Orthomolecular and Botanical Treatments to Help Alleviate the Side Effects of Atypical Antipsychotic Drugs

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Abstract

The current standard of care for schizophrenic patients, such as continual medication with atypical antipsychotic drugs, does more harm than good. A review of the literature revealed that in addition to causing the well known side effects of extrapyramidal symptoms and tardive dyskinesia, side effects such as hyperprolactinemia, sexual dysfunction, weight gain, diabetes, cardiac arrhythmias, and even a worsening of psychosis (when used long-term) are common occurrences. Specific orthomolecular and botanical treatments might help prevent and/or reduce some of these negative side effects. The most effective approach is to institute all the components of an ideal treatment program, as advocated by Dr. Abram Hoffer. This is the only approach that facilitates genuine recovery among chronic schizophrenic patients.

Introduction

The newer atypical class of antipsychotic drugs (APDs) are considered a major advance over the older, "typical" APDs. Like the typical APDs, the atypical ones are just as efficacious at treating the positive symptoms of the illness, such as hallucinations and delusions, yet claim to have a broader spectrum of efficacy over the older drugs which results in fewer side effects.[1] The first part of this report will review the main side effects of atypical APDs. The second part will focus on orthomolecular and botanical treatments that appear to have value in terms of prevention and/or reduction of side effects.

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Extrapyramidal Symptoms

Extrapyramidal symptoms (EPS) are a neurological side effect of antipsychotic medication, involving involuntary movements such as tardive dyskinesia (TD), tremors and rigidity (parkinsonism), body restlessness (akasthisia), muscle contractions (acute dystonia), and changing in breathing and heart rate (neuroleptic malignant syndrome). This latter syndrome is potentially fatal if not treated and can be a sudden occurrence within the first few weeks of treatment. It includes muscle rigidity, tremors, high fever, labile blood pressure, cognitive dysfunction, and autonomic disturbances.

TD usually occurs with prolonged treatment with neuroleptic drugs. The typical manifestations of TD are lip smacking, sucking, and facial grimacing. These symptoms often last for years and can be irreversible.[2] TD is one of the most frequently encountered and distressing side effects of antipsychotic treatment, and often requires antiparkinsonian medications. In general, the atypical APDs are less likely to cause acute EPS and TD than the typical or older class of drugs. For example, quetiapine, a first line atypical antipsychotic drug, has shown low incidence of EPS.[3] On the other hand, with higher doses of other atypicals such as olanzapine and clozapine, these side effects occur more frequently.[4] Risperidone treatment is associated with a lower incidence of TD and may actually attenuate the expression

of orofacial dyskinesia in patients previously treated with haloperidol.[2] However, when risperidone is used at higher doses, it has resulted in levels of EPS similar to the typical APDs.[4]

Hyperprolactinemia

Antipsychotic drugs, through their mechanism of dopamine antagonism, cause elevated serum prolactin levels. Elevated prolactin levels have direct and indirect roles in the development of breast cancer, osteoporosis, cardiovascular disease, and sexual dysfunction.[5] More specifically, sustained hyperprolactinemia induces hypogonadism, causing estrogen deficiency in women and testosterone deficiency in men. In women, the most common consequences of elevated prolactin levels include amenorrhea, dyspareunia (difficult or painful intercourse), galactorrhea, gynecomastia, and impaired mental functioning. In men, the problems with elevated prolactin levels tend to primarily affect sexual function and fertility.[6] With the exception of risperidone, hyperprolactinemia is more of a concern with the typical APDs than with the newer atypical ones.

In women on typical APDs, the ensuing side effects of menstrual irregularities range from 15-91% and galactorrhea from 10-50%. Hyperprolactinemia-induced hypogonadism leads to low estrogen levels and possibly a worsening of the psychopathology in female patients because estrogen is believed to have antipsychotic properties. The estrogen deficiency also leads to symptoms such as vaginal dryness during intercourse and loss of libido. Long-term, it can cause decreased bone mineral density and osteoporosis. Compared to healthy men, male schizophrenics on conventional APDs report galactorrhea.[6]

Haloperidol can raise serum prolactin levels as early as 72 hours after initiating treatment, the rise continuing for 6-9 days then reaching a plateau. Haloperidol at 15 mg/day is associated with sustained hyperprolactinemia.[6] The atypical APDs are weaker dopamine-type 2 receptor (D2) antagonists than the typical class of drugs, and thus do not affect prolactin levels to the same degree. In three trials of quetiapine at certain doses, the drug did not cause a sustained elevation of serum prolactin levels.[7] Risperidone is an exception amongst the atypical APDs, causing dose-related increases in prolactin levels similar to typical drugs such as haloperidol. The increases are seen in both men and women, with the mean increases being greater in women than in men. The early studies on risperidone used the drug in high doses, but current clinical practice uses lower doses (4 mg/day). It is not clear whether the lower doses of atypical APDs have less of an effect on prolactin levels.[6] The conflicting results in the literature may be the result of the following: (1) whether or not tolerance develops to the prolactin-elevating effects of the atypical drugs; and (2) whether there's a correlation between prolactin concentration and psychopathology.[6] Overall, the side effects caused by hyperprolactinemia, such as galactorrhea and sexual dysfunction, lead to noncompliance among schizophrenic patients.[6]

Sexual Dysfunction

Most patients on APDs experience some sort of sexual dysfunction, which may include loss of interest (libido), decreased arousal (poor vaginal lubrication or erectile dysfunction), and anorgasmia (inability to have an orgasm). Surveys suggest that as much as 40% of women and 60% of men on typical APDs report these symptoms.[8] Because of its depressing effects on quality of life, patients rate sexual dysfunction as the most distressing side effects of drug therapy.

