Ms. A, age 45, is hospitalized for abdominal pain. She is noted to have hiccups, the onset of which she reports was >1 month ago and did not have a clear precipitant. Abdominal and head imaging return no acute findings, and data from a serum electrolyte test, hepatic function test, and thyroid function test are within normal limits. The medical team notices that Ms. A’s speech is pressured, she hardly sleeps, and she appears animated, full of ideas and energy.

Ms. A has a history of bipolar I disorder, hypertension, hyperlipidemia, gastroesophageal reflux disease, and hypothyroidism. Her present medications include hydrochlorothiazide 25 mg/d; levothyroxine 25 mcg/d; omeprazole 20 mg/d; and lovastatin 20 mg/d. She states that she was remotely treated for bipolar disorder, but she was cured by a shamanic healer, and therefore no longer needs treatment.

Approximately 35% of adults in the United States age 60 to 79 reported taking ≥5 prescription medications in 2016, compared to 15% of adults age 40 to 59.1 In a study of 372 patients with advanced, life-limiting illness, Schenker et al2 found that those who took multiple medications (mean: 11.6 medications) had a lower quality of life and worse symptoms. Optimizing medications to patients’ specific needs and diagnoses in order to reduce pill burden can be a favorable intervention. In addition, some patients—approximately 30% of those with schizophrenia and 20% of those with bipolar disorder—may not have insight into their mental illness as they do with their medical conditions, and may be more accepting of treatment for the latter.3 Dual-indication prescribing may be a useful way to decrease polypharmacy, reduce potential drug-drug interactions (DDIs), increase patient acceptance and adherence, and improve a patient’s overall health.

Multiple uses for antidepressants and antipsychotics
One of the first medications discovered to have antidepressant effects was iproniazid, a monoamine oxidase inhibitor (MAOI)

Practice Points

- Nonpsychiatric indications for antidepressants and antipsychotics are predominantly off-label use.
- Conduct a judicious evaluation of the evidence, including the population studied, dosing, and limitations, to help weigh the risks vs benefits for dual use of any medication.
- For patients with limited insight into their psychiatric illness, promoting the dual use of an antidepressant or antipsychotic may increase the patient’s buy-in and promote disease state management.
Initially used to treat tuberculosis, since then, numerous classes of antidepressant medications have been developed that capitalize on monoamine reuptake through several different mechanisms of action. These drugs can be grouped into subclasses that include selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, tricyclic antidepressants, MAOIs, and others. True to their roots in iproniazid, these medications can have a myriad of effects not limited to mental health and can therefore be beneficial for a variety of comorbid conditions.

As was the case with antidepressants, the first medication approved in the antipsychotic class, chlorpromazine, was serendipitously discovered to treat psychosis and agitation after being approved and used to treat presurgical apprehension. The term “antipsychotic” is almost a misnomer given these agents’ broad pharmacology profiles and impact on various mental illnesses, including bipolar disorder, depressive disorders, anxiety disorders, and many other mental conditions.

First-generation antipsychotics (FGAs) were the first to enter the market; they work primarily by blocking dopamine-2 (D2) receptors. Second-generation antipsychotics have less movement-based adverse effects than FGAs by having higher affinity for serotonin 5-HT2A receptors than for D2 receptors. However, they tend to carry a higher risk for weight gain and metabolic syndrome.

Antidepressants and antipsychotics are widely utilized in psychiatry. Many have been found to have additional uses beyond their original FDA-approved indication and can therefore be beneficial for a variety of comorbid conditions.

One limitation of using psychiatric medications for nonpsychiatric indications is that different doses of antidepressants and antipsychotics are typically targeted for different indications based on receptor binding affinity. A common example of this is trazodone, where doses below 100 mg are used as needed for insomnia, but higher doses ranging from 200 to 600 mg/d are used for depression. Another important
Potential drug-drug interactions are an important concern when considering using psychotropics for nonpsychiatric indications.

consideration is DDIs. For example, the possibility of adding an agent such as fluoxetine to a complex pain regimen for fibromyalgia could impact the clearance of other agents that are cytochrome P450 (CYP) 2D6 substrates due to fluoxetine’s potent inhibition of the enzyme.6,7 Table 16-51 (page 35), Table 26-60 (page 37), Table 36-107 (page 38), and Table 46-108-123 (page 39) provide information on select antidepressants, while Table 56-124-140 (page 40) and Table 66-41-171 (page 41) provide information on select antipsychotics. Each table lists psychiatric and nonpsychiatric indications for the respective medications, including both FDA-approved (where applicable) and common off-label uses. Most of the indications listed are for adult use only, unless otherwise noted.

CASE CONTINUED

After reviewing Ms. A’s medical history, the treatment team initiates chlorpromazine, 25 mg 3 times a day, for intractable hiccups, and increases the dosage to 50 mg 3 times a day after 3 days. Chlorpromazine is FDA-approved for treating bipolar mania, and also for treating intractable hiccups. Shortly thereafter, Ms. A’s hiccups subside, she sleeps for longer periods, and her manic symptoms resolve.

