Treatment Resistance in Schizophrenia: The Role of Alternative Therapies

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In 1931, Gananath Sen and Kartick Chandra Bose reported on the use of an alkaloid extract from the Rauwolfia serpentina plant in the treatment of hypertension and "insanity with violent maniacal symptoms." They noted that dosages of 20 to 30 grains of the powder twice daily produce not only a hypnotic effect but also a reduction of blood pressure and violent symptoms.

Outside of India, however, Sen and Bose's observations on the use of rauwolfia for psychotic disorders were generally ignored. It was not until 1954, when Nathan Kline reported that both whole root rauwolfia extract and reserpine—a purer preparation—seemed to be somewhat more effective than placebo in more than 400 inpatients with neuropsychiatric conditions, that clinicians in the West took notice. Although it soon became apparent that phenothiazines were generally more tolerable than reserpine, and even after our enthusiastic embrace of clozapine, a respected 1991 review still listed reserpine as 1 of 8 reasonable, evidence-based treatment options for persons affected with the refractory symptoms of schizophrenia.

Was Sen and Bose's root extract treatment "alternative"? Alternative is a fuzzy term; this article will include information on vitamins, dietary supplements, herbal treatments, and—quite broadly—"other." Virtually all of these approaches are meant to be adjunctive and can be considered as additions to traditional antipsychotic therapy, rather than replacing it.

A variety of treatments, some of them quite novel at the time, have been used for schizophrenia over the years. The Figure provides a brief timeline for the introduction of a number of such therapies. Orthomolecular psychiatry

In the 1960s, the idea of treating patients with mental illnesses with high doses of vitamins became popular. Within the realm of what Linus Pauling christened "orthomolecular psychiatry," Hoffer and Osmond championed the use of a high dose of vitamin B₃ (niacin) and suggested that there was some connection between schizophrenia and the vitamin-deficiency disorder pellagra, which can present with a variety of psychiatric symptoms. However, conceptual problems with this hypothesis and negative findings in controlled studies diminished the fervor for this vitamin intervention. A 1991 review of 53 trials that tested niacin or vitamin B₆ in a variety of psychiatric disorders found serious methodologic deficiencies in virtually all of the studies. Mainstream approaches to treatment resistance

A page was turned when Kane and associates published results from a landmark study of clozapine that demonstrated real hope for persons with treatment-resistant symptoms associated with schizophrenia. The researchers used a demanding operationalized definition of treatment resistance for the study that included significant psychotic pathology in the face of at least 3 unsuccessful trials of different neuroleptics at high doses for a minimum of 6 weeks in the previous 5 years. The study findings showed that clozapine was superior to chlorpromazine not only in treating the positive symptoms of treatment-resistant schizophrenia but also in treating the recalcitrant negative symptoms. Previously, clinicians may have been satisfied to treat a person who had an acute exacerbation of schizophrenia to the point where delusions and hallucinations were minimized and he or she was stable and dischargeable. This study raised the bar for treatment goals.

More recently, cognitive symptoms were being appreciated as not only critical core symptoms of schizophrenia, but, along with negative symptoms, a principal cause of the functional disability associated with this disorder. It is a major clinical advance that atypical antipsychotics, such as clozapine, olanzapine, and risperidone, have been found to ameliorate positive, negative, and
cognitive symptoms, and symptoms of excitement/agitation and depression/anxiety in schizophrenia.\textsuperscript{13}

The realization that other symptom domains are treatable has expanded what we expect of ourselves as psychiatrists in treating schizophrenia, and this is reinforced by the growth of the recovery model for treatment. This more appropriate biopsychosocial perspective casts a wider net for how we view treatment-resistant symptoms. Early successes still left patients with much that needed to be addressed regarding symptoms and functionality. It is now accepted that residual symptoms should be viewed as treatment resistant and worthy of appropriate attention.

The current mainstream allopathic-somatic approach focuses on treating patients who have schizophrenia with an atypical antipsychotic; if several of these fail, a trial of clozapine should be considered because it may be specifically more effective in reducing symptoms of aggression\textsuperscript{14} and suicidality.\textsuperscript{15,16}

Adjunctive electroconvulsant therapy is an approach that is clearly beneficial for treating positive symptoms or agitation, although not always practical.\textsuperscript{17} Low-frequency transcranial magnetic stimulation is sometimes effective for intractable hallucinations\textsuperscript{18} and cognitive-behavioral therapy (now a standard of care in the United Kingdom\textsuperscript{19}) and cognitive remediation\textsuperscript{20} address particular refractory areas of psychopathology. Nonetheless, these strategies often leave significant residual symptoms because of lack of response, adverse effects, or patients' rejection of particular treatments.

