

# Watch for nonpsychotropics causing psychiatric side effects

Look behind the scenes for drugs that play a supporting role in new mood symptoms

**M**r. J, age 52, has a history of opioid dependence. Four weeks after starting interferon therapy for hepatitis C, he presents to the outpatient mental health clinic with depressed mood, irritability, decreased energy, poor concentration, insomnia, anhedonia, and suicidal ideation.

Because Mr. J has no history of depression, the psychiatrist diagnoses him with depressive disorder secondary to interferon. Interferon is stopped. Mr. J's mood improves, but he wants to restart interferon.

The psychiatrist starts Mr. J on sertraline, 50 mg/d, then gradually increases the dose to 150 mg/d as Mr. J's mood symptoms return. Subsequently, the patient continues interferon with a combination of sertraline and supportive psychotherapy.

Recognizing a medication as the possible cause of your patient's psychiatric symptoms can avoid inaccurate diagnosis and nonindicated psychiatric treatment. Diligently evaluating patients for drug-related psychiatric side effects is critical because complications usually are reversed when the offending drug is discontinued. Unfortunately, a thin line separates available evidence from anecdotal myths about psychiatric complications of nonpsychotropics.

Almost two-thirds (65%) of drugs included in the *Physicians' Desk Reference* list potential psychiatric side effects, according to a random sample review.<sup>1</sup> In some patients, such as Mr. J, these effects can exacerbate mood symptoms and result in perceptual, cognitive, or behavioral disturbances.



BLAIR KELLY FOR CURRENT PSYCHIATRY

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continued



## Nonpsychotropic medications

### Clinical Point

Beta blockers such as metoprolol and propranolol can cause delirium and psychosis

### Table

## New-onset psychiatric symptoms? Check patient's drug list

Symptom	Documented as a possible cause
<b>Psychosis/agitation</b>	Anabolic androgenic steroids, antihistamines, clonidine, corticosteroids, decongestants, didanosine, ethionamide, H <sub>2</sub> blockers, isoniazid, nitrates, NSAIDs, opioids, proton pump inhibitors, quinolones, salbutamol, skeletal muscle relaxants, sulfonamides/trimethoprim
<b>Anxiety</b>	Acyclovir, anabolic androgenic steroids, clonidine, corticosteroids, cyclosporine, decongestants, didanosine, serotonin 5-HT <sub>1</sub> agonists such as sumatriptan, foscarnet, ganciclovir, nitrates, ondansetron, penicillins, skeletal muscle relaxants
<b>Depression</b>	Anabolic androgenic steroids, beta blockers, chloramphenicol, clonidine, corticosteroids, didanosine, digoxin, efavirenz, foscarnet, GnRH agonists, H <sub>2</sub> blockers, interferons, isoniazid, isotretinoin, NSAIDs, quinolones, statins, tetracyclines
<b>Delirium</b>	ACE inhibitors, anabolic androgenic steroids, antibiotics (most), anticholinergics, beta blockers, centrally acting antihypertensives such as methyldopa and reserpine, cimetidine, clonidine, corticosteroids, didanosine, digoxin, H <sub>2</sub> blockers, lidocaine, naltrexone, nitrates, NSAIDs, opioids
<b>Insomnia</b>	Aminophylline, anabolic androgenic steroids, clonidine, corticosteroids, decongestants, didanosine, opioid antagonists, proton pump inhibitors, quinolone antibiotics, salbutamol, skeletal muscle relaxants, tetracyclines

NSAIDs: nonsteroidal anti-inflammatory drugs; ACE: angiotensin-converting enzyme; GnRH: gonadotropin-releasing hormone  
**Source:** Prepared for CURRENT PSYCHIATRY by Drs. Sidhu and Balon from references cited in this article

A wide range of drugs can cause psychosis, agitation, anxiety, depression, delirium, or insomnia (*Table*). On the other hand, certain psychiatric side effects of nonpsychotropics can be beneficial (*Box 1*).

Improve your assessments by examining the evidence linking psychiatric side effects to commonly prescribed and over-the-counter (OTC) compounds, including:

- cardiovascular medications
- steroids (prescription and illegal)
- hormones
- interferons
- antimicrobials.

