Off-label

7 steps for safer,

Consider risks and benefits for your patient and yourself before grabbing the prescription pad.
Have you noticed two curious patterns in off-label prescribing? Psychiatrists avoid agents approved for treating insomnia but pre-
scribe anticonvulsants for a variety of unapproved uses.

Most of us prescribe medications for therapeutic uses not found in FDA-approved labeling. Among 200 psychiatrists surveyed, 65% said they
had prescribed off label in the previous month, and only 4% had ever received a patient complaint about the practice.¹

But patient complaints are not the only issue. Taking shortcuts as you venture into uncharted Rx territory can leave your patients at risk for ineffective
treatment or injury.

To help protect them from harm and yourself from legal problems, we discuss:

- off-label use of hypnotics, anticonvulsants, and other drugs
- 7 steps to keep you out of trouble before you reach for the prescription pad
- what the law says about informed consent and off-label prescribing.

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A COMMON PRACTICE
Psychiatrists often resort to off-label prescribing, not only for insomnia but also to treat schizophrenia-spectrum disorders, unipolar and bipolar affective disorders, anxiety disorders (especially obsessive-compulsive disorder), mental disorders related to general medical conditions, dementia, and personality disorders. The most common reason for off-label prescribing is to treat childhood-onset disorders, especially severe and complex ADHD and developmental disorders.13

In a Department of Veterans Affairs study, nearly one-half of atypical antipsychotics were prescribed off label, despite a lack of data to support most of the uses.5 In a managed-care system survey, one-third of initial antidepressant prescriptions were written for an intended treatment period of <6 months, often for off-label and nonpsychiatric conditions.6

The FDA’s position. Psychiatrists are not alone; U.S. physicians may write 25% to 60% of prescriptions off-label, depending on the clinical setting.7,8 The FDA regulates drug approvals and safety, but claims no authority over medical practice and acknowledges the legitimacy of off-label prescribing.

PROBING THE ‘CURIous PATTERNS’
Hypnotics. McCall9 reviewed a trend for clinicians to prefer unapproved agents when treating primary chronic insomnia and found prescribers avoiding benzodiazepine receptor agonists—the drugs labeled for insomnia. Instead, trazodone had become the most frequently prescribed sleep agent. This practice developed in the 1990s despite a lack of clinical trials of trazodone in chronic insomnia and minimal support for this use (trazodone has shown efficacy in patients with insomnia for 2 weeks).10

Prescribers choose trazodone off label for insomnia because it is sedating, relatively safe, easy to titrate, and inexpensive in generic form. We believe prescribers choose off-label medications as hypnotics for various reasons, including:
• concern about the labeled limitations on benzodiazepines’ use
• benzodiazepine receptor agonists’ controlled drug status
• misconception that off-label alternatives have shown efficacy and safety
• formulary recommendations or restrictions.11

Anticonvulsants. Psychiatrists seem to have a magnetic attraction to using anticonvulsants to treat bipolar disorder, even though few of these agents have shown efficacy and only carbamazepine, valproate, and lamotrigine are labeled for any phase of bipolar illness.

In the literature and from referrals to our inpatient and outpatient services, we have found anticonvulsants also being used for other psychopathologies, a practice even less securely supported by clinical trial data than their use in bipolar disorder. For example, a retrospective study of more than 48,000 patients in the Georgia Medicaid program12 found that 71% of anticonvulsant prescriptions were written off-label in 1999 and 2000. Among the six anticonvulsants prescribed most often, 19% to 57% of prescriptions were unsupported by evidence from controlled clinical trials.

Gabapentin was used most often (86% of its prescriptions were off label), though its use for pain disorders and by neurologists contributed substantially. Off-label use of gabapentin—including psychiatric use for bipolar disorder, attention-deficit/hyperactivity disorder (ADHD), sleep disorders, and alcohol withdrawal syndromes—exceeds its indicated use.13

As for other anticonvulsants, in a New York State study of hospitalized psychiatric patients,
more than 50% of valproate and divalproex use was off-label, including treatment of schizophrenia and schizoaffective disorder.¹⁴

The Cochrane Collaboration’s repository of systematic reviews (see Related resources, page 28) includes evidence on anticonvulsant use for psychiatric disorders. Analyses of some anticonvulsants for specific psychiatric disorders exist,¹⁵ and others are being prepared. Even so, embracing all anticonvulsants for treating bipolar disorder and other psychopathologies is clearly premature.

