Escitalopram

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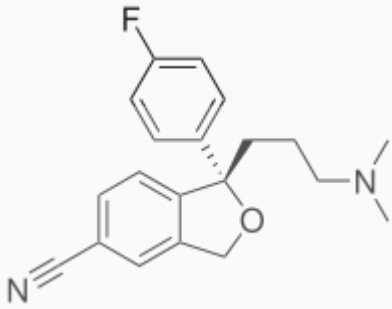

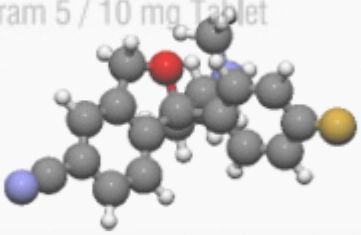

Systematic (IUPAC) name	
(*S*)-1-[3-(Dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile	
Clinical data	
Trade names	Lexapro
AHFS/Drugs.com	monograph
MedlinePlus	a603005
Licence data	US FDA:link
Pregnancy cat.	C (AU) C (US)

Legal status	Prescription Only (S4) (AU) POM (UK) ℞-only (US)
Routes	Oral
Pharmacokinetic data	
Bioavailability	80%
Protein binding	~56%
Metabolism	Liver, specifically the enzymesCYP3A4 and CYP2C19
Half-life	27–32 hours
Identifiers	
CAS number	128196-01-0
ATC code	N06AB10
PubChem	CID 146570
DrugBank	DB01175
ChemSpider	129277
UNII	4O4S742ANY
ChEBI	CHEBI:36791
ChEMBL	CHEMBL1508
Chemical data	

Formula	$C_{20}H_{21}FN_2O$
Mol. mass	324.392 g/mol (414.43 as oxalate)
SMILES	• Fc1ccc(cc1)[C@@]3(OCc2cc(C#N)ccc23)CCCN(C)C
InChI	InChI=1S/C20H21FN2O/c1-23(2)11-3-10-20(17-5-7-18(21)8-6-17)19-9-4-15(13-22)12-16(19)14-24-20/h4-9,12H,3,10-11,14H2,1-2H3/t20-/m0/s1 Key:WSEQXVZVJXJVFP-FQEVSTJZSA-N

Escitalopram is an antidepressant of the selective serotonin reuptake inhibitor (SSRI) class. It is approved by the U.S. Food and Drug Administration (FDA) for the treatment of adults and children over 12 years of age with major depressive disorder (MDD) and generalized anxiety disorder (GAD). Escitalopram is the (*S*)-stereoisomer (enantiomer) of the earlier Lundbeck drug citalopram, hence the name *es*citalopram. Whether escitalopram exhibits superior therapeutic properties to citalopram or merely represents an example of "evergreening" is controversial.[1]

Medical uses

Escitalopram has FDA approval for the treatment of major depressive disorder and generalized anxiety disorder in adults.[2] In European countries, it is approved for depression (MDD) and certain anxiety disorders: general anxiety disorder (GAD), social anxiety disorder (SAD), obsessive-compulsive disorder (OCD), and panic disorder with or without agoraphobia.

Depression

Escitalopram was approved by regulatory authorities for the treatment of major depressive disorder on the basis of four placebo controlled, multi-center, double-blind clinical trials, three of which demonstrated a statistical superiority to placebo.[3] Nonetheless, considerable controversy exists regarding the superiority of escitalopram to its predecessor citalopram. The importance of

this issue follows from the greater cost of escitalopram relative to the generic mixture of isomers citalopram prior to the expiration of the escitalopram patent in 2012, which led to charges of "evergreening". Accordingly, this issue has been examined in at least 10 different systematic reviews and meta analyses. The most recent of these have concluded (with caveats in some cases) that escitalopram is modestly superior to citalopram in efficacy and/or tolerability.[4][5][6][7]

In contrast to these findings, a 2011 review concluded that all second generation antidepressants are equally effective,[8] and treatment guidelines issued by the National Institute of Health and Clinical Excellence and by the American Pyschiatric Association generally reflect this viewpoint.[9][10]

The utility of antidepressant drugs in the treatment of mild-to-moderate depression is itself controversial. This issue is discussed in detail in the SSRI article.

