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In This Issue

This issue of the *Residents' Journal* focuses on the theme of psychopharmacology and therapeutics. In a review article, Amritha Bhat, M.B.B.S., M.D., summarizes available data on the use of psychopharmacological treatment for bipolar disorder and other psychiatric disorders during pregnancy. Nilesh S. Tannu, M.D., M.S., discusses biomarkers in psychopharmacology and how they may impact patient care and the long-term goal of individualized medicine. Marsal Sanches, M.D., Ph.D., provides an overview of perspectives in the medication management of bipolar disorder. Leah C. Susser, M.D., examines the symptoms of serotonin reuptake inhibitor discontinuation. Mark A. Oldham, M.D., presents data on the use of chronotherapy for mood and neurocognitive disorders. Swapnil Gupta, M.B.B.S., M.D., provides a synopsis of the mechanisms of action, therapeutic efficacy, and practical considerations of *N*-acetylcysteine in psychiatric treatment. Last, Samuel T. Wilkinson, M.D., presents data on the unique legal status of marijuana for medical use, highlighting the indications as well as risks.

Pushing Boundaries

Misty Richards, M.D., M.S.
Editor-in-Chief

There has never been a more critical time to stand united on the frontlines of our medical specialty. The field of psychiatry is faced with many challenges and opportunities as we begin to embrace health care reform, tackle unprecedented neuropsychiatric questions, and directly address the battle against mental health stigma. As trainees, we are asked to learn about and contribute to these growing entities while fulfilling our role as healers in a world burdened with psychiatric illness. We do this at a unique time where public interest in mental health issues is at an all-time high. Media coverage of public shootings and violence has increased, pulling at our heartstrings and testing our reserve. What can we do to answer the call for help?

We can get involved. We can write. We can actively learn. We can participate in thoughtful discussions meant to push the boundaries of our mental capacities. We

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can cultivate the *American Journal of Psychiatry Residents' Journal* (AJP-RJ) into more than just a monthly publication; we can create a reliable forum where some of psychiatry's most challenging issues are addressed. We welcome your thoughts, your passion, and, most of all, your literary contributions.

The 2014–2015 Editorial Board has expanded to accommodate the tremendous growth of the Journal. We are pleased to introduce Dr. Rajiv Radhakrishnan (Yale), our new Senior Deputy Editor, and Dr. Tobias Wasser (Yale), our new Deputy Editor, who will work closely with me on issue content, manuscript revision, and development of the overall vision of the Journal. Drs. Ijeoma Chukwu (University of California, Irvine) and Kathy Mary Patchan (University of Maryland) will serve as Associate Editors, with their efforts focused largely on recruitment of authors, as well as contributors, and manuscript revision. Finally, we have Dr. Holly Peek (Tulane University), our new Media Editor, who will manage external relations, advertising, and expanding the Journal's social media presence. Our collective efforts are built on the strong foundation laid by former AJP-RJ leadership and sustained by the dedicated editorial and administrative staff of the *American Journal of Psychiatry*. For their tireless efforts, we are thankful.

For the latest updates on publications, research, resident resources, and leadership opportunities, please follow us on social media at www.twitter.com/AJP_ResJournal and www.facebook.com/AJPResidentsJournal.

Treatment of Bipolar Disorder and Psychotic Disorders During Pregnancy

Amritha Bhat, M.B.B.S., M.D.

A psychiatrist treating pregnant women has to balance the risks and benefits of treatment, keeping in mind the well-being of both the patient and the developing fetus. The risks of untreated mental illness during pregnancy do not receive as much publicity as the risks of psychiatric treatments. Ethical considerations preclude randomized double-blind trials in this population, leaving little in the way of evidence-based guidelines to inform treatment decisions. Studies based on teratology service databases are limited by the fact that women who call for advice and are included in the database may be higher functioning than those who do not. Most studies do not control for confounding factors such as diet, polypharmacy, tobacco use, alcohol and street drug use, and maternal age. The present review is an attempt to summarize recent available knowledge (or the lack thereof) that can inform psychopharmacological management of bipolar and psychotic disorders, for which nonpharmacological treatments alone are often insufficient. Depressive and anxiety disorders are more commonly encountered in women of childbearing age and are extensively reviewed elsewhere (1, 2).

All untreated psychiatric disorders have effects on functioning and quality of life, as well as behavioral effects such as obesity, smoking, alcohol and drug abuse, poor nutrition and suboptimal antenatal care, or intentional harm through suicide or neonaticide. Women with untreated psychosis or mood disorders may also have difficulty parenting, leading to adverse effects on child development. On the other hand, psychotropic medications used during pregnancy are associated with a wide range of adverse effects, not just teratogenicity but also obstetric, neonatal, and long-term neurodevelopmental effects.

Food and Drug Administration (FDA) pregnancy categories are not included in the present review because the FDA is proposing to eliminate these categories.

The new labeling will include subsections on pregnancy and on lactation, each with three components: risk summary, clinical considerations, and a data section (3).

Bipolar Disorder in Pregnancy

Effects of Untreated Bipolar Disorder

Bodén et al. (4) compared pregnant women with bipolar disorder who were treated with a mood stabilizer (N=320; lithium, antipsychotics, lamotrigine, valproate, carbamazepine) or not treated with a mood stabilizer (N=554) with a control group of pregnant women without bipolar disorder (N=331,263). They found a higher risk of preterm birth in both the treated and untreated bipolar disorder groups (increased by 50% compared with the control group). Infants born to untreated mothers had smaller head circumference (3.9% had microcephaly compared with 3.3% born to treated women) and neonatal hypoglycemia (4.3% compared with 3.4% born to treated women), but this difference was not statistically significant after adjusting for confounders (maternal age, smoking, alcohol use, and birth order).

Effects of Treatments for Bipolar Disorder

Lithium is one of the psychotropics for which we have the most data for use during pregnancy, yet it is still surrounded by misconceptions. Although the Lithium Baby Registry indicated increased risk of major congenital malformations, especially Ebstein's anomaly, more recent studies (4) have found no associations with congenital malformations.

Apart from the follow-up study of the lithium registry, an observational retrospective study (5) of 15 children exposed in utero to lithium and examined at 3–15 years of age showed that the children's growth and their behavioral and general development were normal, and cognitive testing results were within normal limits. Clearly, more studies examining larger numbers of lithium-exposed babies are needed before any comment can be made about the long-term effects of lithium exposure.

Most of the data available on the use of other mood stabilizers are based on studies of the use of these treatments in epilepsy, and therefore one cannot completely rule out the confounding effects of epilepsy itself on the outcomes studied. Valproate and carbamazepine use during pregnancy have been associated with prematurity, intrauterine growth retardation, and an increased risk of major malformations (structural abnormalities with surgical medical or cosmetic importance that may need surgical intervention). In one study, the rate of pregnancies resulting in serious adverse outcomes was 8.2% with carbamazepine, 1.0% with lamotrigine, and 20.3% with valproate (6). Valproate exhibited a dose-dependent effect. Valproate has also been associated with adverse neonatal outcomes such as neonatal hemorrhage and hepatic dysfunction (7). Lamotrigine has been implicated in development of oral clefts in some (8) but not all (9) studies.

It is sometimes suggested that mood stabilizers can be safely started in the second trimester because organogenesis has already occurred; however, longer-term consequences include lower IQ scores among offspring exposed to valproate and carbamazepine in utero (10), 6–9 points lower on average compared with unexposed children.

A population-based Danish registry study (11), with less than 3% loss to follow-up, examined children exposed in utero to valproate and found the absolute risk for autism spectrum disorder to be 4.42% (95% confidence interval [CI]=2.20%–7.81%) and the risk for childhood autism to be 2.95% (95% CI=1.42%–6.11%). This risk remained elevated even after

correcting for the effect of epilepsy. However, other prescription medications that may have been taken during pregnancy were not accounted for.

Psychotic Disorders in Pregnancy

Effects of Untreated Psychotic Disorders

In their study, Jablensky et al. (12) found that psychotic illnesses such as schizophrenia were associated with increased risk of antepartum hemorrhage (odds ratio=2.75, 95% CI=1.32–5.74) and cardiovascular malformations. However, data on prescription medication, severity of the mothers' illness, or smoking/use of illicit drugs were not reported.

Effects of Antipsychotics

In a review, no teratogenic risk associated with several first-generation antipsychotics (promethazine, prochlorperazine, haloperidol, perphenazine, trifluoperazine, loxapine, thioridazine, flupenthixol, and fluphenazine) was reported, nor were risks reported for second-generation antipsychotics (clozapine, risperidone, olanzapine, quetiapine, ziprasidone, and aripiprazole) (13).

A later systematic review recommended first-generation antipsychotics in treating drug-naive patients because second-generation antipsychotics "appear to increase risk of gestational metabolic complications and babies large for gestational age" (14). However, more recently conducted cohort studies indicate that second-generation antipsychotics may be preferable. One such study examined 561 women exposed to at least one second-generation antipsychotic (olanzapine, quetiapine, clozapine, risperidone, aripiprazole, ziprasidone, amisulpiride, or zotepine) compared with 284 patients exposed to first-generation antipsychotics (haloperidol, promethazine, or flupenthixol) and 1,122 patients exposed to nonteratogenic drugs (15). The authors found that preterm birth and low birth weight were more common in infants exposed to first-generation antipsychotics. Post hoc analysis revealed an increased rate of septal defects in offspring exposed to second-generation antipsychotics.