There are several ways by which these drugs affect sexual function. One mecha-

nism involves inhibition of dopamine release due to dopamine blockage at D2 receptors that may impair libido and erection. Another mechanism has to do with blockage of the alpha-adrenergic pathway in the periphery, which may lead to priapism (a painful and sustained penile erection which is a urologic emergency), galactorrhea, amenorrhea, gynecomastia and vaginal dryness (due to estrogen deficiency). Alterations in serotonin, which participates in initiating arousal through its vasodilatory effects in the periphery, can negatively affect sexual function. Finally, non-specific central nervous system (CNS) effects, such as sedation, can cause a decrease in the desire for sexual activity.

As a whole, the primary mechanism of sexual dysfunction induced by these drugs is probably the direct dopamine antagonism with some additional indirect effects due to hyperprolactinemia.[8] Sexual dysfunction is an important problem with the typical APDs, and to a lesser extent with the newer atypical drugs. Nonetheless, it remains an under-appreciated problem.

Weight Gain and Diabetes Mellitus (DM)

A common side effect of APDs, especially the atypical APDs, is excessive weight gain. In fact, it is now believed to be the most prominent long-term side effect associated with these newer drugs and should be highly considered when treatment plans are designed, because of the obvious medical consequences of obesity.[1]

The weight gain may be related to increased appetite (due to drug interaction with the brain monoaminergic and cholinergic systems), and to the endocrine effects of hyperprolactinemia.[9] Clozapine and olanzapine both induce glucose dysregulation and dyslipidemia, the development of which may be associated with the combination of sudden body weight gain (BWG), insulin resistance, increased appetite and related endocrine changes.[9] It is hypothesized that clozapine causes weight gain by increasing adipose tissue, which leads to insulin insensitivity, glucose intolerance, and when severe, diabetes mellitus (DM).[4] In one report, 58% of patients on clozapine gained at least 10% over baseline.[4] Several cases of clozapine-induced diabetic ketoacidosis have also been reported.[10]

One cohort study found that patients being treated with typical or atypical APDs are at greater risk of developing DM than the general population.[11] The patients in the risperidone and haloperidol cohorts showed the greatest risk.[11] Patients on olanzapine averaged weight gains of 5.4 kg over the first six to eight months of treatment and had a 20% increased risk of developing DM than patients on risperidone who averaged weight gains of 3.9 kg.[4] Quetiapine has been shown to cause lower levels of weight gain than other atypical APDs. However, the typical APD, haloperidol, causes less BWG than the other drugs.[4] It also appears that adolescents experience more BWG compared to other populations when taking atypical APDs.

Cardiovascular Side Effects

Clozapine poses a risk of myocarditis, especially during the first month of therapy. A 2002 advisory by Health Canada reported an association between clozapine use and pericarditis, myocardial infarction, pericardial effusion, cardiomyopathy, heart failure, and mitral insufficiency.[4] In addition, antipsychotic drugs, including some atypical APDs, may cause electrocardiogram (ECG) changes that can lead to drug-induced arrhythmia and, rarely, sudden unexplained death.[7] In one study, risperidone showed a significant increase in QT interval duration compared to placebo,[12] yet in another study (albeit conducted by the company

who manufactures the drugs), none of the atypical drugs were found to cause QT elevations that were considered clinically significant.[7]

Implications of Use During Pregnancy and Lactation

A study involving lactating women taking clozapine found the level in their foremilk to be 2.8 to 4.3 times the level of clozapine in the maternal plasma, but no studies have been done to accurately assess the direct implication of these levels on the breastfeeding neonate.[13]

Clozapine and olanzapine increase the risk of significant weight gain, and DM puts the infant at greater risk for perinatal mortality, prematurity, congenital abnormalities (e.g., neural tube defects), macrosomia and, as previously stated, increases the chances of developing DM in the future. Physicians should also be aware that stopping antipsychotic medication when pregnant or post-partum, especially abruptly, could have the potential consequence of causing a psychotic relapse in the patient, which may be severe and include maternal suicide and infanticide.

Avoidance of phenothiazines are recommended because of their association with significant increases in congenital abnormalities. As well, clozapine, or combinations of typical APDs, with dosages within their upper ranges should be avoided during pregnancy and lactation, until further evidence determines them to be safe.[13]

Blood Dyscrasias

Clozapine has a well known, albeit, minimal risk, of life-threatening blood dyscrasias (agranulocytosis). This is one of the major reasons why the drug is used primarily for patients refractory to other APDs and is not first-line therapy. Patients on clozapine require regular blood monitoring and surveillance every 1 to 2 weeks, which makes this drug problematic as it disrupts a patient's quality of life.[4]

