Challenges in Pharmacologic Management of the Hospitalized Patient With Psychiatric Comorbidity

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BACKGROUND: Psychiatric comorbidity is common in the inpatient medical population. Hospitalists are frequently faced with decisions regarding the psychopharmacologic management of medically ill patients, yet receive limited psychiatric training. This review aims to assist the hospitalist in making an informed decision about the continuation of home psychotropic medications in the medically ill patient.

METHODS: A PubMed literature review was performed to obtain information on the effects of psychotropic medication discontinuation. In addition, the literature was reviewed regarding the potential challenges of psychotropic medication continuation.

RESULTS: A growing number of studies demonstrate high rates of relapse when medications are discontinued in patients suffering from mood disorders, schizophrenia, and anxiety disorders. Abrupt cessation of psychotropics is especially dangerous, leading to a greater chance of destabilization. Discontinuation syndromes, with prominent physical symptoms, may also result from sudden psychotropic cessation. Conversely, continuing home psychotropic medication may cause adverse effects due to drug-drug interactions or changing pharmacokinetics.

CONCLUSIONS: This review examines the risks of psychotropic discontinuation as well as the challenges of psychotropic continuation in the medically ill patient. When making complex psychopharmacologic decisions, hospitalists should employ all available resources, including pharmacists and consult-liaison psychiatrists. Ultimately, physicians and patients must make collaborative decisions, weighing the risks and benefits of psychiatric medications.

Mental illness is highly prevalent, with approximately 30% of the US population meeting criteria for at least 1 disorder. In the medically ill population, psychiatric disease is even more common; a 2005 survey showed that half of all patients visiting primary care physicians met criteria for a mental disorder. Conversely, those with serious mental illness suffer greater medical morbidity than the general population, with higher rates of obesity, diabetes, metabolic syndrome, cardiovascular disease, chronic obstructive pulmonary disease, human immunodeficiency virus, viral hepatitis, and tuberculosis. When acute medical problems arise, those with mental illness endure longer hospitalizations; the presence of a psychiatric disturbance in the general medical setting has been shown to be a robust predictor of increased hospital length of stay.

Because of the strong correlation between medical and mental illness, hospitalists will care for patients with psychiatric disorders. Despite this, internists generally receive a paucity of formal training in the treatment of mental disturbances. One survey of university-affiliated internal medicine residencies revealed that only 10% of programs offered “any kind of modest curriculum in psychiatric education.” Regardless of this lack of preparation, hospitalists are called upon at each admission to make decisions that affect the psychiatric treatment of patients on psychotropic medication; namely, they must decide whether to continue or discontinue psychiatric medications. Many physicians reflexively discontinue a patient’s chronic medications upon admission to the hospital; one study reported an adjusted odds ratio of between 1.18 and 1.86 for stopping a medication prescribed for a chronic condition.

This review aims to assist the hospitalist in making an informed decision about the continuation of psychotropic medications in the medically ill patient. First, it examines the risks of stopping psychotropic medication, including psychiatric decompensation and discontinuation syndromes. It also explores the challenges of medication continuation in the context of changing pharmacokinetics and emerging side effects. Ultimately, physicians and patients must make collaborative decisions, weighing the risk of medication interactions against the potential adverse effects of psychiatric decompensation.