**Omega-3**

Reported findings of differences in essential plasma unsaturated fatty acid membrane composition in patients with schizophrenia led to the consideration of prescribing omega-3 fatty acids, which was bolstered by a dramatic case report.\textsuperscript{21,22} Controlled studies have resulted in encouraging but somewhat mixed findings, unlike the more robust findings for omega-3 in depression. Two essential omega-3 fatty acids were compared in a 3-month, double-blind pilot study that found that augmentation with eicosapentaenoic acid (EPA) was superior to docosahexaenoic acid (DHA) or placebo in significantly reducing Positive and Negative Syndrome Scale (PANSS) scores\textsuperscript{23}; a second study using EPA suggested that supplementation with omega-3 for extended periods can benefit some patients even without antipsychotics.\textsuperscript{24}

In a 16-week, double-blind study of 40 patients with schizophrenia that augmented antipsychotic treatment with either 3 g/d of ethyl-EPA (e-EPA) or placebo, Emsley and colleagues\textsuperscript{25} found superiority for the e-EPA condition in reducing PANSS scores (mean decrease in PANSS score of 12.6 on e-EPA vs 3.1 on placebo; \( P = .03 \)). Using the PANSS and other scales, an open-label augmentation study of 33 patients with schizophrenia reported an advantage in omega-3 augmentation—in this case using EPA, DHA, and vitamins C and E.\textsuperscript{26}

On the other hand, a 16-week trial in 87 patients that compared 3 g/d of e-EPA with placebo found no difference in positive, negative, mood, or cognitive symptoms of schizophrenia.\textsuperscript{27} Noting that both the active and placebo groups had improvements in their PANSS ratings, these investigators evaluated the placebo response in 37 study participants and found that the 9.5% improvement in the PANSS total score usually occurred by the end of the first 2 weeks of participation, which argues for the value of a placebo run-in phase for future studies.\textsuperscript{28}

Revisiting the initial findings of plasma membrane abnormalities, a 24-hour dietary recall in 146 community-dwelling patients with schizophrenia found little difference in dietary fatty acid and antioxidant intake from controls.\textsuperscript{29} However, a more elaborate evaluation of 72 subjects with schizophrenia found that the previously reported membrane lipid abnormalities could be explained by the fact that many of the subjects were smokers and had a significantly different omega-3 dietary intake from that of the controls.\textsuperscript{30} A recent review of the few randomized controlled trials concluded that while there was some evidence for clinical improvement and decreased need for neuroleptics in patients with schizophrenia who have EPA or e-EPA added to their treatment regimen, larger studies are still needed to establish a clear benefit.\textsuperscript{31} NMDA glutamate receptor and glycine, d-serine, and d-alanine

Sitting between mainstream and alternative therapies are amino acid treatments, derived from the recognition that phencyclidine (PCP) psychosis was a better model for schizophrenia than the previous model of amphetamine psychosis. Among other observations, those with PCP intoxication presented with negative as well as positive symptoms. The mechanism of PCP's action was eventually elucidated; it specifically blocked the ion channel in NMDA (\textit{N}-methyl-d-aspartate) glutamate receptors in the brain. An allosteric modulatory site on this complex receptor has been referred to as the "glycine" site, and its endogenous ligands plausibly may be the amino acids glycine, d-serine, and d-alanine (the latter 2 unusual d-forms present in the brain because of a racemizing enzyme).\textsuperscript{31}
Some lines of evidence suggest that the NMDA glycine site may be the locus of a primary lesion in persons with schizophrenia. Furthermore, Hashimoto and associates\textsuperscript{32,33} have found reduced serum d-serine levels and reduced cerebrospinal fluid d-serine/serine ratios in patients with schizophrenia; other studies suggest that identified genes linked to schizophrenia may be acting at this site.\textsuperscript{34} A meta-analysis of short-term clinical trials found that treatment augmented with the agonists glycine and d-serine moderately reduced negative symptoms, while partial agonist d-cycloserine was less efficacious.\textsuperscript{35} These agents do not appear helpful for patients treated with clozapine, although glycine and d-serine may be effective for those being treated with olanzapine or risperidone.\textsuperscript{36,37} A more recent study supports the efficacy of d-alanine.\textsuperscript{38} Glycine is available to the public as a dietary supplement.\textbf{Early interest in homocysteine and folate metabolism}

Methionine is an essential amino acid that is centrally involved in key methylation reactions in the body; when a methyl group is added to methionine it becomes a homocysteine. In the early 1960s, several reports noted that when persons with schizophrenia were challenged with a methionine load, some experienced worsened psychiatric symptoms, generating the transmethylation hypothesis for the cause of schizophrenia.\textsuperscript{39,40}

In the 1960s and 1970s, interest was sparked by several case reports of patients who had psychotic disorders and genetic-based functional deficiencies of key enzymes in methylation pathways that involved methionine and homocysteine, including deficiencies in cystathionine synthase (associated with homocystinuria)\textsuperscript{41} and of 5,10-methylenetetrahydrofolate reductase (MTHFR).\textsuperscript{42} These patients were treated with high-dose folate, which decreased high homocysteine levels and significantly improved psychiatric symptoms. However, a screening of 949 consecutive psychiatric admissions (one third presenting with schizophrenia) failed to uncover a single case of aminoaciduria,\textsuperscript{43} and it became clear that such interesting case reports had little to do with the cause of most cases of schizophrenia.

