

Worried about high-dose prescribing? Manage risk for you and your patient

Communicate and document informed consent when using medications off-label

Mr. B, age 35, is admitted for the fourth time to the inpatient service with hallucinations and delusions related to chronic schizophrenia. After appropriate attempts to control his symptoms, he has begun to respond to usual treatment with an atypical antipsychotic. He remains a “partial responder,” however, at the maximum FDA-approved dosage listed in the package insert (PI). What do you do next?

Because of this author’s (NSK) dual training in medicine and forensic psychiatry, other clinicians often ask me about patients such as Mr. B. Prescribing for patients who do not respond to standard dosages can create anxiety about going “off-label.” This article describes how to manage potential risk to yourself and your patient by communicating effectively and documenting informed consent.

What are the options?

To effectively treat Mr. B’s symptoms, you could:

- change medications and start over
- augment with a second atypical antipsychotic
- stay with the antipsychotic to which he has shown partial response, but go above the PI dosing.

Each strategy could pose problems, but most psychopharmacologists would choose the third option—the most logical one.

Changing medications is attractive, but the choice of an atypical antipsychotic with relative metabolic neutrality



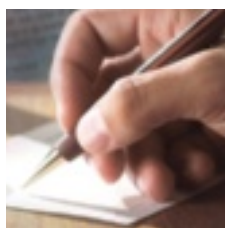
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Off-label prescribing

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Every clinician I've met prescribes drugs off-label in terms of dose, indications, or age limits listed in the package insert

Table 1

Patient factors that influence response to medication

Patient body mass, age, race, ethnicity, and gender
Variability in medication absorption
Hepatic metabolizing factors
How 'sick' the patient is, compared with those in pivotal clinical trials
Patient's behavior, lifestyle, habits, and diet
Comorbid medical conditions
Other psychiatric and nonpsychiatric pharmacotherapy

is limited, and "switching" is time-consuming. When a drug begins to show efficacy, most clinicians won't opt to "change horses midstream"—especially if managed care is pressuring for rapid discharge.

Augmentation introduces polypharmacy and potential drug-drug interactions. Very little evidence guides us in combining antipsychotics, as most manufacturers will never study the coadministration of 2 branded medications with the same indication.

Only a few case reports have described combining atypical antipsychotics.¹⁻⁴ Moreover, many managed care providers and governmental payers/regulators will not pay for polypharmacy with 2 atypical antipsychotics or will allow it only during cross-tapering from one agent to another.

'High-dose' monotherapy is the choice most often taken by clinicians and experts. Pharmaceutical manufacturers study a wide range of doses during medication development. Two pivotal trials form the basis of the New Drug Application for FDA approval and largely dictate the PI language.

Don't misconstrue the PI dosing as optimal for a specific medication or patient. Historically, FDA-approved dosing for atypical antipsychotics has been too high (risperidone, aripiprazole) or too low (ziprasidone, quetiapine) for many patients we treat, even when the medications are used as indicated. This problem is magnified when clinicians try to make

individual patients (N=1) resemble the average pooled analysis of the clinical trial group (N>200) and find that the individual patient may be a low-dose, average-dose, or high-dose responder (*Table 1*).

Informed prescribing. Polypharmacy is a complex issue because essentially no pharmacokinetic or pharmacodynamic studies have examined the simultaneous use of ≥ 3 psychotropics. When a pharmacist or drug interaction computer alerts you to a potential drug-drug interaction, the warning is almost always theoretical. No real data exist about coadministering most medications.

Physicians may query a manufacturer about off-label, above-PI dosing data by contacting the company's medical information department or asking a pharmaceutical representative. What you receive will vary by manufacturer, but in almost every case you will get the safety data you want. Occasionally you also will get efficacy data, which is nice but not crucial. An online literature search of MEDLINE is another way to obtain this information.

Liability risk?

Every clinician I've met prescribes drugs off-label, whether in terms of dose, indication, or age limits in the PI as published in the *Physicians' Desk Reference* (PDR).⁵ Still, nearly all describe to me the following nightmare, in which they "violated" the PI and "something bad" happens.

They are sitting in court on the witness stand, white-knuckled and sweaty, as a plaintiff's attorney strolls up to them, PDR in hand, and says: "Doctor, isn't this the Bible, and you violated the Bible?" And thus is born the fear of a malpractice claim, predicated on off-label dosing.