FIGURE 1. Clinical Recommendations for Treating Psychiatric Disorders During Pregnancy

Prenatal considerations

Ideally, the discussion regarding use of medications during pregnancy should be had with every woman of child-bearing age before conception.

Discuss the risks and benefits of not just the medications but also of untreated psychiatric disorder.

Initiate prenatal vitamins, especially folate, before pregnancy or as early as possible.

The specific drug used should be determined on a case-by-case basis, not just depending on available evidence on teratogenicity and long-term outcomes but also based on the patient's history of response.

Considerations during pregnancy

Monotherapy and lower doses are preferred, but the disorder should not be undertreated because this would expose the fetus to the effects of both the illness and the medication, i.e., titrate up to the minimum *effective* dose.

Although starting a medication in the second trimester (after organogenesis) would reduce risk of teratogenicity, it could still have long-term neurodevelopmental consequences.

The pregnant woman taking psychotropics should be monitored more closely and frequently, with therapeutic drug monitoring (especially for lithium and lamotrigine use), level-2 ultrasound, and fetal echocardiography.

There is insufficient evidence to choose between first- and second-generation antipsychotics based solely on fetal effects.

There does not seem to be a case for discontinuation of psychotropics toward the end of pregnancy because this does not seem to reduce the rate of neonatal complications.

Postpartum considerations

It should be ensured that delivery occurs in a facility with a neonatal intensive care unit. After delivery, the mother and child may need to be observed for longer than the traditional 48 hours for complications.

There may also be a case for closer surveillance of the child, at least up to school age.

McKenna et al. (16) found that there was an increased rate of low birth weight (10% in the exposed group compared with 2% in the comparison group) and therapeutic abortion but no increased rate of major malformation, obstetric complications, or neonatal complications in children of women taking second-generation antipsychotics (olanzapine, N=60; risperidone, N=49; quetiapine, N=36; and clozapine, N=6). This was a prospective database study with the comparison group carefully chosen for exposure to nonteratogenic drugs and absence of both psychiatric disorder and use of psychotropic drugs. In the exposed group, there was a high rate of polytherapy and an increased rate of risk factors independently associated with poor pregnancy outcome (i.e., unplanned pregnancy, not taking folic acid/multivitamins, binge consumption of alcohol and smoking). Transient

extrapyramidal symptoms have been reported in neonates after intrauterine exposure to first-generation antipsychotics (17).

In a prospective controlled study of 309 mother-infant dyads, 6-month-old infants who had intrauterine antipsychotic exposure (N=22; haloperidol, aripiprazole, olanzapine, quetiapine, risperidone, or ziprasidone) had lower INFANIB (Infant Neurological International Battery) scores compared with infants with intrauterine antidepressant exposure (N=202) or no psychotropic exposure (N=85) (18). Visual habituation and mean time looking at a stimulus did not differ across groups. However, half the data for the exposure sample were collected retrospectively and therefore subject to recall bias. Additionally, the antipsychotic exposure group had a small sample size, and, as with most studies of this type, the

study was not powered to distinguish the effects of the illness from the effects of the treatment. Peng et al. (19) reported delayed scores on the Bayley Scales of Infant Development for 2-month-old babies who were exposed to second-generation antipsychotics (N=76; clozapine, risperidone, sulpiride, olanzapine, and quetiapine), but this difference was not statistically significant at 12 months of age, suggesting temporary impairment.

Other Considerations

Changes in drug absorption, distribution, metabolism, and elimination occur during pregnancy and may contribute to changing psychotropic drug levels. Mechanisms include induction of cytochrome P450 enzymes 3A4 and 2D6 (which metabolize clozapine, quetiapine, and risperidone) by sex hormones, reduction in total protein, increasing free drug fraction of medications, and changes in hepatic and renal blood flow and glomerular filtration rate. In addition, increase in body fat during pregnancy results in greater storage of antipsychotics (which are lipophilic). Frequent monitoring of drug levels, as well as dose increases, may be indicated, especially for lithium and lamotrigine use.

When a pregnant woman desires to discontinue psychotropic medication because of concerns of harming the fetus, it is important to inform her that sudden discontinuation has been shown to lead to decompensation of psychiatric illness (20).

Psychopharmacology during lactation is beyond the scope of the present review but is also important to keep in mind to facilitate continuity of treatment.

Conclusions

Despite the lack of conclusive evidence, the benefit from treatment of bipolar and psychotic disorders during pregnancy appears to outweigh the risks. Preconceptional counseling and planning is ideal (Figure 1), but because many pregnancies are unplanned, it is helpful to have a detailed informed consent discussion before making a decision to discontinue or withhold medications.

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Biomarkers in Psychopharmacology: The Present and Future

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As we move toward an era of individualized medicine, the discovery of biomarkers is taking center stage. In other fields of medicine, biomarker research has led to many important discoveries, such as the discovery of troponin as a marker for myocardial infarction, 14-3-3 protein for Creutzfeldt-Jakob disease, and S100β/UCH-L1/alpha-II spectrin for brain trauma (1). Although such advances have yet to be developed for psychiatric disorders, the hope is that biomarkers will not only be able to identify individuals with similar disorders for diagnostic purposes but also guide selection of optimal treatment strategies and monitor therapeutic response and/or adverse events. The challenge will be to have a set of reliable, sensitive, and specific biomarkers for each of these goals. Presently, biomarkers are being explored to validate investigational new drugs as surrogate indices of clinically relevant endpoints, as well as to probe treatment response to established treatment regimens.

There are numerous tools, as well as assessment and physiological measures, for investigating biomarkers in psychiatric disorders: imaging (e.g., functional MRI, diffusion tensor imaging, single-photon emission CT, positron emission tomography, and MR spectroscopy); molecular biology (e.g., proteomics, genomics, metabolomics, and lipidomics); clinical outcome assessment (e.g., the Cocaine Selective Severity Assessment and Addiction Severity Index); cardiovascular (e.g., heart rate and ECG fingerprint); and neurophysiology (e.g., EEG and auditory-evoked response potentials such as P300, N100, mismatch negativity, and spectral analyses) (2). Based on preliminary proteomics studies, a 51 analyte immunoassay, called VeriPsych, was developed, which purported to diagnose schizophrenia with a specificity and sensitivity of 83% (3). While services for the test are currently suspended in order to better refine the assay to fit the needs of patient and health care providers, it remains an initial model for biomarker discovery. Another example is the Neuropsychiatric EEG-Based Assessment Aid system for attention deficit hyperactivity disorder (ADHD), which has been approved by the Food and Drug Administration (FDA). Investigators have identified psychiatric disorder-specific putative diagnostic biomarkers for mood disorders, including genetic markers (the 5-HTT linked polymorphic region, catechol-O-methyltransferase, and the serotonin-2A single-nucleotide polymorphism) and peripheral markers (brain-derived neurotrophic factor, interleukin-6, neuroactive steroids, and the renin-angiotensin aldosterone system) (4). Research in substance use disorder has shown progress in defining possible candidate biomarkers in chronic cocaine dependence. Findings from studies of human and nonhuman primate models for chronic cocaine dependence/toxicity suggest that there is a coordinate dysregulation of proteins related to cell structure, signaling, metabolism, and mitochondrial function (5). These changes underlie long-term compromised cellular function not only in the nucleus accumbens but also in the frontal cortex following chronic cocaine exposure. However, the study of substance use disorder is limited by the small availability of FDA-approved treatment regimens.

To date, no validated and/or clinically accepted biomarker exists as a measure for most psychiatric disorders, including substance use disorder. There are several molecules and pathways that can be considered as potential biomarkers for schizophrenia, chronic cocaine use, depression, autism spectrum disorder, and ADHD (1). However, hurdles for clinical validation remain substantial, such as identifying the relationship of a biomarker to the disorder's biological mechanism and its correlation with prognosis, disorder severity, and treatment. Acceptable standards for reliability, sensitivity, and specificity have yet to be established and are made more complex by the diagnostic classification system used in psychiatry. Notwithstanding the significant challenges to this clinical paradigm, it is an objective worth the pursuit, with the potential for improved patient care and the ultimate goal of individualized medicine.

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Perspectives in the Pharmacological Treatment of Bipolar Disorder: Where Are We Heading?

Marsal Sanches, M.D., Ph.D.

Bipolar disorder is a chronic mental illness associated with significant morbidity, functional impairment, and high rates of suicide (1). Even though some patients with bipolar disorder have their symptoms well controlled by currently available pharmacological agents, existing treatments often fail to provide sufficient management, with elevated rates of relapse and residual symptoms (2). Therefore, there is a clear demand for new medications that are able to provide more long-term mood stability and adequate control of residual symptoms.

The present review focuses on some of the new pharmacological agents currently being tested for the treatment of bipolar disorder (Table 1). Rather than carrying out a comprehensive review on the topic in question, we provide a brief overview on the perspectives in the medication management of bipolar disorder, in light of available evidence.

