

Nonpsychiatric indications for antidepressants and antipsychotics

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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

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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.

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Table 1

Selective serotonin reuptake inhibitors

Medication	Psychiatric indication(s)	Nonpsychiatric indication(s)
Citalopram	<i>FDA-approved:</i> MDD ⁹ <i>Off-label:</i> BPSD, ⁹ BED, ¹⁰ GAD, ^{11,12} OCD, ¹³ PD, ^{14,15} PMDD, ¹⁶ PTSD, ¹⁷ SAD, ¹⁸ AUD ¹⁹	<i>Off-label:</i> Premature ejaculation, ²⁰ vasomotor symptoms of menopause ²¹
Escitalopram	<i>FDA-approved:</i> MDD, ²² GAD ²² <i>Off-label:</i> BED, ²³ BN, ²⁴ OCD, ^{25,26} PD, ²⁷ PMDD, ^{27,28} PTSD ²⁹	<i>Off-label:</i> Vasomotor symptoms of menopause ^{30,31}
Fluoxetine	<i>FDA-approved:</i> Bipolar I depression (when used with olanzapine), ⁶ BN, ⁶ MDD, ⁶ OCD, ⁶ PD, ⁶ PMDD ⁶ <i>Off-label:</i> BED, ³² PTSD, ^{33,34} SAD ³⁵	<i>Off-label:</i> Fibromyalgia, ⁷ premature ejaculation, ³⁶ hot flashes (with history of breast cancer), ³⁷ Raynaud's phenomenon ³⁸
Paroxetine	<i>FDA-approved:</i> GAD, ³⁹ MDD, ³⁹ OCD, ³⁹ PD, ³⁹ PMDD, ³⁹ PTSD, ³⁹ SAD ³⁹ <i>Off-label:</i> None	<i>Off-label:</i> Premature ejaculation, ⁴⁰ fibromyalgia, ⁴¹ headaches, ⁴² pruritus (nondermatologic) ⁴³
Sertraline	<i>FDA-approved:</i> MDD, ⁴⁴ OCD, ⁴⁴ PD, ⁴⁴ PMDD, ⁴⁴ PTSD, ⁴⁴ SAD ⁴⁴ <i>Off-label:</i> BED, ^{45,46} BN, ⁴⁷ GAD ⁴⁸	<i>Off-label:</i> Premature ejaculation, ^{49,50} fibromyalgia ⁵¹

AUD: alcohol use disorder; BED: binge eating disorder; BN: bulimia nervosa; BPSD: behavioral and psychological symptoms of dementia; 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

initially used to treat tuberculosis.⁴ 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.⁵ 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-HT_{2A} 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

Clinical Point

The term 'antipsychotic' is almost a misnomer given these agents' broad pharmacology profiles and impact



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Clinical Point

Potential drug-drug interactions are an important concern when considering using psychotropics for nonpsychiatric indications

Related Resource

- Joshi KG, Frierson RL. Off-label prescribing: how to limit your liability. *Current Psychiatry*. 2020;19(9):12,39. doi:10.12788/cp.0035

Drug Brand Names

Amitriptyline • Elavil	Hydrochlorothiazide •
Aripiprazole • Abilify	Microzide
Bupropion • Wellbutrin	Imipramine • Tofranil
Chlorpromazine • Thorazine	Levothyroxine • Levoxyl
Citalopram • Celexa	Lovastatin • Altoprev
Clomipramine • Anafranil	Mirtazapine • Remeron
Desipramine • Norpramin	Nortriptyline • Pamelor
Desvenlafaxine • Pristiq	Olanzapine • Zyprexa
Doxepin • Sinequan	Omeprazole • Prilosec
Duloxetine • Cymbalta	Paroxetine • Paxil
Escitalopram • Lexapro	Quetiapine • Seroquel
Fluphenazine • Prolixin	Risperidone • Risperdal
Fluoxetine • Prozac	Sertraline • Zoloft
Haloperidol • Haldol	Venlafaxine • Effexor

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 2⁵²⁻⁶⁸ (page 37), Table 3⁶⁹⁻¹⁰⁷ (page 38), and Table 4¹⁰⁸⁻¹²³ (page 39)** provide information on select antidepressants, while **Table 5¹²⁴⁻¹⁴⁰ (page 40) and Table 6¹⁴¹⁻¹⁷¹ (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.

