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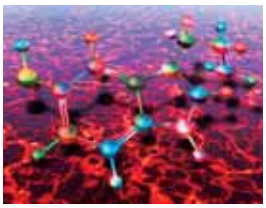

To Abruptly Cross Over or Not: That Is the Question in SSRI Conversion

Kristin Zerumsky, PharmD, Rae Ann Maxwell, RPh, PhD, and Nicole T. Ansani, PharmD

Educational Objectives

After reviewing this article, the reader should be able to:

- Describe the effect of the half-life of an SSRI on the incidence of serotonin withdrawal syndromes when a patient's SSRIs are switched.
- Recognize the signs and symptoms of serotonin syndrome.
- Recognize the signs and symptoms of withdrawal syndrome.

Abstract

Patients are often required to "cross over" between selective serotonin reuptake inhibitors (SSRIs) because of cost savings or a lack of the agent's effectiveness. Pharmacokinetics, serotonin syndrome, and withdrawal symptoms must be considered when therapy is changed.

This review analyzes the data available regarding changing from one SSRI to another; however, the findings are inconclusive in terms of the advisability of safely and abruptly switching from one SSRI to another. Therefore, we recommend evaluating the pharmacokinetic profile of the SSRI agents when a switch is being considered. SSRIs with a longer half-life may cause symptoms of serotonin syndrome if patients are switched, whereas using agents with a shorter half-life may result in withdrawal symptoms. Patients should be aware of the possible excessive serotonin-related symptoms that can occur within the first few days to weeks after a switch.

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Key words: discontinuation, crossover, taper, selective serotonin reuptake inhibitor

Introduction

Selective serotonin reuptake inhibitors (SSRIs) are considered first-line therapy in treating many depressive disorders, and they are among the most commonly prescribed drugs in the U.S.[1,2] Currently, the evidence is insufficient to suggest that one SSRI is superior to another; however, patients may require a change from one SSRI agent to another during their course of therapy. For example, some patients may respond better to a particular SSRI than another.[3] Other reasons for switching SSRI therapy include possible cost savings associated with generic alternatives, drug intolerance, and new or potential drug interactions. Although case reports and clinical trials have evaluated safe and effective conversion of SSRIs, there are no published guidelines or recommendations regarding cross-over agents.

This article summarizes the available literature and provides a practical application of the evidence to guide clinicians in changing SSRI therapy. It specifically addresses whether patients should abruptly stop one SSRI, then begin taking the new agent immediately, or whether they should slowly discontinue the agent before initiating therapy with the new SSRI.

We conducted searches using Medline (from 1966 to January 2005) and PyschInfo (from 1967 to January 2005). We used the key words "selective serotonin reuptake inhibitor," "cross-over," "discontinuation," and "taper" to evaluate the literature and to analyze the safest and most effective methods of changing SSRI regimens. From this search, we consistently identified three factors that need to be considered in safely changing SSRI therapy:

- the pharmacokinetic profile of the current SSRI
- the possibility of serotonin syndrome
- withdrawal symptoms

Selective Serotonin Reuptake Inhibitors

The SSRIs include such drugs as citalopram (Celexa®, Forest), escitalopram (Lexapro®, Forest), fluvoxamine (Luvox®, Solvay), fluoxetine (Prozac®, Eli Lilly), paroxetine HCl (Paxil®, GlaxoSmithKline), paroxetine mesylate (Pexeva®, Synthon), and sertraline (Zoloft®, Pfizer). These agents selectively inhibit presynaptic neuronal serotonin uptake, with a minimal effect on dopamine and norepinephrine.

SSRI agents were developed as an alternative to the tricyclic antidepressants (TCAs) to minimize adverse cardiovascular and anticholinergic effects and to treat numerous psychiatric disorders, including depression and obsessive–compulsive disorder (OCD). The most common adverse drug events (ADEs) reported with all the SSRIs are gastrointestinal disturbances, insomnia, fatigue, and sexual dysfunction. Weight gain is also commonly seen with paroxetine.[4] If patients are unable to tolerate the ADE profile of one SSRI, clinicians may consider choosing an alternative SSRI.