Additional Side Effects

Patients on quetiapine are recommended to have regular follow-up eye examinations every six months, due to speculation that the drug may be linked to lens abnormalities such as cataracts.[4, 7] Thyroid function may also be effected by quetiapine, since higher end doses were shown to cause a 20% decrease in total and free thyroxine.[7] This may be one of the reasons why olanzapine and quetiapine are associated with a fairly high incidence of drowsiness. Unlike some of the other atypical APDs, insomnia is a common adverse effect caused by risperidone therapy.[4] Additionally, risperidone should be used with caution in patients also taking indinavir and ritonavir because such a combination can induce reversible coma.[14] Another atypical APD, clozapine, can induce dose-dependent seizures.[15]

One of the newer atypical drugs on the market is aripiprazole, which is supposed to have fewer side effects compared to the other atypical APDs. It still has been shown to cause headaches, nausea, vomiting, constipation, dyspepsia, orthostatic hypotension, tachycardia, insomnia, somnolence, and tremors.[12] **Table 1** (p.21) summarizes the main side effects caused by selected atypical and typical APDs.

Worsening the Long-term Outcome

Continuous use of APDs has actually been shown to worsen the long-term outcome in schizophrenic patients. Although these drugs are effective in treating acute psychotic symptoms, they do not improve patients' lives in the long run.[16] The first pivotal study to show this was the 1960 National Institute of Mental Health study that found the drugs to have short-term benefit but higher relapse rates if used long-term.[16] The World Health Organization later conducted a study on conven-

Table 1. Summary of the main side effects caused by selected atypical and typical APDs

Anti-psychotic Agent	EPS & TD	Hyperpro-lactinemia	Weight Gain	Sexual	Other
Risperidone (atypical agent)	Dose-dependent increases in EPS. At high doses, incidence of EPS is similar to that seen with Haloperidol	Yes	Yes	Lesser extent	Insomnia, increased QT interval, and interaction with indinavir and ritonavir
Clozapine (atypical agent)	Dose-dependent increases in EPS	Lesser extent	Yes, and increased risk of developing adult-onset DM	Lesser extent	Minimal risk of life-threatening blood dyscrasias (agranulocytosis), cardiovascular toxicity, drowsiness, and dose dependent seizures
Olanzapine (atypical agent)	Dose-dependant increases in EPS	Lesser extent	Yes, and increased risk of developing adult-onset DM	Lesser extent	Orthostatic hypotension and drowsiness
Quetiapine (atypical agent)	Low incidence of EPS across all doses	Lesser extent	Lesser extent	Lesser extent	Orthostatic hypotension and lens abnormalities
Aripiprazole (atypical agent)	Lesser extent	Lesser extent	Lesser extent	Lesser extent	GI symptoms, insomnia, tremors, and tachycardia
Haloperidol (typical agent)	Yes	Yes	Lesser extent	Yes	Higher risk for adult-onset DM, especially with increasing age

tional neuroleptics, which showed that in the developing world, where patients are kept on the drugs for a short period of time, patients had exceptionally good social outcome compared to the poor long-term outcome of patients in the developed world who are kept on the drugs chronically.[16]

In the late 1970s, Canadian investigators at McGill University reported that the brains of patients treated with APDs developed an increased density of D2 receptors by 30% or more in an attempt to compensate for the dopamine antagonistic effects of the drugs. Patients can become super-sensitized to dopamine (thought to be the mediator of psychosis), so that when they abruptly stop the drugs, they have a higher tendency towards psychosis.[16] This mechanism makes medicated patients more biologically vulnerable to psychosis. The need for continued antipsychotic treatment may itself be drug induced.[16]

Atypical APDs have established detrimental effects on metabolic function, similar to the older, typical APDs. They

also increase the density of D2 receptors, making patients more vulnerable to psychosis, and probably reduce lifespan when used long term. Ironically, modern psychiatry seems to be prescribing them to an increasing number of patients, including those "at risk" of developing schizophrenia. The real goal should be to minimize their use and to wean patients off of them very slowly.

Managing the Side Effects of Drowsiness, Exhaustion, Fatigue, and Somnolence

All the atypical APDs cause some combination of drowsiness, exhaustion, fatigue, and somnolence. One of the best orthomolecular methods to combat these side effects is injectable vitamin B_{12} (hydroxocobalamin). Newbold has written about the therapeutic uses of injectable vitamin B_{12} as an antidote for over-sedation.[17] In Newbold's report, he recalled a case involving one of his clients, an actress, who was dealing "bootleg Quaaludes" as a source of income. She apparently treated her clients with 6000 mcg (micrograms) of injectable hydroxocobalamin when they would become over-sedated from these pills and would be unable to leave her premises. From giving them high doses of injectable hydroxocobalamin, she was able to reverse their sedation enabling them to leave her apartment. In the same report, Newbold also discussed another case involving a comatose patient with marked symptoms of over-sedation induced by "bootleg Quaaludes" and excessive amounts of vodka. This patient also responded to injectable hydroxocobalamin, but required 9000 mcg of it in order to regain consciousness and be alert. From these experiences, Newbold suggested that all patients with symptoms of over-sedation from overdoses of sedatives, tranquilizers, and/or alcohol be given a therapeutic trial of 9000 mcg of hydroxocobalamin.

