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Flibanserin Therapy and *CYP2C19* Genotype

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Introduction

Flibanserin (brand name Addyi) is indicated for the treatment of "hypoactive sexual desire disorder" (HSDD) in premenopausal women. It is the first drug to be approved by the FDA for female sexual dysfunction. Flibanserin acts on central serotonin receptors and was initially developed to be an antidepressant. Although it was not effective for depression, flibanserin did appear to increase sex drive.

The use of flibanserin is limited by modest efficacy and the risk of severe hypotension and syncope (fainting). This risk is increased by alcohol, and by medications that inhibit CYP3A4 (the primary enzyme that metabolizes flibanserin). Consequently, alcohol use is contraindicated during flibanserin therapy, and flibanserin is contraindicated in individuals taking moderate or strong CYP3A4 inhibitors, which include several antibiotics, antiviral agents, cardiac drugs, and grapefruit juice.

The CYP2C19 enzyme also contributes to the metabolism of flibanserin, and individuals who lack CYP2C19 activity ("CYP2C19 poor metabolizers") have a higher exposure to flibanserin than normal metabolizers.

The risk of hypotension, syncope, and CNS depression may be increased in individuals who are CYP2C19 poor metabolizers, according to the FDA-approved drug label, which also states that approximately 2–5% of Caucasians and Africans and 2–15% of Asians are CYP2C19 poor metabolizers. However, the drug label does not provide alternative dosing for poor metabolizers (Table 1). The standard recommended dosage of flibanserin is 100 mg once per day, taken at bedtime (1).

Table 1. The FDA (2015) Drug Label for Flibanserin. Recommendations for CYP2C19 Poor Metabolizers.

Phenotype	Recommendations
CYP2C19 poor metabolizer	Increase monitoring for adverse reactions (e.g., hypotension) in individuals who are CYP2C19 poor metabolizers.

This FDA table is adapted from (1).

Drug: Flibanserin

Flibanserin is the first drug to be approved by the FDA to treat premenopausal women with "acquired, generalized hypoactive sexual desire disorder (HSDD), as characterized by low sexual desire that causes marked distress or interpersonal difficulty". The drug label states that flibanserin should not be used when problems with sexual desire are due to a coexisting medical or psychiatric condition, problems within the relationship, or the

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effects of medicine or other drugs. In addition, flibanserin should not be used to treat postmenopausal women or men, and it is not indicated to enhance sexual performance (1, 2).

Approximately 10% of adult women in the US are thought to have HSDD, which can significantly affect quality of life. The symptoms of HSDD vary, but may include a lack of sexual desire, impaired arousal, an inability to achieve orgasm, or a general decrease in sexual satisfaction, with accompanying distress (3, 4).

Note: in the 5th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM5), disorders of desire and arousal were joined into one classification titled female sexual interest/excitement and arousal disorder (FSIAD). However, HSDD is still referred to in the literature, and remains a central element of FSAID (5).

A common reason for sexual problems is insufficient or inadequate sexual stimulation, and the mainstay of treatment is counselling (sex therapy, couples therapy, psychotherapy). Sex therapy includes education on the differences in male and female genital anatomy; e.g., in women, the clitoris is the structure for sexual pleasure, whereas the vagina is a birth canal and not in itself a source of pleasure - therefore, sexual intercourse is unpleasurable and even painful when the woman is insufficiently aroused. Sex therapy provides a safe and respectful space for sexual feelings to emerge and can identify issues such as anxiety and sexual trauma.

In addition to counselling, the management of female sexual dysfunction may also include lifestyle changes (e.g., relaxation techniques, increasing quality time with partner), and physical therapy; e.g., for problems related to pelvic floor hypertonus such as dyspareunia (painful intercourse) and vaginismus (inability for the penis to enter the vagina despite a woman's wish to do so). Medications may include hormone therapy and phosphodiesterase inhibitors (although the latter is not licensed for use in women, and studies report inconsistent results) (6).

Flibanserin is thought to work by targeting central serotonin receptors – it is a postsynaptic 5-HT-1A agonist and 5-HT-2A antagonist. It also has a weak antagonist effect on HT2B, 5-HT2C and dopamine D4 receptors (7-9).

The FDA approval of flibanserin in 2015 was controversial, primarily because of modest efficacy and safety concerns. A daily dose of 100 mg of flibanserin, taken at bedtime, has been associated with a modest increase in sexual desire, and a modest increase of sexually satisfying events – an additional "one half" of an event, per month, on average (9-15). Although only indicated for premenopausal women, one study reported that flibanserin was generally well tolerated and may have efficacy in post-menopausal women (16, 17).