In part inspired by findings that pregnant women exposed to famine conditions are more likely to give birth to offspring with neural tube defects (likely from folate deficiency) as well as offspring with schizophrenia, there has been continuing interest in folate, homocysteine, and the MTHFR gene in the possible pathogenesis of schizophrenia. Thus far, some suggestive findings have failed to be replicated; yet there appear to be unexplained disturbances in this metabolic pathway that are associated with the risk of a diagnosis of schizophrenia.\textsuperscript{44,45} \textbf{Homocysteine and vitamin B redux}

High homocysteine levels have been found to interfere with NMDA receptors in animal studies. Neeman and coauthors\textsuperscript{46} reported finding lower plasma glycine levels and higher homocysteine levels in patients with schizophrenia compared with controls, and glycine levels correlated with increased negative symptoms. Findings of higher homocysteine levels in patients with schizophrenia may often involve folate-deficient dietary choices, obesity, or cigarette smoking, but one study found that these variables explained relatively little of the high homocysteine levels.\textsuperscript{47} In any case, remediation of high homocysteine levels with vitamin supplements is fairly straightforward, accomplished by adding high-dose folate, vitamin B\textsubscript{12}, and sometimes pyridoxine.

Recently, 42 individuals with schizophrenia who had high homocysteine levels received 3 months of treatment with vitamins or placebo in a crossover study. Those receiving the vitamins were found to have significant improvements in clinical symptoms as measured by PANSS and neuropsychological test scores, compared with placebo.\textsuperscript{48} \textbf{Antioxidants}

Oxidative stress/free radical damage has been proposed as mediating pathology in various neuropsychiatric disorders, including schizophrenia. Small initial trials failed to shed adequate light on the value of ascorbic acid (vitamin C) in the treatment of schizophrenia,\textsuperscript{49,50} although a recent 8-week study reported significant improvement in Brief Psychiatric Rating Scale scores for those receiving an adjunctive 500 mg/d dosage of vitamin C.\textsuperscript{51} In addition, one study\textsuperscript{25} with positive findings used adjunctive omega-3 with vitamins C and E. Additional studies are needed to evaluate this approach.

Another putative adjunctive antioxidant strategy in schizophrenia involves the addition of Ginkgo biloba extract. Although several studies have shown fairly consistent preliminary results,\textsuperscript{52-54} larger and more definitive studies are still needed. \textbf{Other modalities}

Recent Cochrane Database Reviews addressing other modalities for the treatment of patients with schizophrenia have found insufficient evidence to recommend acupuncture,\textsuperscript{55} hypnosis,\textsuperscript{56} or art therapy.\textsuperscript{57} However, a review of adjunctive studies of Chinese herbal medicines found some suggestion of efficacy\textsuperscript{58} and a review of music therapy concluded that there was some evidence of benefit, if at least 20 sessions were provided.\textsuperscript{59}

Many patients (80%) who have serious mental illnesses successfully use religious or spiritual beliefs and practices as coping strategies in their daily lives.\textsuperscript{60,61} We have organized a state hospital
inpatient group designed to mobilize religious and spiritual resources to aid patients' coping and recovery\(^2\); it would be helpful to have more efforts exploring the potential value and drawbacks of patients' use of religion and spirituality. **Alternative approaches in other roles for schizophrenia**

Vitamins may be useful as potential prophylaxis. The higher rates of schizophrenia in those born in winter or spring, and the reported association between prenatal exposure to the 1945 famine of the "Dutch Hunger Winter" and later development of schizophrenia in offspring may be rationalized by the hypothesis that schizophrenia is more prevalent in those who have had vitamin D deficiency during the first year of life. The results of a 1966 study of a Finnish-birth cohort lend support to this theory.\(^3\) However, as there were very few children not given the then-recommended vitamin D supplement, and since not receiving the supplement may have been associated with other plausible risk factors, this single study provides only weak support for this interesting idea. **Conclusion**

The term "complementary medicine" may sound better than "alternative medicine" to most physicians. Whatever it is called, open-mindedness should not be an excuse for lowering the standards of evidence-based medicine in establishing definitive opinions. While waiting for better evidence to substantiate or disprove various complementary approaches, let us partner with patients and their families in deciding on rational treatment strategies, and share with each other the findings, case reports, or randomized controlled trials, whether their results are positive or negative.

**References:**


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