EXPERT REVIEWS

Escitalopram for the treatment of major depression and anxiety disorders

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Escitalopram is the S-enantiomer of the selective serotonin reuptake inhibitor (SSRI) citalopram, which contains equal amounts of the S- and R-forms in a racemic mixture. Escitalopram is the most selective SSRI, with almost no significant affinity to other tested receptors. It has been demonstrated that it is escitalopram that carries the therapeutic potential of citalopram, and has statistically superior and clinically relevant properties compared with citalopram. Escitalopram is at least as effective in the treatment of depression and anxiety as other SSRIs, as well as venlafaxine, bupropion and duloxetine. Owing to multiple metabolic degrading pathways, the clinically relevant interactions of escitalopram with other drugs are minimal. Compared with other antidepressants, escitalopram is generally better tolerated, its onset of action is relatively fast, and its use may have cost–effectiveness and cost–utility advantages. Escitalopram is an effective first-line option in the management of patients with major depression, including severe forms, and various anxiety disorders.

KEYWORDS: anxiety • chiral stereoisomer • depression • enantiomer • escitalopram

Until recently, the majority of antidepressant compounds with asymmetric (chiral) carbon atoms were used in the form of the racemate, such as a mixture of stereoisomers (e.g., fluoxetine, reboxetine, mianserin, mirtazapine, venlafaxine, milnacipran). In compounds with a single chiral center, two enantiomorphic stereoisomers occur, S- and R- forms. The S–R classification represents a given convention derived from the formula of glyceraldehyde and does not always correspond with optical rotation. Enantiomers can exert different pharmacological properties, so that isolation of one of them can lead to the separation of the more therapeutically efficient isomer with lower toxicity. Citalopram (Cipralex®, Lexapro®, Seroplex®, Sipralexa® – H Lundbeck A/S) is an example of such an S–R racemate (FIGURES 1 & 2). When compared with the R-form, escitalopram is a substantially more effective serotonin reuptake inhibitor with a somewhat different receptor profile. Pure escitalopram [1] was therefore introduced onto the market by H Lundbeck A/*S* and Forest Laboratories under the brand name Cipralex or Lexapro, respectively [201], as the oxalate salt, compared with citalopram, which is the hydrobromide salt. Its development was initiated in the summer of 1997, and the resulting new drug application was submitted to the US FDA in March 2001. The FDA issued the US approval of escitalopram for major depression in August 2002, and for generalized anxiety disorder (GAD) in December 2003. Escitalopram is also registered for the treatment of major depressive episodes and panic disorder (PD), social anxiety disorder (SAD) and obsessive–compulsive disorder (OCD) in Sweden, Switzerland, Belgium, Denmark, Great Britain, France, Norway, Austria, Czech Republic, Lithuania, Ireland, Canada and other countries.

Pharmacology

Selective serotonin reuptake inhibition in the brain interneural synapses is the main mode of escitalopram action. In rat brain synaptosomes, escitalopram blocks serotonin reuptake to a greater extent (IC_{50}: 2.1 nM) than R-citalopram (IC_{50}: 280 nM) or citalopram (IC_{50}: 3.9 nM) [2,3]. Escitalopram does not directly influence the reuptake of noradrenaline and dopamine [2].

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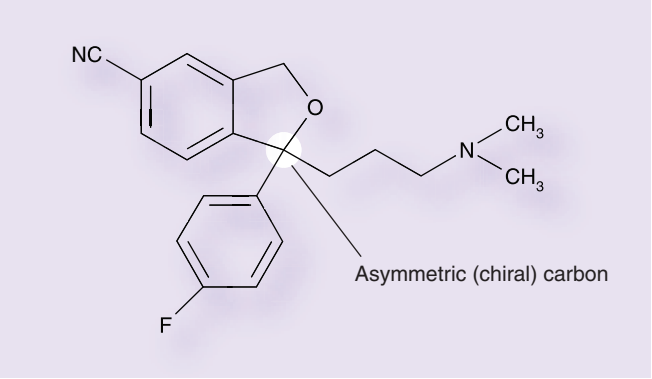

Figure 1. Citalopram.

Using cell membranes, Owens *et al.* directly measured the inhibition of human serotonin, noradrenaline and dopamine transporters by various selective serotonin reuptake inhibitors (SSRIs) [4]. Also in this paradigm, escitalopram exerted a high affinity for the serotonin transporter (receptor affinity [K_i]: 1.1 nM) and negligible affinity for the other two transporters (K_i: 7841 and 27,410 nM, respectively) (Table 1). Out of all tested SSRIs, escitalopram was the most selective; the most potent inhibitors, however, were paroxetine (K_i: 0.1 nM) and sertraline (K_i: 1.1 nM), but paroxetine also inhibits the reuptake of noradrenaline and dopamine. *In vivo*, escitalopram increases the extracellular concentration of serotonin in the rat brain to a significantly greater extent than citalopram, while R-citalopram has no or a minimal effect in this respect [5]. At equipotent doses, the S-enantiomer was significantly more efficient than citalopram (racemate) in increasing the extracellular levels of serotonin within the frontal cortex of freely moving rats bearing a locally implanted microdialysis probe. Further experiments showed that R-citalopram counteracted the capacity of escitalopram to enhance extracellular serotonin levels. In addition, behavioral studies also showed that R-citalopram exerts effects counteracting those of escitalopram (antidepressant- and anxiolytic-like effects). The reason for these differences between the two enantiomers might also concern the secondary molecular targets at which citalopram acts, but with affinities at least two orders of magnitude less than for the serotonin transporter [6,7]. The antagonism of escitalopram by R-citalopram was unexpected; it is hypothesized that a direct interaction between the two enantiomers may occur on a particular site of the serotonin transporter. Results have shown that R-citalopram has a significant affinity only for the allosteric site of the transporter, which regulates the affinity of the ligand for the active site of serotonin reuptake inhibition [8]. As both enantiomers compete in binding to an allosteric site of the transporter and S-citalopram binds to both primary and allosteric sites, it has been suggested to classify escitalopram as an 'allosteric serotonin reuptake inhibitor' [9,10].

