

Adjunct Treatments for Schizophrenia and Bipolar Disorder: What to Try When You Are Out of Ideas

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Abstract

The pharmacologic treatment of schizophrenia and bipolar disorder leaves much to be desired. Repurposed drugs, which are approved for other medical conditions, represent an underutilized therapeutic resource for patients who have not responded to other drugs. Using experience gained from a decade of repurposed drug studies by the Stanley Medical Research Institute and search of the literature, we have identified nine such drugs for which there is some evidence of efficacy for schizophrenia and/or bipolar disorder. These include: aspirin; celecoxib; estrogen/raloxifene; folate; minocycline; mirtazapine; omega-3 fatty acids; pramipexole; and, pregnenolone. The evidence of efficacy is reviewed for each drug. Because there is little or no financial incentive for pharmaceutical companies to promote such drugs, there is a paucity of definitive trials, and these drugs are less widely known than they deserve to be. Biomarker studies should also be carried out to identify subgroups of patients who do respond to these drugs.

Key Words: Aspirin, Celecoxib, Estrogen, Folate, Minocycline, Mirtazapine, Omega-3 Fatty Acids, Pramipexole, Pregnenolone

Introduction

The pharmacological treatment of serious psychiatric disorders is unsatisfactory for many patients. Psychotic symptoms are often only partially resolved (1, 2), and the cognitive and negative symptoms of schizophrenia (3) and the depressive symptoms of bipolar disorder (4) have proven to be especially refractory to present treatments. When confronted with poor therapeutic results, the most common response by clinicians is to try clozapine or to add another antipsychotic or mood stabilizer. All too often that still does

not produce a satisfactory result, and the clinician is left wondering what to try next.

For the past decade, the Stanley Medical Research Institute (SMRI) has supported treatment trials using repurposed drugs for the treatment of schizophrenia and bipolar disorder. Repurposing assumes that drugs that are already available to treat other medical conditions may be useful for these psychiatric disorders. However, because the psychiatric use is off-label, or the drugs are generic or available over-the-counter, pharmaceutical companies have little or no financial incentive to support such treatment trials. It should be recalled that chlorpromazine was discovered as a repurposed drug, having originally been used as a sedative for anesthesia.

SMRI has supported approximately 200 such trials, a list of which is available at www.stanleyresearch.org, List of Awarded Treatment Trials. From these trials and reviews of the literature, nine medications have been identified, all of which have shown some promise for use as adjunct medication for schizophrenia and/or bipolar disorder in SMRI-

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Table 1 Repurposed Drugs for Schizophrenia and/or Bipolar Disorder

Aspirin	May be useful in patients with elevated CRP or other inflammatory markers
Celecoxib	May be useful for schizophrenia in patients with relatively recent onset, but benefits must be weighed against risks of serious side effects
Estrogen and Raloxifene	Studies of women with schizophrenia suggest possible benefit for positive symptoms, but risks of side effects should be considered
Folate	Studies of patients with schizophrenia with low folate levels suggest that it is useful, especially for depressive symptoms
Minocycline	May be useful in relatively recent-onset schizophrenia, especially for negative symptoms; should not be given to pregnant women or children
Mirtazapine	May be useful for the negative symptoms of schizophrenia and for akathisia
Omega-3 Fatty Acids (fish oil)	Some evidence of efficacy in schizophrenia and bipolar disorder, especially if using omega-3 fatty acid with at least 50% EPA; promising results in premorbid individuals considered to be at high risk
Pramipexole	Appears to be useful for bipolar depression; use for schizophrenia unclear because of possible exacerbation of symptoms
Pregnenolone	May have a role in a subset of patients with schizophrenia and for bipolar depression

funded trials. These nine medications are summarized in Table 1. It is recognized that many other medications have been proposed as adjunct medications for these disorders, including various antidepressants, benzodiazepines, amino acids, and indigenous and herbal remedies. It is not the purpose of this paper to include these other medications, but merely to focus on selected compounds with which we have had some direct experience. A summary of these nine drugs follows, listed alphabetically. SMRI has supported many of the previous trials for these drugs and, in each case, is currently supporting additional trials.

None of these medications have yet been conclusively established as proven adjunct medications, but for each there are suggestions that they might be useful and should, thus, be considered in treatment-resistant cases when the clinician is out of other treatment options. The use of drug combinations has been very useful for diseases such as hypertension and AIDS, especially when the drugs act through different mechanisms. Many of these repurposed drugs are thought to act through mechanisms different from mechanisms used by standard antipsychotics and mood stabilizers and, thus, could ultimately lead to new classes of drugs for these conditions.

Aspirin (Acetylsalicylic Acid)

Background

Folk remedies containing salicylic acid have been used for centuries to treat pain and fever. Acetylsalicylic acid was first synthesized in Europe in the mid-19th century. The patent for aspirin, owned by Bayer, expired in 1917 in the United States, and it has been widely available over-the-counter since that time.

Mechanism of Action

Aspirin is a non-steroidal anti-inflammatory drug (NSAID) thought to work by blocking cyclooxygenase (COX), an enzyme needed for the synthesis of prostaglandins and thromboxanes. It is thought to block COX-1 and COX-2 equally. This interferes with pain transmission and the aggregation of platelets, thereby decreasing clots and being useful as a prophylactic against heart attacks. Prostaglandins also play an important role with N-methyl-D-aspartate (NMDA) receptors, important in glutamate transmission. Other possible mechanisms of action include neuroprotection, effects on membrane phospholipids, and effects on pro-inflammatory cytokines such as interleukins and tumor necrosis factor- α .

Use in Schizophrenia

C-reactive protein (CRP) is an enzyme that is a marker of chronic inflammation. At least three studies have reported that CRP is elevated in individuals with schizophrenia, suggesting that inflammation is an important part of the disease process (5-7). In addition, genes associated with inflammation are upregulated in brain tissue in schizophrenia (8), and some antipsychotics have been shown to affect CRP (9). In the only published study to date, 70 patients with schizophrenia spectrum diagnoses were randomized to aspirin 1,000 mg/d or placebo, in addition to their regular medication, for 3 months. All the patients had been sick for less than 10 years. Those on aspirin had a significant decrease in positive PANSS scores and a nonsignificant decrease in negative symptoms. Cognitive symptoms were not improved. The patients who showed the best response were those with the highest levels of some markers of inflammation (10). To minimize effects of the aspirin on the stomach, patients were

also given a proton pump inhibitor. SMRI is supporting a large, ongoing, double-blind, follow-up study using aspirin as an adjunct medication for schizophrenia.

Use in Bipolar Disorder

CRP was reported to be elevated in a study of 122 outpatients with bipolar disorder (11). Other studies have associated bipolar disorder with inflammation through gene expression or altered cytokine levels (12). A study of rats suggested that lithium's effectiveness may be attributable in part to its anti-inflammatory action (13). To date, no study has been published on the use of aspirin in bipolar disorder, but SMRI is supporting a double-blind study in progress.

Assessment

Aspirin is a relatively safe drug except for individuals who have ulcers or other bleeding problems. It should not be used without medical authorization for patients taking inhibitors of blood clotting, such as warfarin (Coumadin) or clopidogrel (Plavix). Its possible role in the treatment of schizophrenia and bipolar disorder is still to be determined, but may be most useful in patients with elevated CRP or other inflammatory markers.

Celecoxib (Celebrex)

Background

Celecoxib was introduced in the U.S. in 1999 as a drug for pain and inflammation and has become one of the most widely prescribed drugs. It is available by prescription in capsules of 50 mg, 100 mg, 200 mg, and 400 mg.

