Off-label and oft-prescribed

Off-label use of medications, ie, prescribing drugs for indications not specified in their US Food and Drug Administration (FDA)-approved labels, is somewhat tainted. Companies have been penalized for promoting such use, and physicians criticized for receiving compensation for advocating this in educational venues. None of us can give a talk that is approved for continuing medical education credit by the Accreditation Council for Continuing Medical Education without stating whether we will be discussing any off-label drug use, with the not-so-subtle implication that we may be hawking a bill of goods for some financial benefit and that the attendees may be unable to determine for themselves the credibility of the speaker and the potential clinical benefits of the cited therapies based on data provided. Then there are issues with insurance payment for medications utilized for off-label indications—without FDA approval, the drugs are deemed to be experimental. Yet, there are situations where off-label use of certain medications is of unequivocal benefit to patients.

In no way do I minimize the value of the imprimatur of FDA approval stating a drug, after appropriate preclinical and clinical studies, is deemed safe and effective. Whatever the agency's shortcomings, the story of thalidomide (a drug never approved by the FDA) gives credence to the value of having a robust approval process. Arguments will likely continue forever as to whether the agency errs on the side of being too permissive or too restrictive in its approval process.

Nonetheless, I believe there are valid clinical reasons why we should continue to prescribe FDA-approved medications for nonapproved indications. In my practice, I treat some conditions that are sufficiently uncommon or heterogeneous in expression that large-scale clinical trials are logistically hard to carry out or deemed financially unviable by the corporate sponsor, even though clinical experience has informed us of a reasonable likelihood of efficacy. Sometimes drugs have "failed" in clinical trials, but experience and post hoc subset analysis of data have indicated a likely positive response in certain patients.

Although a drug that has been FDA approved has passed significant safety testing, the patients exposed to the drug when it was evaluated for treating a certain disease may be strikingly different from patients who have a different disease—the age, sex, comorbidities, and coprescribed medications may all differ significantly in the population of patients with the "off-label" disorder. Hence, appropriate caution is warranted, and if relevant, this should be explained to patients before giving them the medication.

In this issue of the *Journal*, 2 papers address the use of medications in an "off-label" manner. On page 807, Schneider and colleagues discuss several frequent clinical uses of tricyclic antidepressants for reasons other than depression, and on page 815, Modesto-Lowe and colleagues review the more controversial use of gabapentin in patients with alcohol use disorder. The hoped-for benefits in both circumstances are symptomatic, and both benefits and side effects are dose-related in ways not necessarily coinciding with those in the FDA-labeled indications.

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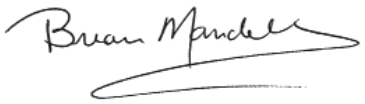
My experience in using tricyclics as adjunctive treatment for fibromyalgia is that patients are quite sensitive to some of the side effects of the drugs (eg, oral dryness and fatigue), even in low doses. Moreover, we should expect only modest benefits, which should be explicitly described to the patient: improved quality of sleep with resultant decreased fatigue (while we watch closely for worsened fatigue from too-high dosing) and a modest reduction in pain over time as part of a multimodality treatment plan. I often find that practitioners who are less familiar with the use of these medications in this setting tend to start at lowish (but higher than often tolerated) doses, have patients take the medication too close to bedtime (resulting in some morning hangover sensation), fail to discuss the timing and degree of expected pain relief, don't titrate the dose over time, and are not aware of the different responses that patients may experience with different medications within the same class. As with all prescribed medications, the benefits and ill effects must be frequently assessed, and particularly with these medications, one must be willing to discontinue them if appropriate outcomes are not achieved.

"Off-label" should not imply off the table as a therapeutic option. But it is incumbent on us to devote sufficient time to explain to each patient the anticipated side effects and hoped-for benefits, particularly since in most cases, we and our patients cannot refer to the results of definitive phase 3 clinical trials or patient online information sites that are totally relevant, reliable, data supported, and FDA reviewed.



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