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Table 2

Serotonin-norepinephrine reuptake inhibitors

Medication	Psychiatric indication(s)	Nonpsychiatric indication(s)
Desvenlafaxine	<i>FDA-approved:</i> MDD ⁵² <i>Off-label:</i> None	<i>Off-label:</i> Vasomotor symptoms of menopause ⁵³
Duloxetine	<i>FDA-approved:</i> GAD, ⁵⁴ MDD ⁵⁴ <i>Off-label:</i> None	<i>FDA-approved:</i> Fibromyalgia, ⁵⁴ musculoskeletal pain (chronic), ⁵⁴ diabetic neuropathy ⁵⁴ <i>Off-label:</i> Stress urinary incontinence after prostatectomy ^{55,56}
Venlafaxine	<i>FDA-approved:</i> GAD, ⁵⁷ MDD, ⁵⁷ PD, ⁵⁷ SAD ⁵⁷ <i>Off-label:</i> OCD, ^{58,59} PTSD, ⁶⁰ ADHD (pediatric patients only), ^{61,62} PMDD ⁶³	<i>Off-label:</i> Migraine prophylaxis (episodic), ^{64,65} diabetic neuropathy, ⁶⁶ hot flashes (history of breast cancer), ⁶⁷ peripheral neuropathy (due to chemotherapy) ⁶⁸

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

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Clinical Point

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

Table 3

Tricyclic antidepressants

Medication	Psychiatric indication(s)	Nonpsychiatric indication(s)
Amitriptyline	<i>FDA-approved:</i> MDD ⁶⁹ <i>Off-label:</i> None	<i>Off-label:</i> 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
Amoxapine	<i>FDA-approved:</i> MDD ⁸² <i>Off-label:</i> None	<i>Off-label:</i> IBS ⁸³
Clomipramine	<i>FDA-approved:</i> OCD ⁸⁴ <i>Off-label:</i> MDD, ⁸⁵ PD ⁸⁶	<i>Off-label:</i> Ejaculatory disorders ^{87,88}
Desipramine	<i>FDA-approved:</i> MDD ⁸⁹ <i>Off-label:</i> None	<i>Off-label:</i> Diabetic neuropathy, ⁹⁰ IBS, ⁹¹ postherpetic neuralgia ⁹²
Doxepin	<i>FDA-approved:</i> MDD, ⁹³ AUD, ⁹³ GAD, ⁹³ insomnia ⁹³ <i>Off-label:</i> None	<i>Off-label:</i> Chronic idiopathic urticaria ⁹⁴
Imipramine	<i>FDA-approved:</i> MDD ⁹⁵ <i>Off-label:</i> BN, ⁹⁶ PD, ⁹⁷ BED ⁹⁸	<i>FDA-approved:</i> Childhood enuresis (age ≥ 6) ⁹⁵ <i>Off-label:</i> Neuropathic pain, ⁹⁹ urinary incontinence, ¹⁰⁰ diabetic neuropathy ⁹²
Nortriptyline	<i>FDA-approved:</i> MDD ¹⁰¹ <i>Off-label:</i> ADHD (pediatric) ¹⁰²	<i>Off-label:</i> Lower back pain (chronic), ¹⁰³ myofascial pain, ¹⁰⁴ postherpetic neuralgia, ¹⁰⁵ mortality secondary to stroke, ¹⁰⁶ neurogenic bladder ¹⁰⁷

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

Clinical Point

Amitriptyline, amoxapine, and desipramine have been used off-label to treat irritable bowel syndrome

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Table 4

Atypical antidepressants

Medication	Psychiatric indication(s)	Nonpsychiatric indication(s)
Bupropion	<i>FDA-approved:</i> MDD, ¹⁰⁸ smoking cessation ¹⁰⁸ <i>Off-label:</i> ADHD, ¹⁰⁹ bipolar depression ¹¹⁰	<i>Off-label:</i> SSRI-induced sexual dysfunction ^{111,112}
Mirtazapine	<i>FDA-approved:</i> MDD ¹¹³ <i>Off-label:</i> PD, ^{114,115} PTSD, ¹¹⁶ insomnia ¹¹⁷	<i>Off-label:</i> Tension-type headache prophylaxis, ¹¹⁸ obstructive sleep apnea ¹¹⁹
Trazodone	<i>FDA-approved:</i> MDD ¹²⁰ <i>Off-label:</i> BPSD ^{121,122}	<i>Off-label:</i> Insomnia ¹²³

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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Clinical Point