The problem of drug interactions can arise when patients begin SSRI therapy or during their treatment. Table 1 lists the pharmacokinetic characteristics of the various SSRIs as well as potential differences in drug interactions caused by interaction with the cytochrome enzyme system. Fluoxetine and paroxetine are both potent inhibitors of the CYP 2D6 isoenzyme and have the highest potential for drug interactions.[8–10]

Factors to Consider in Conversion of SSRI Therapy

Pharmacokinetics

Theory

The pharmacokinetic profile of the existing SSRI regimen should be evaluated before patients begin taking a new SSRI. The elimination half-life of the SSRI and its active metabolites may predict the potential for withdrawal symptoms or excessive serotonin levels (see Table 1). For instance, fluoxetine has a longer half-life than other SSRIs; this can contribute to excess serotonin levels when the new agent is initiated immediately after fluoxetine is discontinued.

Evidence

Randomized, controlled trials evaluating the impact of pharmacokinetics on clinical outcomes of a switch in SSRI therapy have not been published; only limited pharmacokinetic data are available.

Dominquez et al. These authors noted a lack of ADEs on pharmacokinetic parameters after an abrupt switch from fluoxetine to paroxetine.[12] No ADEs were reported in this study, and clinical efficacy outcomes were not measured.

The Potential for Serotonin Syndrome

Theory

Baldessarini, Radomski et al., and Lane and Baldwin. Overlapping treatment with SSRIs has the potential to cause serotonin syndrome as a result of excessive serotonin in the central nervous system.[13] Symptoms include akathisia, muscle twitches or tremor, nervousness, insomnia, sweating, and coma and seizures in extreme cases.[14,15]

Lane and Baldwin reported that pyrexia, neuromuscular symptoms, and changes in mental status must be present for a diagnosis of serotonin syndrome to be confirmed, because an immediate switch of an SSRI can produce a pharmacodynamic interaction and may increase serotonin toxicity symptoms, suggesting the presence of the syndrome.[15]

Evidence

Haider et al. A randomized, single-blinded, crossover study was conducted to determine the efficacy and safety of switching patients from fluoxetine to sertraline.[16] Eligible patients received at least two months of fluoxetine therapy. The patients were randomly selected to abruptly change to sertraline therapy 50 mg (n = 25) or 75 mg (n = 23) for every 20 mg of fluoxetine or to continue taking fluoxetine (n = 22). Study outcomes included improvement, worsening, or no change in depression and drug safety.

The results demonstrated no significant differences in efficacy for either treatment group. Four possible cases of serotonin syndrome were reported with symptoms, including nervousness, shaking, insomnia, dysphoria, anxiety, restlessness, and nightmares. Three cases were reported in those patients who were switched from fluoxetine to sertraline 50 mg and in one patient who switched to sertraline 75 mg. The authors concluded that the symptoms of serotonin syndrome were a result of residual fluoxetine, but they did not note the possibility of a drug interaction.

Kreider et al. In a double-blind, randomized study, these researchers assessed the tolerability of abruptly changing SSRI therapy from fluoxetine to paroxetine, compared with a two-week washout period.[17] Patients who had maintained fluoxetine therapy for at least six weeks were assigned to immediately switch to 20 mg of paroxetine for four weeks (n = 123) or to change to placebo for two weeks, followed by paroxetine for two weeks (n = 119). The primary endpoint was tolerability.

Seven patients in the immediate crossover group withdrew from the study within two weeks, compared to three weeks for patients given a washout period ($P = .22$). Reasons for withdrawal in the immediate crossover group (from fluoxetine to paroxetine) included headache, arthralgia, insomnia, nervousness and sweating (consistent with excessive serotonin), kidney stones, and migraine. Reasons for withdrawal in the washout group were ethanol abuse and chest pain.

The incidence of ADEs was lower in the patients given a washout period during the first two weeks of the study. Insomnia was the only event that was significantly more common in the immediate crossover group ($P < .05$). The authors concluded that patients could safely cross over from fluoxetine to paroxetine with or without a washout period. The authors did not report any efficacy findings for either group.