Novel Approaches in the Pharmacological Management of Bipolar Disorder

Neuroprotective Agents

Some of the medications available for the treatment of bipolar disorder, such as lithium, valproic acid, and some atypical antipsychotics, seem to owe part of their therapeutic efficacy to neuroprotective effects (3). In addition, some neuroprotective agents, currently approved for the treatment of other conditions, have recently been tested for the management of bipolar disorder, with promising results. These include agents with effects on the glutamatergic system (ketamine, D-cycloserine, and riluzole), protein kinase C inhibitors (tamoxifen), and glucocorticoid receptor antagonists, such as mifepristone (4).

Several other drugs with putative effects on the glutamatergic modulation properties are currently under investigation with regard to their possible role in the treatment of bipolar disorder. For example, ceftriaxone (an antibiotic) and felbamate (an anticonvulsant) have been found to have effects on glutamatergic modulation and are both being tested for their efficacy in the treatment of bipolar depression (5). Similarly, metabotropic glutamate receptors (mGluRs) are a subtype of glutamate receptors that seem to be implicated in the pathophysiology of schizophrenia as well as bipolar disorder (6). It is possible that mGluR agonists have a potential role in the treatment of the disorder, but no studies, to our knowledge, have addressed that role.

With respect to hypothalamic-pituitary-adrenal axis hyperactivity, in addition to mifepristone, the antifungal agent ketoconazole (which has antiglucocorticoid properties) displayed positive effects in the treatment of bipolar depression in a

TABLE 1. Pharmacological Agents Under Investigation for the Treatment of Bipolar Disorder

Drug	Putative Mechanism of Action
Ceftriaxone	Glutamatergic modulation
D-cycloserine	
Felbamate	
Ketoconazole	Hypothalamic-pituitary-adrenal axis modulation
Mifepristone	
Acetyl-L-carnitine	Mitochondrial enhancement
Coenzyme Q10	
Lipoic acid	
L-carnosine	Antioxidant effects
N-acetyl cysteine	
Omega-3 fatty acids	
Aspirin	Anti-inflammatory effect
Dextromethorphan	
Curcumin	
Minocycline	
Donepezil	Cholinergic modulation
Galantamine	
Scopolamine	
Allopurinol	Purinergic modulation
Cytidine	Miscellaneous
Triacetyluridine	
Uridine	
Insulin	
Erythropoietin	
Methylphenidate	

preliminary study (7). Corticotrophin-releasing factor antagonists have been tested in the treatment of unipolar depression with mixed results, but no evidence regarding their efficacy in bipolar disorder is currently available (4). Finally, some agents that are able to enhance mitochondrial function (with consequent positive effects on neuroprotection) are currently being tested in the treatment of bipolar disorder, and these agents include acetyl-L-carnitine, coenzyme Q10, and lipoic acid (5).

Antioxidants

Clinical and preclinical studies point to the involvement of oxidative stress in the pathophysiology of bipolar disorder (8). Therefore, a better understanding of the role of antioxidants in the treatment of this condition is of high interest.

In this context, omega-3 fatty acids have been found to have positive effects as an augmentation strategy among adult patients with bipolar depression, as well as in juvenile bipolar patients with depressive and manic symptoms (9). In addition to their antioxidant properties, omega-3 fatty acids seem to inhibit protein kinase C activity, with ultimate neuroprotective properties (10). Similarly, the potential efficacy of *N*-acetyl cysteine, another antioxidant agent, as a treatment strategy in bipolar depression has been previously demonstrated (11).

Moreover, a clinical trial investigated the efficacy of L-carnosine in the treatment of cognitive impairment in bipolar disorder, but the results are not yet available (5). Finally, other antioxidant drugs, such as synthetic triterpenoids, have been tested for the treatment of other conditions associated with oxidative stress but not for the treatment of bipolar disorder (5).

Anti-Inflammatory Drugs

The possible involvement of inflammatory processes in the pathophysiology of bipolar disorder (particularly bipolar depression) has recently been addressed in several studies (12). Moreover, evidence from rodent and human studies suggests that inhibition of the cyclooxygenase-2 pathway may be a shared mechanism of action of mood stabilizers (13).

In this sense, a double-blind, randomized clinical trial examined the possible role of celecoxib, a cyclooxygenase-2 inhibitor, as an augmentation strategy for the treatment of bipolar depression (14). The results indicated an earlier onset of antidepressant effect in the medication group compared with the placebo group, although no differences between groups were present at the end of the follow-up period. Furthermore, several ongoing trials are currently investigating the effect of other anti-inflammatory agents in the treatment of bipolar disorder, including aspirin, dextromethorphan, minocycline, and curcumin, a phytotherapic agent with anti-inflammatory and antioxidant properties (5). It is unclear at this point whether these medications will eventually have a well-established role in the treatment of bipolar disorder or whether their potential benefits will outweigh some of the risks associated with their long-term use.

Agents With Action in the Cholinergic System

The putative implication of the cholinergic system in the pathophysiology of mood disorders led to several proof-of-concept trials involving medications with actions in the cholinergic system for the treatment of bipolar disorder (3). Cholinesterase inhibitors (donepezil and galantamine) have been tested in the treatment of bipolar disorder (4). While results regarding a possible mood stabilizer effect of this class of medications are generally negative, it is possible that they may play a role in the management of the cognitive impairment associated with bipolar disorder. The numerous methodological issues displayed by these studies limit the generalization of the findings.

In addition, the intravenous infusion of scopolamine, an anticholinergic agent, has been found to produce rapid antidepressant effects in patients with unipolar and bipolar depression (15). It is not yet clear whether this agent might have a specific role in the treatment of bipolar disorder.

Drugs Acting on the Purinergic System

The involvement of the purinergic system in the pathophysiology of bipolar disorder is supported by preclinical and clinical evidence (3). Common pathways seem to regulate the purinergic, dopaminergic, and GABA-ergic transmissions, and studies suggest that elevated plasma uric acid may be a state marker for mania in bipolar patients. Allopurinol, commonly used in the treatment of gout, is an inhibitor of the enzyme xanthine oxidase, therefore working as a purinergic modulator.

Three double-blind placebo-controlled studies demonstrated positive effects of allopurinol augmentation in the treatment of mania. Most interesting, the findings from one of these studies revealed a direct correlation between improvement in manic symptoms and decrease in plasma uric acid levels (3).

Pyrimidine Nucleosides

Pyrimidine nucleosides seem to produce positive effects on multiple brain/metabolic pathways. These include glutamatergic transmission, phospholipid metabolism, catecholamine production, and mitochondrial function.

In one randomized clinical trial (16), cytidine (added to valproate as an augmentation strategy) was found to produce early improvement in bipolar depressive symptoms, as well as decreases in the brain glutamate/glutamine levels measured through MR spectroscopy. Similarly, triacetyluridine, another nucleoside, was found to have positive effects in the treatment of bipolar depression, and this improvement was significantly correlated with increases in brain pH measured using phosphorus MR spectroscopy, suggesting a direct relationship between clinical improvement and enhanced mitochondrial function (17).

Finally, short-term use of uridine has been shown to enhance brain membrane phospholipid precursors in healthy control subjects, and one open-label study points toward improvements in depressive symptoms among adolescent bipolar patients treated with uridine (18). At least two randomized controlled studies have focused on the efficacy of that nucleoside in the treatment of bipolar depression, but results from these studies are not yet available.

Other Agents

Many additional proof-of-concept trials have investigated the potential efficacy

of different agents in the treatment of bipolar disorder. For example, the possible involvement of insulin in neuroplasticity modulation led to a randomized trial focusing on the potential benefits of intranasal insulin specific to the cognitive performance of bipolar patients (19). Significant improvements in executive functioning were observed in the treatment group. Likewise, an ongoing clinical trial is investigating the possible effect of erythropoietin on cognitive function and depressive symptoms in patients with unipolar and bipolar depression (5). Among other compounds currently being tested for the treatment of bipolar disorder are valacyclovir, digoxin antibodies, methylene blue, and pentazocine, a kappa-opioid receptor antagonist (5).

Finally, a recently proposed multicenter trial will investigate the putative role of methylphenidate in the treatment of manic symptoms (20). The investigators postulate that primary deficits in brain arousal could lead to manic symptoms through overcompensatory mechanisms (the "vigilance regulation model of mania"), and stimulants may help stabilize vigilance, akin to the use of stimulants in treating symptoms of attention deficit hyperactivity disorder.

Conclusions

Different from the sometimes empirical studies that led to the identification of classic medications used in the treatment of mood disorders, current research on novel treatments for bipolar disorder seems to be following a bottom-up approach, based on multiple pathways for which involvement in the pathophysiology of bipolar disorder has been recently hypothesized.

Even though it is unlikely that new pharmacological agents that are able to revolutionize the core treatment of bipolar disorder will be available within the next 10 years, many of the medications discussed in the present review seem promising as augmentation strategies and might play a role in addressing treatment-resistant bipolar disorder and in the management of specific clusters of symptoms, such as cognitive impairment in bipolar patients.

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Serotonin Reuptake Inhibitor Discontinuation Symptoms

Leah C. Susser, M.D.