DISCONTINUATION
Decompensation of Mental Health
Approximately 10% to 15% of patients hospitalized for medical illness require reduction or discontinuation
of psychotropic medications because they may be contributing to the clinical presentation. The rate and method of drug discontinuation can affect the course of major psychiatric disorders. A growing number of studies demonstrate high rates of relapse when medications are discontinued in patients suffering from mood disorders, schizophrenia, and anxiety disorders. Abrupt cessation of psychotropics is especially dangerous, leading to a greater chance of destabilization than if medications are tapered. Episodes of active illness even appear to occur more frequently with sudden psychotropic cessation than they would in the natural course of untreated disease. This is true for several classes of psychotropics, including antidepressants, mood stabilizers, and antipsychotics. For example, in a study of pregnant women who suddenly stopped their psychotropic medication (both antidepressants and benzodiazepines), nearly one-third experienced suicidal ideation. Depression and suicidality have also been documented in bipolar patients who were abruptly taken off of lithium. More commonly, rapid lithium discontinuation in bipolar patients causes mania, with illness relapse as soon as 4 days after cessation. Additionally, abrupt discontinuation of antipsychotics in patients with schizophrenia leads to early, and often severe, psychosis. One study found a relapse rate of 50% within 30 weeks of sudden oral neuroleptic cessation. Furthermore, restarting medications, even at the previous effective dose, may not return the patient to their prior baseline. Psychiatric decompensation in the hospitalized patient can worsen medical outcomes, with decreased adherence to treatment plans. In extreme circumstances, patients may be at risk of self-harm or suicide.

**DRUG-SPECIFIC DISCONTINUATION SYNDROMES**

**Antidepressants**

Discontinuation of medications presents additional problems, and sudden cessation of psychotropic medications can lead to uncomfortable or even dangerous symptoms. For example, the serotonin discontinuation syndrome has been well documented. Chronic use of serotonin re-uptake inhibitors (generally greater than 6 to 8 weeks) leads to downregulation of postsynaptic serotonin receptors. When selective serotonin re-uptake inhibitors (SSRIs) or serotonin-norepinephrine re-uptake inhibitors are abruptly stopped, the brain experiences a relative decline in serotonin. Symptoms include a flu-like illness, nausea, imbalance, insomnia, sensory disturbances, and dysphoria. Onset may be within hours of missing a dose, but typically occurs within 3 days of medication discontinuation. The syndrome is more likely to occur with cessation of medications of shorter half-life and less likely to occur with medications with a long half-life, such as fluoxetine (Table 1). The symptoms can be ameliorated with a gradual tapering or reintroduction of the antidepressant. Untreated symptoms resolve in 1 to 2 weeks. Although the syndrome in isolation is not life-threatening, a number of the symptoms can complicate medical illness and muddle diagnosis of other diseases.

Older antidepressants, including the tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs), have serotonergic effects, and thus discontinuation may cause the symptoms described above. However, these agents also have effects on other neurotransmitters. The TCAs block muscarinic cholinergic receptors, leading to upregulation. Abrupt cessation can lead to cholinergic rebound, with parkinsonism and mania emerging. Multiple case reports document improvement in these symptoms with an anticholinergic agent, such as benztropine. MAOIs lead to changes in α-2 adrenergic and dopaminergic receptors. Sudden discontinuation has been associated with agitation, delirium, and psychosis; 1 case report even documents catatonia associated with autonomic instability.

In addition, sudden discontinuation of antidepressants (including the SSRIs) may provoke mania or hypomania in some patients, regardless of whether they have experienced previous spontaneous manic episodes.

**Neuroleptics**

Data for an antipsychotic withdrawal syndrome are less convincing than those for serotonergic agents. However, certain symptoms have been associated with abrupt neuroleptic discontinuation. Most frequently, gastrointestinal distress and diaphoresis are described. Anxiety, agitation, and insomnia are also common. These symptoms are thought to be associated with cholinergic rebound, mediated by direct effects of neuroleptics on muscarinic receptors or indirectly through dopamine receptor blockade and the dopamine-cholinergic balance. Symptoms may be more severe when antimuscarinic, antiparkinsonism drugs are simultaneously stopped. Some authors argue that the timing of symptom onset can differentiate antipsychotic withdrawal from illness relapse, with discontinuation syndrome occurring within the first 7 days of medication cessation.
Additionally, abrupt cessation of antipsychotics may be associated with rapid-onset psychosis. The data are strongest for clozapine discontinuation, where overall incidence is approximately 20%. This is hypothesized to be mediated by dopamine receptor upregulation and subsequent hypersensitivity to endogenous dopamine. The emerging psychosis is purportedly distinct from the underlying illness. Episodes have been described in patients on chronic metoclopramide who have no prior psychiatric history, as well as in patients with bipolar disorder without psychosis prior to neuroleptic discontinuation. 21