SAFER OFF-LABEL PRESCRIBING
Though few lawsuits have challenged off-label prescribing per se,³ you can be found liable if your patient injures someone or is injured—such as in a car accident caused by excessive sedation—while taking an off-label drug you prescribed. Just because a drug has shown safety and efficacy for its labeled use does not mean it will be safe and efficacious for other uses.

The following case shows how 7 steps (Table 1) can reduce off-label prescribing risks:
Mr. B, age 49, seeks treatment for insomnia after detoxification for alcohol dependence. He is willing to take sleep medication, but he attends Alcoholics Anonymous meetings regularly and his sponsor has warned him to avoid controlled prescription drugs.

Married and working as a carpenter, Mr. B denies any mood, anxiety, or thought disorders. He is taking no medications and reports no drug or food allergies. His primary care physician reports a normal physical exam, ECG, and lab investigation.

Step 1. Be familiar with evidenced-based reviews and treatment guidelines relating to your patient’s psychiatric disorder. Although these models do not define the standard of care, they point to a prescription decision-making process consistent with clinical trial data. Along with behavioral interventions such as improving sleep hygiene, Mr. B might benefit from sleep medication. Few guidelines and little evidence exist to guide hypnotic therapy for patients with a history of alcohol dependence. However, prescribing sedative-hypnotics to these patients is controversial, and Mr. B wishes to avoid these anyway. He will likely require treatment for several months.

Step 2. Clarify your rationale for off-label prescribing
After behavioral measures fail to improve Mr. B’s insomnia, we consider a sedating antidepressant or an atypical antipsychotic. We favor antidepressants because of their clinical and side-effect profiles.

Step 3. Obtain a second opinion if indicated.
We decide not to seek an opinion from an addictions psychiatry specialist before proceeding with treatment but may seek consultation if the antidepressant trial fails.

Step 4. Weigh risks and potential benefits—
including efficacy and safety factors—of specific agents for your patient. Decide if any medications might be suitable and if any may be more likely to help than others.

Tertiary amine tricyclics such as amitriptyline are sedating, but their anticholinergic side effects are cumbersome and safer alternatives are available. We thus consider a nontricyclic, sedating antidepresant as first-line therapy for Mr. B. Several atypical antidepressants and selective serotonin reuptake inhibitors (SSRIs) are sedating but may cause sexual side effects, weight gain, and hepatic enzyme abnormalities.

We choose trazodone, which is commonly prescribed off label for insomnia, after carefully considering:

- Mr. B’s stated desire to avoid benzodiazepines
- preliminary data on trazodone’s benefit (increased sleep efficiency) in post-alcohol withdrawal insomnia\(^6\)
- the dosage range at which sedation occurs

• easy monitoring of adverse effects
• availability in generic form.

**Step 5.** Obtain informed consent from your patient or appropriate surrogate, following your state’s disclosure requirements.

We share our reasoning for choosing trazodone with Mr. B and advise him of the potentially dangerous side effects of priapism, orthostatic hypotension, confusional states, and oversedation. We warn him:

- to check before adding complementary or alternative agents or medications from any other physicians
- that taking cough and cold preparations while using trazodone increases the risk of serotonin syndrome.

**Step 6.** Document your decision-making process and the patient’s consent to pursue the treatment course you selected together.

In our outpatient clinic notes we document the factors that led to our choosing an off-label psychotropics: our discussion with Mr. B, his request to avoid sedative-hypnotic agents, our informed consent discussion with him, and plans to monitor for treatment benefits and adverse effects.

**Step 7.** Monitor your patient carefully for known and unexpected adverse effects from the medication or potential drug-illness interactions.

We write a limited prescription for trazodone, consistent with the titration schedule, and schedule a follow-up appointment in 2 to 4 weeks. We instruct Mr. B to call if he has any questions or problems.