Mechanism of Action

Celecoxib is a non-steroidal anti-inflammatory drug (NSAID) that selectively targets the cyclooxygenase-2 (COX-2) enzyme; thus, in theory, maintaining its anti-inflammatory and analgesic properties but reducing side effects on the GI tract. It is not as selective a COX-2 inhibitor as rofecoxib (Vioxx), which was taken off the market in 2004 because of cardiovascular complications, including myocardial infarctions. Nevertheless, celecoxib has a black box warning because of possible cardiovascular and GI side effects.

Use in Schizophrenia

Five double-blind, placebo studies have been carried out with mixed results. A study of 50 patients undergoing an acute exacerbation of their symptoms reported a significant improvement in their PANSS total score using 400 mg/d for 5 weeks; a reanalysis showed that it had the most effect in patients with an illness of less than 2 years' duration (14). A follow-up study of 40 patients using 400 mg/d for 8 weeks

reported no overall effect; however, a reanalysis showed that patients with an illness of less than 2 years showed the most improvement (15). One study of 35 patients with chronic schizophrenia, average duration of illness 20 years and using 400 mg/d for 8 weeks, reported negative results (16), but another trial of 60 patients with chronic schizophrenia, average duration of illness 8 years and "in an active phase of illness," also using 400 mg/d for 8 weeks, reported a significant improvement in positive and total symptoms on PANSS (17). Most recently, a study of 49 individuals with first-episode schizophrenia (symptoms of less than 2 years' duration), using 400 mg/d for 6 weeks, reported significant improvement in negative and total symptoms on PANSS (18).

Use in Bipolar Disorder

We are aware of only one study. Twenty-eight patients with bipolar disorder, in a depressed or mixed phase, were treated with 400 mg/d for 6 weeks. Compared to the placebo controls, those on celecoxib had a trend toward decreased depression at the end of the first week, but the difference between the groups was not maintained for the remaining weeks of the trial (19). SMRI is supporting a trial in progress for 80 patients with bipolar depression. Another COX-2 inhibitor, cimicoxib, was used in a large European study of unipolar depression.

Assessment

Celecoxib may turn out to be a useful ancillary drug for schizophrenia for patients with recent-onset disease, but it is probably not useful for patients who have been sick for more than two years. However, given the unknowns regarding its cardiovascular and GI risks, it should be used with much caution. As in all treatment-related decisions, the possible therapeutic benefit should clearly outweigh the risks. It is also possible that other NSAIDs that have some selectivity for COX-2 will prove useful, but they have not yet been tested.

Estrogen and Raloxifene (Evista)

Background

Estrogen is a naturally occurring hormone that has been widely used in women to ameliorate postmenopausal symptoms. Raloxifene (Evista) is a selective estrogen receptor modulator (SERM) that has estrogen-like effects and is marketed to decrease postmenopausal osteoporosis. Both estrogen and raloxifene have been used in trials for women with schizophrenia, based on the theory that estrogens are protective and are the reason women generally develop schizophrenia later and less severely than men. One study using estrogen in men has also been published.

Mechanism of Action

Estrogen is thought to modulate dopamine receptors and to also affect the serotonin and GABAergic systems. There is some evidence that estrogen is also neuroprotective (20).

Use in Schizophrenia

A variety of trials have been carried out, with conflicting findings. All trials were as adjunct medication except for a single case study in which estrogen alone was successfully used to treat a 51-year-old woman who refused antipsychotics for her late-onset schizophrenia (21). One open and six double-blind, placebo-controlled trials have been published using estrogen to treat women of childbearing age with schizophrenia. The open trial treated 11 women with oral 0.02 mg ethinylestradiol for 8 weeks; it reported that “the patients who received adjunctive estradiol made a much quicker recovery” (22). The first double-blind trial treated 36 women: 12 received 50 mcg of transdermal estradiol given by patch for 4 weeks, 12 received 100 mcg, and 12 received a placebo patch. Those receiving 100 mcg compared to the placebo group had a significant improvement in PANSS positive ($p=0.002$), negative ($p=0.039$), and general ($p=0.002$) symptoms, with the 50 mcg group having intermediate values (23). The same research group replicated their findings with a trial of 102 women randomized to 100 mcg transdermal estradiol or placebo for 4 weeks; those on estradiol had a significant reduction in positive ($p<0.04$) and general ($p<0.05$), but not negative symptoms (24).

Two other research groups reported positive results of double-blind studies using oral ethinylestradiol 0.05 mg/d for 8 weeks. In one ($n=32$), the women on estradiol had a significant improvement in PANSS positive and total and general psychopathological symptoms (25). In the other ($n=64$), a significant improvement was reported for these same symptoms and negative symptoms as well (26). In contrast to these positive results, a double-blind study with 17-beta estradiol given to 46 women over 8 months, using the women as their own controls in a crossover design, reported no improvement (27). In addition, a study of 52 postmenopausal women with schizophrenia showed no clinical difference between those who did, and did not, receive hormone replacement therapy (28). Another study randomized 44 women to conjugated estrogens 0.625 mg/d or placebo for 4 weeks; the women on estrogen had a trend ($p<0.10$) toward improvement, but it was not statistically significant (29). Finally, one study using estrogen in men with schizophrenia was published; 53 men were randomized to 2 mg/d estradiol valerate or placebo for 2 weeks without any significant improvement in symptoms (30). SMRI is supporting an ongoing 8-week, placebo-controlled study in which 100 mcg and 200 mcg transdermal estradiol patches are being compared to placebo in 180 women; an interim analysis presented at

a research meeting reported that both doses produced significant improvement in PANSS positive, but not negative symptoms.

Raloxifene has been used in two small trials for postmenopausal women with schizophrenia. In one study, 35 women were randomized to raloxifene 120 mg/d ($n=13$), raloxifene 60 mg/d ($n=9$), or placebo ($n=13$) for 12 weeks. Those on 120 mg, but not 60 mg, had a significant improvement in the PANSS total score (31). In the other study, 33 women were randomized to raloxifene 60 mg/d or placebo for 12 weeks; those on raloxifene showed significant reduction in PANSS positive, negative, and general symptoms (32). SMRI is supporting two large ($n=80$ and 200) raloxifene trials in progress.

Use in Bipolar Disorder

There are case reports of two women with bipolar disorder who were resistant to lithium, but who responded to a combination of estrogen and progesterone (33).

Assessment

Given the known side effects of long-term estrogen on breast and uterine cancer as well as thromboembolism, these drugs should be used very cautiously, with a careful risk-benefit calculation. Raloxifene is thought to not have the same effects on breast and uterine tissue and so may be the drug of choice. If these drugs are effective, it appears more likely that it will be for positive, rather than negative, symptoms.

Folate

Background

Folate is a naturally occurring B vitamin (B9); its synthetic form is folic acid. When it is low during pregnancy, it can cause congenital neural tube defects in the developing fetus. Supplemental folic acid has been widely studied as a possible treatment for depression and cardiovascular disease. It is widely available in pharmacies, health food stores, and on the Internet; as in all such cases, the purity and potency of the compound may vary.

Mechanism of Action

Folate reduces the level of homocysteine, an amino acid thought to exacerbate some psychiatric symptoms. Folate is also involved in the synthesis of neurotransmitters and in many other metabolic pathways.