Movement disorders may emerge during neuroleptic discontinuation. Both parkinsonism and dyskinesias have been described. In some patients, dyskinesias resolve within weeks of drug discontinuation; however, others experience permanent symptoms, termed covert dyskinesia. 22 In rare circumstances, dyskinesias may affect the respiratory muscles, causing distress. Several case reports of withdrawal-emergent respiratory dyskinesia have been reported following risperidone cessation. 23–25 Additionally, several case reports have described catatonia occurring after abrupt discontinuation of clozapine. In all cases, symptoms promptly resolved with reinitiation of clozapine. 26

Neuroleptic malignant syndrome (NMS) is a rare but potentially fatal complication of antipsychotic administration. Symptoms include fever, rigidity, autonomic instability, and mental status changes. 27 Though NMS is hypothesized to occur due to dopamine receptor blockade, rare cases of NMS have also been reported with abrupt cessation of neuroleptics. Of the 8 case reports in the literature, 1 resulted in death. 22,28

Mood Stabilizers
Though some of the atypical antipsychotics are used to treat bipolar disorder, mood stabilizers are the mainstay of pharmacotherapy. The most commonly used mood stabilizers are lithium, valproic acid, lamotrigine, topirimate, carbamezapine, and oxcarbaze- pine. When mood stabilizers are discontinued, patients are at risk of psychiatric relapse, as documented above. However, withdrawal symptoms have not been commonly documented upon abrupt discontinuation of lithium or the anticonvulsants used to treat bipolar disorder. 29,30

Benzodiazepines
Benzodiazepines are widely prescribed for insomnia and anxiety. Chronic legal use of benzodiazepines is approximately 2% in the general population. 31 Like ethanol, benzodiazepines bind nonselectively to the GABA-A receptor, resulting in downregulation of GABA receptors and compensatory increased N-methyl-D-aspartate transmission. Sudden discontinuation of benzodiazepines results in a syndrome that mirrors that of alcohol withdrawal. Symptoms range from mild (tremor, insomnia, and anxiety) to life-threatening (seizures, delirium, and autonomic instability). Serious withdrawal is more likely with substances of shorter half-life and with higher chronic doses. Onset often occurs between 2 and 10 days after discontinuation, depending on the half-life of the benzodiazepine. 32 Other rare serious reactions have been documented following abrupt benzodiazepine cessation, including NMS and catatonia. 30

CONTINUATION
Reflexive discontinuation of psychotropic medications can clearly lead to adverse outcomes. However, when hospitalists decide to continue a patient’s psychotropic medications, they must also be cognizant of potential complications. Modifications may be necessary because of hepatic, renal, or cardiac disease. In addition, physicians need to be aware of drug-drug interactions. Pharmacotherapy for medically ill elderly patients may require dose modifications to account for an increased lipophilic volume of distribution and a decreased rate of metabolism. 33 Finally, pregnancy can present additional challenges regarding dose modifications and teratogenicity.

On the other hand, hospitalists must be aware that continuing a patient’s psychotropic medication may not be the cause of new psychiatric symptoms. Drugs prescribed for medical disorders (eg, corticosteroids) often cause psychiatric symptoms. In addition, psychiatric symptoms may emerge at times of nonpsychotropic medication withdrawal or due to nonpsychotropic drug-drug interactions. 4 Groups of medications commonly associated with psychiatric disturbances include analgesics, sedatives, anesthetics, anticonvulsants, and anticholinergics.

PHARMACOKINETICS: PSYCHOTROPIC TOXICITY
Medical illness alters the body’s steady state, and renal or hepatic metabolism may be impaired when a patient requires hospitalization. Additionally, new medications may increase the effects of psychotropics, whether by intrinsic augmentation of effect or decreased psychotropic clearance. Ultimately, these changes can lead to psychotrophic toxicity.

