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RUDER·FINN

MEMO

TO: Bonnie Rossello
Barry Brand

FR: Sandra Stahl

RE: Discontinuation

5 June 1997

We've written two draft letters to the editor regarding the Lilly discontinuation supplement. One is from Drs. Pollock, Krishnan and Nemeroff. The other would be authored by Ivan.

Here are some points of consideration as you review them:

- We'll have to reference the actual supplement (as opposed to the supplement preview) for statements regarding what Rosenbaum et al. state or allege when?
- In the issue of J. Clin Psych we had around, all the letters were written as case reports. If this is a requirement, we'll need to ask one of the physicians to provide one.
- The references listed for discontinuation symptoms with all SSRIs is the same for both letters, and complete duplication will look fishy if we decide to submit both. Are there other references we could draw on for the various drugs? At the very least, we can't have the references appear in the same order.

Please have a look at these and let us know how you'd like to proceed. Thanks.

All attached
Other references
from Ivan

WB 084726

[Letter from Drs. Nemeroff, Krishnan, and Pollock]

Sir:

Rosenbaum et al.[1] suggest that selective serotonin reuptake inhibitors (SSRIs) with longer half-lives are less likely to cause discontinuation symptoms than those with shorter half-lives. Discontinuation symptoms have been reported with all the SSRIs.[2-7] In our experience they occur infrequently and are usually mild, transient, and less severe than those associated with discontinuation of tricyclic antidepressants.

For SSRIs with long half-lives and active metabolites, such as fluoxetine, the incidence of discontinuation symptoms can be assessed only if the follow-up is long enough. A study of fluoxetine would require 4 to 5 weeks of follow-up after stopping the medication; we are aware of no such study. In the clinical setting, a patient who abruptly stops treatment with a long-acting agent may not associate a symptom that occurs several weeks later with discontinuation of therapy.

In situations where it is desirable to achieve washout quickly, an antidepressant with a short half-life and no active metabolites has clear advantages. Such situations include allergic reactions such as anaphylactoid events and rash; adverse reactions such as nausea or bruising (due to depletion of serotonin from platelets); and severe hyponatremia, which has been reported in elderly patients and attributed to inappropriate antidiuretic hormone secretion induced by SSRIs.[1] In addition, if a patient becomes pregnant, one might wish to discontinue therapy as quickly as possible. With fluoxetine, a woman will have the drug and active metabolites in her blood for 5 weeks after discontinuation. A drug with a shorter half-life, if discontinued immediately after conception, could wash out before the fetal-placental circulation is established.

In the absence of an emergency, however, antidepressants should not be discontinued abruptly, primarily because of the risk that depression will recur. With paroxetine, we taper the dose by 50% every 5 days. If any symptoms occur, we proceed more slowly. For patients who experience symptoms after stopping the drug entirely, we start it again at 10 mg/day and then reduce the dose to 10 mg every other day.

For patients who stop taking an antidepressant on their own, it is important to find out whether they did so because of side effects, a perceived lack of efficacy, or some other reason. We recommend reemphasizing to patients the importance of taking the medication every day, not just when they feel depressed, and of not stopping the medication on their own; and then deciding whether to resume the original therapy or switch to another agent.

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References

Letters to the Editor

Discontinuation Symptoms and SSRIs

Sir: I read with interest the recent supplement[1] to the *Journal* based on the meeting chaired by Dr. Schatzberg and agree that the constellation of symptoms associated with the abrupt discontinuation of selective serotonin reuptake inhibitors (SSRIs) has emerged as a topic of clinical interest. I have difficulty understanding, however, some of the conclusions drawn by the Discontinuation-Consensus Panel of authors in this supplement, namely, that "discontinuation reactions are more likely to occur or to become apparent during discontinuation of SRIs [serotonin reuptake inhibitors] that have shorter half-lives than the extended half-life agent fluoxetine" and that symptoms of discontinuation are "minimized by a slow taper or by using a drug that has an extended half-life."[1(p9A)]

A relatively large and growing body of anecdotal reports, open-label studies, and retrospective chart reviews describes discontinuation symptoms with the SSRIs. Clearly, each of the SSRIs, including fluoxetine,[2-9] paroxetine,[4-6,9] sertraline,[3,10-17,19] and fluvoxamine,[18,20] causes discontinuation symptoms. Abrupt discontinuation of SSRIs is characterized by mild and self-resolving symptoms that can include dizziness, nausea, vomiting, diarrhea, nervousness, and rhinitis.

As suggested by Schatzberg,[2] differences in elimination half-lives among the SSRIs do appear to result in distinct temporal profiles of discontinuation symptoms. Published case reports describe discontinuation symptoms for paroxetine and sertraline that generally persist for 1 to 2 weeks after cessation of treatment,[11-16] which is consistent with the approximately 24-hour elimination half-lives of these SSRIs. The longer acting fluoxetine (with an elimination half-life of 4 to 6 days for the parent compound and 4 to 16 days for the pharmacologically active metabolite, norfluoxetine) has been reported to cause discontinuation symptoms beginning up to 25 days after therapy is stopped. The case report literature describes fluoxetine-related discontinuation symptoms persisting for up to 56 days.[3,5,7-9] Thus, the longer elimination half-life of fluoxetine appears to be associated with discontinuation symptoms that occur later and last longer compared with those associated with shorter-acting SSRIs.

The preliminary findings from one direct comparative study of the SSRIs suggest that fluoxetine, unlike paroxetine or sertraline, is not associated with discontinuation symptoms.[1] However, patients in this study were assessed for only 5 to 8 days after stopping therapy, which is generally not a sufficiently long period of time for discontinuation symptoms with fluoxetine to appear. If clinical trials are to accurately study between-agent differences, they must be designed with sufficiently long follow-up to observe discontinuation symptoms that occur after long-acting agents are stopped.

