



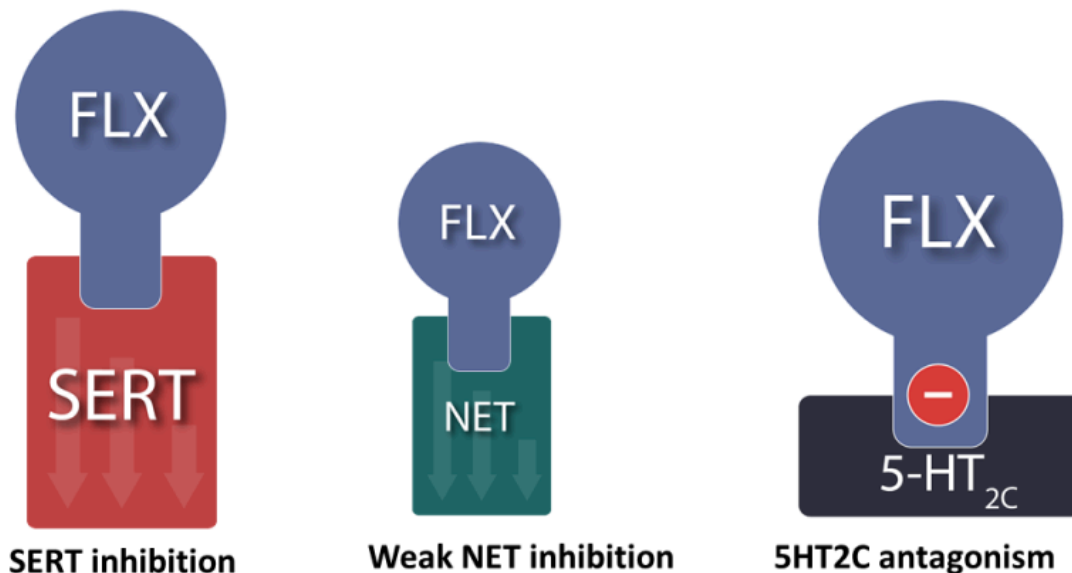
The Psychopharmacology of Fluoxetine: Mechanism of Action, Indications, Pharmacokinetics and Dosing

Flavio Guzman, M.D.
Editor,
Psychopharmacology Institute

Fluoxetine has activating properties that make it a good option for patients with retarded depression or atypical depression. However, we should avoid activation in patients with insomnia and agitation. There is something that makes fluoxetine unique: its long half-life, we will discuss the advantages and disadvantages of this in clinical practice. This long half-life allowed the development of a weekly capsule. The other important pharmacokinetic concept is that fluoxetine is a potent inhibitor of the CYP2D6.

Pharmacology and MOA

Fluoxetine binding profile





As other SSRIs, fluoxetine inhibits the serotonin transporter protein. In addition, it is also a weak norepinephrine reuptake inhibitor, this effect increases with higher doses. However, the clinical relevance of this norepinephrine effect is not clear. Fluoxetine is an antagonist at 5HT_{2C} receptors, this has been proposed as a potential mechanism for its activating properties.

Clinical Uses

FDA-approved indications

Mood disorders	Anxiety disorders	Other
<ul style="list-style-type: none">• Major depressive disorder• Bipolar depression (as OFC)	<ul style="list-style-type: none">• Panic disorder• OCD	<ul style="list-style-type: none">• Bulimia nervosa• Premenstrual dysphoric disorder

Prozac (Fluoxetine) [Prescribing Information]. Indianapolis, IN : Lilly USA. Accessed April 2014



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Fluoxetine is approved for the treatment of major depressive disorder and bipolar depression. In the case of bipolar depression, its use is approved in a combined olanzapine formulation, called olanzapine-fluoxetine combination, or OFC (Symbyax). It is also approved for anxiety disorders such as panic disorder and OCD. Other indications include bulimia nervosa and premenstrual dysphoric disorder. Fluoxetine is the only antidepressant approved for the treatment of bulimia.



Pharmacokinetics

Fluoxetine has a long half-life



Most SSRIs:
approximately 1 day



Fluoxetine: 2 to 4 days

Norfluoxetine: 7 to 15 days

Preskorn, Sheldon H. "Clinically relevant pharmacology of selective serotonin reuptake inhibitors." *Clinical pharmacokinetics* 32.1 (1997): 1-21.



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Fluoxetine has unique pharmacokinetic properties, probably what distinguishes fluoxetine from other SSRIs is its long half-life. Most SSRIs have a half-life of approximately 1 day. On the other hand, fluoxetine has a half-life of 2 to 4 days, its active metabolite, norfluoxetine has a half-life of 7 to 15 days.



Fluoxetine has a long half-life



Advantages

- Good for treatment adherence
- Protects from discontinuation syndrome

Preskorn, Sheldon H. "Clinically relevant pharmacology of selective serotonin reuptake inhibitors." *Clinical pharmacokinetics* 32.1 (1997): 1-21.