I (Prousky) have treated several patients on atypical APDs with injectable hydroxocobalamin due to symptoms of over-sedation. I am impressed with the vitamin's ability to "perk" these patients up and help them make it through the day. It is not a cure-all, but it does improve quality of life. The recommended dose to start with is 5000 mcg once or twice each week. Generally patients respond favorably within 24 to 48 hours after their first injection. Instead of feeling excessively sleepy, many of these patients report more energy and an increased alertness. Patients who do not respond to the injectable vitamin B_{12} should be provided with supplemental calcium and magnesium since these minerals help vitamin B_{12} gain entrance into the cells.[17]

Managing the Side Effects of EPS

Other symptoms that are believed to occur less frequently with the atypical APDs are the EPS. However, I (Prousky) have seen several patients with some degree of EPS while on the atypical APDs, and most of these patients have been prescribed benztropine mesylate to deal with them. Unfortunately, the addition of benztropine mesylate merely adds more mental symptoms to patients already struggling with their psychiatric condition (e.g., confusion, disorientation, and memory impairment). The botanical medicine, ginkgo biloba extract (GBE) might be helpful. In a study involving treatment resistant schizophrenic patients, the addition of 360 mg per day of GBE with haloperidol was shown to decrease EPS and enhance effectiveness of the drug.[18] Even though this study assessed the combination of GBE with a typical APD, similar positive results might also occur when combining GBE with atypical APDs. This drug-botanical combination might reduce EPS and enhance atypical APD effectiveness, possibly preventing further increases in medication dosage. The ability of GBE to enhance medication

effectiveness might also allow patients to reduce their dosages and experience fewer side effects from their medications.[19]

In addition to GBE, there are a number of nutritional treatments that would help reduce and/or prevent EPS that include ascorbic acid, manganese, phosphatidylcholine, pyridoxine hydrochloride, and vitamin E (d-alpha tocopheryl acetate). Werbach has summarized various studies demonstrating the effectiveness of these nutrients to reduce and/or eliminate TD among patients taking typical APDs.[20] Although none of these nutritional agents have been subjected to clinical trials involving patients on atypical APDs, they probably have a similar spectrum of efficacy when used in combination with this class of antipsychotic medications. **Table 2** (below) lists these orthomolecular agents and their corresponding dose ranges.

Managing Sexual Dysfunction

In male schizophrenic patients, a number of viable orthomolecular and/or botanical options exist that should help reverse some of the sexual dysfunction associated with the use of atypical APDs.

L-arginine. One of the first agents to be considered is L-arginine. This amino acid is a biologic precursor to nitric oxide, which plays an important role in endothelium-dependent processes.[21] In fact, problems with penile endothelial L-arginine are thought to be responsible for part of the pathogenesis of erectile dysfunction (ED).[22] In a small clinical trial involving men with ED, 40% of the treatment group on 2.8 g of L-arginine daily for two weeks demonstrated improvements compared to no improvements among men in the placebo group.[23] In a larger trial, 50 men with ED were given 5 g of L-arginine per day or a matching placebo for six weeks. There was a subjective improvement among 31% of the men in the L-arginine group.[24] Another study combined 1.7 g of L-arginine with increasing doses of pycnogenol in a three-month trial involving 40 men with ED.[25] All the men took 1.7 g of L-arginine during the first month, and then during the second month were given 40 mg of pycnogenol twice daily with the same dose of L-arginine. During the third month, the dose of the pycnogenol was increased to 40 mg three times daily with the same dose of L-arginine. At the end of the second month, 80% reported a normal erection, and by the end of the third month this therapeutic response increased to 92.5%. Other benefits that were noted included a quicker erection in response to stimulation, and an increased duration of erection.

Ginseng. Another agent that might benefit male schizophrenic patients is

Table 2. Orthomolecular and botanical agents to reduce and/or eliminate EPS and TD associated with atypical APDs.

Supplement	Recommended Daily Dosage
Ascorbic Acid	1300-4000 mg
Ginkgo biloba extract	360 mg
Manganese	15-60 mg
Phosphatidylcholine	Dose equivalent to 2400-6400 mg of choline
Pyridoxine hydrochloride	250-800 mg
Vitamin E	250-800 mg of d-alpha tocopheryl acetate

panax ginseng. The active compounds in panax ginseng, the ginsenosides, induce relaxation of the smooth muscle of the corpus cavernosum in rabbits by augmenting the release of nitric oxide.[26-27] Clinical trials involving human subjects have demonstrated that panax ginseng can improve erectile function and sexual satisfaction. In one trial, 90 patients were divided into three groups: the panax ginseng group, the placebo, and the trazodone group.[28] Even though parameters such as intercourse frequency, premature ejaculation, and morning erection after treatment were the same in all three groups, the panax ginseng group did have a significant improvement in penile rigidity, girth, duration of erection, libido, and patient satisfaction. The overall efficacy of panax ginseng on ED was 60% compared to only 30% among the placebo and trazodone groups.

A more recent randomized, double-blind, placebo-controlled, crossover study assessed the efficacy of panax ginseng among 45 men with ED.[29] One group of men were given 900 mg of panax ginseng three times daily for eight weeks. The other group was given an identical looking placebo three times daily for eight weeks. After the eight weeks, each group was subjected to a two week washout period and then received crossover treatment with placebo or panax ginseng for an additional eight weeks. The men on panax ginseng scored significantly higher on the International Index of Erectile Function (IIEF) compared to men on placebo. The panax ginseng group also had better penile tip rigidity as measured by a device called the RigiScan, compared to the placebo group. The authors of this study were unable to explain the benefits of panax ginseng in terms of its hemodynamic and hormonal actions. Instead, it was purported that panax ginseng benefited ED due to its effects upon multiple mechanisms.

