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When is off-label prescribing appropriate?

After evaluating all available evidence, carefully consider your patient's individual risks

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Off-label prescribing (OLP)—prescribing a medication in a manner different from that approved by the FDA—is common and can be clinically beneficial. A survey of 200 British psychiatrists found that 65% had prescribed a medication off-label within the previous month.[1] However, OLP often is not supported by strong evidence and carries clinical risks, such as adverse effects and unproven efficacy. A 2006 study found that only 4% of off-label prescriptions of psychiatric medications were supported by strong scientific evidence.[2]

OLP may become unavoidable for several reasons, including:

- lack of data from quality trials on a specific indication or patient population
- patients seen in clinical practice vary from those evaluated in clinical trials (***Figure 1, page 24***)
- the need to treat patients who do not respond to first-line therapies or have treatment-resistant conditions.

At times, OLP may be a psychiatrist's only option: >80% of DSM-IV-TR diagnoses have no FDA-approved medication.[3]

No practice guidelines are available to help clinicians decide when OLP is appropriate. Psychiatrists must rely on multiple, sometimes-conflicting sources to determine whether evidence is sufficient to support off-label use in a specific clinical scenario. This article looks at types of OLP and offers suggestions for clinicians who are considering prescribing a medication outside of its approved use.

The FDA's role

Once the FDA approves a medication for a specific indication, physicians legally are permitted to prescribe that

Off-label prescribing

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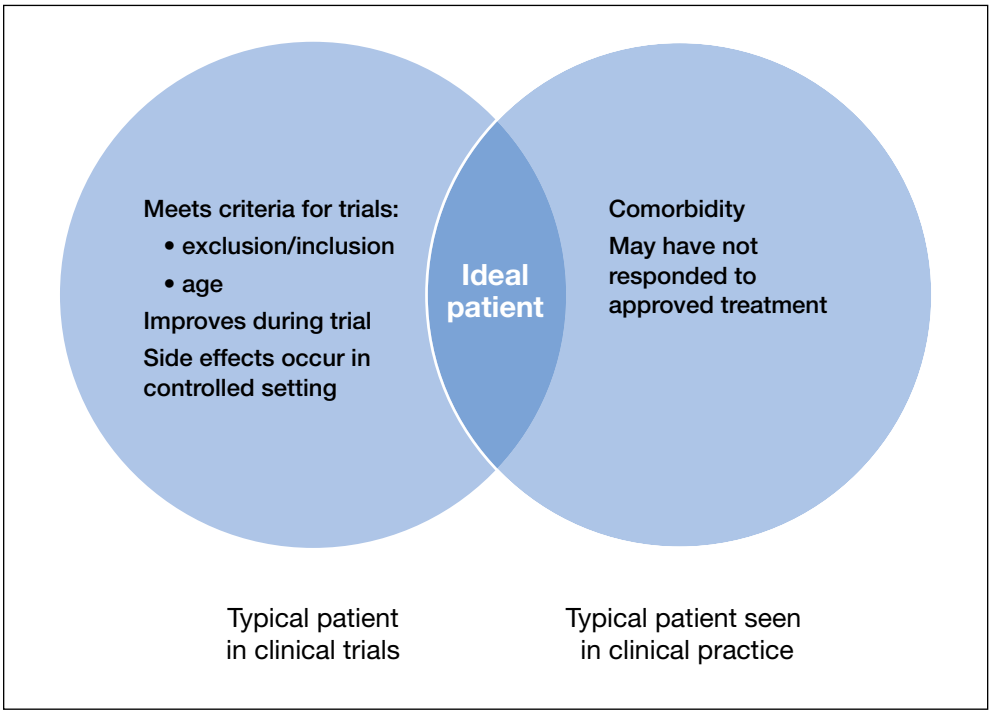
An off-label indication may be a logical extension of an approved indication

Figure 1

Clinical trial patients vs 'real world' patients



drug for indications, patient populations, or dosages not included on the FDA-approved label.[2,4] The FDA oversees and regulates pharmaceutical companies, not physicians.[4] Currently, pharmaceutical companies cannot market a drug for an indication not included on the label, but physicians are free to use the drug for any condition or disease.[5]

When is OLP used?

According to Baldwin et al,[6] prescribing that is considered off-label generally falls into 1 of the following 4 categories:

Indication. This type of OLP is prescribing a medication for an indication other than those included on the FDA-approved label. The off-label indication may be a logical extension of an approved indication. For example, a medication approved for treating erectile dysfunction might be prescribed to a patient who is experiencing antidepressant-induced sexual dysfunction.

If a pharmaceutical company wishes to expand the indications of a medication they must seek supplemental approval from the FDA. This is a long, expensive process. In certain situations, it may be in the patient's best interest to prescribe a medication off-label until that indication becomes approved. When clinicians identify new uses for existing medications while they care for patients, it is considered field discovery, and this innovative process may occur years before such indications receive FDA approval.