Specific toxicities merit discussion. First, serotonin syndrome is a potentially fatal condition. The majority of cases occur with synergistic serotonergic medication administration, though there are case reports of the syndrome occurring with addition of inhibitors of cytochrome P450 2D6 and/or 3A4 to SSRIs. A large number of medications from different classes have been indicated (Table 2). 34 Symptoms generally occur within 24 hours of medication administration and include mental status changes, autonomic instability, and neuromuscular hyperactivity. When serotonin syndrome is suspected, the offending agent should be discontinued immediately. There is no definitive treatment, though supportive care can be lifesaving. 34
TABLE 2. Medications That May Contribute to Serotonin Syndrome

<table>
<thead>
<tr>
<th>Amphetamines and Derivatives</th>
<th>Antidepressants and Mood Stabilizers</th>
<th>Antimigraine Drugs</th>
<th>Analgesics</th>
<th>Antimetics</th>
<th>Miscellaneous</th>
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<tr>
<td>MDMA</td>
<td>Buspirone</td>
<td>Ergot alkaloids</td>
<td>Cyclobenzaprine</td>
<td>Metoclopramide</td>
<td>Cocaine</td>
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<td>Dextroamphetamine</td>
<td>Carbamazepine</td>
<td>Triptans</td>
<td>Fentanyl</td>
<td>Ondansetron</td>
<td>Dexethromorphan</td>
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<td>Methamphetamine</td>
<td>Lithium</td>
<td>Lidocaine</td>
<td>Meperidine</td>
<td>Linezolid</td>
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<td>Sibutramine</td>
<td>MAOIs</td>
<td>Tramadol</td>
<td>Tramadol</td>
<td>5-hydroxytryptophan</td>
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<td></td>
<td>SSRIs</td>
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<td>SNRIs</td>
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<td>Serotonin 2A receptor blockers (eg,</td>
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<td>trazodone)</td>
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<td></td>
<td>St. John’s Wort</td>
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<td></td>
<td>TCAs</td>
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<td>Valproic Acid</td>
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NOTE: Abbreviations: MAOI, monoamine oxidase inhibitors; MDMA, 3,4-methylenedioxymethamphetamine; SNRIs, serotonin-norepinephrine re-uptake inhibitors; SSRIs, selective serotonin re-uptake inhibitors; TCAs, tricyclic antidepressants.

In addition to serotonin syndrome, hypertensive emergency may occur due to drug interactions with MAOIs. MAOIs inhibit the enzyme monoamine oxidase, resulting in elevated levels of serotonin, histamine, and catecholamines in the blood. Co-administration of MAOIs and sympathomimetic agents (such as cough suppressants and analgesics) may dangerously increase adrenergic stimulation, elevating blood pressure to the point of end-organ damage. Please see Table 3 for a full list of drugs indicated in MAOI-associated hypertensive crisis.35 To ensure safety, it is recommended that MAOIs be discontinued for 14 days prior to introducing medications with sympathomimetic properties, and vice versa. Because of its longer half-life, a 5-week washout period is recommended for fluoxetine.35

Lithium toxicity may result from changing patient pharmacokinetics. Lithium is almost entirely renally excreted, and acute kidney injury may precipitously raise serum levels. Within the renal collecting system, lithium is handled similarly to sodium, with 80% reabsorbed from the proximal tubule to the collecting duct. Thus, factors that decrease glomerular filtration rate (GFR) and increase proximal tubule absorption will increase serum lithium levels. For example, decreased effective arterial volume (due to dehydration, cirrhosis, nephrotic syndrome, or heart failure) may elevate lithium levels. Additionally, medications that decrease GFR may increase lithium reabsorption. These include nonsteroidal anti-inflammatory drugs, angiotensin-converting enzyme inhibitors, and thiazide diuretics. Because of lithium’s narrow therapeutic index, small elevations in serum levels can lead to toxicity. Severity of intoxication correlates with serum concentration. Symptoms range from lethargy, weakness, tremor, ataxia, and gastrointestinal distress to coma, seizures, renal failure, and death. Toxicity is also associated with electrocardiograph (ECG) changes, including ST-segment depression and T-wave inversion in the lateral precordial leads. Sinus node dysfunction can also occur. Definitive treatment for lithium toxicity is hemodialysis.36