Abrupt withdrawal or rapid taper of serotonin reuptake inhibitor (SRI) treatment can cause distressing discontinuation symptoms. The experience of withdrawal symptoms can detrimentally affect a patient's attitude toward antidepressants and the patient's willingness to take an antidepressant in the future. Early recognition that symptoms are due to withdrawal of an SRI prevents unnecessary medical workup and allows for appropriate and timely treatment. While antidepressants from many classes are SRIs, the present review is limited to selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs). There are many reasons, both intentional and unintentional, for abruptly discontinuing an antidepressant. Patients may discontinue antidepressants without consultation with a health care professional because of improved mood or because of financial reasons, such as a change in copay, financial status, or insurance coverage. A patient, alternatively, may not consistently adhere to the medication regimen. The medication might be abruptly discontinued by medical professionals during emergency hospitalization, either because the nature of the medical emergency would make SRI use dangerous or because the medical team is not yet aware of the patient's home medication list. It is important to be aware of the potentially distressing withdrawal symptoms and to educate patients and physicians in other specialties about these symptoms to allow for rapid recognition and treatment.

Frequency

SRI discontinuation symptoms are common, and their frequency and severity are particularly increased with SRIs with shorter half-lives, such as venlafaxine, paroxetine, and fluvoxamine (1–4). Discontinuation symptoms can occur when the SRI is withdrawn or when it is rapidly tapered. One study with a small sample size found that 78% of patients tapered off of extended-release venlafaxine experienced withdrawal symptoms, compared with 22% of patients treated with placebo (3). A double-blind placebo-controlled trial compared symptoms when the SRI was continued in patients taking paroxetine, sertraline, or fluoxetine with symptoms when the SRI was substituted for placebo for 5 days. Results showed that paroxetine withdrawal was associated with the most change in adverse events (2). A retrospective chart review revealed that 17.2% of patients who discontinued fluvoxamine or paroxetine experienced discontinuation symptoms, compared with 1.5% of those who discontinued fluoxetine or sertraline (5). In a study of fluvoxamine, 28% of patients who were tapered off of the drug experienced withdrawal symptoms (1). While discontinuation symptoms are common when SRIs with short half-lives are stopped or tapered, discontinuation symptoms are rare when fluoxetine, which has a long half-life and a metabolite with a long half-life, is discontinued (2, 6).

Symptoms

Withdrawal of SSRIs and SNRIs is associated with similar discontinuation symptoms, and these symptoms range in severity. The most common symptoms associated with withdrawing an SSRI are dizziness/lightheadedness, nausea, headache, and lethargy (7). Other reported symptoms include ataxia, vertigo, anxiety, paresthesias, numbness, electric shock sensations, flu-like symptoms, memory problems, confusion, tremor, sweating, insomnia, irritability, and diarrhea (7–9). Common symptoms observed after SNRI withdrawal include dizziness, lightheadedness, sweating, irritability, dysphoria, and insomnia, and patients can also sense electric shocks (3, 7, 10, 11). The electric shock sensation associated with withdrawal of SSRIs and SNRIs can be very painful and transiently debilitating (1, 7, 10). The sensation can occur in the head, can radiate to the back and arms, and can be triggered by neck movement (10, 12). This has been described by patients as "brain shocks" or "electric shocks" (10, 12).

Discontinuation Syndrome

Some researchers define a "discontinuation syndrome" to distinguish more severe states from milder symptoms associated with discontinuing SRIs. For example, Black et al. (9) proposed criteria for an SSRI discontinuation syndrome. Beginning within 1–7 days of stopping or tapering an SSRI after treatment with it for at least 1 month, patients must have two of the following symptoms that cause distress or impairment: dizziness/lightheadedness/vertigo, paresthesias, anxiety, diarrhea, fatigue, gait instability, headache, insomnia, irritability, nausea/vomiting, tremor, or visual disturbances (9). Medical illness and relapse of the psychiatric illness that was being treated must be ruled out as the cause of these symptoms (9). Haddad (7) proposed a similar syndrome, with slight variation in the time of onset and symptom list, and he recommended specifying severity.

Timing

Onset and duration of symptoms aid in distinguishing discontinuation symptoms from other etiologies. Symptoms of SRI discontinuation typically begin within the first few days (7). The median time between discontinuation of paroxetine and developing symptoms of discontinuation is 2.1 days, with 21% of patients developing symptoms in the first day, 86% within 4 days, and 93% within 1 week (4). In another study of paroxetine withdrawal, patients had statistically significant changes in adverse events by the second missed dose, and these adverse events increased during the 5-day study period (2). Venlafaxine withdrawal can start around

2–12 hours after the time of the missed scheduled dose (13). In one study, 78% of patients on a venlafaxine taper regimen experienced unwanted symptoms within 3 days of stopping extended-release venlafaxine, compared with 22% of patients treated with placebo instead of venlafaxine (3).

A study of SSRIs and clomipramine demonstrated that symptoms of SRI discontinuation last for an average of 11.8 days, with a maximum duration of 21 days (5). In a study of SSRI discontinuation symptoms, findings revealed that after discontinuation of paroxetine, symptoms could last for 1–52 days, with a mean and median duration of 10.5 and 8 days, respectively (4). However, there have been case reports of SRI discontinuation symptoms lasting longer, including up to 13 weeks, which was reported in one case after sertraline taper (12).

Treatment

It is imperative to rapidly identify whether symptoms are a result of SRI discontinuation in order to provide timely treatment, which can often lead to immediate resolution of symptoms. Symptoms usually improve within 24 hours of restarting an SRI (5). Venlafaxine discontinuation symptoms respond to both venlafaxine and other SRI medications (13). If venlafaxine is used to treat venlafaxine withdrawal, symptoms of withdrawal can improve within 1–8 hours after the administered venlafaxine dose (13).

Mechanism

One main proposed mechanism for SRI discontinuation symptoms is serotonin depletion, although acetylcholine rebound has been hypothesized to play a role in paroxetine withdrawal and norepinephrine in venlafaxine withdrawal. Serotonin's involvement in discontinuation symptoms is supported both mechanistically and with evidence from studies. When an SRI is stopped, there is a decrease in available serotonin, but the serotonin receptors transiently remain down-regulated, which could lead to discontinuation symptoms (14, 15). The symptoms observed after withdrawal of an SRI, including headache and gastrointestinal symptoms, can be explained by this transient relative depletion of serotonin. Serotonin is used to treat headaches (13). There are serotonin receptors and serotonin in the gut, which could explain gastrointestinal symptoms (13). Other evidence to support serotonin's role in SRI discontinuation symptoms includes the inverse relationship between the half-life of an SRI and the incidence of discontinuation symptoms, independent of the SRI's anticholinergic properties (1–3, 13). Discontinuation symptoms are similar among SSRIs, as well as between SSRIs and SNRIs (7, 10). Both SNRI and SSRI (even the anticholinergic paroxetine) discontinuation symptoms can be treated with another SRI (13, 16, 17). However, paroxetine discontinuation symptoms may not be relieved by anticholinergic medication, and venlafaxine discontinuation symptoms may not always be relieved by noradrenergic medication (13, 16, 17).

Acetylcholine is thought to be a mechanism for tricyclic antidepressant discontinuation symptoms, and it has been hypothesized as a mechanism for withdrawal symptoms from paroxetine, which also has anticholinergic properties (5, 14, 18). However, there are case reports in which desipramine, which has anticholinergic properties, did not relieve paroxetine withdrawal symptoms, suggesting that acetylcholine may not be the only or the main mechanism for paroxetine withdrawal symptoms in these cases (17).

While venlafaxine discontinuation symptoms have been shown to be relieved by SSRI treatment, the brain shocks associated with venlafaxine have also been shown to respond to atomoxetine, which affects norepinephrine, suggesting that norepinephrine may also play a role in venlafaxine discontinuation symptoms in some cases (13, 19).

Conclusions

In summary, abrupt withdrawal or rapid tapering of SRIs can cause uncomfortable and potentially debilitating symptoms that, if not recognized, could lead to unnecessary medical workup and distress. Symptoms are more common with SRIs with shorter half-lives. Common symptoms include dizziness, nausea, headache, and lethargy. Symptoms often start within a few days, and they can vary in duration from days to weeks. Symptoms usually rapidly resolve with administration of an SRI.

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Chronotherapy: When the Tincture of Time is Potent Medicine

Mark A. Oldham, M.D.

Whereas time may not heal all wounds, growing evidence suggests that alterations in "biological time" may improve many psychiatric conditions. The growing field of chronotherapy (*chronos* for "time") involves interventions that modulate circadian rhythms, and researchers continue to expound upon the clinical application and neurobiological underpinnings of this class of therapies (1). The present introduction to chronotherapy is intended as a practical treatise, divided into two sections. The first half introduces readers to the principal chronotherapies. The second half surveys emerging data on psychiatric disorders for which chronotherapy has been investigated as a treatment model.

Interventions

Common chronotherapeutic interventions include applications of controlled illuminance and modification of sleep-wake cycles (see Wirz-Justice et al. [2] for a more detailed description of the treatments presented in this article).

Controlled Illuminance
Light serves as the primary biological *zeit-geber* ("time giver") and synchronizes the body's internal clock regarding day and night. Bright light therapy is the most widely known and used type of chronotherapy, but several other variations have been used, including narrow-band wavelength blue or green light, dawn simulation, dark therapy, and amber-tinted glasses that filter out short wavelength (blue) light.