Off-label prescribing is rarely the only issue in a lawsuit, according to Denny Rodriguez, assistant vice president, claims, Professional Risk Management Services (PRMS), Inc.—manager of The Psychiatrists' Program endorsed by the American Psychiatric Association. When raised, allegations related to off-label prescribing

are among many presented by the plaintiff under the rubric of treatment that violated the standard of care.

Contrary to the plaintiff's allegations, off-label prescribing rarely violates the standard of care because it has valid clinical and scientific bases. And don't acknowledge the PDR as "the Bible," which it is not; it's a compilation of PIs. The FDA affirms that once a product is approved for marketing, a physician may choose to prescribe it for off-label use (**Box**).⁵

Standard of care

The real issue for practitioners is the "standard of care." Violating the standard of care—what a similarly trained clinician would do under similar circumstances—is the first step on the slippery slope to malpractice. Here we can be quite sure that the standard of care and evidence-based medicine are in sync and support the use of off-label, high-dose monotherapy.

Properly documenting your reasoning helps to demonstrate that your prescribing meets the standard of care. Always document and obtain informed consent. Also stay up-to-date about:

- medications you prescribe
- emerging evidence and safety information
- appropriate patient monitoring for clinical response and adverse effects.⁸

Black boxes and bold lettering

The FDA may mandate that a manufacturer highlight certain information on a PI in 3 ways—bold lettering, black-box warning, and red lettering, in order of presumed increasing seriousness. This system is meant to draw prescribers' attention to potential safety problems with pharmaceutical agents. No psychiatric medications carry red-letter warnings, a classification usually reserved for antineoplastic agents.

At one time the FDA relied on evidenced-based data to determine the need for warnings. Recently, however, when a problem has been identified with one agent, the FDA has tended to require all drugs in that agent's class to carry similar—if not

Box

FDA statement on off-label prescribing

The FDA acknowledges that doctors need to treat patients and may prescribe medications off-label. As stated in the foreword to the *Physicians' Desk Reference*:

*The FDA has also recognized that the [Federal Food, Drug, and Cosmetic] Act does not, however, limit the manner in which a physician may use an approved drug. Once a product is approved for marketing, a physician may choose to prescribe it for uses or in treatment regimens or patient populations that are not included in approved drug labeling. The FDA also observes that accepted medical practice includes drug use that is not reflected in approved drug labeling.*⁵

identical—PI warnings. In psychiatry, the FDA has ordered suicide precautions on all antidepressants and metabolic syndrome/hyperglycemia warnings on all atypical antipsychotics, despite evidence of differences in potential risks associated with medications within classes. For example, clinical trials have shown a higher risk of obesity and diabetes among patients receiving olanzapine compared with those receiving ziprasidone.⁷

The FDA's action appears to "level the playing field," giving patients the misperception that any treatment would carry an equal risk. Therefore, when you prescribe a drug that carries a class-wide warning in its PI, present the evidence in a balanced, objective manner so that the patient can make an informed decision.

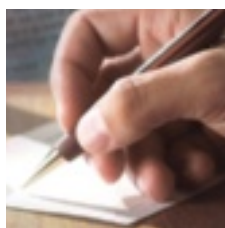
Managing risk

Your best protection against liability is to communicate effectively with the patient and document that communication—including informed consent—in the medical record.⁸ Obtain and document informed consent whenever:

- you initiate a drug or other treatment
- treatment extends beyond the PI-recommended maximum dose.

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Off-label prescribing rarely violates the standard of care because it has valid clinical and scientific bases



Off-label prescribing

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Update the informed consent discussion with your patient when a new warning or safety information about a drug emerges

Table 2
**Informed consent:
Pertinent points to document**

Proposed treatment
Potential side effects (most common)
Potential side effects (most dangerous)
Potential side effects that might make a patient anxious, such as those included in recent FDA statements, changes in labeling, or advertisers' consumer marketing messages
Alternatives, including their potential side effects
Course without treatment
Demonstration of patient's comprehension of warnings and opportunity to ask questions

Similarly, when a new side-effect warning or safety information about a medication emerges, update the informed consent discussion and re-obtain and re-document the patient's consent. When warnings are discussed on the nightly news or the Internet, patients prescribed that medication will expect you to address this. Informed consent discussions are an excellent way to discover and address patients' concerns and ensure that they have realistic expectations about treatment.

