Preparation of Lower Dosages of SNRI Antidepressants to Ameliorate Discontinuation Symptoms: Two Case Studies

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There is a large body of evidence showing that adverse effects experienced with antidepressant treatment ameliorate over time and that disease-state symptoms improve for many patients (1). However, there is a paucity of information relating to how to stop these medications when a patient’s depression has remitted. Presented here are two cases that demonstrate the role pharmacists play in helping patients discontinue SNRI medications through the preparation of lower strength dosage forms.

Introduction

Duloxetine (Cymbalta®, Lilly) and desvenlafaxine (Pristiq®, Wyeth/Pfizer) are selective serotonin and norepinephrine reuptake inhibitors (SNRIs) approved for use in Canada for the treatment of major depressive disorder. Duloxetine is also indicated for the treatment of neuropathic pain associated with diabetic peripheral neuropathy, fibromyalgia, generalized anxiety disorder, osteoarthritis of the knee, and chronic low back pain. Duloxetine is available in 30 and 60 mg capsules containing enteric-coated pellets; a 20 mg capsule is available in other countries (2). Desvenlafaxine is available as a 50 mg or 100 mg extended release tablet, with a 25 mg tablet available in other markets (3).

There is scant information in the published literature regarding the process of weaning off either SNRI. While discontinuation reactions from selective serotonin reuptake inhibitors (SSRIs) are well recognized in both the adult and pediatric populations (4), there are no clear guidelines for tapering schedules. SNRIs have also been shown to cause discontinuation symptoms including dizziness, insomnia, irritability, nausea, abnormal dreams, and hyperhidrosis (5). These symptoms can mimic major depression and result in re-treatment due to a misdiagnosis of a relapse (6). Discontinuation symptoms typically manifest within one to seven days of stopping these medications (4). For SSRIs, the availability of fluoxetine, an agent with a longer half-life, can facilitate the weaning process. However, for SNRIs, the medications all have similarly short elimination half-lives, meaning a switch to an alternative SNRI is unlikely to lessen discontinuation symptoms.

Case 1

A 49-year-old male with a diagnosis of multiple sclerosis was initiated on duloxetine for neuropathic pain. The physician was targeting a dose of 60 mg for treatment, however, the patient was instructed to adjust his dose as needed and was provided with 30 mg capsules. While duloxetine is not approved in Canada for this indication, there is some evidence for its use (7). According to the patient, the physician told him that discontinuation would not be an issue with this medication. Concomitant medications included dalfampridine 10 mg twice daily and a tapering dose of prednisone.

The patient initiated treatment with duloxetine 30 mg daily, and, over a period of 4 months, made attempts to maintain the target dose of 60 mg. He decided to stop the medication, as it did not seem to impact his pain even when taking the 60 mg dose. Prior to discontinuing, the patient had been taking the 30 mg daily dose for two weeks (the lowest dose commercially available). Despite being stable at this low dose, he experienced dizziness, nausea, and ‘brain zaps’ upon stopping, which affected his ability to work. These symptoms would begin within three days of stopping the duloxetine and necessitated him to reintroduce the medication.
We offered to compound a lower dosage of duloxetine to provide a more gradual taper. An experienced pharmacy assistant opened a duloxetine 30 mg capsule and weighed the pellets inside on a digital scale; the contents of one capsule, including excipients, weighed 180 mg. She then weighed out half the amount (90 mg), placed it in a size 3 empty gel capsule and prepared a two-week supply. The patient felt well on the 15 mg dose and the decision was made to prepare two weeks of 7.5 mg capsules. The patient was able to successfully wean off duloxetine with a decrease in the withdrawal symptoms he found most intolerable; however, after completely stopping the medication, he continued to experience ‘brain zaps’ several times a day for a few more days. Despite this, the taper did seem to prevent the development of dizziness and nausea.

Case 2

In another case, a 36-year-old female presented a prescription from a psychiatrist for a tapering course of desvenlafaxine, with dose decreases of 5 mg weekly starting at 45 mg. The patient had been taking desvenlafaxine for nine months for the treatment of major depressive disorder. Her medical history was insignificant otherwise. Notably, desvenlafaxine is formulated as a hypromellose polymer matrix extended-release tablet that cannot be split, chewed, or crushed. Because of the design of the tablet and how the release of drug is controlled, it is not possible to compound it into a capsule while retaining an extended release profile (8). This was confirmed in discussion with the manufacturer [personal communication, 21/04/15].