### Cardiovascular medications

**Beta blockers** have CNS effects—some of which cause psychiatric syndromes—that might depend on an ancillary property such as lipophilicity.<sup>2</sup> Unlike hydrophilic agents such as atenolol that are excreted unchanged by the kidneys, lipophilic drugs such as metoprolol and propranolol are metabolized by the liver and are believed to enter the brain. Metoprolol has a brain/plasma concentration ratio about 20 times higher than that of atenolol.<sup>3</sup>

Metoprolol and propranolol can induce delirium and psychosis.<sup>4,5</sup> Psychiatric side effects with metoprolol are frequent,<sup>4</sup> and propranolol has been associated with:

- sedation (affecting >10% of patients)
- nightmares
- visual impairment
- hallucinations
- delirium
- depression.<sup>5</sup>

In 1967, it was reported that up to 50% of patients taking propranolol may experience dysphoria and at times severe depression.<sup>6</sup> These effects may occur acutely or develop gradually.<sup>5</sup>

The relationship between depressive symptoms and beta blockers has been increasingly questioned, however. One study did not find a higher prevalence of depression in patients receiving beta blockers vs those receiving other medications, although this trial had major methodologic limitations.<sup>7</sup> One large study found no significant association between beta-blocker use and major depression, regardless of patient age, gender, or race.<sup>8</sup>

These studies stress the importance of carefully assessing the individual patient

before assigning neurotoxicity to beta blockers, as these drugs have considerable benefits for cardiovascular disease.<sup>9</sup>

**Angiotensin-converting enzyme (ACE) inhibitors** also affect the CNS. About 4% to 8% of patients taking an ACE inhibitor experience altered mental status—typically increased arousal and psychomotor activity—although <2% discontinue the medication because of neuropsychiatric side effects. These include:

- anxiety
- mania
- insomnia
- fatigue
- paresthesias
- hallucinations.<sup>5</sup>

Sedation occurs in about 5% of patients taking ACE inhibitors. Depression and suicide ideation as a result of ACE inhibition have been reported;<sup>13</sup> however, ACE inhibitors have also been known to improve depression. Episodes of frank delirium have been reported.<sup>5</sup>

**Clonidine** is a centrally acting alpha-agonist. The alpha-adrenergic system regulates arousal and has an important role in major depression, anxiety states, and other arousal disorders.

More than one-third (35%) of patients taking clonidine experience sedation or lethargy; less commonly, the drug causes anxiety (3%), agitation (3%), depression (1%), and insomnia (1%).<sup>5</sup> Acute confusion, delirium, hypomania, and psychosis related to clonidine use have long been recognized, occurring in <1% of patients—primarily those with preexisting cerebrovascular disease.<sup>5</sup>

**Other cardiovascular drugs.** Side effects of nitrates/nitrites include delirium, psychosis (including delusions), anxiety, restlessness, agitation, and hypomania.<sup>5</sup> Digoxin can cause cardiac glycoside-induced encephalopathy, which may present as sedation, apathy, depression, and psychosis. Patients may develop delirium, even when digoxin/digitoxin serum levels are within a therapeutic range.

Cholesterol-lowering statins might be linked to an increased risk of depression and

**Box 1**

## Not all psychiatric side effects are harmful

In some instances, mood-elevating side effects of nonpsychotropic medications might be beneficial. This might be the case if your patient experiences a sudden, otherwise unexplainable improvement.

### CASE Helped by corticosteroids

Ms. Q, age 44, has a history of asthma and major depressive disorder and is being treated by a resident psychiatrist with a combination of paroxetine, 60 mg/d, mirtazapine, 15 mg at night, and cognitive-behavioral therapy. Her treatment has been challenging, and the psychiatrist has tried multiple medications and psychotherapy modalities.

At a recent psychotherapy session, Ms. Q says she has been feeling much better, with improved mood and greater energy. Upon further questioning, she reports having an asthma exacerbation a week before that resulted in hospitalization. During her stay, Ms. Q was started on a tapering dose of prednisone, which elevated her mood. Depressive symptoms returned when the effects of the prednisone wore off.