Use in Schizophrenia

In 1994, Goff et al. reported a correlation between low folate levels and negative symptoms in schizophrenia, thereby increasing interest in folate as a possible treatment (34). Five double-blind studies have been completed, three

of which have been published. A study of 17 patients on methylfolate 15 mg/d for 6 months reported “significantly improved clinical and social recovery” (35). A study of 42 patients given folic acid 2 mg/d for 3 months reported significant improvement on PANSS positive and total, but not negative symptoms (36). Both of these studies used only patients with low serum folate levels. However, a study of 32 patients with normal serum folate levels, using folate 2 mg/d for 3 months, reported no effect on negative symptoms (37). A study being submitted for publication of 100 patients treated with folic acid 5 mg/d for 3 months found significant improvement in depression and in some cognitive function, but another unpublished study of 42 patients given folic acid 4 mg/d for 3 months found no differences between patients taking folic acid and placebo. SMRI is supporting three other large, ongoing, double-blind trials.

Use in Bipolar Disorder

Although folate has been studied extensively for patients with depression, limited studies have been carried out for bipolar disorder. One study in bipolar patients demonstrated that elevated homocysteine levels were associated with impaired cognition (verbal learning, delayed memory, and executive function) (38). SMRI is supporting two small studies: one using folate to improve cognition, and the other to retard the development of clinical disease in young adults with multiple risk factors for bipolar disorder.

Assessment

If folate proves to be useful for serious psychiatric disorders, it is most likely to do so for depressive symptoms. Although widely used and relatively free of side effects, it is not entirely innocuous and at high doses has been suspected of possibly enhancing growth in developing cancers.

Minocycline

Background

Minocycline is a broad-spectrum tetracycline antibiotic that has been available since the 1970s. It has better penetration into the central nervous system and a longer half-life than other tetracyclines. It has been widely used as an antibacterial for acne and a variety of other infections. It has excellent penetration of the blood-brain barrier. In recent years, it has generated interest among neurologists for its neuroprotective effects in animal models of multiple sclerosis; Parkinson’s disease; amyotrophic lateral sclerosis; Huntington’s disease; methamphetamine-induced neurotoxicity; and, focal cerebral ischemia. It has also been used in clinical trials of patients with multiple sclerosis, Huntington’s disease, and autoimmune encephalitis (39). It is generic and available in tablets of 50 mg and 100 mg, as well as in extended-release tablets under the trade name Solodyn.

Mechanism of Action

Minocycline appears to have a wide variety of actions in addition to being antibacterial. Its anti-inflammatory and neuroprotective effects are thought to be related to some combination of its inhibition of inducible nitric oxide synthase (iNOS); capsase 1 and 3; p-38 mitogen-activated protein kinase (MAPK); cytochrome C release; cyclooxygenase-2 expression; prostaglandin E₂ formation; and, microglial activation. It has also been reported to have antiviral effects against HIV and antiprotozoal effects against *Toxoplasma gondii*. Its use in individuals with schizophrenia has been encouraged by its effects in rodent models of this disease. In one study, minocycline attenuated the behavioral changes following the administration of an NMDA antagonist in mice (40). In another study, minocycline reversed the effects of an NMDA antagonist in rats (41).

Use in Schizophrenia

Two case report series have been published: one including two patients with schizophrenia (42), and the other including three patients with recent-onset acute paranoid schizophrenia (43). An open-label study of 22 patients with treatment-resistant schizophrenia, using 150 mg/d for 4 weeks, reported an improvement in both PANSS positive and negative symptoms (44, 45). Two placebo-controlled, double-blind trials have been carried out. In one study, 73 patients with schizophrenia of less than 5 years’ duration were randomized to minocycline 200 mg/d or placebo for 12 months; “all symptoms measures improved significantly,” especially the negative symptoms (46). In the other study, 54 “early phase” (symptoms of less than 5 years) patients were randomized to minocycline 200 mg/d or placebo for 6 months; the authors reported a significant improvement on negative symptoms on SANS and CGI, and a significant improvement in some tests of executive function (47). SMRI is supporting two large studies of minocycline as an adjunct medication for schizophrenia.

Use in Bipolar Disorder

There is a single case report of significant improvement of depression in a woman with bipolar disorder being treated with minocycline 150 mg/d for sinusitis (48). SMRI is supporting a large study in progress.

Assessment

Minocycline may be useful as an adjunct medication for the negative symptoms of schizophrenia, especially in patients with a relatively recent onset. It is generally well tolerated, with dizziness and ataxia occurring occasionally. Minocycline should not be used in pregnant women or young children, as it can permanently stain the children’s teeth. It should also not be used past the medication’s expiration date, as it can be toxic.

Mirtazapine (Remeron)

Background

Mirtazapine came onto the market in 1994 as a tetracyclic antidepressant, thus being structurally different from the selective serotonin reuptake inhibitors (SSRIs). It has been used to treat depression, posttraumatic stress disorder, obsessive-compulsive disorder, and social anxiety. It is now generic and available in 15 mg, 30 mg, and 45 mg tablets.

Mechanism of Action

Mirtazapine affects a variety of neurotransmitters, including serotonergic, adrenergic, histamine, and muscarinic receptors. In affecting the 5HT-2 serotonergic, but not dopamine, receptors, it bears some resemblance to clozapine.

Use in Schizophrenia

Five small ($n=24$ to 40), double-blind trials have used mirtazapine 30 mg/d as an adjunct to treat schizophrenia. All the trials lasted between 6 and 8 weeks. Four of the five trials reported statistically significant improvement of the symptoms of schizophrenia, especially the negative symptoms (49-52). Two of the four positive studies also reported a statistically significant improvement in positive symptoms. The fifth study ($n=40$) reported no improvement in either positive or negative symptoms (53), but had a nonsignificant trend favoring mirtazapine. Mirtazapine was also shown in three studies to be effective in decreasing antipsychotic-induced akathisia (54-56). SMRI is supporting two large, multi-site studies in progress using mirtazapine as an adjunct to treat schizophrenia.

Use in Bipolar Disorder

Mirtazapine has been widely used to treat unipolar depression, and there are reports of its inducing manic episodes in selected patients (57).

Assessment

Given the paucity of effective drugs for treating the negative symptoms of schizophrenia, mirtazapine appears to be promising. For treating depression, mirtazapine has been used in doses up to 120 mg/d. The main side effects of mirtazapine are drowsiness, increased appetite, and weight gain. When starting and stopping the drug, the dose should be increased and decreased slowly.

Omega-3 Fatty Acids (Fish Oil)

Background

Polyunsaturated fatty acids (PUFA) include omega-3 and omega-6. Omega-3 fatty acids include eicosapentaenoic acid (EPA) and docosahexaenoic (DHA), which together are

important ingredients in fish oil. EPA and DHA are essential for normal brain development and are the most widely sold dietary supplements in the U.S., surpassing even multivitamins. Possible links between PUFA and serious psychiatric disorders have been investigated for more than two decades (58). Some studies have suggested that the geographical prevalence of schizophrenia or affective disorders correlates with fish consumption; a lower fish consumption was associated with a higher prevalence of bipolar disorder, but the results for schizophrenia were less clear (59, 60). Some studies have reported that PUFA levels are reduced in individuals with bipolar disorder, but a study of DHA levels in women who gave birth to children who developed psychotic disorders found DHA levels to be elevated (61). Confounding factors such as smoking make the interpretation of these studies difficult (59, 60).

Mechanism of Action

PUFA are essential ingredients in cell membranes and are thought to affect signal transduction pathways. They are known to inhibit phospholipase A-2 and cyclo-oxygenase and thought to modulate oxidative stress (62, 63), but their precise mechanism of action in psychiatric disorders is not known.