Bright light therapy typically involves illuminance of at least 2,500 lux at the level of the cornea applied in the morning. The current established application of bright light therapy is full-spectrum white light of 10,000 lux for 30 minutes at the same time each morning, including weekends, although historically 2,500 lux was often employed for 2 hours (2). The light is typically delivered by means of a light box, which may be purchased online or, less commonly, at local supermarkets. When fluorescent bulbs are involved, the device should have a diffusing screen that filters out ultraviolet light less than 400 nm to avoid harm to the eyes and skin (3). Alternative light-delivery devices include light-therapy desk lamps, hand-held devices, and visors with light-emitting diodes. When used for seasonal or nonseasonal depression, mood improvement often occurs within 1–2 weeks of treatment onset; however, improvements may abate within days of treatment discontinuation. Common side effects include headache, eye strain, nausea, insomnia, and irritability. Similar to antidepressant medication, bright light therapy may contribute to manic switch or treatment-emergent suicidal ideation, and it is recommended that the use of bright light therapy always be convened under the supervision of a health care professional (2).

Interventions that emit narrow-band wavelength light appearing blue or green have been implemented with preliminary success but presently remain nonstandard methods of treatment. Green-appearing wavelengths of light, which are slightly longer than blue-appearing light, have been proposed in response to concerns that persistent short-wavelength blue or ultraviolet light may cause skin or eye damage.

Dawn simulation, dark therapy, and blue-blocking glasses are all considered experimental. Dawn simulation involves the use of a diffuse light-emitting system that slowly increases in light intensity over 90 minutes at the end of the sleep cycle. Eyelids are translucent and allow for light to be received by the retina and thus may help to entrain circadian rhythms in the morning. Dark therapy and the related use of blue-blocking glasses that limit circadian activation in the evening represent a natural corollary to light therapy and have been investigated as treatments for mania and sleep disorders.

Sleep-Wake Cycles
Circadian sleep-wake interventions include wake therapy (the preferred term for total or partial sleep deprivation), sleep-phase advance therapy, and melatonin agonists. Most interns can attest to the fact that staying up all night gives rise to mood-elevating properties, often causing a "subjective buzz." As such, week-long protocols of every-other-night wake therapy may greatly hasten antidepressant response when added to antidepressant treatment and bright light therapy (4). Such protocols also tend to incorporate advancing of the sleep phase. Wake therapy has been shown to improve depression symptoms within 24 hours; however, it must be combined with other interventions such as antidepressant medication or other chronotherapies such as bright light therapy to prevent relapse after the next sleep period. Wake therapy is among the select few interventions (including ECT and *N*-methyl-D-aspartate receptor antagonists) that provide antidepressant effects over the course of hours to days.

Agents that modulate circadian rhythms, sometimes called chronobiotics, have been shown to improve circadian rhythm sleep disorders; however, research on their role in a range of other sleep-wake disorders is ongoing. The melatonin agonists ramelteon and tasimelteon are approved for use in the United States, but melatonin is neither approved nor regulated by the Food and Drug Administration.

Evidence From Efficacy Studies

Depression
The description of seasonal affective disorder (or major depressive disorder with seasonal pattern as described in DSM-5) ushered in the age of chronotherapy in the 1980s, and since that time more than 70 controlled clinical trials have investigated the efficacy of bright light therapy

TABLE 1. Recommendations for Bright Light Therapy and Wake Therapy in Major Depression[a]

Organization	Bright Light Therapy	Wake Therapy
American Psychiatric Association	May be considered as a first-line acute-phase treatment for major depression.	n/a
British Association for Psychopharmacology	Effective in short-term treatment of seasonal and non-seasonal depression. Sustained benefits are unclear.	Temporary improvement in depression. Sustained benefits unclear.
Canadian Network for Mood and Anxiety Treatments	First-line treatment in acute seasonal depression. Second-line treatment in mild-to-moderate nonseasonal depression.	Third-line treatment for acute treatment of mild-to-moderate major depression.
National Institute for Health and Clinical Excellence	Methodological limitations in trials for seasonal depression are cited (uncertain role). Not considered for nonseasonal depression	n/a
Texas Medication Algorithm Project[b]	n/a	n/a
World Federation of Societies of Biological Psychiatry	Bright light therapy is an option in the treatment of seasonal affective disorder if administration is possible and protocol adherence can be ensured.	May be used for nonmedicated patients with depression or started with antidepressant medication. May be added to potentiate ongoing antidepressant medication.

[a] The guidelines presented are described in detail by Kuiper et al. (19) and Bauer et al. (20).
[b] Only medications are included in this guideline.

in seasonal affective disorder (5), and bright light therapy is often considered a first-line treatment for this condition (Table 1). The role of bright light therapy for the treatment of nonseasonal depression continues to be investigated. Nearly a decade ago, an APA-sponsored meta-analysis demonstrated that monotherapy bright light has an effect size comparable to that of antidepressant medications in the treatment of nonseasonal depression, and several subsequent studies have demonstrated its efficacy in this form of depression (1, 6). Moreover, antidepressant response to bright light therapy is generally seen within 1–2 weeks in both seasonal and nonseasonal depression. Week-long protocols of every-other-day wake therapy combined with antidepressants, bright light therapy, or sleep-phase advance may yield antidepressant effects within days of treatment onset (4).

Bipolar Disorder

Mood episodes in bipolar disorder appear highly influenced by circadian factors. For example, sleep restriction may precipitate manic episodes in bipolar disorder, and a leading psychotherapeutic intervention recommended for bipolar patients is interpersonal and social rhythms therapy, which focuses on stabilizing circadian rhythms in the patient's social context. In fact, the Systematic Treatment Enhancement Program for Bipolar Disorder found that interpersonal and social rhythms therapy improved outcomes in bipolar disorder when combined with mood stabilizers (7). Wake therapy and bright light therapy have been demonstrated in several studies to improve bipolar depression (8), and preliminary data suggest that adjunctive dark therapy or blue-blocking glasses may hasten antimanic response (9).

Sleep-Wake Disorders

Common behavioral treatments for insomnia incorporate specific chronotherapeutic elements. For example, stimulus control therapy involves consistent wake times, sleep hygiene limits light exposure at night, and sleep restriction therapy enhances sleep propensity. First-line treatments for circadian rhythm sleep disorders include bright light therapy, sleep-phase modification (with or without controlled sleep deprivation), and melatonin agonists.

Neurocognitive Disorders

Poor sleep is as common as inattention among patients with delirium, and a variety of studies have demonstrated dysregulated circadian rhythms in these patients (10). Pilot trials have found that monotherapy and adjunctive bright light therapy added to risperidone may prevent or improve delirium (11). Among patients with Alzheimer's disease, confusion commonly displays a reliably evening presentation and may be associated with behavioral disturbances ("sundowning") and sleep fragmentation, implicating chronobiological disruption. Although select trials have found that controlled environmental light/dark patterns improve sleep quality and may improve agitation in this population (12), the data remain inconclusive (13).

Attention Deficit Hyperactivity Disorder (ADHD)

Early evidence has found that morning bright light therapy may improve core features of ADHD (14), and melatonin (15) or blue-blocking glasses before bedtime (16) may improve ADHD-related sleep disruption.

Biological Mechanisms

Although precise biological mechanisms of chronotherapy remain unknown, studies have demonstrated biological effects of bright light therapy and wake therapy. Light received by the retina orchestrates clock gene expression (e.g., CLOCK, BMAL1, Per1, etc.) in the suprachiasmatic nucleus. Projections from the suprachiasmatic nucleus to the paraventricular nucleus of the hypothalamus synchronize cellular clocks throughout the body by means of a time-keeping neural network and melatonin, which acts through the melatonin receptors MT_1

and MT_2 (1). Specifically, antidepressant response to bright light therapy is associated with enhanced serotonergic activity and healthy circadian rhythms. Wake therapy appears to confer antidepressant response through acute alterations in clock gene transcription, effects that may be shared with ketamine (17).

Limitations

Although the body of evidence in support of chronotherapy continues to grow, limitations remain. For example, questions regarding study designs, adequate blinding, appropriate control groups, and small cohorts often hinder the degree of conclusions that can be made. Longer-term efficacy trials, effectiveness trials, and rigorous "dose-finding" studies of light intensity, duration, and spectral emission would help to define the role of bright light therapy for psychiatric disorders. Additionally, the ability to patent or brand "light" or "wake" generates its own set of practical limitations.

Conclusions

Results from a recent survey of practicing psychiatrists in Massachusetts who evaluated use and perceptions of bright light therapy suggested that the leading potentially modifiable barrier to its use was lack of knowledge (18), and although this does not imply that greater information will necessarily increase prevalent use of bright light therapy and other chronotherapies, it does suggest a need for education in this area. Perhaps the most compelling reason to date to consider chronotherapy remains the potential to hasten antidepressant response. These interventions can be grafted seamlessly into traditional psychiatric practice. With ongoing research in this field and increasing acceptance among mental health professionals, chronotherapy is certain to see its brightest days ahead.

At the time this article was accepted for publication, Dr. Oldham was a fifth-year fellow in psychosomatic medicine in the Department of Psychiatry, Yale University School of Medicine, New Haven, Conn.

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N-Acetylcysteine in Psychiatry: Panacea or Placebo?

Swapnil Gupta, M.B.B.S., M.D.