The safety concerns of flibanserin therapy include the risk of severe hypotension, syncope, and CNS depression (e.g., daytime sleepiness). These risks are further increased if flibanserin is taken during the day (it should be taken at bedtime), is taken with alcohol, or taken with CYP3A4 inhibitors (flibanserin is primarily metabolized by CYP3A4). Both alcohol use and the use of strong or moderate CYP3A4 inhibitors are contraindicated with flibanserin use (18, 19). There have been no studies of flibanserin in pregnant women, and it is unknown whether flibanserin causes fetal harm.

Inhibitors of CYP3A4 include antibiotics (e.g., clarithromycin, ciprofloxacin, telithromycin), antifungals (e.g., ketoconazole, itraconazole, posaconazole, fluconazole), HIV drugs – antiretrovirals (e.g., ritonavir, saquinavir, nelfinavir, indinavir, atazanavir) and protease inhibitors – (e.g., amprenavir, fosamprenavir); hepatitis C virus protease inhibitors (e.g., boceprevir, telaprevir), calcium channel blockers (e.g., diltiazem, verapamil), the diuretic conivaptan, the antidepressant nefazodone, and grapefruit juice.

In addition, several drugs can induce CYP3A4 and although concomitant use of these drugs with flibanserin therapy is not contraindicated, it is not recommended. This is because exposure to flibanserin will be decreased, potentially to subtherapeutic levels. The antibiotic rifampin, which is a strong CYP3A4 inducer, decreased concentrations of flibanserin by 95% (20).

The CYP2C19 enzyme has a less prominent role in the metabolism of flibanserin. However, strong CYP2C19 inhibitors may increase flibanserin exposure, and individuals who lack CYP2C19 activity ("CYP2C19 poor metabolizers") may have higher drug levels of flibanserin compared with normal metabolizers (20).

Gene: CYP2C19

The cytochrome P450 superfamily (CYP450) is a large and diverse group of hepatic enzymes that form the major system for metabolizing lipids, hormones, toxins, and drugs. The *CYP450* genes are very polymorphic and can result in reduced, absent, or increased drug metabolism.

The CYP2C19 enzyme contributes to the metabolism of a range of clinically important drugs, such as benzodiazepines, antiplatelet agents, some proton pump inhibitors, antidepressants, and flibanserin –– flibanserin was originally developed to be an antidepressant.

The *CYP2C19* gene is highly polymorphic, as currently there are 35 variant star (*) alleles catalogued by the Pharmacogene Variation (PharmVar) Consortium. The *CYP2C19*1* is considered the wild-type allele when no variants are detected and is associated with normal enzyme activity and the "normal metabolizer" phenotype.

The *CYP2C19*17* allele is associated with increased enzyme activity and is found among individuals with "rapid" (**1/*17*) and "ultrarapid" (**17/*17*) metabolizer phenotypes. Heterozygous carriers of nonfunctional alleles (e.g., **2* and **3*) are classified as "intermediate metabolizers" (e.g. **1/*2*), and individuals who have 2 nonfunctional alleles are classified as "poor metabolizers" (e.g., **2/*2*, **2/*3*) (Table 2).

Table 2. CPIC (2016). Assignment of CYP2C19 Phenotype based on Genotype.

Phenotype	Genotype	Examples of diplotypes
CYP2C19 ultrarapid metabolizer (approximately 2–5% of individuals)[a]	An individual who has 2 increased function alleles	**17/*17*
CYP2C19 rapid metabolizer (approximately 2–30% of individuals)	An individual who has one normal function allele and one increased function allele	**1/*17*
CYP2C19 normal metabolizer (approximately 35–50% of individuals)	An individual who has 2 normal function alleles	**1/*1*
CYP2C19 intermediate metabolizer (approximately 18–45% of individuals)	An individual who has one normal function allele and one no function allele, or one no function allele and one increased function allele	**1/*2* **1/*3* **2/*17*[b]
CYP2C19 poor metabolizer (approximately 2–15% of individuals)	An individual who has 2 no function alleles	**2/*2* **2/*3* **3/*3*

[a] CYP2C19 metabolizer status frequencies are based on average multi-ethnic frequencies. See the *CYP2C19* Frequency Tables for population-specific allele and phenotype frequencies (21).
[b] The predicted metabolizer phenotype for the**2/*17* genotype is a provisional classification. The currently available evidence indicates that the *CYP2C19*17* increased function allele is unable to completely compensate for the *CYP2C19*2* no function allele.
This table is adapted from (21).

Approximately 2% of Caucasians, 4% of African Americans, and 15–25% of East Asians are CYP2C19 poor metabolizers, and up to 45% of individuals are CYP2C19 intermediate metabolizers (2, 22-24).

The most common no function allele is *CYP2C19*2*, which is defined by a c.681G>A variant in exon 5 that creates an aberrant splice site that translates a truncated and nonfunctioning protein. The *CYP2C19*2* allele frequencies are ~15% in Caucasians and Africans, and ~29–35% in Asians (25).