Prednisone is not indicated for depression and has harmful effects when used long term. The psychiatrist adds bupropion, 300 mg/d, to Ms. Q's regimen, and her symptoms improve.

suicide, but the evidence is inconclusive. Some studies have supported this link,<sup>10,11</sup> whereas others have strongly refuted it<sup>12,13</sup> or had mixed results.<sup>14</sup> A recent review<sup>15</sup> recommends being vigilant for psychiatric side effects in patients taking these drugs.

### Steroids: prescription and illegal

**Corticosteroids** are prescribed for a variety of immune system-related diseases, including asthma, allergic rhinitis, rheumatoid arthritis, inflammatory bowel disease, and dermatologic disorders. Mood changes are the most common psychiatric symptoms caused by corticosteroid use; delirium is less common. Psychiatric side effects include:

### Clinical Point

Mood changes are the most common psychiatric symptoms caused by corticosteroids



## Nonpsychotropic medications

### Clinical Point

Some studies suggest a link between estrogen and depression but in others estrogen had a positive effect on mood

- lethargy
- insomnia
- euphoria
- depression
- psychosis
- “personality changes”
- anxiety
- agitation.<sup>5</sup>

Multiple studies have linked corticosteroids and mood symptoms. The Boston Collaborative Drug Surveillance Program<sup>16</sup> confirmed a direct relationship between corticosteroid dosage and psychiatric effects. More than 18% of patients had severe psychiatric symptoms at corticosteroid dosages >80 mg/d.

A prospective study of asthma patients found statistically significant changes in mood—primarily manic symptoms—during brief corticosteroid courses at modest dosages. Depressed persons did not become more depressed during prednisone therapy, however; in fact, some improved. Some patients with posttraumatic stress disorder reported increased depression and memories of the traumatic event during prednisone therapy.<sup>17</sup>

In a study of 50 ophthalmologic patients who did not have psychiatric illness receiving prednisolone (mean starting dose 119 mg/d) for 8 days, 26% developed mania and 10% depression.<sup>18</sup> None reported psychotic symptoms.

The most common adverse effects of short-term corticosteroid therapy are euphoria and hypomania. Long-term therapy tends to induce depressive symptoms.<sup>19</sup> A review of 79 cases of psychiatric syndromes induced by corticosteroids found that 41% reported depression, 28% mania, 6% mixed symptoms, and 14% psychosis.<sup>20</sup>

A group of 16 healthy volunteers receiving 80 mg/d of prednisone over 5 days exhibited depressed or elevated mood, irritability, lability, increased energy, anxiety, and depersonalization.<sup>21</sup> Numerous case studies have reported anxiety, agitation, mania, and psychotic symptoms in children and adults taking inhaled corticosteroids.

In general, psychiatric side effects of corticosteroids occur within 2 weeks of starting therapy and resolve with dosage reduction or discontinuation. In severe

cases or situations in which the dosage cannot be reduced, the patient may require antipsychotics or mood stabilizers.<sup>19</sup>

Female gender and past psychiatric history might be risk factors for developing psychiatric symptoms with corticosteroids,<sup>22</sup> although not all studies have confirmed these findings.<sup>18</sup>

**Anabolic androgenic steroids (AAS)** have limited therapeutic benefits but are used illegally by some bodybuilders, wrestlers, and other amateur and professional athletes to increase muscle mass, enhance performance, and gain a competitive edge. AAS can cause acute paranoia, delirium, mania or hypomania, homicidal rage, aggression, and extreme mood swings, as well as a marked increase in libido, irritability, agitation, and anger.