Gingko Biloba. Another botanical medicine, GBE, ought to be tried when helping both male and female schizophrenic patients suffering from sexual dysfunction. Although the reports on GBE assessed its value in treating sexual dysfunction induced by antidepressant medications, it might offer some benefit to schizophrenic patients on atypical APDs. The first report of GBE's ability to improve ED involved male geriatric patients taking antidepressant medications.[30] While these patients were taking GBE to improve their memory, many of them noticed an improvement with their erections. The dosages used in this trial were 40-60 mg capsules taken twice daily, and was increased to 120 mg twice daily. The average dose during the trial was 207 mg/day. Around 76% of the patients found GBE to be effective at restoring all aspects of their sexual response, including erectile function. The mechanism responsible for GBE's positive effects upon sexual function had to do with its ability to augment nitric oxide synthase (e.g., increase nitric oxide availability). These positive effects occurred in the presence of serotonin, which can impede nitric oxide production.[31]

Another trial evaluated the effectiveness of GBE for antidepressant-induced sexual dysfunction.[32] Twenty-four patients participated in the trial, with an equal number of men and women. There was a significant improvement in sexual response after three and six weeks of use. However, the data was inconclusive since the therapeutic response to GBE was so variable among the patients. In a smaller trial involving both male and female patients, GBE was not successful at helping any of the nine male patients, and was only helpful among three of the 13 female patients tested.[33] In a placebo-controlled, double-blind trial for antidepressant-induced sexual dysfunction,[37] patients were randomized to receive GBE or a placebo.[34] The participants on GBE received 120 mg for the first two weeks,

160 mg for the next two weeks, and 240 mg for the remaining four weeks of the trial. All participants were given a questionnaire before taking either GBE or placebo, and after the second, forth, and eighth weeks. Unfortunately, no statistical significance was achieved for patients on GBE compared to those on placebo. Nonetheless, GBE might be helpful. It should be prescribed to male and female schizophrenic patients suffering from sexual dysfunction induced by the atypical APDs. **Table 3,** (below) lists the orthomolecular and botanical agents that might reduce the sexual dysfunction associated with atypical APDs.

Managing Hyperprolactinemia

The most well known botanical agent that lowers prolactin levels is vitex agnus castus. In a review of its prolactin-reducing effects, Brown reported: (1) that vitex in vitro inhibited the basal and the thyrotropin-releasing hormone (TRH) stimulation of prolactin levels; and (2) that it contains constituents that directly bind to the dopamine receptors of the anterior pituitary.[35] For these reasons, it is inadvisable for any schizophrenic patient currently taking any of the atypical APDs to concomitantly use vitex as a means to lower prolactin levels. Atypical APDs are dopamine-receptor blocking agents, and taking vitex would reduce their effectiveness.

The orthomolecular agent, gamma-aminobutyric acid (GABA), should also be avoided. GABA is an inhibitory neurotransmitter with anxiolytic properties similar to clonazepam and other benzodiazepines.[36] Like vitex, GABA has the ability to augment dopamine release and reduce prolactin secretion. GABA's exact biochemical mechanisms are not well understood, but studies using animal models have been helpful in elucidating some of them. In one in vitro study, the GABA (B) receptor agonist, baclofen, was shown to inhibit the basal and thyrotropic releasing hormone-stimulated prolactin secretion in anterior pituitary cells.[37] In another rat experiment, it was concluded that endogenous GABA, by acting through GABA (A) receptors, influences the basal and diurnal changes of tuberoinfundibular dopaminergic neuronal activity, and consequently prolactin secretion.[38] Since there are GABA receptors (A and B types) located in the anterior pituitary, orally administered GABA might stimulate these pituitary receptors causing a release of dopamine and a drop in prolactin secretion. Although it is unclear if orally administered GABA can effectively gain entrance into the CNS, the use of this agent should be avoided due to its potential effects upon dopamine, and its potential antagonistic effects upon atypical APDs. At present, the authors of this report are unaware of any orthomolecular and/or botanical agents that can lower prolactin levels without possibly compromising the effectiveness of the atypical APDs.

Table 3. Orthomolecular and botanical agents to reduce and/or eliminate sexual dysfunction associated with atypical APDs

Supplement	Recommended Daily Dosage
L-Arginine (male patients only)	1.7-2.8 g
Pycnogenol (male patients only)	120 mg
Panax Ginseng (male patients only)	2700 mg
Ginkgo Biloba Extract (male & female patients)	240 mg

Managing Weight Gain

Besides the well known lifestyle measures that are time-tested in terms of losing weight (e.g., diet and exercise), supplementation with green tea extract should help to control some of the weight gain produced by the atypical APDs. In one human trial involving ten healthy men, the administration of green tea extract containing 50 mg of caffeine and 90 mg of epigallocatechin gallate (EGCG) given three times daily with meals produced statistically significant results.[39] Specifically, green tea extract increased the 24-hour energy expenditure, reduced the 24-hour respiratory quotient, and increased the 24-hour urinary excretion of norepinephrine (NE). The investigators concluded that green tea extract, apart from caffeine's thermogenic properties, controlled body composition through its sympathetic activation of thermogenesis, fat oxidation, or from a combination of these two factors.

