of Memoral Herbal on Prevention of Electroconvulsive Therapy-Induced Memory Impairment in Mood Disorder Patients (isfahan - Iran 2011)." International Journal of Preventive Medicine 3, no. 7 (July 2012): 499–503.

- *"The Memoral herbal capsules, each contains 360 mg of Boswellia oleo-gum resin and 36 mg of Zimgiber rhizome. The most important constituent of Boswellia is gum resin 60%, mosilage 20-23% and essence 5-9%, which contains a-b-Thujon, p-cymen and linanol. Boswellia Serrata has Boswellic acid and acetyl- 11- keto-beta boswellic acid too, which are responsible for many therapeutic effect. The volatile oils in Boswellia dilate the vasculator of the brain thus can increase the blood passage through the brain. Boswellia extract has been demonstrated by a battery of rigorous tests to have anti-inflammatory effect. Boswellic acid has memory enhancing and anti-dementia properties. The mechanism by which Boswellia can improve memory is through its anti-inflammatory effect on the brain."*
- *"Our work showed the effective prevention of ECT-induct cognitive impairment by using Memoral herbal. The cognitive status of patients not only declined, but also improved. The memory, attention and orientation, verbal fluency, and MMSE of patients showed improvement by Memoral use."*

Nitrous Oxide

Nitrous Oxide Inhalation as an Alternative to Electroconvulsive Therapy

Milne, Brian. "Nitrous Oxide (laughing Gas) Inhalation as an Alternative to Electroconvulsive Therapy." Medical Hypotheses 74, no. 5 (May 2010): 780–81. doi:10.1016/j.mehy.2009.11.021.

- *"Electroconvulsive therapy (ECT) is used widely in the treatment of psychiatric conditions; however, its use is not without controversy with some recommending a moratorium on its clinical use. Complications and side effects of ECT include memory loss, injury, problems originating from sympathetic stimulation such as arrhythmias and myocardial ischemia and the risk of general anesthesia. Nitrous oxide (laughing gas) could potentially substitute for ECT as it shares some similar effects, has potential beneficial properties for these psychiatric patients and is relatively safe and easy to administer. Nitrous oxide induces laughter which has been described as nature's epileptoid catharsis which one might surmise would be beneficial for depression. It also produces a central sympathetic stimulation similar to ECT and causes release of endogenous opioid peptides, which are potential candidates for the development of antidepressant drugs. Nitrous oxide is also associated with seizure like activity itself. Administration of nitrous oxide as a substitute for ECT is eminently feasible and could be given in a series of treatments similar to ECT therapy."*

Percutaneous Electrical Nerve Stimulation

Percutaneous Electrical Nerve Stimulation (PENS) Proves Useful for Treating ECT-induced Headaches

Ghoname, E. A., "Use of Percutaneous Electrical Nerve Stimulation (PENS) for Treating ECT-Induced Headaches." Headache 39, no. 7 (August 1999): 502–5.

- *"Five patients who experienced migrainelike attacks associated with electroconvulsive therapy (ECT) were treated using a novel nonpharmacologic therapy known as percutaneous electrical nerve stimulation (PENS). In this sham-controlled preliminary evaluation, PENS therapy proved to be a useful alternative to opioid analgesics for the acute treatment and/or prevention of ECT-induced headache."*

Phenylbutyric Acid

Phenylbutyric Acid Protects against Spatial Memory Deficits form ECT

Yao, Zhao-Hui, "Phenylbutyric Acid Protects against Spatial Memory Deficits in a Model of Repeated Electroconvulsive Therapy." Current Neurovascular Research 11, no. 2 (May 2014): 156–67.

- *"Intraperitoneal injection of phenylbutyric acid (PBA), an aromatic short chain fatty acid acting as a molecule chaperon, could prevent rats from the rECS-induced memory deficits and synaptic potential enhancement by decreasing the levels of the abnormally increased memory-associated proteins and enhanced axon reorganization in hippocampus. Our data suggested that PBA might be potentially used to attenuate the rECS-induced memory impairment."*

Transcutaneous Acupoint Electrical Stimulation

Transcutaneous Acupoint Electrical Stimulation Has a Good Response in Reliving Nausea and Vomiting in Patients Receiving Electroconvulsive Therapy

Kramer, Barry Alan, "Transcutaneous Acupoint Electrical Stimulation in Preventing and Treating Nausea and Vomiting in Patients Receiving Electroconvulsive Therapy." The Journal of ECT 19, no. 4 (December 2003): 194–96.