Stock and Kofoed. A retrospective review was performed to

Table I **Pharmacokinetic Characteristics of Available Selective Serotonin Reuptake Inhibitors**

	Citalopram	Escitalopram	Fluoxetine	Fluvoxamine	Paroxetine HCl	Paroxetine Mesylate	Sertraline
Half-life	35 hours	27–35 hours	Initial: 24–72 hours Steady state: 96–144	16 hours	21 hours	33.2 hours	26 hours
Active metabolite half-life	N/A	N/A	Norfluoxetine: 4–16 days	N/A	N/A	N/A	*N*-desmethyl-sertraline: 2–4 days
CYP-450 interactions	2C19,3A4 substrate	2C19, 3A4 2D6 substrate	2D6 substrate and potent inhibitor	2C9 substrate and 2C9 and 2C19 inhibitor	2D6, 3A4 substrate potent 2D6 inhibitor	2D6, 3A4 substrate potent 2D6 inhibitor	2D6, 3A4, 2C19 substrate

Data from references 5 to 11.
N/A = not applicable.

evaluate the impact of an SSRI interchange program on clinical efficacy and safety endpoints in depressed patients.[18] Of the 126 patients who were evaluated, 31 and 41 patients received only fluoxetine or sertraline, respectively; 54 patients were enrolled in the SSRI therapeutic interchange from fluoxetine to sertraline. The evaluated outcomes included reasons for discontinuation and dosage adjustment.

The results revealed that 34 of the 54 patients in the interchange program were considered to have successfully switched from fluoxetine to sertraline, as judged by clinicians. Ten patients whose therapy was changed from fluoxetine to sertraline were deemed to have had an unsuccessful change in SSRI therapy secondary to intolerable side effects such as nervousness, jitteriness, nausea, and headache. The authors attributed these ADEs to a possible increase in central serotonin activity.

For the remaining unsuccessful patients whose SSRI agent was changed, two patients stopped treatment because of the medication's lack of efficacy; data were not reported for the remaining eight patients. Significantly more patients in the fluoxetine to sertraline group (37%) discontinued therapy than in the sertraline group (12%) ($P < .009$). The discontinuation rates for the fluoxetine group were not reported.

The authors discussed the possibility of an unexpected drug interaction of fluoxetine and sertraline causing serotonin syndrome–associated symptoms attributable to the long-half life of fluoxetine.

Miner et al. An additional study evaluated the safety and efficacy of changing patients maintained on paroxetine, citalopram, or sertraline for six to 52 weeks to once-weekly fluoxetine.[19] In this multicenter, open-label study, 246 patients who were receiving citalopram 20–40 mg/day (n = 83), paroxetine 20 mg/day (n = 86), or sertraline 50–100 mg/day (n = 77) were switched to 90 mg of fluoxetine weekly with no washout period. The primary endpoints were the percentage of patients who discontinued therapy because of a relapse of depressive symptoms or because of the agent's lack of efficacy. Secondary endpoints included safety evaluations.

The results showed that the rate of relapse and lack of efficacy were similar between groups. The most common ADEs after the crossover were rhinitis, headache, nervousness, and insomnia; these effects were similar among all groups of patients. The incidence of nervousness decreased over time in all three groups.

The authors concluded that a crossover to once-weekly fluoxetine was both safe and efficacious.

Withdrawal Symptoms

Theory

Withdrawal symptoms have been reported in 0.06 to 5.1% of patients who discontinue SSRI therapy. These symptoms include disequilibrium, gastrointestinal disturbances, influenza-like symptoms, paresthesia, insomnia, and vivid dreams. More serious effects include mania and "electrical shock" sensations.[20]

Withdrawal symptoms have also been experienced by patients who abruptly discontinued therapy as well as those whose doses were tapered.[11,17,19–21] Symptoms generally occur within one to three days after drug cessation and resolve within two to several weeks.

Symptoms are also more common in SSRIs with shorter half-lives, such as paroxetine and fluvoxamine.[20] Withdrawal symptoms, however, are rapidly reversed when the original SSRI or another SSRI is reintroduced.[20] If the clinician prefers a washout period when switching patients from one SSRI to another, these symptoms must be monitored, most notably when the SSRI that is being discontinued has a short half-life.

Evidence

Rosenbaum et al. These investigators studied the abrupt cessation of SSRI treatment in 242 patients who were main-

tained on fluoxetine (n = 81), sertraline (n = 79), or paroxetine (n = 82) for four to 24 months in a randomized, multicenter, double-blind, placebo-controlled study.[1] The primary endpoint was the difference in discontinuation-emergent ADEs, which occurred within seven days of treatment cessation. These 43 possible signs or symptoms of withdrawal were derived from the literature and were formulated into a checklist by the investigators.