For CYP2C19, another commonly tested no function variant is *CYP2C19*3*, which contains a c.636G>A variant in exon 4 that causes a premature stop codon. The *CYP2C19*3* allele frequencies are ~2-9% in Asian

populations, but rare in other racial groups. Other no function variants occur in less than 1% of the general population, and include *CYP2C19*4-*8* (25).

Linking Gene Variation with Treatment Response

Currently, data are lacking on the influence of the CYP2C19 genotype on the efficacy and toxicity of flibanserin.

The drug label for flibanserin cites one study that compared 100 mg daily flibanserin in CYP2C19 poor metabolizers and normal metabolizers. In nine women who were poor metabolizers, the maximum serum concentration of flibanserin was 1.5 times higher, compared with normal metabolizers. In addition, exposure to flibanserin was 1.3 times higher, and the drug's half-life increased by over 2 hours (from 11.1 hours in normal metabolizers to 13.5 hours in poor metabolizers).

Because CYP2C19 poor metabolizers have increased exposure to flibanserin, the FDA recommends increasing monitoring for adverse reactions (e.g., hypotension) in individuals who are CYP2C19 poor metabolizers.

In contrast to CYP3A4, the concurrent use of strong CYP2C19 inhibitors is not contraindicated with flibanserin therapy. However, the drug label does caution that the concomitant use of strong CYP2C19 inhibitors may increase flibanserin exposure, which in turn increases the risk of hypotension, syncope, and CNS depression. The label recommends discussing the use of a strong CYP2C19 inhibitor with the patient when prescribing flibanserin.

Drugs that are CYP2C19 inhibitors include selective serotonin reuptake inhibitors and other types of antidepressants (e.g., fluoxetine, fluvoxamine, moclobemide), antibiotics (e.g., chloramphenicol, isoniazid), antifungals (e.g., fluconazole, voriconazole), proton pump inhibitors and histamine antagonists (e.g., cimetidine, esomeprazole, omeprazole), HIV drugs (e.g., delavirdine, efavirenz), benzodiazepines, and other types of anti-seizure drugs (e.g., oxcarbazepine, felbamate, topiramate), and antiplatelet agents (e.g., clopidogrel, ticlopidine) (1, 20).

Genetic Testing

Clinical genotyping tests are available for several *CYP2C19* alleles. The NIH's Genetic Testing Registry (GTR) provides examples of the genetic tests that are currently available for the *CYP2C19* gene and flibanserin response. In addition, variant CYP2C19 alleles to be included in clinical genotyping assays have been recommended by the Association for Molecular Pathology (AMP) (27).

Clinical *CYP2C19* genotyping results are reported as a diplotype, such as *CYP2C19 *1/*1*, that typically also include an interpretation of the individual's predicted metabolizer phenotype (ultrarapid, normal, intermediate, or poor). Table 2 summarizes common CYP2C19 phenotypes.

Therapeutic Recommendations based on Genotype

This section contains excerpted[1] information on gene-based dosing recommendations. Neither this section nor other parts of this review contain the complete recommendations from the sources.

2015 Statement from the US Food and Drug Administration (FDA): CYP2C19 poor metabolizers had increased flibanserin exposures compared to CYP2C19 extensive metabolizers. Additionally, syncope occurred in a subject who was a CYP2C19 poor metabolizer. Therefore, increase monitoring for adverse reactions (e.g.,

[1] The FDA labels specific drug formulations. We have substituted the generic names for any drug labels in this excerpt. The FDA may not have labeled all formulations containing the generic drug. Certain terms, genes and genetic variants may be corrected in accordance to nomenclature standards, where necessary. We have given the full name of abbreviations, shown in square brackets, where necessary.

hypotension) in patients who are CYP2C19 poor metabolizers. The frequencies of poor CYP2C19 metabolizers are approximately 2–5% among Caucasians and Africans and approximately 2– 15% among Asians.

Please review the complete therapeutic recommendations that are located here: (1).

Nomenclature for selected *CYP2C19* alleles

Common allele name	Alternative names	HGVS reference sequence		dbSNP reference identifier for allele location
		Coding	Protein	
*CYP2C19*2*	681G>A Pro227Pro	NM_000769.1:c.681G>A	NP_000760.1:p.Pro227=	rs4244285
*CYP2C19*3*	636G>A Trp212Ter	NM_000769.1:c.636G>A	NP_000760.1:p.Trp212Ter	rs4986893
*CYP2C19*17*	-806C>T	NM_000769.1:c.-806C>T	Not applicable - variant occurs in a non-coding region	rs12248560

Note: the normal "wild type" allele is *CYP2C19*1*.
Guidelines for the description and nomenclature of gene variations are available from the Human Genome Variation Society (HGVS): http://www.hgvs.org/content/guidelines
Nomenclature for Cytochrome P450 enzymes is available from the Human Cytochrome P450 (CYP) Allele Nomenclature Database: http://www.cypalleles.ki.se/

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