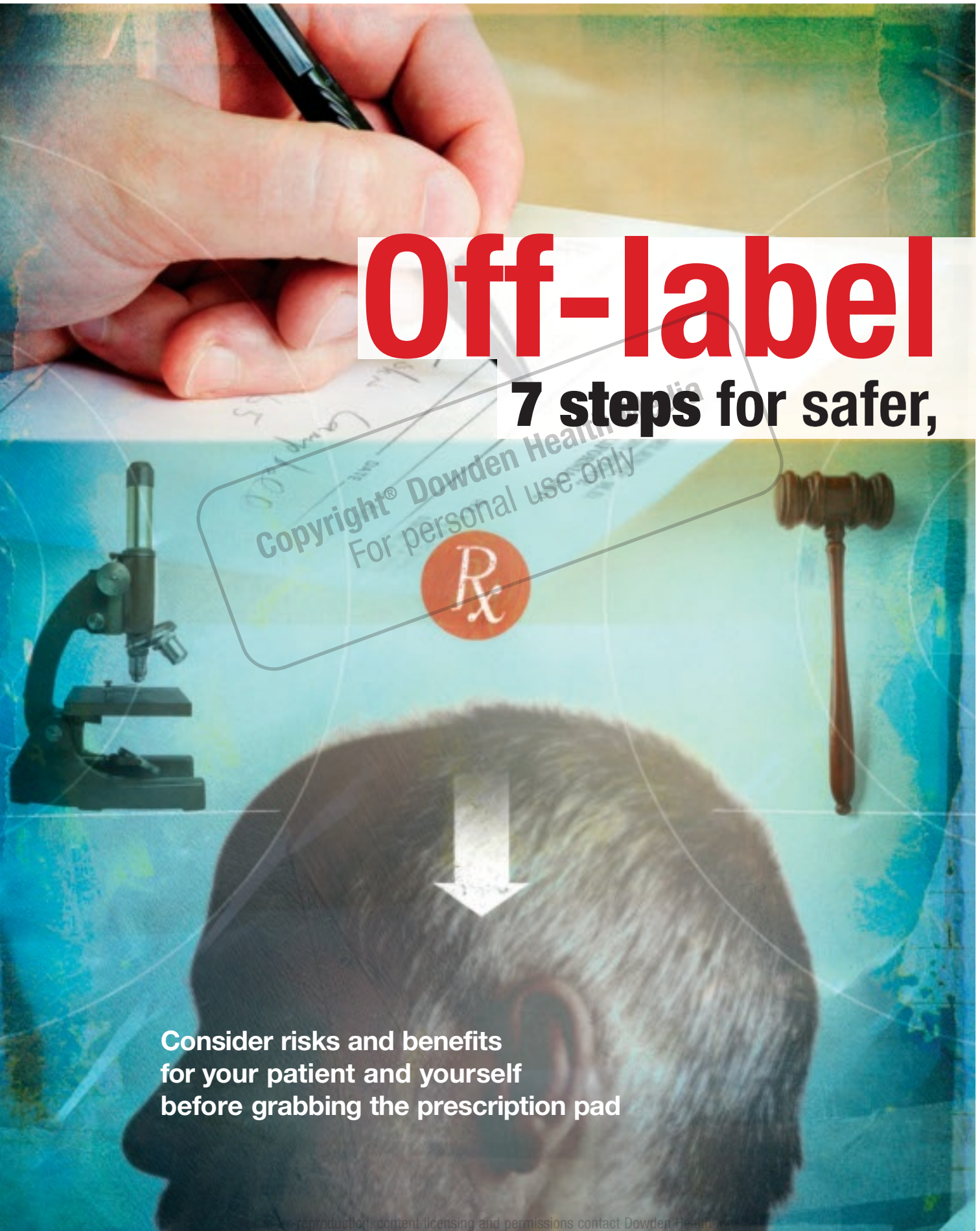

Off-label

7 steps for safer,

Consider risks and benefits for your patient and yourself before grabbing the prescription pad

Current PSYCHIATRY

prescribing
more effective treatment

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Have you noticed two curious patterns in off-label prescribing? Psychiatrists avoid agents *approved* for treating insomnia but prescribe 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.

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.[2,3]

In a Department of Veterans Affairs study, nearly one-half of atypical antipsychotics were prescribed off label,[4] 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.

More than 50% of valproate and divalproex use was off-label in one inpatient study

PROBING THE 'CURIOUS PATTERNS'

Hypnotics. McCall[9] 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 program[12] 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,

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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.