Though the therapeutic index is much wider for valproic acid than for lithium, valproate toxicity may also occur in the medically ill patient with previously stable serum levels. Valproic acid is highly protein-bound at therapeutic levels, and is metabolized largely through hepatic glucuronidation. Initiation of medications that compete for protein-binding sites, including aspirin, has led to valproate toxicity. Moreover, acute liver failure or addition of drugs that compete with hepatic microsomal enzymes may lead to decreased excretion of valproic acid. Poisoning may result in central nervous system (CNS) and respiratory depression, hypotension, cerebral edema, and pancreatitis. True hepatotoxicity is rare, though hyperammonemia is widely documented. Thrombocytopenia is the most common hematologic abnormality associated with overdose. However, thrombocytopenia may also occur without complication in patients on stable therapeutic doses. Treatment is largely supportive, though hemoperfusion and hemodialysis may be used when serum levels are >300 μg/mL, as only 35% of the drug is protein-bound at that level. Naloxone has been shown in case reports to reverse valproic acid-induced coma, and L-carnitine has been increasingly recommended for hyperammonemia.37,38

PHARMACOKINETICS: DRUG-DRUG INTERACTIONS

As discussed above, the addition of a new medication can increase previously stable levels of psychotropic drugs, leading to toxicity. Conversely, mental health...
medications can alter the expected metabolism of a drug being used to treat acute medical illness. Many psychotropics are metabolized via the cytochrome p450 enzyme, particularly the SSRIs (Table 4). A number of antimicrobial and antipathetic medications are also cleared via this route, leading to potential toxic or subtherapeutic levels when drug-drug interactions occur.

PSYCHOTROPIC ADVERSE EFFECTS

Psychotropic medications may also cause side effects that contribute to the clinical presentation, requiring ongoing monitoring, a dose reduction, or psychotropic discontinuation. Potential adverse effects that commonly impact psychopharmacologic management include anticholinergic side effects, cardiac effects, and sedation.

ANTICHOLINERGIC EFFECTS AND TOXICITY

Newly emerging anticholinergic effects may be particularly troubling. Dry mouth may cause swallowing difficulty and aspiration. Pupillary dilatation and dry eyes can increase risk of falls. Constipation may evolve into fecal impaction, and urinary retention can contribute to increased catheter use and infection. CNS effects are perhaps the most serious, ranging from drowsiness and memory impairment to frank delirium.

Many psychotropic drugs are anti cholinergic. Among the antidepressants, the TCAs and paroxetine have the highest anticholinergic activity. Anticholinergic effects have also been reported with the low potency first generation neuroleptics and with the atypical antipsychotics olanzapine and clozapine. Additionally, medications used to treat the extrapyramidal symptoms associated with antipsychotics (such as benzotropine and diphenhydramine) are strongly anticholinergic. Patients without previous overt anticholinergic symptoms from these medications may experience adverse effects when hospitalized. Medical illness or new medications may alter psychotropic drug metabolism and elimination, leading to accumulation of their anticholinergic effects. Many medications used in the hospital also have intrinsic anticholinergic activity. These include some antiemetics, antispasmodics, antiarrhythmics, and histamine H2 receptor blockers. Elderly patients are particularly prone to anticholinergic effects due to age-related deficits in cholinergic transmission.

QTc PROLONGATION

QTc prolongation is a potentially lethal side effect of certain medications. Prolonged QTc increases the risk of cardiac mortality and sudden death, presumably related to onset of torsades de pointe. Certain antidepressants have consistently been associated with QTc prolongation, particularly the TCAs. In addition, the US Food and Drug Administration recently issued the recommendation that the SSRI citalopram not be used at doses >40 mg (and 20 mg in those with hepatic impairment or age >60 years) due to results of a randomized controlled trial that showed a dose-response increase in QTc. Antipsychotic medications have also been shown to increase QTc, with the greatest evidence for thioridazine and the first-generation, low-potency neuroleptics. Haloperidol (particularly the intravenous formulation) has also been linked to both long QTc and torsades, though data may be confounded by the degree of medical illness of patients receiving the medication. Of the atypicals, ziprasidone causes the greatest QTc prolongation. However, a large retrospective cohort study showed similar risk increase of sudden cardiac death (2-fold) among all antipsychotics (including typicals and atypicals) when examined individually.