**LIMITS TO OFF-LABEL USE**

Some insurers have adopted policies to discourage off-label prescribing of psychotropics—particularly atypical antipsychotics and antidepressants—because of concerns about the annual 13% increase in prescription drug costs (Box).\(^17\)

Thus, psychiatrists have valid therapeutic reasons...
Off-label prescribing

Off-label prescribing is legal, common, necessary, and recognized in some states by statute and by U.S. Supreme Court decisions.

**Court decisions.** In a class action suit before the top court (Buckman Company vs. Plaintiff’s Legal Commission, 2001), 5,000 plaintiffs claimed damages from orthopedic screws and plates that were FDA-approved for use in long bones but not for use in the spine. A unanimous court held that such off-label use is an accepted practice of medicine and necessary offshoot of FDA regulatory function and does not interfere with the practice of medicine.

**WHAT THE LAW SAYS**

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**Professional ethics require us to consider the most-effective, safest treatments and to involve patients in decision-making.**

- We also are vulnerable to malpractice claims, particularly if a patient dies by suicide from overdose or from the prescribed dose of an off-label product (see *Malpractice Verdicts, page 52*).

**Informed Consent.** Failing to obtain informed consent can result in a patient’s right to be informed of the risk of malpractice litigation if a patient is injured, although state laws generally do not require you to disclose that you are prescribing off-label. In our experience, disclosure helps prevent patient confusion and anxiety when materials help patients receive their own medical records from the Internet or do not list their diagnoses among prescriptions prescribed.

Most state medical practice laws spell out the information required in the patient chart to demonstrate informed consent, defined variously as:

- what a reasonable provider would tell a patient
- what a reasonable patient would expect to hear from the provider
- what a patient would need to hear before deciding on a treatment course.

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The courts also have determined that off-label use does not mean “experimental” and itself is not a risk. Off-label use may be consistent with the standard of care and does not categorically indicate negligence (though a practitioner who prescribes negligently—such as prescribing a drug to which a patient is known to be allergic—may be found liable).

**Drug manufacturers’ risk.** The courts recognize that patients receive prescription drugs from doctors, not directly from the manufacturers. The law thus provides some immunity to manufacturers if your patient is injured by a drug you prescribe off-label. The learned-intermediary rule says manufacturers must warn you adequately of a drug’s foreseeable risks, and you then assume the responsibility to warn the patient.

The courts recognize exceptions, though, and have required manufacturers to warn patients directly about vaccines given in mass immunizations, drugs withdrawn from the market, drugs advertised directly to consumers, and other risks.

**References**
9. O’Reilly JD, Dalal A. Off-label or out of bounds? Prescriber and

**Table 2**

<table>
<thead>
<tr>
<th>Why psychiatrists prescribe off-label</th>
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<tbody>
<tr>
<td><strong>Therapeutic reasons</strong></td>
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<tr>
<td>Patient has a disorder for which no drug is labeled</td>
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<tr>
<td>Patient falls outside of labeled age or demographic group, such as children, older patients, and pregnant women</td>
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<tr>
<td>Patient fails to respond to labeled products</td>
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<tr>
<td>Off-label product may potentiate response to a labeled agent or minimize its adverse effects</td>
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<tr>
<td><strong>Preferences</strong></td>
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<tr>
<td>Manufacturers and respected peers promote use of off-label products as first- or second-line agents</td>
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<tr>
<td>Practitioner wishes to foster innovative treatments</td>
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<td>Patients or families request an off-label drug instead of labeled alternatives</td>
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<tr>
<td>Practitioner avoids using a particular labeled drug or drug class</td>
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**Don’t be afraid to prescribe psychotropics off-label, but use appropriate caution to protect the patient and yourself. Become familiar with evidence-based findings/guidelines, and carefully weigh risks and benefits specific to individual patients and psychiatric disorders.**
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Related resources


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<tr>
<th>DRUG BRAND NAMES</th>
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<tr>
<td>Amitriptyline • Elavil, others</td>
</tr>
<tr>
<td>Carbamazepine • Carbatrol, Epitol, Equetro, Trigaretal</td>
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<tr>
<td>Lamotrigine • Lamictal</td>
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<td>Trazodone • Desyrel, Triavil, Valporate</td>
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<td>Gabapentin • Gabarone, Neurontin</td>
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<td>Depakote, Depakene</td>
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DISCLOSURES

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