Use in Schizophrenia

At least seven double-blind adjunct treatment trials have been carried out, four with positive findings and three negative. All used between 1 and 4 gms of EPA and lasted 12 to 16 weeks. The three negative studies involved 69, 87, and 115 patients, both first-episode and chronic; one of the studies reported positive symptom improvement only for the patients on clozapine (64-66). The first three positive studies were smaller ($n=30$, 40, and 45). They were noteworthy because one showed EPA as superior to DHA (67); another reported 6 out of 14 patients maintained on EPA without antipsychotics (67); and, the third claimed "remarkable" symptom improvement in chronic patients (68). However, a meta-analysis of all six studies concluded that "omega-3 EPA did not alleviate the symptoms of schizophrenia" (59). In perhaps the most interesting of the positive studies, young people thought to be at ultra-high risk for developing psychoses were randomized to 1.2 gms/d of omega-3 fatty acids or placebo for 12 weeks. Nine months after completion of the trial, 2/41 individuals (5%) in the omega-3 group but 11/40 individuals (28%) in the placebo group had transitioned to a psychotic disorder (69). SMRI is supporting a five-year follow-up of the individuals in this trial as well as a large ($n=320$) replication of this study and a study using omega-3 fatty acids to try to prevent the recurrence of schizophrenia in individuals who have recovered from their initial episodes.

Use in Bipolar Disorder

At least three double-blind, placebo-controlled adjuvant trials have utilized omega-3 to treat adult bipolar disorder. A study of 30 bipolar patients, both types I and II, used 9.6 mg/d of EPA and DHA and reported a “striking difference in relapse rates and response” for patients on omega-3 compared to placebo (70). A study of 75 patients with bipolar depression, using EPA 1 gm or 2 gms for 12 weeks, reported a significant improvement in depression for patients on either dose compared to placebo (71). However, a study of 121 bipolar patients (59 depressed, 62 rapid cyclers) reported no marked effect of EPA 6 gm/d for 4 months (72). In addition, an open-label study of 12 bipolar depressed patients, using EPA 1.5–2.0 gm/d for up to 6 months, reported an improvement in depressive symptoms (73). Finally, an open-label study of 18 children with juvenile bipolar disorder reported improvement in manic and depressive symptoms using a combination of EPA and DHA for 6 weeks (74).

Assessment

The possible role of omega-3 in treating schizophrenia is unclear. As a recent Cochrane Review summarized it: “There is currently still no reason for clinicians to either encourage or discourage the use of polyunsaturated fatty acids. If a person with schizophrenia wishes to use one then, perhaps, an omega-3 preparation should be the preferred option” (75). For bipolar disorder, especially the depressed symptoms, omega-3 appears to be more promising. One meta-analysis of ten studies of omega-3 for treating depression also suggests the same conclusion (76). We have performed, but not yet published, a meta-analysis of omega-3 in depression and found DHA-predominant preparations to be without clinical efficacy; however, preparations that contain at least 50% or more EPA are consistently superior to placebo in treating depression. Since omega-3 supplements are widely available and apparently without serious side effects, they are probably worth trying.

Pramipexole (Mirapex)

Background

Pramipexole has been available since 1997 and is used to treat Parkinson’s disease and restless legs syndrome. It is available as a generic in tablets of 0.125 mg, 0.25 mg, 0.5 mg, and 1.5 mg.

Mechanism of Action

Pramipexole is a dopamine agonist, especially targeting the D-3 receptor. Thus, it increases the level of dopamine, which is why it is useful for treating Parkinson’s disease. It is also thought to have neuroprotective properties.

Use in Schizophrenia

Two open-label and two placebo-controlled, double-blind studies have been carried out. The former included a study of 37 patients, of which only 8 completed 3 weeks on the drug; 4 were said to be responders (77). The other open-label study included 15 patients and used up to 10.25 mg for 6 days; 4 patients dropped out (2 due to worsening of symptoms), and 5 others were said to be “much improved” (78). In a double-blind trial, 41 patients with residual schizophrenia were randomized to pramipexole up to 5 mg/d or placebo for 10 weeks; 7 pramipexole patients dropped out, and 9 were said to improve on the PANSS total score (77). In the other trial, 24 patients were treated with pramipexole 0.375–4.5 mg/d or placebo for 12 weeks; 2 out of 11 pramipexole patients dropped out, but the others showed a significant decrease in PANSS positive ($p=0.006$) and PANSS total scores (79). SMRI is supporting a large ($n=200$) double-blind study in progress.

Use in Bipolar Disorder

Two small double-blind trials have been published involving 22 bipolar I and II depressed patients and 21 bipolar II depressed patients, respectively. In the first, 8 of 12 patients on pramipexole had “an improvement of at least 50% in their Hamilton depression scale scores” (80). In the second study, 6 of 10 patients on pramipexole had “a significant treatment effect” (81). A third study, publicly reported but not yet published, randomized 35 patients with bipolar I to pramipexole 1.5 mg/d or placebo; those on pramipexole had significant cognitive improvement on processing speed and working memory (82). An open-label study of 21 bipolar depressed patients also reported that two-thirds improved on pramipexole (83). In addition, two retrospective chart studies both reported evidence of pramipexole’s efficacy for bipolar depression (84, 85), and a large ($n=174$) study of unipolar depression reported pramipexole to be efficacious (86). Many of these studies are summarized in a review by Aiken (87). Pramipexole is listed as an alternate treatment for bipolar depression by the Texas Implementation of Medication Algorithms for Bipolar Disorder and by the Canadian Network for Mood and Anxiety Treatments.

Assessment

Pramipexole may have a therapeutic role in schizophrenia for a subset of patients if they can be identified. However, the risk of exacerbation of symptoms appears to be substantial. By contrast, pramipexole appears to be potentially useful as an adjunct drug for bipolar depression. The main problem is side effects, the most common of which are headache, nausea, and somnolence. Of greater concern are rare but serious side effects: compulsive behaviors such as patho-

logical gambling; sleep attacks; and, psychotic symptoms. Side effects appear to be dose-related, and all patients being put on pramipexole should be very slowly titrated upward (e.g., 0.125 mg per week).

Pregnenolone

Background

Pregnenolone is a neurosteroid made naturally in the brain. It is widely sold in health food stores (10 mg, 25 mg, 50 mg, and 100 mg) for improvement of sleep and memory. It was used in the 1940s and 1950s for inflammatory conditions, especially rheumatoid arthritis, at doses of up to 500 mg/d before better drugs became available.

Mechanism of Action

Pregnenolone is synthesized from cholesterol and is a precursor of other hormones, including those made in the testes and ovaries; thus, it has been called the mother of all steroid hormones. Its possible effect on psychiatric symptoms is thought to be associated with its effect on NMDA receptors in the glutamate system, although it is also thought to affect GABA, sigma, acetylcholine, and dopamine receptors. Some researchers have noted in animal models that pregnenolone may increase brain myelination and synaptogenesis and, thus, be neuroprotective. Studies in rodents have also shown that pregnenolone improves memory and learning. When given orally, pregnenolone easily passes the blood-brain barrier and enters the brain. Also of interest are studies in rodents showing that olanzapine and clozapine increase the levels of pregnenolone in rat brains.