Dosage. The most common example of this type of OLP in psychiatry is prescribing higher-than-approved dosages of antidepressants or antipsychotics for patients who do not respond to the maximum approved dosages. The effectiveness of this strategy is unknown.[6]

Duration. This typically entails prescribing a medication for a period of time longer than specified on the label. For example, many antidepressants are approved only for treating depressive illness. Therefore, continuing an antidepressant as maintenance therapy for a patient who is

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in remission could be considered off-label. Benzodiazepines are approved primarily for short-term management of anxiety, but commonly are prescribed for patients with chronic, disabling anxiety disorders who do not respond to other medications.[6]

Patient age. The FDA approves medications for use in patients within a specified age range based on patients evaluated in clinical trials, and most trials of psychotropics include patients age 18 to 65. However, it is highly unlikely that a 17-year-old patient's drug metabolism changes substantially when he or she reaches age 18, or when a 65-year-old turns 66. Research has demonstrated that medications can be effective outside of strict age ranges. For example, randomized controlled trials (RCTs) have shown that antidepressants are efficacious in treating depression in geriatric patients, and selective serotonin reuptake inhibitors are efficacious in treating obsessive-compulsive disorder (OCD) in children and adolescents.[6]

Few medications have been approved for treating geriatric patients with psychiatric illness. For example, no drugs are approved for treating psychotic, behavioral, and mood symptoms that may accompany dementia. For this reason, clinicians often prescribe psychotropics off-label to these patients.

The rate of psychotropic prescriptions to children and adolescents—particularly antidepressants and antipsychotics—has been increasing.[7-9] The British Association for Psychopharmacology suggested that it may be reasonable to apply what we know regarding adults' responses to drug treatment to children and adolescents with schizophrenia or OCD, but more caution is required in young patients with mood or anxiety disorders.[10]

Combination therapy is another type of OLP. Often a disease state consists of multiple underlying syndromes, and treating individual syndromes is a common strategy. For example, in addition to depressed mood, a patient with major depressive disorder also may have insomnia and poor concentration. A medication approved for treating depressed mood may not improve insomnia or poor concentration. Therefore, combination therapy may be necessary, but likely would be off-label. Combination therapy also may be tried when a patient does not respond to monotherapy. For example, although the evidence supporting the practice is inconclusive, clinicians commonly prescribe >1 antipsychotic to patients with schizophrenia or other psychotic disorders.

Help for making OLP decisions

Position statements/policies. The American Psychiatric Association (APA) and the American Medical Association support OLP when the practice is based on sound scientific evidence and medical opinion.[11] The APA position statement encourages clinicians to use various compendia, including the American Hospital Formulary Service (AHFS) Drug Information, in conjunction with peer-reviewed literature to determine the medical acceptability of off-label uses.[11]

Evidence-based medicine includes a hierarchy of scientific and clinical evidence that can justify medical decisions. At the top of this hierarchy are large RCTs and smaller RCTs; cohort studies, case-control studies, poorly controlled or uncontrolled studies, case reports, and expert opinion are less valuable (***Figure 2, page 26***).[4]

Searching through all available resources for evidence supporting a specific off-label use is a cumbersome, time-consuming process. For this reason, clinicians may refer to compendia that evaluate and rate the available evidence supporting off-label use of medication, such as the AHFS Drug Information and DrugDex. Other resources include peer-reviewed medical journals. Physicians can contribute to knowledge of off-label uses by sharing their experiences, both good and bad, with their colleagues via presentations, publications, and/or initiating a study.

Other resources. Gazarian et al[12] delineated 3 situations where OLP might be considered appropriate: use justified by

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The APA supports off-label prescribing when the practice is based on sound scientific evidence and medical opinion

Off-label prescribing

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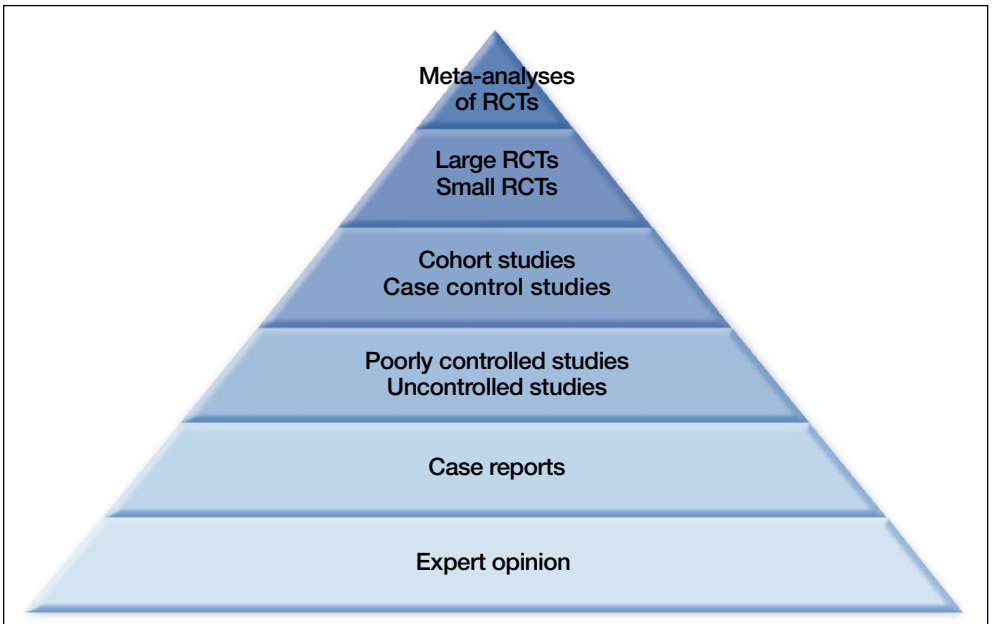
Explain to patients the risks and benefits of any proposed off-label medication use, and obtain informed consent