In another study, the catechin-polyphenols and caffeine found in green tea extract stimulate thermogenesis by sympathetically releasing norepinephrine.[40] The catechin-polyphenols from green tea extract increases norepinephrine via their inhibition of catechol-O-methyl-transferase (the enzyme that degrades NE), and the caffeine content inhibits transcellular phosphodiesterases (enzymes that breakdown NE-induced cyclic adenosine monophosphate). The possible net effects are sympathetic stimulation of thermogenesis and improved weight control. The beneficial effects of green tea extract have been more formally studied in an open trial of moderately obese patients.[41] An 80% ethanolic dry extract of green tea standardized to 25% catechins (expressed as EGCG), was found to decrease both body weight and waist circumference after three months of use. The authors of this study suggested that green tea extract might favorably influence body composition by inhibition of gastric and pancreatic lipases and from the stimulation of thermogenesis.

These studies demonstrate that green tea extract can have a favorable effect upon body composition. However, the use of green tea extract also increases the production of NE and should be used with caution in all schizophrenic patients. The oxidized derivative of norepinephrine, noradrenochrome, likely contributes to the psychosis of schizophrenia. Any increase in norepinephrine, therefore, could be detrimental. To offset this problem, make sure that green tea extract is given with a complement of antioxidants. Caffeine-free green tea extracts would produce less NE since it would not have the same type of sympathetic stimulation when compared to extracts containing caffeine. The optimal dose of green tea extract appears to be 270 mg daily that is standardized to 25% catechins (expressed as EGCG).

Managing Diabetes

Patients on atypical APDs can develop drug-induced glucose intolerance and have a syndrome that mimics adult-onset diabetes. In terms of diabetes control and prevention, the most important orthomolecular agent appears to be chromium. For many years, chromium was thought to be involved in the glucose-tolerance factor (GTF) molecule that presumably increases insulin sensitivity. The composition of GTF, as isolated from yeast, is made of chromic ion, nicotinic acid, and the amino acids glycine, glutamic acid, and cysteine.[42] However, GTF of any type has never been found in human tissues. More recently, a naturally occurring oligopeptide low-molecular weight chromium-binding substance (LMWCr) has been proposed to be the biologically active form of chromium.[43] This compound has been found in many different types of mammals, and is widely distributed in numerous tis-

sues (e.g., liver, kidney, spleen, intestine, testicles, and brain). This oligopeptide is also comprised of the amino acids glycine, cysteine, glutamic acid, aspartic acid, and has a multinuclear chromic assembly in which the chromic centers are bridged by the anionic ligands, oxide and/or hydroxide.[43] This LMWCr compound is part of an insulin amplification system that regulates glucose homeostasis through a complex series of biochemical reactions occurring at the insulin receptor.[44,45] In a study involving 185 adult-onset diabetic patients, there were significant decreases in the concentration of fasting and two-hour glucose levels, insulin, hemoglobin A1C, and total cholesterol among patients supplemented with 1000 mcg of chromium picolinate compared to those on 200 mcg of chromium picolinate or placebo.[46] Thus, chromium as part of the LMWCr, should have the ability to improve glucose tolerance and increase insulin sensitivity in schizophrenic patients with poor glucose control.

In terms of toxicity, Lamson and Plaza have summarized the chromium literature, and have evaluated its mechanisms of action and exceptional safety profile. According to these investigators, "there is no demonstration of general chromium toxicity in animals at a dose that would extrapolate to humans as 1050 mg daily."[47] One of these investigators has even used 3000-4000 mcg of chromium as nicotinate given twice daily to adult-onset diabetic patients for months to years resulting in tremendous reductions of glucose and lipid levels without any increases in blood urea nitrogen, liver enzymes, or other laboratory abnormalities. It is interesting to note that high supplemental doses of chromium would never come even close to 1050 mg per day.

While on atypical APDs, many schizophrenic patients develop insulin resistance, increased appetite, and related endocrine changes. I (Prousky) speculate that the glucose intolerance resulting from atypical APDs disrupts chromium homeostasis and creates an increased metabolic need that can be met only through high-dose supplementation. I can recall one patient who had positive body composition changes, such as weight loss, following a few months of taking 3000 mcg of chromium from yeast each day. Although fasting glucose measurements were not done prior to and after the chromium intervention, the body composition changes in this one patient were probably a reflection of improved glucose homeostasis. The dose ranges that are likely of value among schizophrenic patients on atypical APDs are 1000-4000 mcg of chromium given twice daily.