Use in Schizophrenia

There have been three published studies. Thirty-two patients with schizophrenia were given adjunct pregnenolone 100 mg/d, 500 mg/d, or placebo for 8 weeks (88). Those on 500 mg had an improvement in negative symptoms, verbal memory, and attention. Patients liked taking the drug, and five patients continued taking it for 3 years. A study of 21 patients on escalating doses of adjunct pregnenolone up to 500 mg/d or placebo for 8 weeks reported significant improvement in negative symptoms and nonsignificant improvement in cognitive symptoms ($p=0.048$) (89). A study of 58 patients with schizophrenia or schizoaffective disorder who took pregnenolone 30 mg/d, 200 mg/d, or placebo for 8 weeks reported significant improvement in positive (but not negative) symptoms ($p=0.010$), and nonsignificant improvement in attention and working memory on the 30 mg dose but not the 200 mg dose (90). Pregnenolone was well tolerated in all three studies and side effects (e.g., headache and restlessness) were minimal. One of the men who took pregnenolone for 3 years developed an enlarged prostate (88),

although another study reported that pregnenolone had no effect on testosterone levels (90).

There are three large, ongoing, follow-up studies of pregnenolone, one SMRI-supported and two others, all using 500 mg/d. There is also a completed study, not yet published, that used 50 mg/d.

Use in Bipolar Disorder

A single study has been published using pregnenolone 100 mg/d or placebo for 8 weeks as adjunctive medication in a heterogeneous sample of 70 patients with bipolar disorder or recurrent major depression; all subjects also had a history of substance abuse (91). Those on pregnenolone had a significant improvement in depression (Hamilton Rating Scale for Depression; $p=0.03$) compared to the placebo group and a trend toward improvement in manic symptoms. No improvement in memory or other cognitive symptoms was observed. SMRI is supporting an ongoing study using pregnenolone 500 mg/d or placebo for 12 weeks in 80 patients with bipolar depression.

Assessment

Pregnenolone may turn out to be useful, but its effectiveness has not been established. Ongoing studies for both schizophrenia and bipolar disorder will hopefully clarify this issue.

Discussion

Given the need for better treatments for schizophrenia and bipolar disorder, it is important to explore all available resources. The repurposing of drugs being used to treat other diseases, over-the-counter drugs, and nutraceuticals represent a neglected resource. NIMH's recent publication *From Discovery to Cure* also noted that "repurposing medications used for other indications remains a very real opportunity" (92). Repurposing trials are especially timely, since major pharmaceutical companies are currently reducing efforts to find novel treatment for these diseases.

One major problem with repurposed drug trials is making the information available to clinicians. Since there is little or no financial incentive for pharmaceutical companies to promote repurposed drugs, there are no three-page, glossy ads or drug representatives to purchase pizza for the clinician's office staff. In the U.S., pharmaceutical companies employ 90,000 drug representatives, one for every 4.7 office-based clinicians, and support more than 60% of the cost of continuing medical education (93-95). Drugs for schizophrenia and bipolar disorder are major sources of revenue for pharmaceutical companies, and it is unrealistic to expect the companies to promote less expensive alternatives. One can argue that the results of repurposed drug trials are avail-

able in psychiatric journals, but studies of physicians have shown that such articles, by themselves, play a very small role in clinician decisions to try new drugs (96).

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Another consideration in doing studies of repurposed drugs is cost. Many of these drugs are very inexpensive compared to drugs still under patent. If some of these prove useful, they could help reduce the costs of psychiatric care, both in the U.S. and especially in less developed countries, where medication costs are critical.

For many of these drugs, there are suggestions that some patients respond and others do not. One of the major challenges is to identify biomarkers that will allow us to predict who will respond. For example, do markers of inflammation predict responders to aspirin or celecoxib, or do serum folate levels predict response to folate? Given the heterogeneity of both schizophrenia and bipolar disorder, we should not expect everyone to respond. Also missing, to date, are head-to-head trials of repurposed drugs against each other and against traditional treatments.

Another problem with evaluating the results of repurposed drug trials is that some studies are initiated by enthusiasts who zealously seek confirmatory data and positive results. It is, thus, important to verify the findings from one or more initial positive studies by doing larger, confirmatory studies using different investigators. In many cases, the confirmatory study will be negative, as has been the case with some of our own studies.

It is premature to outline an algorithm for the use of these repurposed drugs since sufficient data are not yet available regarding their effectiveness and target population. Among them, omega-3 fatty acids with EPA have promise for unipolar and some bipolar patients, and other benefits of taking omega-3 are well established. Folate may also have other benefits. Mirtazapine and estrogen also have shown promise in schizophrenia, but the definitive trials are not yet complete.

As with all treatment decisions, repurposed drugs should not be utilized without a careful assessment of possible risks and benefits. Even drugs such as aspirin, folic acid, and omega-3 fish oil can have side effects in some individuals, and drugs like celecoxib and estrogen should be used very cautiously. The risks of aspirin, celecoxib, estrogen and raloxifene, folate, minocycline, mirtazapine, and the omega-3 fatty acids are well known, since they have been well

studied for many indications in general medicine. There is an unknown risk of pramipexole in patients with schizophrenia and bipolar disorder because of the possibility that it could exacerbate these disorders, a risk that may not occur in patients with Parkinson's disease or restless legs syndrome. Pregnenolone, although used for many years and sold in health food stores, has not been well studied in contemporary studies.

As with all treatment decisions, repurposed drugs should not be utilized without a careful assessment of possible risks and benefits.

In summary, a number of repurposed drugs are available as adjunct treatment of treatment-resistant patients with schizophrenia and bipolar disorder. If used with attention to their possible side effects, they may be reasonable therapeutic alternatives when you are out of ideas.

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References

1. Rummel-Kluge C, Komossa K, Schwarz S, Hunger H, Schmid F, Kissling W, et al. Second-generation antipsychotic drugs and extrapyramidal side effects: a systematic review and meta-analysis of head-to-head comparisons. *Schizophr Bull* 2010 May 31 [Epub ahead of print].
2. Rummel-Kluge C, Komossa K, Schwarz S, Hunger H, Schmid F, Lobos CA, et al. Head-to-head comparisons of metabolic side effects of second generation antipsychotics in the treatment of schizophrenia: a systematic review and meta-analysis. *Schizophr Bull* 2010;123(2-3):225-233.
3. Buckley PF, Stahl SM. Pharmacological treatment of negative symptoms of schizophrenia: therapeutic opportunity or cul-de-sac? *Acta Psychiatr Scand* 2007;115(2):93-100.
4. DePaulo JR Jr. Bipolar disorder treatment: an evidence-based reality check (editorial). *Am J Psychiatry* 2006;163(2):175-176.
5. Fan X, Pristach C, Liu EY, Freudenreich O, Henderson DC, Goff DC. Elevated serum levels of C-reactive protein are associated with more severe psychopathology in a subgroup of patients with schizophrenia. *Psychiatry Res* 2007;149(1-3):267-271.
6. Dickerson F, Stallings C, Origoni A, Boronow J, Yolken R. C-reactive protein is associated with the severity of cognitive impairment but not of psychiatric symptoms in individuals with schizophrenia. *Schizophr Res* 2007;93:261-265.
7. Suvisaari J, Loo B-M, Saarni SE, Perala J, Saarni S, Jula A. Inflammation in psychotic disorders: a population-based study (abstract). *Schizophr Res* 2010;117:488.
8. Saetre P, Emilsson L, Axelsson E, Kreuger J, Lindholm E, Jazin E. Inflammation-related genes up-regulated in schizophrenia brains. *BMC Psychiatry* 2007;7:46.
9. Diaz FJ, Pérez-Iglesias R, Mata I, Martínez-García O, Vázquez-Barquero JL, de Leon J, et al. Possible effects of some antipsychotic drugs on C-reactive protein in a drug-naïve psychotic sample. *Schizophr Res* 2010;121(1-3):207-212.