N-acetylcysteine (NAC) is the prodrug of the sulfur-containing nonessential amino acid cysteine. It has been used in intravenous form to treat acetaminophen poisoning and for the prevention of contrast nephropathy. For several decades, inhaled NAC has been used as a mucolytic for bronchopulmonary disorders such as pulmonary alveolar proteosis. Its antioxidant actions at the intracellular level have been known for years, but in the past 10 years, there has been increasing focus on its potential as a glutamatergic agent and thereby as pharmacotherapy for a range of substance use and other psychiatric disorders (1, 2). The present review provides a synopsis and update on the mechanisms of action, therapeutic efficacy, practical considerations, and future directions of NAC.

Mechanisms of Action

NAC has its most prominent effects on cellular redox status, inflammation, and glutamatergic neurotransmission (Figure 1). There is growing evidence for the role of oxidative stress in the pathophysiology of several psychiatric disorders, including schizophrenia, bipolar disorder, depression, attention deficit hyperactivity disorder, and autism. In these psychiatric disorders, there are demonstrated abnormalities in enzymes that are responsible for clearing free radicals, such as glutathione peroxidase and superoxide dismutase. Moreover, mitochondria, which are the seat of cellular oxidative processes, have been shown to be dysfunctional in these disorders. Furthermore, these disorders are also associated with markers of oxidative damage to neurons, as well as to DNA coding for neuronal proteins (3). In addition, there is extensive data supporting a role for inflammatory pathways in the pathophysiology of schizophrenia and mood disorders coming from the measurement of circulating inflammatory markers and from the effect of psychotropic agents on these markers, as well as

lipopolysaccharide-induced inflammation models for these disorders (4).

The most well-established role of NAC is in supplying cysteine for the synthesis of the primary endogenous antioxidant, glutathione. NAC may also directly act as an antioxidant by reducing hydroxyl radicals and hypochlorous acid (5). Either independently or through its antioxidant effect, NAC also reduces levels of various inflammatory markers in lipopolysaccharide-activated macrophages (6). This accounts for its "broad-spectrum" psychotropic effects.

The effect of NAC on glutamatergic neurotransmission has especially been explored in substance-related and addictive disorders (1, 2). Long-term administration of addictive drugs causes downregulation of presynaptic metabotropic glutamate receptor type 2 (mGluR2), which functions to provide negative feedback and reduce the release of glutamate into the synapse. Additionally, addictive drugs also cause downregulation of the glutamate transporter type 1 in glial cells, resulting in reduced clearance of, and thereby increasing, synaptic glutamate. This is referred to as the glutamate spillover. NAC, by getting converted to cystine, stimulates the cystine-glutamate antiporter, which in turn increases the level of extrasynaptic glutamate. Extrasynaptic glutamate stimulates presynaptic mGluR2 that causes a reduction in synaptic glutamate release. At the same time, NAC also increases the activity of glutamate transporter type 1 in glial cells, further clearing synaptic glutamate and reducing the glutamate spillover. Both these mechanisms have been associated with the prevention of relapse in drug use in animal models. NAC regulation of the cystine/glutamate antiporter and mGluR2 can also regulate dopamine release from presynaptic terminals. Through its antioxidant effects, NAC may also regulate dopamine release by modulation of the redox status of the cell. Animal studies have shown

that NAC reduces dopamine release by increasing intracellular glutathione levels.

Clinical Trials of NAC

There are several studies of NAC in substance use and other psychiatric disorders, but these studies are limited by small sample sizes and open-label design.
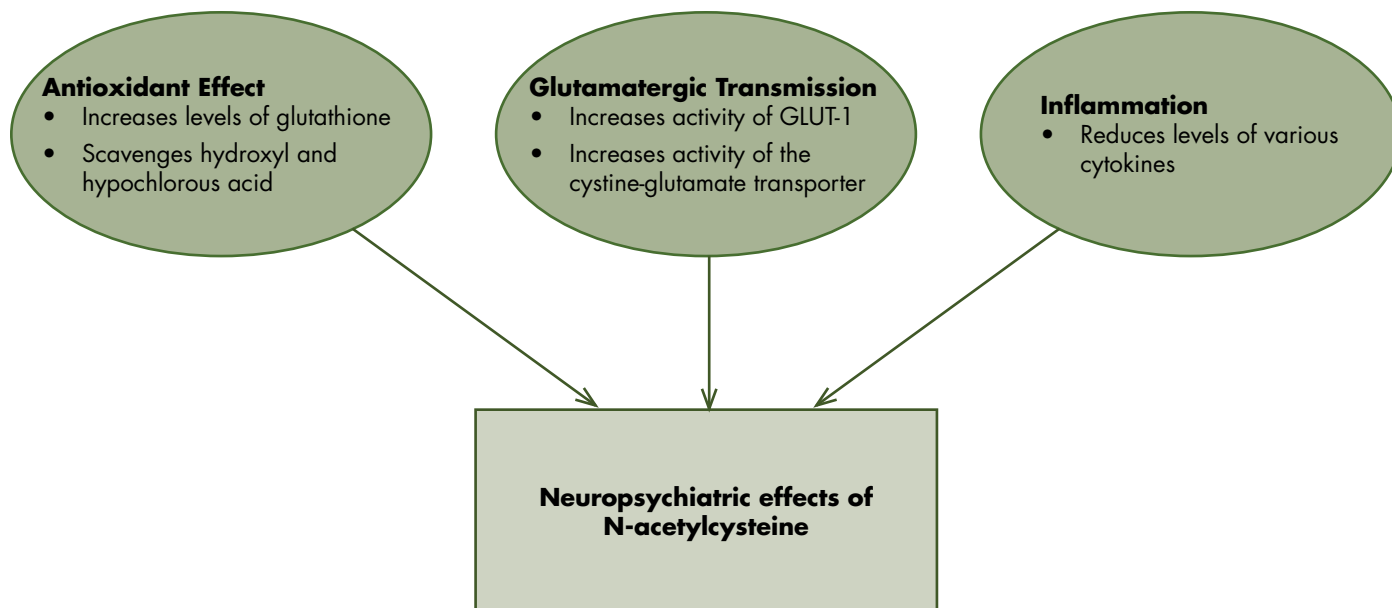
Substance Use Disorder

NAC has been tested for its effects on craving, relapse, and reward in cocaine, nicotine, and cannabis dependence (1, 7). It was shown to reduce craving in treatment-seeking cannabis-dependent adolescents (8) but not in nicotine- (9) or cocaine-dependent adults (10, 11). NAC also doubled the odds of a negative urine screen for cannabinoids at the end of 6 weeks in another study of cannabis-dependent adolescents (12) and reduced cue-reactivity to cocaine stimuli (10). It has been tried in combination with naltrexone for the treatment of methamphetamine dependence but did not show a statistically significant effect in any of the outcome measures.

Schizophrenia

In the largest randomized controlled trial of NAC in schizophrenia to date (N=140), it was shown to reduce negative symptoms, as measured by the Positive and Negative Syndrome Scale, but improvements were lost at the 1-month follow-up (13). In the same study, NAC was also shown to reduce abnormal movements, including akathisia, and to improve global functioning. It is noteworthy that in patients with schizophrenia, NAC improved mismatch negativity, which is an electrophysiological marker of auditory sensory processing and a rough measure of glutamatergic function (14). Plasma glutathione levels were found to be elevated in patients in whom mismatch negativity improved, thus illuminating one mechanism of action. One case report described the beneficial effect

FIGURE 1. Mechanisms of Action of *N*-Acetylcysteine

Antioxidant Effect
- Increases levels of glutathione
- Scavenges hydroxyl and hypochlorous acid

Glutamatergic Transmission
- Increases activity of GLUT-1
- Increases activity of the cystine-glutamate transporter

Inflammation
- Reduces levels of various cytokines

Neuropsychiatric effects of N-acetylcysteine

of NAC when it was added to risperidone for a young woman with treatment-resistant schizophrenia (15).

Other Psychiatric Disorders
Both an open-label (N=75) and a randomized controlled trial (N=149) demonstrated the effect of NAC as an adjunct to mood stabilizers in treating bipolar depression (2). Similar to schizophrenia patients, these bipolar patients also showed improvement in functioning. There is accumulating evidence for the use of NAC in obsessive-compulsive disorder, trichotillomania, nail-biting, skin-picking, and pathological gambling, based on several case reports, a case series, and two randomized controlled trials. In these conditions, NAC has been prescribed as monotherapy, as well as an adjunctive treatment to selective serotonin reuptake inhibitors. It improved cognitive performance in Alzheimer's disease patients in three trials (total N=49) (2). These patients were treated with NAC for 6 months and showed significant improvements in performance on the letter fluency task, as well as in immediate number recall on the Wechsler Memory Scale. NAC has also been shown to reduce irritability and repetitive

behaviors while improving social responsiveness in individuals with autism.

Formulations

NAC is available in oral (tablets and capsules), intravenous, and nebulized forms. Only oral NAC, which is available through prescription and over-the-counter, has been used for neuropsychiatric indications. There are no recommendations for oral dosing, and consequently a broad range of doses has been used in clinical trials. In Australia, regulatory authorities have recommended a maximum dose of 1,000 mg/day for over-the-counter preparations. However, in trials for psychiatric indications, it has been prescribed in daily doses ranging from 600 to 3,600 mg (7).