Additional risk factors for QTc prolongation abound in the hospitalized patient. These include many medical problems, including electrolyte abnormalities, heart conditions, renal and hepatic dysfunction, and CNS injury. Hospitalized patients are also exposed to the cumulative effects of medications that increase duration of QTc, such as class I and class III antiarrhythmics. Additionally, certain antimicrobials, including macrolide antibiotics and antifungals, have been associated with QTc prolongation via pharmokinetic interactions.

Because of this, QTc should be measured upon admission in patients on stable doses of psychotropics that predispose to prolongation. Addition of other medications known to contribute to increased QTc should prompt further ECGs. Electrolytes, particularly potassium and magnesium, should be aggressively repleted. When QTc extends beyond 500 ms, consideration should be given to discontinuing or changing medications that can contribute to QTc prolongation (whether psychotropics or drugs used to treat acute medical problems).
SEDATION

Sedation is another potential side effect of psychotropic medications. Although sedation is beneficial for agitation and anxiety, sedated patients may be unable to participate in treatment. They are also at greater risk of aspiration and falls.

Antipsychotics cause sedation through antagonism of α1 adrenergic and H1 histaminergic receptors. Effects are most pronounced with the low-potency, first-generation antipsychotics and the atypicals quetiapine and clozapine. Some antidepressants, including the TCAs and mirtazapine, also cause somnolence by histamine H1-receptor antagonism. If a patient has been psychiatrically stable on a particular antipsychotic or antidepressant, but has psychotropic-induced sedation that interferes with treatment, hospitalists may want to consider temporarily decreasing the dose.

Benzodiazepines induce sedation by increasing γ-aminobutyric acid-ergic transmission. There is significant overlap between anxiolytic and sedating doses of benzodiazepines. The amount of sedation is related to dose, speed of absorption, and onset of CNS penetration. Thus, sedation may be minimized by using a lower dose or switching to an equivalent dose of a slower-onset benzodiazepine.45,46

CONCLUSION

The decision to continue or discontinue psychotropic medications is often challenging. It requires the hospitalist to carefully weigh the risks and benefits of the ongoing treatment versus discontinuation, while also considering the patient’s preference whenever possible. Sudden cessation of psychotropics can lead to a number of unwanted complications, from mild withdrawal to life-threatening autonomous instability and psychiatric decompensation. Yet psychotropic continuation can also lead to unwanted drug-drug interactions and newly emergent side effects.

To improve patient safety and outcomes, hospitalists must take a cautious and well-thought-out approach to treating patients on psychotropic drugs. Reflexive cessation of home medications must be avoided. If hepatic or renal insufficiency develops, medication doses may need to be adjusted. When available, drug levels should guide dose adjustments. If side effects occur, the patient’s medication list should be carefully reviewed for potential drug-drug interactions. Maintaining mental health may mean substituting another drug for one that interferes with home psychotropic medications. Psychotropic doses may also be minimized to decrease side effects. When a psychotropic must be discontinued, tapering is recommended over an abrupt discontinuation, except in the case of an acute toxicity. Moreover, cross-titration to another effective agent may prevent psychiatric decompensation.

Additionally, hospitalists should use all available resources when deciding on a patient’s psychotropic regimen. Mobile devices and online resources can assist with pharmacokinetics. Pharmacists can help with more complex questions or potential drug substitutions. Consultation-liaison psychiatrists can be a valuable resource in ensuring the safety and stability of a patient with psychiatric comorbidity within the medical environment. The consultant may assist by assessing a patient’s current psychiatric state and recommending psychotropic medication changes when needed.

Disclosure: Nothing to report.

References