Potential benefits for patients from updating informed consent include:

- changes in medications or dosages based on the new information
- closer monitoring of potential side effects and other actions
- empowerment to make decisions about stopping a medication or trying alternate medications or treatments.

Documentation also reflects individualization of care, the patient's involvement, and your clinical judgment and decision-making—all critical elements of a record that supports good patient care and protects both patient and clinician.

Documenting informed consent

What to include. View informed consent as an ongoing discussion, not a document that needs to be put into a chart to comply with a legal mandate. Documenting informed consent may be as simple as going through the process and then including pertinent points in the medical record (*Table 2*). The following is an example of a medical record entry used by one author (NSK) to document an initial informed consent discussion:

"I have explained to the patient the reasons for prescribing the above medication, the expected benefits and potential side effects, the treatment alternatives and possible risks and benefits of the alternatives, and the expected course w/o treatment. The patient asked appropriate questions and appeared to understand the answers. (I discussed off-label use.) I provided information from the manufacturer (or some other source). The patient has decided to try this medication and to be followed."

Caveats. Avoid "cutting and pasting" language for each informed consent discussion into each medical record. Make your discussion and its documentation reflect each individual's treatment plan. If you use a preprinted consent/medications side-effect form (as required by many institutions and clinics), consider entering a personalized notation into the progress notes as needed, such as when:

- you prescribe medications with high risk for serious side effects
- you use off-label prescribing that is not customary
- a patient needs extra assistance to follow the treatment plan.⁸

The procedure's formality helps a patient focus on the consent process, making it less likely that he/she will later believe he/she was not adequately informed. The signed form supports the assertion that the consent process took place and establishes at least some of what was disclosed. The signed form and the clinician's entry in the record documenting the informed consent discussion will be beneficial should malpractice litigation allege consent issues.

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Preprinted forms. A disadvantage of preprinted forms is the difficulty in knowing what information to include. If the form's content is very broad, then important information may not be disclosed. If the form is very specific and attempts to list all possible complications, one could presume that any complication not listed was not disclosed. If you incorporate an informed consent form into your practice:

- include all significant and material risks on the form
- state on the form that the risks "include, but are not limited to" those listed on the form
- have thorough informed consent discussions with patients
- enter into the medical record your discussion and a copy of the form signed by the patient.

What to disclose. Clinicians often struggle with how much information to disclose to patients. In general, include what a reasonable person would need to know to make an informed decision. A practical way to think about this is to ask yourself the following questions:

- What information would I want a physician to disclose to my loved one (parent, child, spouse, etc.) if I was not present and my loved one needed to give consent to a treatment recommendation?
- Is this information of the type that a reasonable person could say: "I wouldn't have consented if the doctor had told me that"? If you think so, then provide this information to your patient.

Patient resources. Medication information sheets can enhance informed consent and patients' understanding and retention

Related Resources

- Food and Drug Administration (FDA). Information sheets on hundreds of FDA-approved drugs, listed alphabetically. www.fda.gov/cder/drug/DrugSafety/DrugIndex.htm.
- FDA. Drug safety information for consumers and healthcare professionals. www.fda.gov/cder/index.html.

Drug Brand Names

Aripiprazole • Abilify	Risperidone • Risperdal
Olanzapine • Zyprexa	Ziprasidone • Geodon
Quetiapine • Seroquel	

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Jacqueline Melonas is a full-time employee of PRMS, Inc. PRMS, Inc. contracts with Eli Lilly and Company to provide risk management content related to the management of medical malpractice liability.

of information about medications you prescribe. The FDA's Web site (www.fda.gov) offers printable patient education sheets on hundreds of medications, medication guides, and other resources (see *Related Resources*).⁶ Many manufacturers also offer patient education information at their Web sites, via pharmaceutical representatives, and as part of the PI.

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Disclose to the patient as much information as a reasonable person would need to know to make an informed decision

Bottom Line

When you prescribe off-label medication dosages, demonstrate that your decision is within the standard of care. Discuss alternatives with the patient, based on data from drug manufacturers or the literature. Document this discussion and the patient's consent to treatment in the medical record. If using a preprinted form, document the informed consent discussion in the progress notes.