Table 1

7 steps to safer, more effective off-label prescribing

1. **Be familiar** with evidence-based findings/guidelines
2. **Clarify** your rationale for off-label prescription
3. **Obtain** second-opinion consultation if indicated
4. **Perform** risk-benefit analysis
5. **Obtain** informed consent from patient or appropriate surrogate
6. **Document** steps 1 through 5 in the patient's record
7. **Monitor** for known and unexpected adverse events

SAFER OFF-LABEL PRESCRIBING

Though few lawsuits have challenged off-label prescribing per se,[9] 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—

Box

'Experimental'? How insurers view off-label prescribing

Private insurance. Psychotropic costs are rising 20% a year, contributing to the nation's annual 13% overall prescription drug cost increase.[15] To control rising costs, some medical insurance plans consider off-label use as "unapproved and experimental" and deny coverage. Pharmacy benefit and self-insured employer plans may act similarly, although some states require insurers to cover off-label use of all approved medications.

Government programs. Medicaid does not exclude coverage of off-label prescriptions. How the new Medicare prescription drug plan (Part D) handles off-label prescribing remains unclear.

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 antidepressant 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[16]
- 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 psychotropic: 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

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nausea and dizziness), but less to other effects (e.g., dry mouth, somnolence, and asthenia). ***Male and Female Sexual Dysfunction with SSRIs:*** Although changes in sexual desire, sexual performance, and sexual satisfaction often occur as manifestations of a psychiatric disorder, they may also be a consequence of pharmacologic treatment. In particular, some evidence suggests that selective serotonin reuptake inhibitors (SSRIs) can cause such untoward sexual experiences. Reliable estimates of the incidence and severity of untoward experiences involving sexual desire, performance and satisfaction are difficult to obtain, however, in part because patients and physicians may be reluctant to discuss them. Accordingly, estimates of the incidence of untoward sexual experience and performance cited in product labelling are likely to underestimate their actual incidence. In placebo-controlled clinical trials involving more than 1,800 patients, the ranges for the reported incidence of sexual side effects in males and females with major depressive disorder, OCD, and panic disorder are displayed in Table 4. **Table 4. Incidence of Sexual Adverse Events in Controlled Clinical Trials (in males only: paroxetine: n=925; placebo: n=655):** decreased libido (6% - 14% vs. 0% - 5%), ejaculatory disturbance (13% - 28% vs. 0% - 1%), impotence (2% - 8% vs. 0% - 1%); **(in females only: paroxetine: n=932; placebo: n=694):** decreased libido (1% - 9% vs. 0% - 2%), orgasmic disturbance (2% - 9% vs. 0% - 1%). There are no adequate and well-controlled studies examining sexual dysfunction with paroxetine treatment. Paroxetine treatment has been associated with several cases of priapism. In those cases with a known outcome, patients recovered without sequelae. While it is difficult to know the precise risk of sexual dysfunction associated with the use of SSRIs, physicians should routinely inquire about such possible side effects. ***Weight and Vital Sign Changes:*** Significant weight loss may be an undesirable result of treatment with paroxetine for some patients but, on average, patients in controlled trials had minimal (about 1 pound) weight loss vs. smaller changes on placebo and active control. No significant changes in vital signs (systolic and diastolic blood pressure, pulse and temperature) were observed in patients treated with paroxetine in controlled clinical trials. **Other Events Observed During the Premarketing Evaluation of Paroxetine:** During its premarketing assessment in major depressive disorder, multiple doses of paroxetine were administered to 6,145 patients in phase 2 and 3 studies. The conditions and duration of exposure to paroxetine varied greatly and included (in overlapping categories) open and double blind studies, uncontrolled and controlled studies, inpatient and outpatient studies, and fixed-dose and titration studies. During premarketing clinical trials in OCD and panic disorder, 542 and 469 patients, respectively, received multiple doses of paroxetine. Untoward events associated with this exposure were recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of untoward events into a smaller number of standardized event categories. In the tabulations that follow, reported adverse events were classified using a standard COSTART-based Dictionary terminology. The frequencies presented, therefore, represent the proportion of the 9,089 patients exposed to multiple doses of paroxetine who experienced an event of the type cited on at least one occasion while receiving paroxetine. All reported events are included except those already listed in Tables 1 and 2, those reported in terms so general as to be uninformative and those events where a drug cause was remote. It is important to emphasize that although the events reported occurred during treatment with paroxetine, they were not necessarily caused by it. Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring on one or more occasions in at least 1/100 patients (only those not already listed in the tabulated results from placebo-controlled trials appear in this listing); infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients. Events of major clinical importance are also described in the PRECAUTIONS section. ***Body as a Whole:*** *infrequent:* allergic reaction, chills, face edema, malaise, neck pain; *rare:* adrenergic syndrome, cellulitis, moniliasis, neck rigidity, pelvic pain, peritonitis, sepsis, ulcer. ***Cardiovascular System:*** *frequent:* hypertension, tachycardia; *infrequent:* bradycardia, hematoma, hypotension, migraine, syncope; *rare:* angina pectoris, arrhythmia nodal, atrial fibrillation, bundle branch block, cerebral ischemia, cerebrovascular accident, congestive heart failure, heart block, low cardiac output, myocardial infarct, myocardial ischemia, pallor, phlebitis, pulmonary embolus, supraventricular extrasystoles, thrombophlebitis, thrombosis, varicose vein, vascular headache, ventricular extrasystoles. ***Digestive System:*** *infrequent:* bruxism, colitis, dysphagia, eructation, gastritis, gastroenteritis, gingivitis, glossitis, increased salivation, liver function tests abnormal, rectal hemorrhage, ulcerative stomatitis; *rare:* aphthous stomatitis, bloody diarrhea, bulimia, cardiospasm, chlolelithiasis, duodenitis, enteritis, esophagitis, fecal impactions, fecal incontinence, gum hemorrhage, hematemesis, hepatitis, ileitis, ileus, intestinal obstruction, jaundice, melena, mouth ulceration, peptic ulcer, salivary gland enlargement, sialadenitis, stomach ulcer, stomatitis, tongue discoloration, tongue edema, tooth caries. ***Endocrine System:*** *rare:* diabetes mellitus, goiter, hyperthyroidism, hypothyroidism, thyroiditis. ***Hemic and Lymphatic Systems:*** *infrequent:* anemia, leukopenia, lymphadenopathy, purpura; *rare:* abnormal erythrocytes, basophilia, bleeding time increased, eosinophilia, hypochromic anemia, iron deficiency anemia, leukocytosis, lymphedema, abnormal lymphocytes, lymphocytosis, microcytic anemia, monocytosis, normocytic anemia, thrombocythemia, thrombocytopenia. ***Metabolic and Nutritional:*** *frequent:* weight gain; *infrequent:* edema, peripheral edema, SGOT increased, SGPT increased, thirst, weight loss; *rare:* alkaline phosphatase increased, bilirubinemia, BUN increased, creatinine phosphokinase increased, dehydration, gamma globulins increased, gout, hypercalcemia, hypercholesteremia, hyperglycemia, hyperkalemia, hyperphosphatemia, hypocalcemia, hypoglycemia, hypokalemia, hyponatremia, ketosis, lactic dehydrogenase increased, non-protein nitrogen (NPN) increased. ***Musculoskeletal System:*** *frequent:* arthralgia; *infrequent:* arthritis, arthrosis; *rare:* bursitis, myositis, osteoporosis, generalized spasm, tenosynovitis, tetany. ***Nervous System:*** *frequent:* emotional lability, vertigo; *infrequent:* abnormal thinking, alcohol abuse, ataxia, dystonia, dyskinesia, euphoria, hallucinations, hostility, hypertonia, hypesthesia, hypokinesia, incoordination, lack of emotion, libido increased, manic reaction, neurosis, paralysis, paranoid reaction; *rare:* abnormal gait, akinesia, antisocial reaction, aphasia, choreoathetosis, circumoral paresthesias, convulsion, delirium, delusions, diplopia, drug dependence, dysarthria, extrapyramidal syndrome, fasciculations, grand mal convulsion, hyperalgesia, hysteria, manic-depressive reaction, meningitis, myelitis, neuralgia, neuropathy, nystagmus, peripheral neuritis, psychotic depression, psychosis, reflexes decreased, reflexes increased, stupor, torticollis, trismus, withdrawal syndrome. ***Respiratory System:*** *infrequent:* asthma, bronchitis, dyspnea, epistaxis, hyperventilation, pneumonia, respiratory flu; *rare:* emphysema, hemoptysis, hiccups, lung fibrosis, pulmonary edema, sputum increased, stridor, voice alteration. ***Skin and Appendages:*** *frequent:* pruritus; *infrequent:* acne, alopecia, contact dermatitis, dry skin, ecchymosis, eczema, herpes simplex, photosensitivity, urticaria; *rare:* angioedema, erythema nodosum, erythema multiforme, exfoliative dermatitis, fungal dermatitis, furunculosis, herpes zoster, hirsutism, maculopapular rash, seborrhea, skin discoloration, skin hypertrophy, skin ulcer, sweating decreased, vesiculobullous rash. ***Special Senses:*** *frequent:* tinnitus; *infrequent:* abnormality of accommodation, conjunctivitis, ear pain, eye pain, keratoconjunctivitis, mydriasis, otitis media; *rare:* amblyopia, anisocoria, blepharitis, cataract, conjunctival edema, corneal ulcer, deafness, exophthalmos, eye hemorrhage, glaucoma, hyperacusis, night blindness, otitis externa, parosmia, photophobia ptosis, retinal hemorrhage, taste loss, visual field defect. ***Urogenital System:*** *infrequent:* amenorrhea, breast pain, cystitis, dysuria, hematuria, menorrhagia, nocturia, pyuria, polyuria, urinary incontinence, urinary retention, urinary urgency, vaginitis; *rare:* abortion, breast atrophy, breast enlargement, endometrial disorder, epididymitis, female lactation, fibrocystic breast, kidney calculus, kidney pain, leukorrhea, mastitis, metrorrhagia, nephritis, oliguria, salpingitis, urethritis, urinary casts, uterine spasm, urolith, vaginal hemorrhage, vaginal moniliasis. **Postmarketing Reports:** Voluntary reports of adverse events in patients taking paroxetine that have been received since market introduction and not listed above that may have no causal relationship with the drug include acute pancreatitis, elevated liver function tests (the most severe cases were deaths due to liver necrosis, and grossly elevated transaminases associated with severe liver dysfunction), Guillain-Barré syndrome, toxic epidermal necrolysis, priapism, syndrome of inappropriate ADH secretion, symptoms suggestive of prolactinemia and galactorrhea, neuroleptic malignant syndrome-like events; extrapyramidal symptoms which have included akathisia, bradykinesia, cogwheel rigidity, dystonia, hypertonia, oculogyric crisis which has been associated with concomitant use of pimozide, tremor and trismus; serotonin syndrome, associated in some cases with concomitant use of serotonergic drugs and with drugs which may have impaired paroxetine metabolism (symptoms have included agitation, confusion, diaphoresis, hallucinations, hyperreflexia, myoclonus, shivering, tachycardia and tremor), status epilepticus, acute renal failure, pulmonary hypertension, allergic alveolitis, anaphylaxis, eclampsia, laryngismus, optic neuritis, porphyria, ventricular fibrillation, ventricular tachycardia (including torsade de pointes), thrombocytopenia, hemolytic anemia, events related to impaired hematopoiesis (including aplastic anemia, pancytopenia, bone marrow aplasia, and agranulocytosis), and vasculitic syndromes (such as Henoch-Schönlein purpura). There has been a case report of an elevated phenytoin level after 4 weeks of paroxetine and phenytoin co-administration. There has been a case report of severe hypotension when paroxetine was added to chronic metoprolol treatment.