Anxiety disorder

There may be a significant improvement in GAD symptoms as early as the first week and the majority of patients respond by week eight with a significant improvement in functioning.[11] It also seems effective in the long-term with relapse on escitalopram (20%) less than placebo (50%).[12]

Escitalopram and citalopram appear equally effective in panic disorder.[13]

Other

Escitalopram as well as other SSRIs are effective in reducing the symptoms of premenstrual syndrome, whether taken in the luteal phase only or continuously.[14] There is no good data available for escitalopram for seasonal affective disorder as of 2011.[15]

Adverse effects

Escitalopram, like other SSRIs, has been shown to affect sexual functions causing side effects such as decreased libido, delayed ejaculation, genital anesthesia,[16] andanorgasmia.[17][18]

An analysis conducted by the FDA found a statistically insignificant 1.5 to 2.4-fold (depending on the statistical technique used) increase of suicidality among the adults treated with escitalopram for psychiatric indications.[19][20][21] Similarly, the UK MHRA data indicate an 80% increase of suicide-related events, not reaching statistical significance, in the escitalopram vs. placebo patients.[22] The authors of a related study note the general problem with statistical approaches: due to the rarity of suicidal events in clinical trials, it is hard to draw firm conclusions with a sample smaller than two million patients.[23]

Escitalopram is not associated with significant weight gain. For example, 0.6 kg mean weight change after 6 months of treatment with escitalopram for depression was insignificant and similar to that with placebo (0.2 kg).[24] 1.4–1.8 kg mean weight gain was reported in 8-month trials of escitalopram for depression,[25] and generalized anxiety disorder.[26] A 52-week trial of escitalopram for the long-term treatment of depression in elderly also found insignificant 0.6 kg mean weight gain.[27] Escitalopram may help reduce weight in those treated forbinge eating associated obesity.[28]

Citalopram and escitalopram are associated with dose-dependent QT interval prolongation[29] and should not be used in those with congenital long QT syndrome or known pre-existing QT interval prolongation, or in combination with other medicines that prolong the QT interval. ECG measurements should be considered for patients with cardiac disease, and electrolyte disturbances should be corrected before starting treatment. In December 2011, the UK implemented new restrictions on the maximum daily doses:

- for citalopram, 40 mg for adults; 20 mg for patients older than 65 years; and 20 mg for those with hepatic impairment.
- for escitalopram, 10 mg for patients older than 65 years; other doses remain unchanged.[30][31]

Escitalopram should be taken with caution when using Saint John's wort.[32] Exposure to escitalopram is increased moderately, by about 50%, when it is taken with omeprazole. The

authors of this study suggested that this increase is unlikely to be of clinical concern.[33] Caution should be used when taking cough medicine containing dextromethorphan (DXM) as serotonin syndrome, liver damage, and other negative side effects have been reported.

List of adverse effects

[34][35][36][37]

Very common (>10% incidence) adverse effects include:

- Headache
- Nausea

Common (1-10% incidence) adverse effects include:

- Insomnia
- Somnolence
- Dizziness
- Paraesthesia
- Tremor
- Decreased appetite
- Increased appetite
- Anxiety
- Restlessness
- Abnormal dreams
- Libido decreased
- Anorgasmia
- Sinusitis
- Yawning
- Diarrhea
- Constipation
- Vomiting
- Dry mouth
- Excessive sweating
- Arthralgia (joint pain)
- Myalgia (muscular aches and pains)
- Fatigue
- Pyrexia (fever)
- Ejaculation disorder,
- Impotence (erectile dysfunction)

Discontinuation symptoms

Main article: SSRI discontinuation syndrome

Escitalopram discontinuation, particularly abruptly, may cause certain withdrawal symptoms such as "electric shock" sensations[38] (also known as "brain shivers" or "brain zaps"), dizziness, acute depressions and irritability, bladder control issues, as well as heightened senses of akathisia.[39]

Human data suggests there's a risk when taking Lexapro in the third trimester of pregnancy.[40]

Overdose

Excessive doses of escitalopram usually cause relatively minor untoward effects such as agitation and tachycardia. However, dyskinesia, hypertonia, and clonus may occur in some cases. Plasma escitalopram concentrations are usually in a range of 20-80 µg/L in therapeutic situations and may reach 80-200 µg/L in the elderly, patients with hepatic dysfunction, those who are poor CYP2C19 metabolizers or following acute overdose. Monitoring of the drug in plasma or serum is generally accomplished using chromatographic methods. Chiral techniques are available to distinguish escitalopram from its racemate, citalopram.[41][42][43] Escitalopram seems to be less dangerous than citalopram in overdose and comparable to other SSRIs.[44]