In a large observational cohort study of 320 bodybuilding amateur and recreational athletes,<sup>23</sup> AAS use induced many of these psychiatric side effects. The extent intensified as the abuse escalated. A study that used the Structured Clinical Interview for DSM-III-R to compare 88 athletes using steroids with 68 nonusers found that 23% of the AAS users reported major mood syndromes, including mania, hypomania, and major depression.<sup>24</sup>

In a 2-week, double-blind, fixed-order, placebo-controlled, crossover study of healthy male inpatient volunteers, AAS had both:

- mood-elevating effects—euphoria (“steroid rush”), increased energy, and increased sexual arousal and drive
- mood-dysphoric effects, such as irritability, mood swings, increasingly violent feelings, increased hostility, and cognitive impairments.<sup>25</sup>

As with corticosteroids, psychiatric symptoms from AAS become more prevalent and severe as dosage increases. They usually resolve within a few weeks after users discontinue steroids but may persist for up to 1 month, even if adequately treated with antipsychotic medication.

## Hormones

**Gonadotropin-releasing hormone (GnRH) agonists** such as leuprolide and nafarelin

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## Nonpsychotropic medications

### Clinical Point

Watch for depressive symptoms in patients taking interferon, especially in those with a family history of mood disorders

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are approved for treating endometriosis, advanced prostate cancer, precocious puberty, and uterine leiomyomata. Some studies and case reports suggest that these agents cause depressive symptoms.<sup>26</sup>

**Progestins** have complex and variable psychiatric effects. Clinical trials have investigated the antidepressant effects of exogenous estrogens on psychiatric patients, but results have been inconsistent—possibly because of small numbers of subjects and design flaws.<sup>26</sup> Some studies suggest a link between estrogen and depression in premenopausal and menopausal women with and without psychiatric illness, but findings remain controversial because other studies have found that estrogens have positive effects on mood.<sup>26,27</sup>

### Interferon

Various forms of interferon are used to treat hepatitis C, melanoma, multiple sclerosis, chronic myelogenous leukemia, and other illnesses. Psychiatric complications—particularly depression—are the most frequent side effect of interferon therapy and mainly occur within the first 12 weeks of therapy.<sup>28</sup>

In a prospective observational study of veterans undergoing interferon-alfa/ribavirin treatment for chronic hepatitis C:

- 48% of patients not receiving psychiatric care at baseline required treatment for neuropsychiatric side effects
- 23% developed symptoms of major depression.<sup>29</sup>

Treatment with a selective serotonin reuptake inhibitor stabilized these symptoms and allowed patients to continue hepatitis treatment.

Because patients who receive interferon are far more likely to require psychiatric intervention if they have a family history of mood disorders, closely monitor them for depressive symptoms and treat such symptoms aggressively. Also closely monitor patients with multiple psychiatric diagnoses receiving interferon-alfa therapy.<sup>30</sup>

Jeungling et al<sup>31</sup> speculated that hypometabolism in the prefrontal cortex may predispose patients to interferon-associated

neuropsychological syndromes. Neuropsychiatric symptoms may be a characteristic of hepatitis C, interferon treatment, or both.<sup>32</sup>

### Antimicrobial agents

Antibiotic and antiviral drugs can cause psychiatric side effects:

- directly by affecting neuronal functions
- indirectly by entering the brain rapidly, taking advantage of the compromised blood-brain barrier during sepsis or infection.

Delirium is the most common psychiatric complication associated with these agents.<sup>5</sup>

**Antibiotics.** Penicillin and its analogues are associated with sedation, anxiety, and hallucinations. Delirium has been reported as a side effect of most cephalosporins, especially in patients with compromised renal function. Quinolones such as ciprofloxacin and ofloxacin rarely cause restlessness, irritability, lethargy, tremors, insomnia, mania, depression, psychosis, delirium, seizures, or catatonia (incidence  $\leq 1\%$ ).<sup>5</sup> Though not commonly used, chloramphenicol may cause depression, confusion, and delirium. Many case reports have strongly associated clarithromycin with delirium.<sup>33</sup>

Isoniazid is one of the most commonly used antibiotics that can cause psychiatric side effects; it has been linked to delirium, mania, depression, and psychosis. Ethionamide is associated with sedation, irritability, depression, restlessness, and psychosis. Tetracyclines have been known to cause depression, insomnia, and irritability at high dosages.