References
13. Montgomery SA, Kasper S, Stein DJ, et al. Citalopram 20 mg, 40 mg and 60 mg are all effective and well tolerated compared with placebo in obsessive-compulsive disorder. Int Clin Psychopharmacol. 2001;16(2):75-86.
20. Safariannejad MR, Hosseni SY. Safety and efficacy of citalopram in the treatment of premature ejaculation: a double-blind...
Clinical Point

Venlafaxine has been used off-label to treat migraines, diabetic neuropathy, and hot flashes in patients with breast cancer.

Table 2
Serotonin-norepinephrine reuptake inhibitors

<table>
<thead>
<tr>
<th>Medication</th>
<th>Psychiatric indication(s)</th>
<th>Nonpsychiatric indication(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Desvenlafaxine</td>
<td>FDA-approved: MDD,62</td>
<td>Off-label: Vasomotor symptoms of menopause,53</td>
</tr>
<tr>
<td>Duloxetine</td>
<td>FDA-approved: GAD,54, MDD</td>
<td>Off-label: Fibromyalgia,54 muscular skeletal pain (chronic),54 diabetic neuropathy,54</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>FDA-approved: GAD,57, MDD,57, PD,57 SAD,57</td>
<td>Off-label: Migraine prophylaxis (episodic),65,66 diabetic neuropathy,65 hot flashes (history of breast cancer),65 peripheral neuropathy (due to chemotherapy),66</td>
</tr>
</tbody>
</table>

ADHD: attention-deficit/hyperactivity disorder; GAD: generalized anxiety disorder; MDD: major depressive disorder; OCD: obsessive-compulsive disorder; PD: panic disorder; PMDD: premenstrual dysphoric disorder; PTSD: posttraumatic stress disorder; SAD: social anxiety disorder
Table 3

Tricyclic antidepressants

<table>
<thead>
<tr>
<th>Medication</th>
<th>Psychiatric indication(s)</th>
<th>Nonpsychiatric indication(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amitriptyline</td>
<td>FDA-approved: MDD(^9), Off-label: None</td>
<td>Off-label: Fibromyalgia,(^{70}) functional dyspepsia,(^{71}) interstitial cystitis,(^{72,73}) IBS,(^{74}) migraine prophylaxis,(^{75,76}) neuropathic pain (chronic),(^{77,78}) postherpetic neuralgia,(^{79,80}) sialorrhea (clozapine-induced)(^{81})</td>
</tr>
<tr>
<td>Amoxapine</td>
<td>FDA-approved: MDD(^92), Off-label: None</td>
<td>Off-label: IBS(^93)</td>
</tr>
<tr>
<td>Clomipramine</td>
<td>FDA-approved: OCD(^94), Off-label: MDD, PD(^96)</td>
<td>Off-label: Ejaculatory disorders(^{85,86})</td>
</tr>
<tr>
<td>Desipramine</td>
<td>FDA-approved: MDD(^99), Off-label: None</td>
<td>Off-label: Diabetic neuropathy,(^{89}) IBS,(^{91}) postherpetic neuralgia(^92)</td>
</tr>
<tr>
<td>Doxepin</td>
<td>FDA-approved: MDD(^99), AUD,(^93) GAD,(^93) insomnia(^93), Off-label: None</td>
<td>Off-label: Chronic idiopathic urticaria(^94)</td>
</tr>
<tr>
<td>Imipramine</td>
<td>FDA-approved: MDD(^95), Off-label: BN, PD,(^97) BED(^98)</td>
<td>FDA-approved: Childhood enuresis (age ≥6)(^99), Off-label: Neuropathic pain,(^99) urinary incontinence,(^100) diabetic neuropathy(^92)</td>
</tr>
<tr>
<td>Nortriptyline</td>
<td>FDA-approved: MDD(^101), Off-label: ADHD (pediatric)(^102)</td>
<td>Off-label: Lower back pain (chronic),(^103) myofascial pain,(^103) postherpetic neuralgia,(^105) mortality secondary to stroke,(^106) neurogenic bladder(^107)</td>
</tr>
</tbody>
</table>

AdHD: attention-deficit/hyperactivity disorder; AUD: alcohol use disorder; BED: binge eating disorder; BN: bulimia nervosa; GAD: generalized anxiety disorder; IBS: irritable bowel syndrome; MDD: major depressive disorder; OCD: obsessive-compulsive disorder; PD: panic disorder

References

### Clinical Point

Mirtazapine has been used off-label to treat panic disorder, PTSD, insomnia, and obstructive sleep apnea.