- *"Transcutaneous acupoint electrical stimulation (TAES) is a nonpharmacologic method for preventing and treating nausea and vomiting. TAES can alleviate motion sickness, reduce the incidence of vomiting caused by chemotherapy, and treat pregnancy-induced nausea and vomiting. TAES has been shown to reduce the incidence of postoperative nausea after general anesthesia. This is the first report to review the effectiveness of TAES in preventing and treating nausea and vomiting in 11 patients receiving ECT. Nine of these patients had a good response to TAES. One patient had a mixed response, and 1 did not respond to TAES. "*

T3 Thyroid

T3 Thyroid Hormone May Protect ECT Related Memory Impairment

Stern, R. A., "Antidepressant and Memory Effects of Combined Thyroid Hormone Treatment and Electroconvulsive Therapy: Preliminary Findings." Biological Psychiatry 30, no. 6 (September 15, 1991): 623–27.

- *The most parsimonious explanation for pos- sible °F~ protection against ECT-related memory impairment is that the T3 group received fewer ECT treatments. This would be consistent wit=h past observations that there is a direct relation- ship between number of ECT treatments and neurocognitive impairment (Daniel and Crovitz 1983). However, one additional explanation in- volves an alteration of available central thyroid hormone. It is known that diminished "1"4i n vitro markedly reduces neuronal actin polymerization and that replacement of "1"4n ormalizes the actin cytoskeleton (Siegrist-Kaiser et al 1990). It is possible that temporary disorg~ization of the actin cytoskeleton in neurons located in the amygdala and hippocampus (structures that are highly susceptible*

to seizure and play important roles in learning and memory) may protect the cells from potential disruption by the seizure.

T3 Thyroid Hormone Accelerated the Antidepressant Effects and Diminished the Amnestic Effects of ECT

Stern, R. A., "Influence of L-Triiodothyronine on Memory Following Repeated Electroconvulsive Shock in Rats: Implications for Human Electroconvulsive Therapy." Biological Psychiatry 37, no. 3 (February 1, 1995): 198–201. doi:10.1016/0006-3223(94)00227-T.

- *"In tests of retrograde and anterograde amnesia, rats that received the thyroid hormone T3 in addition to ECS performed better than rats that received ECS with placebo. Stem and colleagues (1991) found that T3 administration in humans both accelerated the antidepressant effects and diminished the amnestic side effects of ECT; however, ECT in that study was discontinued as soon as clinical improvement was observed, which may have confounded the results. That is, the diminished amnesia may have been due to the reduced number of ECT exposures in the T3 group. In the present study, T3 diminished ECS-related amnesia in rats, when all groups received an equal number of ECS exposures. Other agents have been shown to diminish the amnestic side effects of ECS and ECT (Krueger et al 1992; Nobler and Sackeim 1993); however, the findings of the present animal study, along with those of our preliminary clinical report, suggest that T3 may be one of the first agents to reduce ECS/ECT-associated amnesia and also improve the antide- pressant efficacy of ECT. Replication of this animal study with a larger sample size, as well as additional clinical investigation with follow-up, is needed to support these promising results"*

Wintergreen Oil

Topical Wintergreen Oil is Effective for Treatment of Post ECT Headache

Logan, Christopher J., "Treatment of Post-Electroconvulsive Therapy Headache with Topical Methyl Salicylate." The Journal of ECT 28, no. 2 (June 2012): e17–18. doi:10.1097/YCT.0b013e318245c640.

- *"Headache after administration of electroconvulsive therapy (ECT) is common, affecting approximately half of patients treated. Post-ECT headache is typically treated with acetaminophen or nonsteroidal anti-inflammatory drugs but occasionally requires agents such as sumatriptan, opioids, or β-blockers. We report on a patient whose severe post-ECT headaches responded completely to methyl salicylate ointment, applied to the area of his temporalis and masseter muscles. Topical methyl salicylate is generally well tolerated and may be a viable option for some patients with post-ECT headache."*

Vitamin B1

Vitamin B1 Helps Reduce Post-ECT Confusion

Linton, C. R., "Using Thiamine to Reduce Post-ECT Confusion." International Journal of Geriatric Psychiatry 17, no. 2 (February 2002): 189–92.