It was found that the fluoxetine-treated patients (14%) had significantly fewer symptoms of withdrawal than patients who received maintenance sertraline (60%) and paroxetine (66%) ($P < .001$). The most commonly occurring symptoms included dizziness, headache, gastrointestinal disturbances, insomnia, irritability, change in mood, and emotional liability.

The proposed reason for the decreased incidence of withdrawal symptoms with fluoxetine was its long half-life. There was also a significant worsening in depression scales in the sertraline and paroxetine groups after interruption of therapy compared with the fluoxetine group. Therefore, patients maintained on fluoxetine may be able to better tolerate abrupt discontinuation of therapy than those treated with sertraline or paroxetine.

Henry et al. Henry and colleagues evaluated the effect of SSRI treatment interruption by examining concentrations of paroxetine and fluoxetine in the brain after cessation of a three-day treatment.[21] Patients received maintenance therapy with either 20 mg of fluoxetine (n = 5) or paroxetine (n = 5) for six to 12 months. Drug concentrations were measured 48 to 60 hours after the last dose of medication.

After this abrupt cessation, 75% of the serum fluoxetine concentration remained, whereas only 12% of the paroxetine concentration remained ($P < .0001$). In addition, 88% of the fluoxetine and 38% of the paroxetine remained in the brain, as confirmed by changes in fluorine magnetic resonance spectroscopy ($P = .004$). The paroxetine patients reported a significant increase in ADEs after discontinuing treatment ($P < .02$), but the fluoxetine patients reported no difference in ADEs ($P = .75$). The type and frequency of the ADEs were not reported.

The authors concluded that the slower elimination of SSRIs in the brain might contribute to a decreased incidence of withdrawal symptoms for the fluoxetine patients. They noted that this difference might be multifactorial and might include differences in lipophilicity between serum and brain compartments. Further inquiry is needed to validate this theory.

Keuthen et al., Barr et al., and Pacheco et al. In addition to the studies just described, case reports have documented withdrawal symptoms after patients discontinued paroxetine therapy. In the studies by Keuthen,[20] Barr,[22] and Pacheco[23] and their collegaues, withdrawal symptoms occurred in three, five, and five patients, respectively, when paroxetine was tapered over a period of two to 14 days. Patients experienced gastrointestinal tract ADEs (e.g., emesis, nausea) and central nervous system ADEs (e.g., dizziness, headache). These effects were thought to be related to the tapered SSRI.

Discussion

When clinicians are deciding whether to switch patients from one SSRI to another, they should consider the current agent's pharmacokinetic profile and the possibility of serotonin syndrome and withdrawal symptoms. No published guidelines are yet in place for conversion between the various SSRIs. Data are derived primarily from small, randomized, controlled and blinded studies; open-label studies; retrospective reviews; and pharmacokinetic analyses. Case reports do not permit a blanket recommendation for all patients or SSRI agents. A summary of this evidence demonstrates that abrupt switching of SSRIs is generally well tolerated, but clinicians should recognize that serotonin syndrome and withdrawal symptoms have been documented. Therefore, clinicians must also make decisions after considering the current SSRI and the proposed switch agent.

Drugs with a long half-life, such as fluoxetine, tend to be associated with an increased risk of serotonin syndrome if patients are abruptly switched to another SSRI without a suitable washout period. By contrast, withdrawal symptoms have been most commonly reported with agents that have a short half-life, especially if a new agent is not initiated when the current agent is discontinued. The potential for withdrawal symptoms has been illustrated in several case studies with paroxetine, which has one of the shortest half-lives among the SSRIs, and the clinical impact should be considered when patients are discontinuing SSRI therapy.[1,17,19,21,22]

Patients should be counseled about possible adverse effects related to excessive serotonin levels (e.g., nervousness, insomnia, and tremor), particularly if they are using an SSRI with a long half-life, and they should be instructed to notify their health care provider if these ADEs occur. The use of concomitant medications should be taken into consideration, because these may increase the concentration or prolong the half-life of the agent that is to be discontinued.