10. Laan W, Grobbee DE, Selten J-P, Heijnen CJ, Kahn RS, Burger H. Adjuvant aspirin therapy reduces symptoms of schizophrenia spectrum disorders: results from a randomized, double-blind, placebo-controlled trial. *J Clin Psychiatry* 2010;71(5):520-527.
11. Dickerson F, Stallings C, Origoni A, Boronow J, Yolken R. Elevated serum levels of C-reactive protein are associated with mania symptoms in outpatients with bipolar disorder. *Prog Neuropsychopharmacol Biol Psychiatry* 2007;31(4):952-955.
12. Goldstein BI, Kemp DE, Soczynska JK, McIntyre RS. Inflammation and the phenomenology, pathophysiology, comorbidity, and treatment of bipolar disorder: a systematic review of the literature. *J Clin Psychiatry* 2009;70(8):1078-1090.
13. Basselin M, Kim H-W, Chen M, Ma K, Rapoport SI, Murphy RC, et al. Lithium modifies brain arachidonic and docosahexaenoic metabolism in rat lipopolysaccharide model of neuroinflammation. *J Lipid Res* 2010;51(5):1049-1056.
14. Müller N, Riedel M, Scheppach C, Brandstätter B, Sokullu S, Krampe K, et al. Beneficial antipsychotic effects of celecoxib add-on therapy compared to risperidone alone in schizophrenia. *Am J Psychiatry* 2002;159(6):1029-1034.
15. Müller NE, Riedel M, Dehning S, Spellmann I, Mueller-Arends A, Ceroveck A, et al. Is the therapeutic effect of celecoxib in schizophrenia depending on duration of disease? (abstract). *Neuropsychopharmacology* 2004;29(Suppl 1):S176.
16. Rapaport MH, Delrahim KK, Bresee CJ, Maddux RE, Ahmadpour O, Dolnak D. Celecoxib augmentation of continuously ill patients with schizophrenia. *Biol Psychiatry* 2005;57(12):1594-1596.
17. Akhondzadeh S, Tabatabaee M, Amini H, Ahmadi Abhari SA, Abbasi SH, Behnam B. Celecoxib as adjunctive therapy in schizophrenia: a double-blind, randomized and placebo-controlled trial. *Schizophr Res* 2007;90(1-3):179-185.
18. Muller N, Krause D, Dehning S, Musil R, Schennach-Wolff R, Obermeier M, et al. Celecoxib treatment in an early stage of schizophrenia: results of a randomized, double-blind, placebo-controlled trial of celecoxib augmentation of amisulpride treatment. *Schizophr Res* 2010;121(1-3):118-124.
19. Nery FG, Monkul ES, Hatch JP, Fonseca M, Zunta-Soares GB, Frey BN, et al. Celecoxib as an adjunct in the treatment of depressive or mixed episodes of bipolar disorder: a double-blind, randomized, placebo-controlled study. *Hum Psychopharmacol Clin Exp* 2008;23(2):87-94.
20. Littleton-Kearney MT, Ostrowski NL, Cox DA, Rossberg MI, Hurn PD. Selective estrogen receptor modulators: tissue actions and potential for CNS protection. *CNS Drug Rev* 2002;8(3):309-330.
21. Bergemann N, Abu-Tair F, Strowitzki T. Estrogen in the treatment of late-onset schizophrenia (letter). *J Clin Psychopharmacol* 2007;27(6):718-720.
22. Kulkarni J, de Castella A, Smith D, Taffe J, Keks N, Copolov D. A clinical trial of the effects of estrogen in acutely psychotic women. *Schizophr Res* 1996;20(3):247-252.
23. Kulkarni J, Riedel A, de Castella AR, Fitzgerald PB, Rolfe TJ, Taffe J, et al. Estrogen—a potential treatment for schizophrenia. *Schizophr Res* 2001;48(1):137-144.
24. Kulkarni J, de Castella A, Fitzgerald PB, Gurvich CT, Bailey M, Bartholomeusz C, et al. Estrogen in severe mental illness. *Arch Gen Psychiatry* 2008;65(8):955-960.
25. Akhondzadeh S, Nejatiasafa AA, Amini H, Mohammadi MR, Larijani B, Kashani L, et al. Adjunctive estrogen treatment in women with chronic schizophrenia: a double-blind, randomized, and placebo-controlled trial. *Prog Neuropsychopharmacol Biol Psychiatry* 2003;27(6):1007-1012.
26. Behdani F, Hebrani P, Mohamad Nejad M. Adjunctive estrogen treatment in women with chronic schizophrenia admitted in Hejazi and Ibn-e-Sina (abstract). *Eur Neuropsychopharmacol* 2008;18(Suppl):S390.
27. Bergemann N, Mundt C, Parzer P, Pakrasi M, Eckstein-Mannspurger U, Haisch S, et al. Estrogen as an adjuvant therapy to antipsychotics does not prevent relapse in women suffering from schizophrenia: results of a placebo-controlled double-blind study. *Schizophr Res* 2005;74(2-3):125-134.
28. Lindamer LA, Buse DC, Lohr JB, Jeste DV. Hormone replacement therapy in postmenopausal women with schizophrenia: positive effect on negative symptoms? *Biol Psychiatry* 2001;49:47-51.
29. Lousã MR, Marques AP, Elkis H, Bassitt D, Diegoli M, Gattaz WF. Conjugated estrogens as adjuvant therapy in the treatment of acute schizophrenia: a double-blind study. *Schizophr Res* 2004;66(2-3):97-100.
30. Kulkarni J, de Castella A, Headey B, Marston N, Sinclair K, Lee S, et al. Estrogens and men with schizophrenia: is there a case for adjunctive therapy? *Schizophr Res* 2011;125(2-3):278-283.
31. Kulkarni J, Gurvich C, Lee SJ, Gilbert H, Gavrilidis E, de Castella A, et al. Piloting the effective therapeutic dose of adjunctive selective estrogen receptor modulator treatment in postmenopausal women with schizophrenia. *Psychoneuroendocrinology* 2010;35(8):1142-1147.
32. Usall J, Huerta-Ramos E, Iniesta R, Cobo J, Araya S, Roca M, et al. Raloxifene as an adjunctive treatment for postmenopausal women with schizophrenia: a double-blind, randomized, placebo-controlled trial. *J Clin Psychiatry* 2011 Aug 23 [Epub ahead of print].
33. Chouinard G, Steinberg S, Stein W. Estrogen-Progesterone combination: another mood stabilizer? (letter). *Am J Psychiatry* 1987;144(6):826.
34. Goff DC, Bottiglieri T, Arning E, Shih V, Freudenreich O, Evins AE, et al. Folate, homocysteine, and negative symptoms in schizophrenia. *Am J Psychiatry* 2004;161(9):1705-1708.
35. Godfrey PSA, Toone BK, Carney MWP, Flynn TG, Bottiglieri T, Laundry M, et al. Enhancement of recovery from psychiatric illness by methylfolate. *Lancet* 1990;336(8712):392-395.
36. Levine J, Stahl Z, Sela B-A, Ruderman V, Shumaico O, Babushkin I, et al. Homocysteine-reducing strategies improve symptoms in chronic schizophrenic patients with hyperhomocysteinemia. *Biol Psychiatry* 2006;60:265-269.
37. Hill M, Shannahan K, Jasinski S, Macklin EA, Raeke L, Roffman JL, et al. Folate supplementation in schizophrenia: a possible role for MTHFR genotype. *Schizophr Res* 2011; Feb 18 [Epub ahead of print].
38. Dittmann S, Seemüller F, Grunze HC, Schwarz MJ, Zach J, Fast K, et al. The impact of homocysteine levels on cognition in euthymic bipolar patients: a cross-sectional study. *J Clin Psychiatry* 2008;69(6):899-906.
39. Yong VW, Wells J, Giuliani F, Casha S, Power C, Metz LM. The promise of minocycline in neurology. *Lancet Neurol* 2004;3(12):744-751.
40. Zhang L, Shirayama Y, Ioy M, Hashimoto K. Minocycline attenuates hyperlocomotion and prepulse inhibition deficits in mice after administration of the NMDA receptor agonist dizocipine. *Neuropsychopharmacology* 2007;32(9):2004-2010.
41. Levkovitz Y, Levi U, Braw Y, Cohen H. Minocycline, a second-generation tetracycline, as a neuroprotective agent in animal model of schizophrenia. *Brain Res* 2007;1154:154-162.
42. Miyaoka T, Yasukawa R, Yasuda H, Hayashida M, Inagaki T, Horiguchi J. Possible antipsychotic effects of minocycline in patients with schizophrenia. *Prog Neuropsychopharmacol Biol Psychiatry* 2007;31(1):304-307.
43. Chaves C, Marque CR, Chaudhry IB, Husain N, Minhas F, Oliveira JP, et al. Short-term improvement by minocycline added to olanzapine antipsychotic treatment in paranoid schizophrenia (abstract). *Schizophr Bull* 2009;35:354.
44. Miyaoka T. Clinical potential of minocycline for schizophrenia. *CNS Neurol Disord* 2008;7(4):376-381.
45. Miyaoka T, Yasukawa R, Yasuda H, Hayashida M, Inagaki T, Horiguchi J. Minocycline as adjunctive therapy for schizophrenia: an open-label study. *Clin Neuropharmacology* 2008;31(5):287-292.
46. Chaudhry IB, Husain N, Hallak J, Minhas FA, Dursun S, Richardson P, et al. Preventing clinical deterioration in first episode psychosis: potential role of minocycline in neuroprotection (abstract). *Biol Psychiatry* 2009;64:915.
47. Levkovitz Y, Mendlovich S, Riwkes S, Braw Y, Levkovitch-Verbin H, Gal G, et al. A double-blind, randomized study of minocycline for the treatment of negative and cognitive symptoms in early-phase schizophrenia. *J Clin Psychiatry* 2010;71(2):138-149.
48. Levine J, Cholestoy A, Zimmerman J. Possible antidepressant effect of minocycline (letter). *Am J Psychiatry* 1996;153(4):582.
49. Berk M, Ichim C, Brook S. Efficacy of mirtazapine add on therapy to haloperidol in the treatment of the negative symptoms of schizophrenia: a dou-