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**Table 4**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Psychiatric indication(s)</th>
<th>Nonpsychiatric indication(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bupropion</td>
<td><strong>FDA-approved:</strong> MDD, smoking cessation&lt;sup&gt;108&lt;/sup&gt;</td>
<td><strong>Off-label:</strong> SSRI-induced sexual dysfunction&lt;sup&gt;111,112&lt;/sup&gt;</td>
</tr>
<tr>
<td>Mirtazapine</td>
<td><strong>FDA-approved:</strong> MDD&lt;sup&gt;113&lt;/sup&gt;</td>
<td><strong>Off-label:</strong> Tension-type headache prophylaxis, obstructive sleep apnea&lt;sup&gt;119&lt;/sup&gt;</td>
</tr>
<tr>
<td>Trazodone</td>
<td><strong>FDA-approved:</strong> MDD&lt;sup&gt;120&lt;/sup&gt;</td>
<td><strong>Off-label:</strong> Insomnia&lt;sup&gt;123&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

ADHD: attention-deficit/hyperactivity disorder; BPSD: behavioral and psychological symptoms of dementia; MDD: major depressive disorder; PD: panic disorder; PTSD: posttraumatic stress disorder; SSRI: selective serotonin reuptake inhibitor

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First-generation antipsychotics

<table>
<thead>
<tr>
<th>Medication</th>
<th>Psychiatric indication(s)</th>
<th>Nonpsychiatric indication(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorpromazine</td>
<td>FDA-approved: Bipolar mania, 124 Schizophrenia, 124 presurgical apprehension 144</td>
<td>FDA-approved: Intractable hiccups, 124 nausea/vomiting (acute), 124 tetanus (adjunct), 124 acute intermittent porphyria 124 Off-label: Migraine treatment (severe), 125,126 nausea/vomiting in pregnancy 127</td>
</tr>
<tr>
<td>Fluphenazine</td>
<td>FDA-approved: Psychotic disorders 128 Off-label: None</td>
<td>Off-label: Chorea of Huntington’s disease 129</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>FDA-approved: Schizophrenia, 130 Tourette syndrome 130 Off-label: BPSD, 131 bipolar mania, 132 hyperactive delirium 133</td>
<td>Off-label: Nausea/vomiting due to chemotherapy, 124 terminal illness, or postoperative prevention in moderate- to high-risk patients 135</td>
</tr>
<tr>
<td>Perphenazine</td>
<td>FDA-approved: Schizophrenia 136 Off-label: None</td>
<td>FDA-approved: Nausea/vomiting 136 Off-label: None</td>
</tr>
<tr>
<td>Prochlorperazine</td>
<td>FDA-approved: Schizophrenia 137 Off-label: None</td>
<td>FDA-approved: Nausea/vomiting (acute) 137 Off-label: Chemotherapy-induced nausea/vomiting, 138 postoperative nausea/vomiting prophylaxis or treatment, 139 pregnancy-related nausea/vomiting 140</td>
</tr>
</tbody>
</table>

BPSD: behavioral and psychological symptoms of dementia

Clinical Point

Several first-generation antipsychotics are FDA-approved for treating nausea/vomiting

<table>
<thead>
<tr>
<th>Medication</th>
<th>Psychiatric indication(s)</th>
<th>Nonpsychiatric indication(s)</th>
</tr>
</thead>
</table>
| Aripiprazole  | **FDA-approved:** Bipolar disorder (mania/mixed), 141 MDD, 144 schizophrenia, 141 Tourette syndrome 141  
**Off-label:** BPDS, 142 delusional disorder, 143 delusional infestation, 144 OCD 145 | **Off-label:** Chorea of Huntington’s disease, 146 antipsychotic-induced hyperprolactinemia 147 |
| Olanzapine    | **FDA-approved:** Bipolar disorder (mania/mixed), 148 MDD, 148 schizophrenia 148  
**Off-label:** AN, 148 bipolar II disorder (hypomania), 150 hyperactive delirium, 151 delusional infestation, 152 MDD with psychotic features 153 154 | **Off-label:** Chemotherapy-induced acute and delayed nausea/vomiting prophylaxis (high-emetic risk), 155 chorea of Huntington’s disease 156 |
| Quetiapine    | **FDA-approved:** Bipolar disorder (mania/mixed/depression), 155 MDD, 157 schizophrenia 157  
**Off-label:** GAD, 158 OCD, 159 PTSD, 160 Parkinson disease psychosis 161 | **Off-label:** Insomnia 162 |
| Risperidone   | **FDA-approved:** Bipolar I disorder (mania/mixed), 163 schizophrenia 163  
**Off-label:** BPDS, 164, 165 bipolar hypomania, 166 delusional infestation, 167 MDD, 148 OCD, 149 Tourette syndrome 170 | **Off-label:** Chorea of Huntington’s disease 171 |

AN: anorexia nervosa; BPDS: behavioral and psychological symptoms of dementia; GAD: generalized anxiety disorder; MDD: major depressive disorder; OCD: obsessive-compulsive disorder; PTSD: posttraumatic stress disorder

Clinical Point

Several second-generation antipsychotics have been used off-label to treat chorea of Huntington’s disease.
Clinical Point

Promoting the dual use of an antidepressant or antipsychotic may increase the patient’s acceptance of the medication.