Pharmacokinetics

Most studies demonstrate extensive intersubject variation in plasma NAC concentrations following oral administration (16, 17). Oral bioavailability of NAC is estimated at 6%–10% due to extensive first-pass metabolism, with the time to peak concentration 1–2 hours after dosing (17). The volume of distribution ranges from 0.33 l/kg to 0.47 l/kg (17).

Metabolism

NAC forms the dimers *N*-acetylcystine and N,N´-diacetylcystine. The latter is the rate-limiting precursor for the endogenous antioxidant glutathione. NAC covalently bonds to plasma proteins and can be deactylated to form cysteine (17).

Side Effects

Typically, oral NAC is well tolerated and less likely than the intravenous form to cause serious side effects, such as bronchospasm and anaphylaxis (18). Less serious side effects of oral NAC include unpleasant taste, rashes, and gastrointestinal disturbances such as nausea, flatulence, and abdominal cramps (19). Most of these side effects are mild and usually do not require discontinuation of treatment. NAC can also have a mildly stimulating effect causing insomnia. It should be administered with caution in patients with asthma and is contraindicated in patients with NAC allergy.

Drug Interactions

NAC has serious interactions with nitroglycerins and should not be used with this group of medications.

Future Directions

Pharmacokinetic parameters, including transport across the blood-brain barrier and brain concentrations following oral and intravenous dosing, have not been identified in humans and are very relevant to neuropsychiatric disorders. It would be helpful to ascertain mechanisms of action of NAC in specific disorders, including the antioxidant mechanism that can be tested by biochemical measures of oxidative stress such as reduced glutathione and ascorbic acid. Furthermore, the effect of NAC on glutamate and GABA levels can be examined using MR spectroscopy, as exemplified in select studies of cocaine dependence (20). Clinical trials to ascertain doses, duration of treatment, and potential synergistic combinations with other psychotropic medications are needed.

Conclusions

Given its safety and tolerability, further mechanism-oriented, dose-finding, and efficacy studies of the use of NAC in treating substance use and other psychiatric disorders are warranted.

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Medical Marijuana: A Review for the Psychiatric Trainee

Samuel T. Wilkinson, M.D.

Medical marijuana is now legal in at least 20 states and the District of Columbia, with more states expected to follow suit. The present article is an overview of medical marijuana, including cannabis composition, the unique legal status of marijuana as a medication, evidence supporting the efficacy of marijuana in psychiatric conditions, and the risks associated with use.

Cannabis Composition

Crude marijuana consists of more than 70 cannabinoids and other compounds (1). Delta-9-tetrahydrocannabinol is one of the major components and is responsible for the euphoria (as well as psychotic-like experiences) associated with smoked marijuana. Cannabidiol is another major compound, which can comprise over 15% of the crude plant. Cannabidiol is thought to have anxiolytic, antiepileptic, and antipsychotic properties and is not associated with the psychotogenic effects of the drug (2). Other constituents include other cannabinoids (such as cannabidivarin, cannabigerol, and cannabichromene), as well as flavonoids and terpinoids. These other chemicals may produce interactive or individual effects and may moderate the effects of tetrahydrocannabinol (referred to as "entourage effects"). Comparatively, little is known about these lesser but potentially important components of marijuana.

A Unique Legal Status

In the United States, the legal status of medical marijuana is unique. Unlike other medications, medical marijuana has only been approved at the state level, by either legislature or ballot box, and not at the federal level through the Food and Drug Administration (FDA). By bypassing the FDA, marijuana has not been subject to rigorous clinical trials typically required of a medication for each indication. Furthermore, unlike most medications, which are single- or double-agent compounds, crude marijuana consists of more than 70 cannabinoids that produce individual and interactive effects (1). Crude marijuana does not have the same purity and regulated concentration of active ingredients in contrast to medications dispensed by federally regulated pharmacies. Finally, whereas other medications are prescribed with a dosage, schedule, and refill options, a prescription for medical marijuana involves disbursing a recommendation that allows patients to buy up to the legal limit of marijuana (which varies by state) and use it at the dose and schedule they see fit. Hence, the word "prescribe" is somewhat misleading (for the purpose of this article, the words "authorize" and "recommend" are used). Thus, marijuana as medicine is qualitatively different than FDA-approved medications and indications (e.g., metformin for diabetes). Furthermore, although marijuana for medical purposes is legal in at least 20 states and the District of Columbia, it remains illegal at the federal level.

Indications

Depending on the state, legal indications for medical marijuana vary considerably (Table 1). Most states give indications not only for diseases but also for specific symptoms, such as muscle spasticity, seizures, cachexia, and pain. Laws in some states leave open the possibility of additional indications, as determined by a physician in specific circumstances. The most commonly approved conditions include cancer, HIV/AIDS, glaucoma, cachexia/wasting syndrome, severe pain, nausea/vomiting, muscle spasms, and seizures.

Notably, several cannabinoids have been approved by the FDA (or equivalent regulatory bodies) for medical use. Dronabinol is purified tetrahydrocannabinol available in an oral pill and has two FDA-approved indications: 1) nausea associated with chemotherapy and 2) HIV/AIDS-associated cachexia. Nabilone, a synthetic analog of tetrahydrocannabinol, is also available in the United States, Canada, the United Kingdom, and Mexico. Additionally, nabiximols, a 1:1 mixture of tetrahydrocannabinol and cannabidiol, has been approved as an oral-mucosal spray in Canada and the United Kingdom for treatment of spasticity in multiple sclerosis.

Neuropathic Pain

One of the indications for which the most evidence exists for the effectiveness of crude marijuana is neuropathic pain. A number of placebo-controlled trials suggest that smoked marijuana may have modest efficacy in treating neuropathic pain and pain associated with cancer (3, 4). However, negative side effects, including cognitive impairment, alterations in perception, and mood disturbances, have been shown to be common and may limit the utility of marijuana for chronic pain (4). There is less evidence for the role of marijuana in treating other types of pain (5, 6).

Agitation in Alzheimer's Disease

Agitation in the setting of Alzheimer's disease is the most commonly approved psychiatric indication for medical marijuana. However, to date, there are very few studies examining the effects of cannabinoids in patients with Alzheimer's disease or other dementia (7). While preclinical studies of cannabinoids for Alzheimer's disease show some therapeutic promise, including anti-inflammatory and neuroprotective effects (8), clinical data are lacking. The studies that exist are either pilot data with no comparison group (9) or trials with very small sample sizes (10). It is noteworthy that in all these trials, the drug tested was dronabinol (purified tetrahydrocannabinol) and not crude marijuana. To date, there has been no trial evaluating the efficacy of crude marijuana, either smoked or through oral consumption, in dementia-related agitation.

TABLE 1. Qualifying Medical Conditions in States Where Medical Marijuana is Legal[a]

State	Cancer	HIV/AIDS	Glaucoma	Crohn's Disease	Amyotrophic Lateral Sclerosis	Hepatitis C Virus	Epilepsy/Seizures	Muscle Spasm/Multiple Sclerosis	Agitation in Alzheimer's Disease	Cachexia/Anorexia	Pain	Nausea/Vomiting	Other Qualifying Medical Conditions/Treatments
Alaska	x	x	x				x	x		x	x	x	
Arizona	x	x	x	x	x	x	x	x	x	x	x	x	
California[b]	x	x	x							x	x		Arthritis (unspecified), migraines
Connecticut	x	x	x	x				x	x	x			Posttraumatic stress disorder (PTSD), Parkinson's disease
Colorado	x	x	x				x	x		x	x	x	
Delaware	x	x			x	x	x	x	x	x	x	x	PTSD
Hawaii	x	x	x	x			x			x	x	x	Multiple sclerosis
Illinois	x	x	x	x	x	x			x	x			Muscular dystrophy, fibromyalgia, rheumatoid arthritis, traumatic brain injury (TBI), Parkinson's disease, Tourette's syndrome, multiple others
Maine	x	x	x	x	x	x	x	x	x	x	x	x	Nail-patella syndrome, PTSD
Massachusetts[b]	x	x	x	x	x	x		x					Multiple sclerosis, Parkinson's disease
Michigan	x	x	x	x	x	x	x	x	x	x	x	x	PTSD, nail-patella syndrome
Montana	x	x	x	x			x	x		x	x	x	Neuropathy, hospice care
Nevada	x	x	x				x	x		x	x	x	PTSD
New Hampshire	x	x	x	x	x	x	x	x	x	x	x	x	Muscular dystrophy, pancreatitis, TBI, spinal cord injury
New Jersey	x	x	x	x	x		x	x					Muscular dystrophy, less than 1 year life expectancy
New Mexico	x	x	x	x	x	x	x	x		x	x	x	PTSD, arthritis, hospice, neuropathy, spinal cord injury, cervical dystonia, Parkinson's disease, Huntington's disease
Oregon	x	x	x				x	x	x	x	x	x	PTSD
Rhode Island	x	x	x	x		x	x	x	x	x	x	x	
Vermont	x	x					x	x		x	x	x	
Washington	x	x	x	x		x	x	x		x	x	x	Renal failure
District of Columbia	x	x	x					x					Undergoing chemotherapy, radiotherapy, or highly active antiretroviral therapy

[a] The data presented were obtained from information available to the public in state government statues and websites. At the time this article was accepted for publication, Maryland passed a medical marijuana bill, with details still under discussion.

