

### Basic Pharmacokinetic Parameters of SSRIs<sup>20</sup>

Parameter	Fluvoxamine	Fluoxetine	Paroxetine	Sertraline
<b>GI absorption</b>	<b>&gt; 94%</b>	<b>80%</b>	<b>&gt; 64%</b>	<b>&gt; 44%</b>
<b>Tmax(Hr)(range)<sup>a</sup></b>	<b>5(1-8)</b>	<b>6-8</b>	<b>5(0.5-11)</b>	<b>2-4</b>
<b>Bioavailability</b>	<b>53%</b>	<b>94%</b>	<b>100%</b>	<b>NA</b>
<b>Protein binding</b>	<b>77%</b>	<b>95%</b>	<b>95%</b>	<b>99%</b>
<b>Half life</b>		<b>360 hours</b>	<b>21 hours</b>	<b>26 hours(96)</b>
<b>parent</b>	<b>15 hours<sup>b</sup></b>	<b>1.9 days</b>	<b>18-24 hours</b>	<b>26 hours</b>
<b>active metabolite</b>	<b>NA</b>	<b>7-9 days</b>	<b>NA</b>	<b>62 hours<sup>c</sup></b>
<b>Renal excretion<sup>d</sup></b>	<b>94%</b>	<b>80%</b>	<b>64%</b>	<b>44%</b>
<b>Fecal excretion<sup>d</sup></b>	<b>-</b>	<b>15%</b>	<b>36%</b>	<b>44%</b>
	<b>Luvox</b>	<b>Prozac</b>	<b>Paxil</b>	<b>Zoloft</b>

**Prozac –72 hours active metabolite 360 hours**

**Paxil (Aropax) 21 hours no active metabolite**

**Zoloft 26 hours inactive metabolite 96 hours**

**Effexor – 5 hours metabolite 11 hours**

**Celexa – 36 hours**

**Luvox – 6 hours**

**Table 2. Suggested SSRI and SSNRI Tapering Schedule**

<b>Fluoxetine*</b>	<b>Reduce by 5 mg every two weeks until dose is 5 mg/day, then 2.5 mg every two weeks</b>
<b>Fluvoxamine</b>	<b>Reduce by 25 mg every two weeks until dose is 25 mg/day, then 12.5 mg every two weeks</b>
<b>Paroxetine</b>	<b>Reduce by 10 mg every two weeks until dose is 10 mg/day, then 5 mg/day every two weeks</b>
<b>Sertraline</b>	<b>Reduce by 25 mg every two weeks until dose is 25 mg/day, then 12.5 mg every two weeks</b>
<b>Venlafaxine</b>	<b>Reduce by 25 mg every two weeks until dose is 25 mg/day, then 12.5 mg/day every two weeks</b>

\*A liquid preparation may be used for the 5 mg and 2.5 mg dose.

**Example Case:** A patient with depression is receiving 20 mg/day of fluoxetine. Upon discontinuation she experiences symptoms of SSRI withdrawal. Resume fluoxetine at a dose of 20 mg/day until symptoms abate. Then decrease the dose by 5 mg to 15 mg/day for two weeks. If the patient tolerates the lower dose without withdrawal symptoms decrease the dose to 10 mg/day for two weeks. Continue the taper according to the above schedule.

## Conclusion

From the literature, paroxetine appears to be the SSRI most likely to cause withdrawal syndrome, with fluvoxamine and sertraline a close second, possibly due to their high inhibition constants and their shorter half-lives. Published fluoxetine withdrawal reports are scarce, possibly due to the long half-life of fluoxetine and the active metabolite norfluoxetine. Adequate controlled studies are needed to determine the true incidence of withdrawal syndrome, describe patient risk factors, and design the best regimen for tapering the dose of each SSRI. Considering the relatively few published reports available concerning this syndrome compared to the large number of patients who are prescribed SSRIs, we consider withdrawal syndrome to be an uncommon event. Until studies are completed, we recommend that consultant pharmacists monitor for withdrawal symptoms (Table 3) for a minimum of seven days in all patients who discontinue SSRI therapy. If symptoms occur, advise prescribers to restart the SSRI and slowly taper patients off the medication.

**Table 3. Symptoms associated with SSRI Withdrawal Syndrome**

- **Lightheadedness**
- **Dizziness**
- **Vertigo**
- **Gait instability**
- **Headaches**
- **Fatigue**
- **Insomnia**
- **Bizarre dreams**
- **Confusion**
- **Problems with concentration and memory**
- **Gastrointestinal distress**
- **Electric shock sensations**
- **Anxiety**
- **Paresthesia**
- **Irritability**



Paroxetine does not improve symptoms and impairs cognition in frontotemporal dementia: a double-blind randomized controlled trial.

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**RATIONALE.** Patients with frontal variant frontotemporal dementia (fvFTD) present with disinhibition, impulsiveness, apathy, altered appetite and stereotypic behaviors. A non-randomized clinical trial found improvement in these symptoms after treatment with a selective serotonin reuptake inhibitor (SSRI). **OBJECTIVES.** We aimed to subject a SSRI, paroxetine, to a more rigorous test of its efficacy using a double-blind, placebo-controlled experimental design. **METHODS.** Ten subjects meeting the consensus criteria for FTD were entered into a double-blind, placebo-controlled crossover trial. Doses of paroxetine were progressively increased to 40 mg daily. The same regimen was used for placebo capsules. Subjects were assessed with a battery of cognitive tests in the sixth week of paroxetine and placebo treatment. At each assessment, caregivers were interviewed using the Neuropsychiatric Inventory and asked to complete the Cambridge Behavioral Inventory. **RESULTS.** There were no significant differences on the Neuropsychiatric Inventory or the Cambridge Behavioral Inventory. Paroxetine caused a decrease in accuracy on the paired associates learning task, reversal learning and a delayed pattern recognition task. There were no changes on the decision-making task, in spatial span, spatial recognition, spatial working memory, digit span and verbal fluency. **CONCLUSIONS.** This study finds no evidence for the efficacy of paroxetine in the treatment of fvFTD. The results suggest that a chronic course of paroxetine may selectively impair paired associates learning, reversal learning and delayed pattern recognition. This pattern of deficits closely resembles that seen after tryptophan depletion. Results are discussed with respect to current theories on serotonergic modulation of orbitofrontal/ventromedial prefrontal cortex.