Drug/Food Interactions

Escitalopram, similarly to other SSRIs (with the exception of fluvoxamine), inhibits CYP2D6 and hence may increase plasma levels of a number of CYP2D6 substrates such as aripiprazole, risperidone, codeine, etc. Escitalopram can also prolong the QT interval and hence it is not recommended in patients that are concurrently on other medications that have the ability to prolong the QT interval. Being a SSRI escitalopram should not be given concurrently with MAOIs or other serotonergic medications.[45]

Pharmacology

Escitalopram increases intrasynaptic levels of the neurotransmitter serotonin by blocking the reuptake of the neurotransmitter into the presynaptic neuron. Of the SSRIs currently on the market, escitalopram has the highest affinity for the human serotonin transporter (SERT). The enantiomer of escitalopram ((*R*)-citalopram) counteracts to a certain degree the serotonin-enhancing action of escitalopram. As a result, escitalopram has been claimed to be a more potent antidepressant than citalopram, which is a racemic mixture of the two enantiomers. In order to explain this phenomenon, researchers from Lundbeck proposed that escitalopram enhances its own binding via an additional interaction with another allosteric site on the transporter.[46] Further research by the same group showed that (*R*)-citalopram also enhances binding of escitalopram,[47] and therefore the allosteric interaction cannot explain the observed counteracting effect. In the most recent paper, however, the same authors again reversed their findings and reported that (*R*)-citalopram decreases binding of escitalopram to the transporter.[48] Although allosteric binding of escitalopram to the serotonin transporter is of unquestionable research interest, its clinical relevance is unclear since the binding of escitalopram to the allosteric site is at least 1000 times weaker than to the primary binding site.

Escitalopram is a substrate of P-glycoprotein and hence P-glycoprotein inhibitors such as verapamil and quinidine may improve its blood-brain penetrability.[49] In a preclinical study in rats combining escitalopram with a P-glycoprotein inhibitor enhanced its antidepressant-like effects.[49]

History

Escitalopram was developed in close cooperation between Lundbeck and Forest Laboratories. Its development was initiated in the summer of 1997, and the resulting new drug application was submitted to the U.S. FDA in March 2001. The short time (3.5 years) it took to develop escitalopram can be attributed to the previous extensive experience of Lundbeck and Forest with citalopram, which has similar pharmacology.[50] The FDA issued the approval of escitalopram for major depression in August 2002 and for generalized anxiety disorder in December 2003. On May 23, 2006, the FDA approved a generic version of escitalopram by Teva.[51] On July 14 of that year, however, the U.S. District Court of Delaware decided in favor of Lundbeck regarding the patent infringement dispute and ruled the patent on escitalopram valid.[52]

In 2006 Forest Laboratories was granted an 828 day (2 years and 3 months) extension on its US patent for escitalopram.[53] This pushed the patent expiration date from December 7, 2009 to September 14, 2011. Together with the 6-month pediatric exclusivity, the final expiration date was March 14, 2012.

Society and culture

Allegations of illegal marketing

In 2004, two separate civil suits alleging illegal marketing of citalopram and escitalopram for use by children and teenagers by Forest were initiated by two whistleblowers, one by a non-practicing physician named Joseph Piacentile, and the other by a Forest salesman named Christopher Gobble.[54] In February 2009, these two suits received support from the US Attorney for Massachusetts and were combined into one. Eleven states and the District of Columbia have

also filed notices of intention to intervene as plaintiffs in the action. The suits allege that Forest illegally engaged in off-label promoting of Lexapro for use in children, that the company hid the results of a study showing lack of effectiveness in children, and that the company paid kickbacks to doctors to induce them to prescribe Lexapro to children. It was also alleged that the company conducted so-called "seeding studies" that were, in reality, marketing efforts to promote the drug's use by doctors.[55][56] Forest responded to these allegations that it "is committed to adhering to the highest ethical and legal standards, and off-label promotion and improper payments to medical providers have consistently been against Forest policy.[57]"

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