- ble-blind randomized placebo-controlled study. *Int Clin Psychopharmacol* 2001;16(2):87-92.
50. Zoccali R, Muscatello MR, Cedro C, Neri P, La Torre D, Spina E, et al. The effect of mirtazapine augmentation of clozapine in the treatment of negative symptoms of schizophrenia: double-blind, placebo-controlled study. *Int Clin Psychopharmacol* 2004;19(2):71-76.
51. Joffe G, Terevnikov V, Joffe M, Stenberg J-H, Burkin M, Tiihonen J. Add-on mirtazapine enhances antipsychotic effect of first generation antipsychotics in schizophrenia: a double-blind, randomized, placebo-controlled trial. *Schizophr Res* 2009;108(1-3):245-251.
52. Abbasi S-H, Behpourian H, Ghoresli A, Salehi B, Raznahan M, Rezazadeh S-A, et al., The effect of mirtazapine add on therapy to risperidone in the treatment of schizophrenia: a double-blind randomized placebo-controlled trial. *Schizophr Res* 2010;116(2-3):101-106.
53. Berk M, Gama CS, Sundram S, Hustig H, Koopowitz L, D'Souza R, et al. Mirtazapine add-on therapy in the treatment of schizophrenia with atypical antipsychotics: a double-blind, randomized, placebo-controlled clinical trial. *Hum Psychopharmacol* 2009;24(3):233-238.
54. Hieber R, Dellenbaugh T, Nelson LA. Role of mirtazapine in the treatment of antipsychotic-induced akathisia. *Ann Pharmacother* 2008;42(6):841-846.
55. Poyurovsky M, Pashinian A, Weizman R, Fuchs C, Weizman A. Low-dose mirtazapine: a new option in the treatment of antipsychotic-induced akathisia: a randomized, double-blind, placebo- and propranolol-controlled trial. *Biol Psychiatry* 2006;59(11):1071-1077.
56. Poyurovsky M, Epshtein S, Fuchs C, Schneidman M, Weizman R, Weizman A. Efficacy of low-dose mirtazapine in neuroleptic-induced akathisia: a double-blind randomized placebo-controlled pilot study. *J Clin Psychopharmacol* 2003;23(3):305-308.
57. Goyal N, Sinha VK. Mirtazapine-induced manic switch in adolescent unipolar depression (letter). *Aust N Z J Psychiatry* 2008;42(12):1070-1071.
58. Horrobin DF, Glen AIM, Vaddadi K. The membrane hypothesis of schizophrenia. *Schizophr Res* 1994;13(3):195-207.
59. Freeman MP, Hibbeln JR, Wisner KL, Davis JM, Mischoulon D, Peet M, et al. Omega-3 fatty acids: evidence basis for treatment and future research in psychiatry. *J Clin Psychiatry* 2006;67(12):1954-1967.
60. Kinney DK, Teixeira P, Hsu D, Napoleon SC, Crowley DJ, Miller A, et al. Relation of schizophrenia prevalence to latitude, climate, fish consumption, infant mortality, and skin color: a role for prenatal vitamin D deficiency and infections? *Schizophr Bull* 2009;35(3):582-595.
61. Harper KN, Hibbeln JR, Deckelbaum R, Quesenberry CP Jr, Schaefer CA, Brown AS. Maternal serum docosahexaenoic acid and schizophrenia spectrum disorders in adult offspring. *Schizophr Res* 2011;128(1-3):30-36.
62. Fenton WS, Hibbeln J, Knable M. Essential fatty acids, lipid membrane abnormalities, and the diagnosis and treatment of schizophrenia. *Biol Psychiatry* 2000;47(1):8-21.
63. Evans DR, Parikh VV, Khan MM, Coussons C, Buckley PF, Mahadik SP. Red blood cell membrane essential fatty acid metabolism in early psychotic patients following antipsychotic drug treatment. *Prostaglandins Leukot Essent Fatty Acids* 2003;69(6):393-399.
64. Fenton WS, Dickerson F, Boronow J, Hibbeln JR, Knable M. A placebo-controlled trial of omega-3 fatty acid (ethyl eicosapentaenoic acid) supplementation for residual symptoms and cognitive impairment in schizophrenia. *Am J Psychiatry* 2001;158(12):2071-2074.
65. Peet M, Horrobin DF. A dose-ranging exploratory study of the effects of ethyl-eicosapentaenoate in patients with persistent schizophrenic symptoms. *J Psychiatr Res* 2002;36(1):7-18.
66. Berger GE, Proffitt T-M, McConchie M, Yuen H, Wood SJ, Amminger GP, et al. Ethyl-eicosapentaenoic acid in first-episode psychosis: a randomized, placebo-controlled trial. *J Clin Psychiatry* 2007;68(12):1867-1875.
67. Peet M, Brind J, Ramchand CN, Shah S, Vankar GK. Two double-blind placebo-controlled pilot studies of eicosapentaenoic acid in the treatment of schizophrenia. *Schizophr Res* 2001;49(3):243-251.
68. Emsley R, Myburgh C, Oosthuizen P, van Rensburg SJ. Randomized, placebo-controlled study of ethyl-eicosapentaenoic acid as supplemental treatment in schizophrenia. *Am J Psychiatry* 2002;159(9):1596-1598.
69. Amminger GP, Schäfer MR, Papageorgiou K, Kleir CM, Cotton SM, Harrigan SM, et al. Long-chain omega-3 fatty acids for indicated prevention of psychotic disorders: a randomized, placebo-controlled trial. *Arch Gen Psychiatry* 2010;67(2):146-154.
70. Stoll AL, Severus WE, Freeman MP, Rueter S, Zboyan HA, Diamond E, et al. Omega 3 fatty acids in bipolar disorder: a preliminary double-blind, placebo-controlled trial. *Arch Gen Psychiatry* 1999;56(5):407-412.
71. Frangou S, Lewis M, McCrone P. Efficacy of ethyl-eicosapentaenoic acid in bipolar depression: randomized double-blind placebo-controlled study. *Br J Psychiatry* 2006;188:46-50.
72. Keck PE, Mintz J, McElroy SL, Freeman MP, Suppes T, Frye MA, et al. Double-blind, randomized, placebo-controlled trials of ethyl-eicosapentaenoate in the treatment of bipolar depression and rapid cycling bipolar disorder. *Biol Psychiatry* 2006;60(9):1020-1022.
73. Osher Y, Bersudsky Y, Belmaker RH. Omega-3 eicosapentaenoic acid in bipolar depression: report of a small open-label study. *J Clin Psychiatry* 2005;66(6):726-729.
74. Clayton EH, Hanstock TL, Hirneth SJ, Kable CJ, Garg ML, Hazell PL. Reduced mania and depression in juvenile bipolar disorder associated with long-chain omega-3 polyunsaturated fatty acid supplementation. *Eur J Clin Nutr* 2009;63(8):1037-1040.
75. Irving CB, Mumby-Croft R, Joy LA. Polyunsaturated fatty acid supplementation for schizophrenia (review). *The Cochrane Collaboration*. John Wiley and Sons, 2010, pp. 1-64.
76. Lin P-Y, Su K-P. A meta-analytic review of double-blind, placebo-controlled trials of antidepressant efficacy of omega-3 fatty acids. *J Clin Psychiatry* 2007;68(7):1056-1061.
77. Benkert O, Müller-Siecheneder F, Wetzel H. Dopamine agonists in schizophrenia: a review. *Eur Neuropsychopharmacol* 1995;5(Suppl):43-53.
78. Kasper S, Barnas C, Heiden A, Volz HP, Laakmann G, Zeit H, et al. Pramipexole as adjunct to haloperidol in schizophrenia: safety and efficacy. *Eur Neuropsychopharmacol* 1997;7(1):65-70.
79. Kelleher JP, Centorrino F, Huxley NA, Hennen J, Eakin M, Kidwell J, et al. Pilot, randomized controlled trial of pramipexole to augment antipsychotic treatment. *Eur Neuropsychopharmacol*, in press.
80. Goldberg JF, Burdick KE, Endick CJ. Preliminary randomized, double-blind, placebo-controlled trial of pramipexole added to mood stabilizers for treatment-resistant bipolar depression. *Am J Psychiatry* 2004;161(3):564-566.
81. Zarate CA Jr, Payne JL, Singh J, Quiroz JA, Luckenbaugh DA, Denicoff KD, et al. Pramipexole for bipolar II depression: a placebo-controlled proof of concept study. *Biol Psychiatry* 2004;56(1):54-60.
82. Malhotra AK, Braga RJ, Nnadi C, Shaya Y, Stearns WH, Burdick KE. Cognitive enhancement in euthymic bipolar I patients with pramipexole: a placebo-controlled adjunctive trial (poster). Presented at the 49th annual meeting of the American College of Neuropsychopharmacology, Miami, Fla., December 5-9, 2010.
83. Lettanz L, Dell'Osso L, Cassano P, Pini S, Rucci P, Houck PR, et al. Pramipexole in treatment-resistant depression: a 16-week naturalistic study. *Bipolar Disord* 2002;4(5):307-314.
84. Perugi G, Toni C, Ruffolo G, Frare F, Akiskal H. Adjunctive dopamine agonists in treatment-resistant bipolar II depression: an open case series. *Pharmacopsychiatry* 2001;34(4):137-141.
85. Sporn J, Ghaemi SN, Sambur MR, Rankin MA, Recht J, Sachs GS, et al. Pramipexole augmentation in the treatment of unipolar and bipolar depression: a retrospective chart review. *Ann Clin Psychiatry* 2000;12(3):137-140.
86. Corrigan MH, Denahan AQ, Wright CE, Ragual RJ, Evans DL. Comparison of pramipexole, fluoxetine, and placebo in patients with major depression. *Depress Anxiety* 2000;11(2):58-65.
87. Aiken CB. Pramipexole in psychiatry: a systematic review of the literature. *J Clin Psychiatry* 2007;68(8):1230-1236.