Figure 2

The hierarchy of sources for evidence-based medicine



RCTs: randomized controlled trials

Source: Reference 4

high-quality evidence, use in research trials, and exceptional use justified by individual clinical circumstances. Exceptional use would require all of the following:

- the patient has a serious disease or condition
- evidence supports a potential beneficial effect of the off-label treatment
- potential benefits outweigh potential risks
- standard therapy has failed or is inappropriate
- an institutional drug committee approved the off-label use
- the patient provides written informed consent.[12]

Other authors[13,14] have offered recommendations for psychiatrists considering OLP:

- Study available literature and assess whether sufficient evidence supports the proposed off-label use.
- If evidence is lacking, learn about the medication and its potential risks (interactions, adverse effects, and FDA "black-box" warnings). Also consult other resources for additional information and research, including peers and experts in the field.
- Consider and document risks and benefits of the proposed off-label use. Explain these, as well as uncertainties and potential costs, to patients and/or their families, and obtain and document informed consent.
- Cautiously initiate the off-label therapy, monitor patients closely, and meticulously document efficacy and tolerance.

Prescribing medications on-label does not guarantee safety or efficacy. Likewise, OLP does not imply a safety hazard or lack of efficacy. OLP may be in the best interest of the patient. Nonetheless, the practice must be carried out responsibly with utmost caution and consideration of acute and long-term burdens to patients, along with an assessment of the risk vs benefit of the proposed therapy.

References

1. Lowe-Ponsford F, Baldwin D. Off-label prescribing by psychiatrists. Psychiatric Bulletin. 2000;24:415-417.
2. Radley DC, Finkelstein SN, Stafford RS. Off-label prescribing among office-based physicians. Arch Intern Med. 2006;166(9):1021-1026.
3. Devulapalli K, Nasrallah HA. An analysis of the high

psychotropic off-label use in psychiatric disorders: the majority of psychiatric diagnoses have no approved drug. Asian Journal of Psychiatry. 2009;2(1):29-36.
4. Dresser R, Frader J. Off-label prescribing: a call for heightened professional and government oversight. J Law Med Ethics. 2009;37(3):476-486, 396.
5. Food, Drug, and Cosmetic Act, 21 USC §396 (2010).
6. Baldwin DS, Kosky N. Off-label prescribing in psychiatric practice. Advances in Psychiatric Treatment. 2007;13: 414-422.
7. Zito JM, Safer DJ, dosReis S, et al. Trends in the prescribing of psychotropic medications to preschoolers. JAMA. 2000; 283(8):1025-1030.
8. Tournier M, Greenfield B, Galbaud du Fort G, et al. Patterns of antidepressant use in Quebec children and adolescents: trends and predictors. Psychiatry Res. 2010;179(1):57-63.
9. Cooper WO, Arbogast PG, Ding H, et al. Trends in prescribing of antipsychotic medications for US children. Ambul Pediatr. 2006;6(2):79-83.
10. Child and learning disability psychopharmacology. J Psychopharmacol. 1997;11(4):291-294.
11. American Psychiatric Association. Position statement on patient access to treatments prescribed by their physicians. 2007. http://www.psychiatry.org/advocacy--newsroom/position-statements/apa-position-statements. Accessed May 24, 2012.
12. Gazarian M, Kelly M, McPhee JR, et al. Off-label use of medicines: consensus recommendations for evaluating appropriateness. Med J Aust. 2006;185(10):544-548.
13. Kramer SI, McCall WV. Off-label prescribing: 7 steps for safer, more effective prescribing. Current Psychiatry. 2006; 5(4):14-28.
14. Royal College of Psychiatrists. Use of licensed medicines for unlicensed applications in psychiatric practice. College report CR142. http://www.rcpsych.ac.uk/files/pdfversion/cr142.pdf. Accessed May 24, 2012.

Related Resource

- Mossman D. Why off-label isn't off base. Current Psychiatry. 2009;8(2):19-22.

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When initiating off-label therapy, monitor patients closely and meticulously document efficacy and tolerance

Bottom Line

Off-label prescribing (OLP) can be necessary and clinically beneficial, but the practice often is not supported by strong research. Determining when OLP is appropriate requires carefully considering not only available evidence and expert opinion, but also the potential risks and benefits for individual patients, who often vary from those evaluated in clinical trials.