If the patient has previously experienced serotonin-related ADEs or if the clinician wants to be more certain of preventing serotonin syndrome when switching from an agent with a long half-life to one with a shorter half-life agent, it might be prudent to wait for three to five half-lives for the existing agent to be eliminated before a new agent is initiated.

Conversely, if patients are switching from a shorter-half-life agent to another SSRI, regardless of its half-life, and if the physician wants to prevent discontinuation symptoms, the new agent can be initiated within one to two days after the first agent is stopped.

If the patient is taking a higher dose of any agent, it is reasonable to taper the drug to a lower dose before discontinuing the agent and starting another.

Conclusion

Before firm guidelines can be made to assist health care providers in stopping one SSRI and changing to another, further controlled studies are needed. There is no clinical evidence of the efficacy of switching a patient from one SSRI

with a short half-life to one with a longer half-life (i.e., paroxetine to fluoxetine). Clinicians are encouraged to report their findings when they switch patients from one SSRI to another.

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Conflict-of-Interest (COI) Statement

The content of this article has been reviewed under Jefferson's Continuing Medical Education COI policy.

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TOPIC: To Abruptly Cross Over or Not: That Is the Question in SSRI Conversion

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Multiple Choice

Select the one correct answer.

1. **Among patients who discontinue SSRI therapy, approximately what proportion report withdrawal symptoms?**
   a. 0%–5%
   b. 10%–20%
   c. 25%–30%
   d. 40%–50%

2. **The most common symptoms associated with SSRI withdrawal include all of the following *except:***
   a. disequilibrium.
   b. electric shock sensations.
   c. gastrointestinal disturbances.
   d. sexual dysfunction.

3. **After discontinuation of SSRI therapy, what is the approximate onset of withdrawal symptoms among patients who experience them?**
   a. within 24 hours
   b. 1–3 days
   c. 7–10 days
   d. 2 weeks to several weeks

4. **According to the literature, which of the following drugs has the lowest incidence of withdrawal symptoms upon cessation?**
   a. fluoxetine
   b. sertraline
   c. paroxetine
   d. The incidence of withdrawal symptoms is the same for all of these drugs.

5. **Which of the following has an active metabolite with a half-life of 2 to 4 days?**
   a. citalopram
   b. fluoxetine
   c. sertraline
   d. paroxetine

6. **All of the following are symptoms of serotonin syndrome *except:***
   a. akathisia.
   b. muscle twitches and tremors.
   c. nervousness.
   d. influenza-like symptoms.

7. **According to the study by Lane and Baldwin, all of the following need to be present in order to confirm a diagnosis of serotonin syndrome *except:***
   a. pyrexia.
   b. neuromuscular symptoms.
   c. seizures.
   d. mental status changes.

8. **All of the following SSRIs are metabolized by CYP-450 3A4 *except:***
   a. citalopram.
   b. fluoxetine.
   c. paroxetine.
   d. sertraline.

9. **All of the following are CYP-450 2D6 substrates *except:***
   a. sertraline.
   b. fluoxetine.
   c. escitalopram.
   d. citalopram.

10. **Which drug has the shortest half-life among SSRIs?**
    a. citalopram
    b. fluvoxamine
    c. paroxetine
    d. sertraline

CE Registration and Evaluation Form

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3.	a ☐	b ☐	c ☐	d ☐	8.	a ☐	b ☐	c ☐	d ☐
4.	a ☐	b ☐	c ☐	d ☐	9.	a ☐	b ☐	c ☐	d ☐
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9. Which ONE of the following best describes the impact of this activity on your performance:
   - ☐ This program will not change my behavior because my current practice is consistent with what was taught.
   - ☐ This activity will not change my behavior because I do not agree with the information presented.
   - ☐ I need more information before I can change my practice behavior.
   - ☐ I will immediately implement the information into my practice.

10. Will you take any of the following actions as a result of participating in this educational activity (check all that apply)
   - ☐ Discuss new information with other professionals
   - ☐ Discuss with industry representative(s)
   - ☐ Other _____
   - ☐ Consult the literature
   - ☐ Participate in another educational activity
   - ☐ None

Send the completed form and $10 payment (make checks payable to P&T) to: Department of Health Policy, Thomas Jefferson University, Attn: Continuing Education Credit, 1015 Walnut Street, Suite 115, Philadelphia, PA 19107.