[b] The state has flexible clauses allowing physicians to recommend marijuana for any condition that the physician feels marijuana might help treat.

Post-Traumatic Stress Disorder (PTSD)

Although there is growing evidence that patients with PTSD self-medicate with marijuana (11), there have been no clinical trials evaluating the efficacy of marijuana in treating PTSD. According to self-reports, individuals with PTSD frequently cite coping and insomnia aid as their reasons for marijuana use, as opposed to enjoyment, boredom, or social/other reasons (12). Although this association is significant and warrants further study, the finding that PTSD patients self-medicate does not substitute for objective evidence from controlled clinical trials that marijuana improves PTSD symptoms. Thus, while there is preclinical evidence demonstrating that cannabinoids affect aversive memory consolidation (13) (implicating its utility in PTSD), clinical data are lacking.

Risks

Contrary to prevailing public opinion, the legal status of marijuana does not translate to it being safe. A growing body of literature shows side effects that may include psychosis, addiction, and pulmo-

nary complications, as well as cognitive impairment.

Marijuana and Psychosis
There is a large body of literature supporting an association between marijuana and psychosis, including persistent psychotic disorders such as schizophrenia (1). Whether marijuana can cause a persistent psychotic state continues to be debated. Marijuana may act in concert with other factors, such as genetic vulnerability and a history of childhood abuse (14), as a causal component to schizophrenia. The association between marijuana and psychosis is strongest when use is heavy, chronic, and begins in adolescence (1).

Addiction
Approximately 4.3% of Americans have been dependent on marijuana at some point in their lives, and about 9% of adults who try cannabis develop addiction (15). Cannabis is among the first substances that adolescents try, and substantial evidence suggests that it plays a role as a gateway to other, "harder" illicit drugs (16). A cannabis withdrawal syndrome is recognized in DSM-5 and includes symptoms such as irritability, anxiety, sleep difficulty, changes in weight or appetite, and depressed mood. Currently, there are no standardized or accepted treatments for cannabis use disorder.

Pulmonary Complications
Although still controversial, there are legitimate concerns about the long-term effects of smoked marijuana on the development of lung cancer and obstructive lung disease (17).

Intelligence/Cognitive Impairment
A number of studies have investigated the association between cannabis use and cognitive impairment. Controlled laboratory experiments have shown that cannabinoids induce transient cognitive deficits in a dose-related fashion (1). While earlier studies have been mixed as to whether cognitive impairment persists beyond the period of intoxication (for a review, see reference 14), a prospective, longitudinal cohort sample from the general population revealed a significant reduction in IQ associated with chronic marijuana use, ranging from 6 to 8 points (18). Cannabis intoxication also impairs

motor coordination and may contribute to motor vehicle fatalities, especially in combination with alcohol (19).

Conclusions

Medical marijuana maintains a unique legal status within medicine. It has not been subject to the same rigorous approval process, involving large placebo-controlled clinical trials, as other medications. Furthermore, crude marijuana does not have the same purity and regulated concentration of active ingredients.

Indications for which psychiatrists might be asked to authorize medical marijuana include pain, agitation in Alzheimer's disease, and PTSD. There is some evidence that marijuana is effective in treating neuropathic pain, but almost no evidence for Alzheimer's disease and PTSD. Given the burdensome side-effect profile of marijuana, medical marijuana should be reserved as an option of last resort.

Before recommending medical marijuana, consideration should be given to prescribing dronabinol, which has undergone rigorous clinical trials. Additionally, use of dronabinol (as opposed to authorizing the use of medical marijuana) circumvents problems of purity, concentration, composition, and route of administration. If clinicians feel that it is appropriate to recommend medical marijuana in crude form, they should do so in a responsible manner. Reasonable guidelines on the practice of authorizing medical marijuana include recommendations that physicians should establish and maintain a longitudinal therapeutic relationship, conduct a thorough history and physical examination, regularly review efficacy, and seek consultation from associates when appropriate (20).

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1. Two to three Board review-style questions with four to five answer choices.

2. Answers should be complete and include detailed explanations with references from pertinent peer-reviewed journals, textbooks, or reference manuals.

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August Deadlines

Fellowship/Award and Deadline	Organization	Brief Description	Eligibility	Contact	Website
Academy of Psychosomatic Medicine (APM) Trainee Travel Awards **Deadline:** August 1, 2014	Academy of Psychosomatic Medicine	To encourage Psychosomatic Medicine (PM) fellows, residents, and medical students to join APM, attend the annual meeting, and eventually become new leaders of the Academy, a limited number of monetary awards are given to help offset the cost of attending the annual meeting.	PM fellows, residents, and medical students	N/A	http://www.apm.org/awards/trainee-travel.shtml
Webb Fellowship Program **Deadline:** August 1, 2014	Academy of Psychosomatic Medicine	One-year appointment that fosters the career development and leadership potential of advanced psychiatry residents and PM fellows through mentorship, networking, sustained involvement, and affirmation and consolidation of professional identity.	PGY-3 or 4 PM fellow Recent graduates of PM fellowship (within 1 year of graduation)	N/A	http://www.apm.org/awards/webb-fship.shtml
PRITE and Child PRITE Fellowships **Deadline:** August 29, 2014	The American College of Psychiatrists	The PRITE (Psychiatry Resident In-Training Examination) Fellowship Selection Committee chooses PRITE Fellows to serve at least 1 year on the PRITE Editorial Board. They provide a resident perspective to the exam as they participate in the question writing process, developing an assigned number of questions and then editing and referencing exam items.	PRITE: PGY-2 or 3; Child PRITE: First-year child fellow	Kathy@ACPsych.org	http://www.acpsych.org/resident-fellowships/the-prite-fellowship-program/application-process

September Deadlines

Fellowship/Award and Deadline	Organization	Brief Description	Eligibility	Contact	Website
APA Resident-Fellow Member Trustee (RFMT) and Trustee-Elect (RFMTE) **Deadline:** September 1, 2014	American Psychiatric Association	Each year, an RFMTE is elected nationally by the membership and serves on the APA Board of Trustees for 1 year without a vote. At the end of that year, they advance to the Trustee position with voting privileges. These positions provide national leadership opportunities for RFMs. The Board is the governing body of the APA, and its primary function is to formulate and implement the policies of the APA.	APA RFM PGY-2 or 3	Chiharu Tobita ctobita@psych.org (703-907-8527)	http://www.psychiatry.org/learn/residents-fellows/leadership-opportunities
National Institute on Drug Abuse (NIDA)-American Academy of Child and Adolescent Psychiatry (AACAP) Resident Research Award in Substance Abuse and Addiction **Deadline:** September 20, 2014	NIDA & AACAP	Offers significant financial support for research in substance abuse in children and adolescents. Includes travel to AACAP's Annual Meeting and travel to the NIDA Clinical Trials Network's Steering Committee meeting. Awardee(s) will conduct a pilot/preliminary research study, present a scientific poster at the AACAP Annual Meeting, and develop a submission of a research manuscript for publication in a peer-reviewed journal.	PGY-2 or higher in psychiatry, child psychiatry, or triple Board program AACAP member	cjohnson@aacap.org	http://www.aacap.org/AACAP/Awards/Resident_and_ECP_Awards/NIDA_AACAP_Resident_Research_Award_in_Substance_Abuse_and_Addiction.aspx

Author Information for *The Residents' Journal* Submissions

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The Residents' Journal accepts manuscripts authored by medical students, resident physicians, and fellows; manuscripts authored by members of faculty cannot be accepted. To submit a manuscript, please visit http://mc.manuscriptcentral.com/appi-ajp, and select "Residents" in the manuscript type field.

1. **Commentary:** Generally includes descriptions of recent events, opinion pieces, or narratives. Limited to 500 words and five references.

2. **Treatment in Psychiatry:** This article type begins with a brief, common clinical vignette and involves a description of the evaluation and management of a clinical scenario that house officers frequently encounter. This article type should also include 2-4 multiple choice questions based on the article's content. Limited to 1,500 words, 15 references, and one figure.

3. **Clinical Case Conference:** A presentation and discussion of an unusual clinical event. Limited to 1,250 words, 10 references, and one figure.

4. **Original Research:** Reports of novel observations and research. Limited to 1,250 words, 10 references, and two figures.

5. **Review Article:** A clinically relevant review focused on educating the resident physician. Limited to 1,500 words, 20 references, and one figure.

6. **Letters to the Editor:** Limited to 250 words (including 3 references) and three authors. Comments on articles published in *The Residents' Journal* will be considered for publication if received within 1 month of publication of the original article.

7. **Book Review:** Limited to 500 words and 3 references.

Abstracts: Articles should not include an abstract.

Upcoming Themes

Please note that we will consider articles outside of the theme.

Addiction Psychiatry

If you have a submission related to this theme, contact the Section Editor, Juliet Muzere, D.O. (jmuzere@gmail.com).

Women's Health

If you have a submission related to this theme, contact the Section Editor, Kathleen Mary Patchan, M.D. (kpatchan@psych.umaryland.edu).

*If you are interested in serving as a **Guest Section Editor** for the *Residents' Journal*, please send your CV, and include your ideas for topics, to Misty Richards, M.D., M.S., Editor-in-Chief (mcrichards@mednet.ucla.edu).