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

Table 5

First-generation antipsychotics

Medication	Psychiatric indication(s)	Nonpsychiatric indication(s)
Chlorpromazine	<i>FDA-approved:</i> Bipolar mania, ¹²⁴ schizophrenia, ¹²⁴ presurgical apprehension ¹²⁴ <i>Off-label:</i> None	<i>FDA-approved:</i> Intractable hiccups, ¹²⁴ nausea/vomiting (acute), ¹²⁴ tetanus (adjunct), ¹²⁴ acute intermittent porphyria ¹²⁴ <i>Off-label:</i> Migraine treatment (severe), ^{125,126} nausea/vomiting in pregnancy ¹²⁷
Fluphenazine	<i>FDA-approved:</i> Psychotic disorders ¹²⁸ <i>Off-label:</i> None	<i>Off-label:</i> Chorea of Huntington's disease ¹²⁹
Haloperidol	<i>FDA-approved:</i> Schizophrenia, ¹³⁰ Tourette syndrome ¹³⁰ <i>Off-label:</i> BPSD, ¹³¹ bipolar mania, ¹³² hyperactive delirium ¹³³	<i>Off-label:</i> Nausea/vomiting due to chemotherapy, ¹³⁴ terminal illness, or postoperative prevention in moderate- to high-risk patients ¹³⁵
Perphenazine	<i>FDA-approved:</i> Schizophrenia ¹³⁶ <i>Off-label:</i> None	<i>FDA-approved:</i> Nausea/vomiting ¹³⁶ <i>Off-label:</i> None
Prochlorperazine	<i>FDA-approved:</i> Schizophrenia ¹³⁷ <i>Off-label:</i> None	<i>FDA-approved:</i> Nausea/vomiting (acute) ¹³⁷ <i>Off-label:</i> Chemotherapy-induced nausea/vomiting, ¹³⁸ postoperative nausea/vomiting prophylaxis or treatment, ¹³⁹ pregnancy-related nausea/vomiting ¹⁴⁰

BPSD: behavioral and psychological symptoms of dementia

Clinical Point

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

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Table 6

Second-generation antipsychotics

Medication	Psychiatric indication(s)	Nonpsychiatric indication(s)
Aripiprazole	<i>FDA-approved:</i> Bipolar disorder (mania/mixed), ¹⁴¹ MDD, ¹⁴¹ schizophrenia, ¹⁴¹ Tourette syndrome ¹⁴¹ <i>Off-label:</i> BPSD, ¹⁴² delusional disorder, ¹⁴³ delusional infestation, ¹⁴⁴ OCD ¹⁴⁵	<i>Off-label:</i> Chorea of Huntington's disease, ¹⁴⁶ antipsychotic-induced hyperprolactinemia ¹⁴⁷
Olanzapine	<i>FDA-approved:</i> Bipolar disorder (mania/mixed), ¹⁴⁸ MDD, ¹⁴⁸ schizophrenia ¹⁴⁸ <i>Off-label:</i> AN, ¹⁴⁹ bipolar II disorder (hypomania), ¹⁵⁰ hyperactive delirium, ¹⁵¹ delusional infestation, ¹⁵² MDD with psychotic features ^{153,154}	<i>Off-label:</i> Chemotherapy-induced acute and delayed nausea/vomiting prophylaxis (high-emetic risk), ¹⁵⁵ chorea of Huntington's disease ¹⁵⁶
Quetiapine	<i>FDA-approved:</i> Bipolar disorder (mania/mixed/depression), ¹⁵⁷ MDD, ¹⁵⁷ schizophrenia ¹⁵⁷ <i>Off-label:</i> GAD, ¹⁵⁸ OCD, ¹⁵⁹ PTSD, ¹⁶⁰ Parkinson disease psychosis ¹⁶¹	<i>Off-label:</i> Insomnia ¹⁶²
Risperidone	<i>FDA-approved:</i> Bipolar I disorder (mania/mixed), ¹⁶³ schizophrenia ¹⁶³ <i>Off-label:</i> BPSD, ^{164,165} bipolar hypomania, ¹⁶⁶ delusional infestation, ¹⁶⁷ MDD, ¹⁶⁸ OCD, ¹⁶⁹ Tourette syndrome ¹⁷⁰	<i>Off-label:</i> Chorea of Huntington's disease ¹⁷¹

AN: anorexia nervosa; BPSD: 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

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continued

Clinical Point

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

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