Managing Cardiovascular Side Effects

The most worrisome cardiovascular side effects are the cardiac arrhythmias that in rare cases can lead to unexplained death. The best way to manage and/or prevent cardiac arrhythmias is through daily supplementation with fish oil. In a randomized, double-blind, placebo-controlled trial, 65 patients with cardiac arrhythmias (without coronary heart disease or heart failure) were followed for six months, and were divided into two groups.[48] One group was given 3 g daily of encapsulated fish oil (equivalent to 1 g daily of omega-3 PUFA), whereas the other group was given 3 g daily of olive oil as placebo. In the fish oil group there were considerable lipid-modifying benefits that included a decrease of serum triglycerides, total cholesterol, low-density lipoprotein cholesterol, plasma free fatty acids, and thromboxane B2, and an increase in high-density lipoprotein cholesterol. The subjects in the fish oil group also had 46.9%, 67.8%, 71.8%, and 100% fewer incidences of the four types of arrhythmia monitored in this study (atrial premature complexes, ventricular premature complexes, couplets, and trip-

lets). Unlike the fish oil group, no positive changes occurred in the placebo group. The results of this study demonstrated that fish oil supplementation has anti-arrhythmic effects, and can reduce the incidence of fatal myocardial infarction and sudden cardiac death. For the reasons cited in this study, and from the conclusions of other investigators,[49,50] its seems prudent that all schizophrenic patients taking atypical APDs are supplemented with fish oils due to their anti-arrhythmic and lipid-modifying effects. In terms of the optimum dosage, schizophrenic patients should consume a daily amount of fish oil that is recommended for patients with and without coronary heart disease (CHD). For cardioprotection, the daily dose should contain 450-1000 mg of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA).[51]

Case Report

The following case report is an excellent example of the effectiveness of the orthomolecular and botanical approach. The patient was eventually able to discontinue most of his mainstream treatments (except for risperidone), and significantly recover from his diagnosis of schizoaffective disorder.

The patient, a 24-year-old Hispanic male, first presented to Dr. Prousky's private naturopathic practice on November 13, 2004, for chief complaints of schizoaffective disorder and obesity. He described a history of being unwell emotionally from the age of 15 onwards. His symptoms became more severe at the age of 16 when he started hearing messages from billboards, would spend countless hours surfing the Internet, was emotionally very flat, had a belief that 100% of the bible was true, and that the devil was forcing him to do things. He would read excessively and did report some occasional thoughts of violence. Due to his moods, he participated in a hospital-based program for depression that helped very much. His past medical history did include a suicide attempt at the age of 21, for which he was hospitalized and released shortly thereafter. Review of systems illuminated other problems that consisted of glaucoma, mild musculoskeletal complaints, obesity, and shortness of breath. His weight was about 200 pounds in the year 2000. Since being prescribed risperidone in 2001, his weight increased to 260 pounds. His current prescription medications were risperidone (3 mg daily), olanzapine (20 mg daily), and bupropion hydrochloride (150 mg daily). The patient's family history revealed some genetic predisposition to schizophrenia, as his paternal grandmother was diagnosed with this disorder at 60 years old. On physical examination, the patient was well nourished, clinically obese, had high to normal blood pressure, and mild tachycardia. All of his main systems were

Table 4. Patient's First Set of HOD Results.

HOD Test Items	December 2004 Results
Total Score (TS)	40
Perceptual Score (PerS)	4
Paranoid Score (PS)	2
Depression Score (DS)	10
Ratio Score (RS)	4
Short Form (SF)	1

within normal limits. He was prescribed vitamin B_6 (250 mg daily), niacinamide (1000 mg three times daily), vitamin C (1000 mg three times daily), chromium (1000 mcg three times daily), liquid fish oil (1 teaspoon twice daily) providing close to 2 g of EPA, zinc (50 mg daily), and was told to discontinue all dairy and milk products. Regular use of dairy and milk products can be associated with psychosis and depression.[52]

On December 13, 2004, the patient returned for a follow-up. He reported an increased sense of alertness and vigor from the treatments. He also described symptoms of social anxiety where he would feel scared to talk to people, and would even avoid teachers and classmates while completing his auto mechanic program. He did have some depression since the last visit, and experienced suicidal ideation on three separate occasions since the initial visit. His vitals were within normal limits. The patient was given the Beck Anxiety Inventory (BAI) and the Beck Depression Inventory (BDI) to fill-out. His BAI score was 33, indicating moderate anxiety. His BDI score was 26, indicating moderate depression. Laboratory tests showed a normal CBC, normal fasting plasma glucose, and an abnormal lipid profile showing the patient to be at an "above average risk" for coronary heart disease. The patient was switched from the niacinamide to niacin at a dose of 1500 mg three times daily to help control his psychiatric symptoms and to favorably impact his lipid profile. He was also given L-glycine for his symptoms of panic, at a dose of 2000 mg sublingually as needed. An intramuscular injection of vitamin B_{12} (1500 mcg) was also provided. The patient was given the Hoffer-Osmond Diagnostic (HOD) test to determine the severity of his schizoaffective disorder.

The patient's HOD test was received and scored on December 17, 2004 (**Table 4,** p.28). The higher the total score, the greater the probability of that patient having schizophrenia. For a patient with a pre-established diagnosis, the HOD test can also be used to evaluate the severity of mental disturbances and assess a patient's response to treatment. In this patient's case, his total score did indicate that he was symptomatic. If his total scores were to decline over time, it would be an indication of improvement.

About six weeks later, on January 26, 2005, the patient returned for another appointment. He felt that he was no longer symptomatic in terms of his diagnosis of schizoaffective disorder. The niacin caused the patient to vomit, so he reduced the dose to 1000 mg three times daily. He did not like the taste of L-glycine so he never really tried the treatment. He did feel that his anxiety had improved about 10%. The patient was given another intramuscular injection, but the dose was different as it now contained folic acid (0.5 mL or 2.5 mg) and had a greater concentration of vitamin B_{12} (1 mL or 5000 mcg). He was asked to retry the L-glycine and return in another 5 to 6 weeks.