- *"Cognitive side-effects are commonly seen following electroconvulsive therapy which convey no therapeutic benefit but are troublesome to both patient and clinician. Various efforts have been made in the past to minimize these symptoms. Although modification of technical parameters related to ECT administration has led to some limited improvement in this regard, attention is now being increasingly focussed on pharmacological approaches. A number of agents have been explored in this context, however, as far as we are aware, the use of thiamine has not yet been investigated. We present three cases of elderly patients undergoing ECT for major depression in whom thiamine administration was associated with beneficial effects on post-ECT confusion. We review the evidence suggesting that thiamine deficiency may be implicated in the confusional state following ECT and recommend that consideration be given to its use in preventing and treating this problematic side-effect, especially in elderly patients."*

Vitamin B1 is Effective in the Treatment of Post-Electroconvulsive Therapy Delirium

Ogihara, T., "Use of Thiamine in the Treatment of Post-Electroconvulsive Therapy Delirium." Pharmacopsychiatry 42, no. 1 (January 2009): 36–37. doi:10.1055/s-0028-1085440.

- *"In the present case, a series of ECT sessions led to the development of severe delirium, which was immediately resolved by thiamine administration. Additionally, further occurrence of post-ECT delirium was prevented. Unfortunately, we did not evaluate the blood thiamine levels prior to administration. However, the patient's response to thiamine indicates that the clinical manifestation of delirium is closely associated with thiamine deficiency.*

- *Both a decrease in thiamine supply and an increase in the need for thiamine promote a state of thiamine deficiency. Elderly patients with depression undergoing ECT are at a high risk of developing thiamine deficiency. This is because these patients often have an inadequate diet or suffer from anorexia. We speculate that thiamine deficiency caused by decreased dietary intake of thiamine and the effect of ECT procedures may together contribute to the development of post-ECT delirium. Linton et al. also suggested that thiamine deficiency arising from anorexia may mediate severe post-ECT delirium, and they reported that thiamine supplementation has a beneficial effect in treating post-ECT delirium. ECT-associated thiamine shortage may also be caused by another factor: neuronal discharges induced by ECT result in increased neuronal glucose metabolism, which in turn leads to thiamine consumption and hence results in relative thiamine deficiency. A previous study investigating the elevation levels of lactic acid and pyruvic acid in the rat brain following ECT seizure demonstrated that the rats treated with thiamine had significantly lower lactic acid level at 20 min following seizure, and*

suggested the possible advantages of thiamine use in human ECT To date, only a few studies, including this report, have suggested that thiamine supplementation has a beneficial effect in treating post-ECT delirium. Further clinical trials are required to clarify its efficacy in treating post-ECT delirium."

Miscellaneous Disorder Side Effect Treatments

Salt

Salt Supplements Reduce the Side-effects of Lithium Treatment

Bleiweiss, H. "Salts Supplements with Lithium." Lancet 1, no. 7643 (February 21, 1970): 416.

- *"Treatment initially consisted of 600mg. lithium carbonate thrice daily, and the dose was gradually increased to up to 2.7 g daily, together with sodium chloride, 0.5—1.0 g thrice daily. Peak plasma-lithium levels ranged from 0.55 to 1.03 meq. Per litre. "*

Melatonin

Melatonin is Useful for Inhibition of Antipsychotic-induced Side Effects

Anderson, George, "Melatonin: An Overlooked Factor in Schizophrenia and in the Inhibition of Anti-Psychotic Side Effects." Metabolic Brain Disease 27, no. 2 (June 2012): 113–19. doi:10.1007/s11011-012-9307-9.

- *"This paper reviews melatonin as an overlooked factor in the developmental etiology and maintenance of schizophrenia; the neuroimmune and oxidative pathophysiology of schizophrenia; specific symptoms in schizophrenia, including sleep disturbance; circadian rhythms; and side effects of antipsychotics, including tardive dyskinesia and metabolic syndrome. Electronic databases, i.e. PUBMED, Scopus and Google Scholar were used as sources for this review using keywords: schizophrenia, psychosis, tardive dyskinesia, antipsychotics, metabolic syndrome, drug side effects and melatonin. Articles were selected on the basis of relevance to the etiology, course and treatment of schizophrenia. Melatonin levels and melatonin circadian rhythm are significantly decreased in schizophrenic patients. The adjunctive use of melatonin in schizophrenia may augment the efficacy of antipsychotics through its anti-inflammatory and antioxidative effects. Further, melatonin would be expected to improve sleep disorders in schizophrenia and side effects of anti-psychotics, such as tardive dyskinesia, metaboilic syndrome and hypertension. It is proposed that melatonin also impacts on the tryptophan catabolic pathway via its effect on stress response and cortisol secretion, thereby impacting on cortex associated cognition, amygdala associated affect and striatal motivational processing. The secretion of melatonin is decreased in schizophrenia, contributing to its*

etiology, pathophysiology and management. Melatonin is likely to have impacts on the metabolic side effects of anti-psychotics that contribute to subsequent decreases in life-expectancy."

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