Following discussion with the physician, a new prescription for venlafaxine was provided, with an initial dose of 100 mg daily for one week, decreasing by 10 mg weekly. There is little guidance available for switching patients from desvenlafaxine to venlafaxine. Fifty-five percent of a dose of venlafaxine is metabolized to desvenlafaxine (3) and thus many clinicians use a doubling of the desvenlafaxine dose to provide the equivalent venlafaxine dose.

We followed a similar procedure to compound the venlafaxine capsules as we had for the duloxetine. We weighed the contents of five 150 mg PMS-venlafaxine XR capsules, of which the average weight was 401 mg. We then used this to calculate the amount needed for each week of the taper. At follow-up with the pharmacy, three weeks after beginning the taper, the patient had experienced no adverse effects and was happy with the therapy.

Discussion

Interestingly, when we contacted the medical information department at Eli Lilly, we were provided with a summary of discontinuation-emergent adverse events that included more detailed information than the product monograph.

The product monographs for both duloxetine (Cymbalta®) and desvenlafaxine (Pristiq®) provide information about discontinuation symptoms. Following abrupt or tapered discontinuation in placebo-controlled clinical trials, the following symptoms occurred at a rate greater than or equal to 1% and at a significantly higher rate in Cymbalta®-treated patients compared to those discontinuing from placebo: dizziness, nausea, headache, paresthesia, fatigue, vomiting, irritability, nightmares, insomnia, diarrhea, anxiety, hyperhidrosis, vertigo, somnolence, and myalgia. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, dose titration should be managed on the basis of the patient’s clinical response.

We performed a search of Index Medicus and Medline (OvidSP) using the search terms duloxetine, desvenlafaxine, Cymbalta, or Pristiq, and withdrawal or discontinuation. In a letter, Hou reported long-term withdrawal syndrome in a patient of Asian ancestry treated for depression (9). Indeed, the patient experienced intermittent duloxetine withdrawal syndrome for 10 months. There is a report of withdrawal syndrome in a newborn whose mother was taking 90 mg of duloxetine before and during her pregnancy (10). Another case report described shock-like sensations associated with duloxetine discontinuation (11).

There has been a phase IV, manufacturer-sponsored trial investigating the discontinuation of desvenlafaxine (12). This trial included 357 patients taking a 24-week course of desvenlafaxine who were randomly assigned to three groups: abrupt discontinuation of 50 mg dosages, continuation, or a one-week taper to 25 mg prior to discontinuation. No statistically significant difference in discontinuation events was found in DESS (Discontinuation-Emergent Signs and Symptoms) scores assessed by the trial investigators. However, there was a trend to greater adverse events with abrupt discontinuation, and the fact that both discontinuation groups had higher rates of adverse events suggest there is still a need for strategies to ameliorate withdrawal. Further, this study did not address relapse, was only conducted in patients taking a relatively short course of medication, and did not address previous treatment for depression. Curiously, Pfizer’s USA market monograph still mentions the availability of the 25 mg dosage form to assist with discontinuation, despite the results of this trial.
**Conclusion**

Although not recommended by the manufacturer [personal communication, 02/02/15], preparing lower dosages of duloxetine is effective for blunting withdrawal reactions. In the case of desvenlafaxine, the monograph states that tapering is an option; however, there is no practical way of achieving this with commercially available dosage forms. Switching to venlafaxine XR compounded capsules provides the ability to slowly taper a patient’s dose and reduce discontinuation symptoms.

A recent article published in the Journal of Pharmacy Practice acknowledges the difficulty in selecting a medication regimen for discontinuing antidepressants (13). The authors noted that many trials are not designed to effectively track outcomes after discontinuation. This reiterates the need for including discontinuation outcomes in clinical trials of new antidepressant medications. For those medications already on the market, this represents an area where further research needs to be conducted. It would be helpful to have established guidelines for tapering, such as alternate day scheduling or decreasing by a certain percentage of the dose over time, to try to lessen the likelihood of withdrawal symptoms. Pharmaceutical companies manufacturing SSRIs and SNRIs should be encouraged to produce tapering dosage suggestions in conjunction with initiation schedules.

We encourage pharmacists to highlight to patients and prescribers considering cessation of treatment with duloxetine or desvenlafaxine the possibility of withdrawal symptoms on discontinuation. There is potential for patients and their health care professionals to mistake withdrawal symptoms for a recurrence of depression (6). Pharmacists should follow-up with patients in the weeks following discontinuation to monitor for changes in depressive and withdrawal symptoms.

**References**