On March 7, 2005, the patient felt that his diagnosis was better described as social anxiety disorder with some symptoms of schizoaffective disorder. He did not try the L-glycine as he was instructed to do. In terms of his anxiety, he felt about 20-30% better than the last visit. He was given another intramuscular injection of folic acid (2.5 mg) and vitamin B_{12} (5000 mcg).

The patient returned for another appointment on April 20, 2005. He had seen a new psychiatrist who recommended that the patient complete a series of cognitive behavior therapy for his social anxiety disorder. The patient was also attending a weekly group for patients with social anxiety disorder. The psychiatrist prescribed 20 mg of citalopram, and took him off the olanzapine. He was sleeping less since discontinuing the olanzapine. The

psychiatrist also instructed the patient to continue with risperidone (4 mg at bedtime), and bupropion hydrochloride (150 mg daily). The patient did report a better sense of well being, even though he felt more depressed during the previous week. His only problem was fear. He was unable to look at people when riding the subway because of the way people looked back at him. He also thought that people were judging him. For his anxiety, the patient was prescribed L-taurine at a dose of 1500 mg twice daily to be taken away from food. He was also prescribed ginkgo biloba extract (180 mg daily) to help with depression, the side effects of risperidone, and for erectile dysfunction. Another intramuscular injection of folic acid (2.5 mg) and vitamin B_{12} (5000 mcg) was given to the patient.

The patient had one more follow-up on June 27, 2005. He reduced the risperidone to 2 mg daily on his own. He also discontinued the citalopram and bupropion hydrochloride. He did not feel worse than before and, in fact, indicated that he was more alert and required less sleep. He did not complain of any withdrawal symptoms from discontinuing the medications. His social anxiety seemed much improved. He was able to cover for his father as a courier and interact with people. This would not have been possible just a few months previously. The patient just completed his auto mechanic program, and was excited about going to college in the fall for accounting. He also remarked that his paranoid thoughts were gone, and were much better since stopping the two medications. The patient was instructed to stay on the orthomolecular and botanical treatments. He was also advised to continue avoiding all milk and dairy products. I assured him that as long as he remained consistent with the program, he had very little chance of a relapse.

I received the patient's final set of HOD results on June 30, 2005. As evident, the patient's scores dramatically improved demonstrating the effectiveness of the orthomolecular and botanical approach. (See **Table 5,** below).

Discussion

The goals of this report were to review the known side effects of the atypical APDs, and clarify some of the best orthomolecular and botanical strategies that might have value in terms of side effect prevention and/or reduction. Even with this knowledge, schizophrenic patients find themselves in an unfortunate predicament. Should they stay on the atypical APDs and suffer extreme metabolic consequences despite using adjunctive orthomolecular and botanical treatments? Hoffer has written about the "tranquilizer psychosis," and how the atypical APDs make chronic schizophrenic patients sick.[53] In that same report, he mentions

Table 5. Patient's final set of HOD results

HOD Test Items	June 2005 Results
Total Score (TS)	5
Perceptual Score (PerS)	0
Paranoid Score (PS)	0
Depression Score (DS)	1
Ratio Score (RS)	5
Short Form (SF)	0

how "these drugs damage the brain and decrease the odds these patients can ever recover." Even with adjunctive orthomolecular and botanical treatments, it is extremely difficult for schizophrenic patients to fully recover or considerably improve while remaining on atypical APDs.

Another option is for schizophrenic patients to go off of their atypical APDs and suffer the consequences of having terrible withdrawal symptoms and a recurrence of their psychoses. This choice is also inadequate. We propose a third and more reasonable solution, which is to very slowly (over months and sometimes years) withdraw from the atypical APDs and include the components of an ideal treatment program. The components of such an ideal treatment, as reported by Hoffer, include: (1) shelter; (2) decency, understanding, support, safety, and privacy; (3) psychiatric treatment; and (4) orthomolecular treatment.[53] All of these components are equally important. Much of the success of this ideal treatment program depends on the skill of the treating clinician and the compliance and patience of the patient. Orthomolecular interventions do not work immediately, and many months might go by before therapeutic effects are noticed. We do recommend that during the lengthy process of recovery, clinicians utilize many of the orthomolecular and botanical approaches to minimize the damaging metabolic effects of these drugs. Patients need to know that they cannot begin the process of drug withdrawal until they begin to feel better. Once this happens, the atypical APD can be slowly reduced over many months and even years. If the drug is withdrawn too rapidly, very unpleasant withdrawal symptoms occur, in addition to an increased likelihood of psychosis. For more information on the components of an ideal treatment plan, please refer to Hoffer's latest book on schizophrenia.[54]

Conclusion

The atypical APDs cause numerous side effects such as EPS, hyperprolactinemia, weight gain, diabetes, fatigue, and cardiac arrhythmias. Some of these side effects might be reduced and/or prevented by using specific orthomolecular and botanical treatments. Controlled clinical trials are needed to properly evaluate the effectiveness that orthomolecular and botanical agents have upon mitigating the side effects of atypical APDs. At present, Hoffer's ideal treatment plan appears to be the only effective approach that enables chronic schizophrenic patients the opportunity to fully recover without metabolic dysfunction and long-term brain damage.

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