Regardless of the suggestion by Rosenbaum and Zajecka[21] in the supplement that the abrupt discontinuation of SSRIs with longer elimination half-lives results in self-tapering, discontinuation symptoms nevertheless occur. Unlike agents with shorter half-lives, drugs with prolonged elimination half-lives are associated with an extended duration of adverse effects, drug accumulation, complicated titration schedules, and extended fetal exposure for women who conceive during therapy. All SSRIs should be tapered when therapy is stopped unless there is a medical reason for immediate removal of the drug. The time course of adverse effects is prolonged for SSRIs with long elimination half-lives, which, in the case of serious sequelae (e.g., serotonergic syndrome[22] or syndrome of inappropriate antidiuretic hormone secretion[23]) or a frail, elderly patient, represents a real clinical problem.

Each of the SSRIs causes discontinuation symptoms, and the time course of symptoms is directly related to the elimination half-life of the drug and the duration of therapy. The majority of published clinical data on this topic is derived from anecdotal case reports,[24] which generally rely on patients' observations of adverse effects. Clearly, patients are more likely to attribute discontinuation symptoms to a drug when symptoms occur shortly after therapy is stopped (as would occur with a shorter half-life agent) than when symptoms occur 1 week or more after discontinuing treatment (as with an agent with a longer half-life). Thus, the suggestions by some investigators that SSRIs with prolonged elimination half-lives are associated with a minimal rate of discontinuation symptoms[25,26] may be based on data that are spuriously low and not representative of actual prevalence.

The Discontinuation Consensus Panel[27] argues in the supplement that cholinergic rebound is one putative mechanism for discontinuation symptoms, particularly with paroxetine. This theory is based on in vitro findings that, among the SSRIs, paroxetine possesses the highest affinity for muscarinic receptors.[28] However, recent data from our laboratory do not support the extrapolation of these in vitro findings to the clinical setting as was done by the authors of the supplement. We compared serum anticholinergicity and anticholinergic side effects in 54 depressed, elderly patients who were being treated with therapeutic doses of paroxetine or nortriptyline. Under these clinically relevant conditions, paroxetine exhibited an 8-fold lower level of serum anticholinergicity (0.07 ± 0.19 pmol atropine equivalents) than nortriptyline (0.57 ± 0.45, $p = .0004$). In addition, nortriptyline was associated with significantly more dry mouth and tachycardia than paroxetine.[29] Paroxetine has also been shown to be devoid of adverse anticholinergic cardiovascular effects in depressed patients with ischemic heart disease as compared with nortriptyline, which, like other tricyclic antidepressants, has clinically significant cardiac effects in this population.[30] Manufacturers' prescribing information for paroxetine and sertraline describes similar rates of dry mouth for these agents,[31,32] despite differences in in vitro affinities for the muscarinic receptor.[28] Thus, although paroxetine is the most anticholinergic SSRI in an in vitro setting, clinical data obtained both under rigorously controlled conditions and from clinical experience do not support the argument made in the supplement.

As stated in the supplement,[1] the available evidence demonstrates that abrupt cessation of SSRI therapy can be associated with a mild, transient constellation of somatic and psychological symptoms. Some of the conclusions drawn by the authors of the supplement warrant a closer look. Clinical experience and published reports demonstrate that, regardless of elimination half-life, all of the SSRIs cause discontinuation symptoms after abrupt withdrawal and all SSRIs should be gradually tapered

when stopping therapy. Should it be needed, management consists of restarting the SSRI and gradually tapering the dose. Alternatively, patients can be educated about the transient nature of these symptoms and encouraged to wait until the symptoms resolve. Rather than directing our efforts toward the relatively infrequent, minor, and transient discontinuation symptoms associated with SSRI therapy, clinicians may be well advised to focus their energies on the greater issues of efficacy, safety, and patient outcome.

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Dr. Schatzberg Replies

Sir: We appreciate the comments of Dr. Pollock regarding the special supplement on SSRI discontinuation. He notes that fluoxetine can be associated with discontinuation symptoms but that these occur several weeks after discontinuation. We agree that they can occur. However, these rebound symptoms have been very frequently reported with fluoxetine than with almost all the other SSRIs and are rarely a problem. In a 6-week follow-up, double-blind study[7] of discontinuation from fluoxetine, the percentage of patients reporting any adverse events was 30% for patients continuing on fluoxetine and 40% for those switched to placebo. The incidence of dizziness at 6 weeks was 5% for those who discontinued versus 1% for those who switched to placebo. Thus, the problem does appear to be less of an issue with fluoxetine, which has a long half-life, than with other SSRIs.

The apparently higher rates of discontinuation symptoms with the shorter acting agents should not be construed as an indication that we need not be aware of the possibility of such symptoms with longer acting agents. Rather, they are more likely to occur and to be apparent with shorter acting agents where there is less time to achieve homeostasis. Of interest is the recent analysis of the World Health Organization database that noted higher rates of reporting of such symptoms in patients discontinuing from paroxetine and sertraline than in those discontinuing from fluoxetine.[32] Moreover, they noted that fluoxetine was more commonly associated with psychiatric reactions (nervousness, anxiety, depression, etc.) than with CNS manifestations (dizziness, headache, etc.) The opposite was true for paroxetine and sertraline. Thus, they concluded that these data indicated "a possible qualitative difference between the SSRIs with respect to the nature of the withdrawal syndrome."[32(p1001)] This study reported mean days off drug to point of symptoms of 9.5, 24, and 6.6 days for paroxetine, fluoxetine, and sertraline, respectively. The respective medians were 2, 3, and 2 days, indicating a skewing of the data and suggesting that some patients may demonstrate earlier discontinua-