88. Savitz AJ. Multi-year continuation study of pregnenolone in patients with schizophrenia (abstract). *Biol Psychiatry* 2010;67:22S.
89. Marx CE, Keefe RSE, Buchanan RW, Hamer RM, Kilts JD, Bradford DW, et al. Proof-of-concept trial with the neurosteroid pregnenolone targeting cognitive and negative symptoms in schizophrenia. *Neuropsychopharmacology* 2009;34(8):1885-1903.
90. Ritsner MS, Gibel A, Shleifer T, Boguslavsky I, Zayed A, Maayan R, et al. Pregnenolone and dehydroepiandrosterone as an adjunctive treatment in schizophrenia and schizoaffective disorder: an 8-week, double-blind, randomized, controlled, 2-center, parallel-group trial. *J Clin Psychiatry* 2010;71(10):1351-1362.
91. Osuji IJ, Vera-Bolaños E, Carmody TJ, Brown ES. Pregnenolone for cognition and mood in dual diagnosis patients. *Psychiatry Res* 2010;178(2):309-312.
92. From Discovery to Cure: Accelerating the Development of New and Personalized Interventions for Mental Illnesses, Report of the National Advisory Mental Health Council's Workgroup, August 2010, www.nimh.nih.gov/about/advisory-boards-and-groups/namhc/reports/fromdiscoverytocure.pdf, last accessed on March 8, 2011.
93. Wazana A. Physicians and the pharmaceutical industry: is a gift ever just a gift? *JAMA* 2000;283(3):373-380.
94. Blumenthal D. Doctors and drug companies. *N Engl J Med* 2004;351(18):1885-1890.
95. Brodkey A. The role of the pharmaceutical industry in teaching psychopharmacology: a growing problem. *Acad Psychiatry* 2005;29(2):222-229.
96. Prosser H, Almond S, Walley T. Influences on GPs' decision to prescribe new drugs—the importance of who says what. *Fam Pract* 2003;20(1):61-68.