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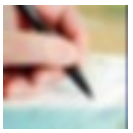

Off-label prescribing

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to prescribe off label and other rationales related to personal or others' preferences (*Table 2*),[18] but off-label prescribing has limits as well:

- 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 increase your 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 they receive at the pharmacy or find on the Internet do not list their diagnoses among prescribed medications' approved indications.

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.

WHAT THE LAW SAYS

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

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 and necessary offshoot of FDA regulatory function and does not interfere with the practice of medicine.

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.

Table 2

Why psychiatrists prescribe off-label

Therapeutic reasons
Patient has a disorder for which no drug is labeled
Patient falls outside of labeled age or demographic group, such as children, older patients, and pregnant women
Patient fails to respond to labeled products
Off-label product may potentiate response to a labeled agent or minimize its adverse effects
Preferences
Manufacturers and respected peers promote use of off-label products as first- or second-line agents[18]
Practitioner wishes to foster innovative treatments
Patients or families request an off-label drug instead of labeled alternatives
Practitioner avoids using a particular labeled drug or drug class

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Bottom Line

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.

marketer liability for unapproved uses of FDA-approved drugs. *Ann Health Law* 2003;12:295-324.

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Related resources

- BMJ Publishing Group. Clinical evidence. Summary of what is known—and not known—about more than 200 medical disorders and 2,000 treatments. www.clinicalevidence.com.
- Cochrane Library of evidence-based clinical reviews. www.cochrane.org.
- Agency for Health Care Research and Quality. Draft comparative effectiveness review of off-label use of atypical antipsychotic drugs. http://effectivehealthcare.ahrq.gov/synthesize/reports/draft.cfm.

DRUG BRAND NAMES

Amitriptyline • Elavil, others
Carbamazepine • Carbetrol; Epitol; Equetro; Tegretol
Gabapentin • Gabarone; Neurontin
Lamotrigine • Lamictal
Trazodone • Desyrel; Trialodine
Valproate • Depakote; Depakene

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