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Long half-life has advantages and disadvantages. One advantage is that this is beneficial in terms of treatment adherence, patients who skip daily doses are still covered. The other is that this long half-life protects the patient from SSRI discontinuation syndrome.

Fluoxetine has a long half-life



Disadvantages

- Longer washout period for switching to MAOIs: 5 weeks

Lane, Roger, and David Baldwin. "Selective serotonin reuptake inhibitor-induced serotonin syndrome: review." *Journal of clinical psychopharmacology* 17.3 (1997): 208-221.

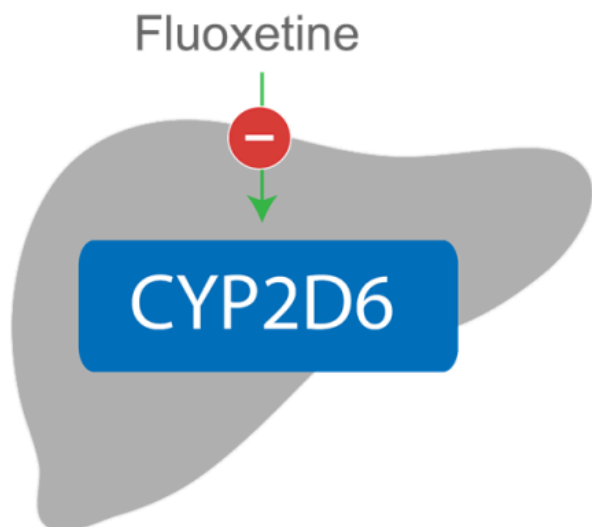


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A clear disadvantage involves drug-drug interactions. If you need to switch a patient from fluoxetine to an MAOI, you will have to wait a longer washout period before initiating the MAOI. It is generally recommended to wait 5 weeks.

Fluoxetine and CYP2D6



- Fluoxetine: potent CYP2D6 inhibitor
- Norfluoxetine: moderate CYP3A4 inhibitor

Preskorn, Sheldon H. "Clinically relevant pharmacology of selective serotonin reuptake inhibitors." *Clinical pharmacokinetics* 32.1 (1997): 1-21.



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Fluoxetine is a potent CYP2D6 inhibitor, the drug shares this feature with two other SSRIs: paroxetine and fluvoxamine. This opens the possibility of drug-drug interactions with CYP2D6 substrates. Norfluoxetine, its active metabolite is a moderate CYP3A4 inhibitor, but this is not clinically relevant.

Adverse effects



Adverse effects

Similar side effects as other SSRIs

Activation

- Nervousness, insomnia
- Usually transient, usually at the beginning, then remits

Pregnancy risk category C



Regarding side effects, it has a similar profile to other members of the SSRI class. There is one distinctive side effect related to its clinical profile: the possibility of causing activation. This is seen as nervousness or insomnia, it is usually transient, appears usually at the beginning of therapy and then remits. This should be kept in mind when prescribing fluoxetine to depressed patients with anxiety.

Prescribing information

Dosage range

Indication	Dose
Depression	20-60 mg/day
Anxiety disorders (lower starting dose)	20-60 mg/day
Bulimia	60 mg/day



Fluoxetine is generally doses between 20 and 60 mg/day for depression and anxiety disorders. The recommended starting dose for depression is 20 mg/day, it can be titrated to 60 mg/day. For anxiety disorders, the starting dose is lower, 10 mg/day, this is because of fluoxetine's activating properties. For bulimia the dose is higher, clinical trials showed efficacy only when dosed at 60 mg/day.

Formulations

- Capsules: 10 mg, 20 mg, 40 mg
- Tablet: 10 mg
- Liquid: 20mg/5ml -120 ml bottles
- Weekly capsule 90 mg

Prozac (Fluoxetine) [Prescribing Information]. Indianapolis, IN : Lilly USA. Accessed April 2014



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Fluoxetine is available in a number of formulations.

- Capsules of 10 mg, 20 mg and 40 mg
- 10 mg tablet
- Liquid formulation of 20 mg/5ml, this is available in 120 ml bottles
- Weekly capsule of 90 mg, this allows once weekly dosing

Other SSRI videos

- [Fluvoxamine Essentials: Mechanism of Action, Indications, Pharmacokinetics and Dosing](#)
- [Sertraline Essentials: Mechanism of Action, Indications, Pharmacokinetics and Dosing](#)
- [Citalopram and Escitalopram: A Summary of Key Differences and Similarities](#)
- The Psychopharmacology of Paroxetine: An Illustrated Summary for Prescribers

Note: this video has been translated to Spanish ["Fluoxetina: farmacodinamia, indicaciones, efectos adversos, farmacocinética y posología"](#)



References

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2. Schatzberg, Alan F., and Charles B. Nemeroff, eds. [The American psychiatric publishing textbook of psychopharmacology](#). American Psychiatric Pub, 2009.
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