Sulfonamides can cause delirium. Psychosis and confusion also have been reported, especially when sulfa drugs are combined with trimethoprim.<sup>5</sup>

**Antivirals.** When used intravenously and at high doses, acyclovir and ganciclovir can cause lethargy, anxiety, hallucinations, and frank delirium.<sup>5</sup> Foscarnet—an antiviral used to treat herpes viruses—can cause depression, anxiety, hallucinations, and aggressive irritability.



Didanosine—an antiretroviral agent to treat HIV infections—can cause lethargy (5% to 7% of patients), depression (2%), anxiety (2%), emotional lability (25%), delirium (2%), insomnia (1%), and psychotic delusions (1%).<sup>5</sup> Efavirenz treatment may be associated with major depression and severe suicidal ideation.<sup>34</sup> Tenofovir, a nucleotide reverse transcriptase inhibitor, has not been associated with psychiatric side effects.<sup>27</sup>

**Antifungals.** Psychiatric side effects are rare.

### OTC and other agents

Many common nonprescription agents can cause psychiatric symptoms. The most frequently used classes include cold and allergy preparations, reflux medications, and analgesics (*Box 2*).<sup>5,35</sup>

**Cold preparations.** Combined antihistamines and decongestants—such as phenylpropanolamine, azatadine, loratadine, ephedrine, phenylephrine, pseudoephedrine, and naphazoline—can cause an atropine-like psychosis that typically manifests as confusion, disorientation, agitation, hallucinations, and memory problems. Decongestants can cause dangerously high levels of norepinephrine when combined with monoamine oxidase inhibitors (MAOIs) and are contraindicated in patients taking MAOIs. Ephedrine can induce restlessness, dysphoria, irritability, anxiety, and insomnia.

**Reflux medications.** Two primary classes of reflux medications are proton pump inhibitors (omeprazole and lansoprazole) and H<sub>2</sub> receptor antagonists (famotidine, nizatidine, ranitidine, and cimetidine). Although generally considered to have a benign side-effect profile, these medications have been reported to cause serious neuropsychiatric complications—including mental confusion, agitation, depression, and hallucinations—mainly in geriatric patients with impaired hepatic-renal function.<sup>36</sup> These occur in only <0.2% of outpatients but are much more common among patients who are hospitalized, elderly, or have hepatic or renal failure.<sup>37</sup>

Time to onset of psychiatric side effects from H<sub>2</sub> antagonists varies. Ranitidine can cause depression 4 to 8 weeks after treatment begins. Cimetidine has been reported to cause adverse events within 2 to 3 weeks and delirium within 24 to 48 hours.<sup>38</sup> These effects usually resolve within 3 days of discontinuing the drug. Cimetidine is also associated with sexual dysfunction.

Discontinuing ranitidine or cimetidine can induce a withdrawal syndrome that includes anxiety, insomnia, and irritability.<sup>39</sup> Cimetidine can increase

*[The following text is extremely faint and largely illegible, appearing to be a continuation of a clinical trial or research report. It contains various headings and data points.]*

**WARNING: RISK OF DEATH**  
Discontinue treatment with DIDANOSINE if you experience any of the following symptoms:  
For more information on symptoms and treatment of lactic acidosis, see full Prescribing Information.  
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## Psychiatric effects of OTC and prescription analgesics

Up to 70% of persons in Western countries use analgesics regularly, primarily for headaches, other specific pains, and febrile illness. Nonsteroidal anti-inflammatory drugs (NSAIDs)—including aspirin, naproxen, ibuprofen, and indomethacin—are efficacious and have a wide safety margin, but potentially serious psychiatric side effects can occur even when these drugs are taken in recommended doses.

Salicylate intoxication, which can present as frank delirium, often goes unrecognized. Any NSAID can produce delirium in the elderly. Case reports have also implicated NSAIDs in mania, psychosis, and depressive disorders with suicidal ideation.<sup>35</sup>

Opioids may cause sedation, psychic slowing, dysphoria, mood changes, psychosis, and delirium. Epidural administration of morphine may induce hallucinations and catatonia. Opioid antagonists—such as naloxone and, particularly, naltrexone—can induce dysphoria, fatigue, sleep disturbances, suicidality, hallucinations, and delirium. The serotonin 5-HT<sub>1</sub> agonist sumatriptan (an antimigraine medication) has been associated with fatigue, anxiety, and panic disorder.<sup>5</sup>

Skeletal muscle relaxants such as baclofen and dantrolene may induce sleep disturbances, anxiety, agitation, mood disturbances, hallucinations, and delirium.

the blood level and action of tricyclic antidepressants. Blood levels of these antidepressants can become toxic, resulting in tachycardia and other adverse effects.

**Other medications.** Ondansetron is a 5-hydroxytryptamine subclass 3 (5-HT<sub>3</sub>) antagonist used for antiemetic therapy. In case reports, it has been strongly associated with anxiety.<sup>40</sup> This association is complex, however, and studies are evaluating 5-HT<sub>3</sub> receptor antagonists for the treatment of anxiety, depression, phobia, and schizophrenia.

Isotretinoin—a retinoid used for severe acne—can cause severe depression and suicidal behavior.<sup>41</sup>

Aminophylline and salbutamol are associated with agitation, insomnia, euphoria, and delirium. Methotrexate is known to cause personality changes, irritability, and delirium.<sup>27</sup>

### Treating drug-related mood effects

If you suspect a nonpsychotropic medication is causing your patient's psychiatric symptoms, discuss this with the patient and the prescribing physician. Switching to another similar agent may be an option. If this is not possible:

- work closely with the patient's primary physician

- treat mood symptoms with appropriate psychotropics.

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### Clinical Point

Combined antihistamines and decongestants can cause psychosis



## Nonpsychotropic medications

### Clinical Point

The acne drug isotretinoin can cause severe depression and suicidal behavior

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## Related Resources

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### Drug Brand Names

Acyclovir • Zovirax	Methyldopa • Aldomet
Aminophylline • Phyllocontin, Truphylline	Metoprolol • Lopressor
Atenolol • Tenormin	Mirtazapine • Remeron
Azatadine • Optimine	Nafarelin • Synarel
Baclofen • Lioresal	Naloxone • Suboxone
Chloramphenicol • Chloromycetin	Naltrexone • Vivitrol
Cimetidine • Tagamet	Naphazoline • Naphcon-A, Clearine
Ciprofloxacin • Cipro	Naproxen • Aleve, others
Clarithromycin • Biaxin	Nizatidine • Axid
Clonidine • Catapres	Ofloxacin • Floxin
Cyclosporine • Neoral, Sandimmune, others	Omeprazole • Prilosec
Dantrolene • Dantrium	Ondansetron • Zofran
Didanosine • Videx	Paroxetine • Paxil
Efavirenz • Sustiva	Peginterferon alfa • PEG-Intron, Pegasys
Ethionamide • Trecator	Phenylephrine • Neo-Syneprine
Famotidine • Pepcid	Prednisolone • Blephamide, Pred Forte, others
Foscarnet • Foscavir	Propranolol • Inderal
Ganciclovir • Cytovene	Pseudoephedrine • Actifed, Sudafed
Indomethacin • Indocin	Ranitidine • Zantac
Interferon alfa • Intron, Roferon	Reserpine • Serpasil
Isoniazid • Nydrizid	Ribavirin • Copegus, Rebetol
Isotretinoin • Accutane	Salbutamol • Aerolin, Airomir, others
Lansoprazole • Prevacid	Sertraline • Zoloft
Leuprolide • Lupron	Sumatriptan • Imitrex
Lidocaine • Xylocaine, Xylocard	Tenofovir • Viread
Loratadine • Claritin	Trimethoprim • Proloprim
Methotrexate • Rheumatrex, Trexall	

### Disclosure

The authors report no financial relationship with any company whose products are mentioned in this article or with manufacturers of competing products.

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## Bottom Line

Always investigate whether any changes in prescription or over-the-counter (OTC) medications could be causing your patients' new psychiatric symptoms. Be especially vigilant for common culprits such as beta blockers, ACE inhibitors, corticosteroids, interferon, analgesics, isotretinoin, and OTC reflux drugs. Most psychiatric complications can be reversed by discontinuing the offending drug or replacing it with a different medication. Consult the prescribing physician before making a medication change.