Selective inhibition of serotonin reuptake was also demonstrated *in vivo* using single photon emission computer tomography scanning, which has shown highly significant blockade of the serotonin transporter in healthy volunteers after clinically relevant doses of escitalopram [11].

Escitalopram and its metabolite demethylescitalopram do not exert significant affinity to any of 140 types of receptors and binding sites, with some exception of σ_{1+2} receptors [4]. Unlike R-citalopram, escitalopram was not a significant antagonist of 5-hydroxytryptamine (serotonin; 5-HT_{2C}) and histamine H_1 receptors, and only slightly influences σ_{1+2} receptors [2,6]. In this way, escitalopram differs from fluoxetine with its affinity for 5-HT_{2C} receptors, paroxetine with its binding to muscarinic M receptors, and from citalopram with its blockade of histamine H_1 receptors [2].

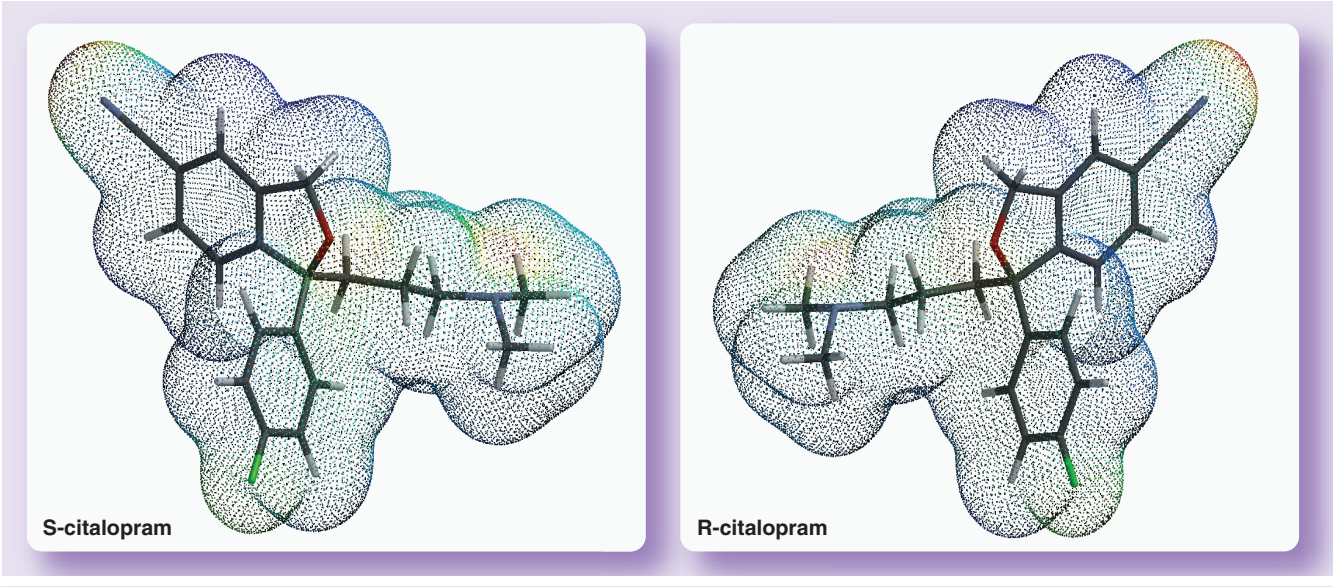

Figure 2. Structural formula of citalopram.

Table 1. Affinity of escitalopram to human serotonin, noradrenaline and dopamine transporters in comparison to other SSRIs

SSRI	Human monoamine transporters				
	K_i (nM)			Ratio	
	5-HT	*NA*	*DA*	*NA/5-HT*	*DA/5-HT*
Escitalopram	1.1	7841	27,410	7100	25,000
Citalopram	1.6	6190	16,540	3900	10,000
R-citalopram	36	12,270	18,720	340	520
Sertraline	0.26	714	22	2700	85
Fluvoxamine	2.3	1427	16,790	620	7300
Fluoxetine	1.1	599	3764	540	3400
Paroxetine	0.1	45	268	450	2700

5-HT: 5-hydroxytryptamine; DA: Dopamine; K_i: Rreceptor affinity; NA: Noradrenaline; SSRI: Selective serotonin reuptake inhibitor.
Data from [4].

The most likely scientific explanation for the clinical effect of escitalopram is inhibition of serotonin reuptake by binding to the serotonin transporter. Using brain imaging techniques (PET or single photon emission computer tomography) and appropriate radiolabeled ligands, it has been demonstrated that the occupancy (binding) to the serotonin transporter is significantly higher with escitalopram than citalopram at steady state (equilibrium: intake of active substance equals that removed from the body). The mean occupancies at 6 and 54 h after last doses were 82 and 63% for escitalopram, and 64 and 49% for citalopram, respectively. The differences between escitalopram and citalopram reported are statistically significant [12].

Pharmacokinetics

Escitalopram 10 mg is equivalent to 20 mg of racemic citalopram. Escitalopram is quickly absorbed from the GI tract and reaches maximum plasma concentration (C_{max}) 3–4 h after ingestion [13]. Bioavailability of escitalopram is similar to that of citalopram (i.e., 80%) [14]. Escitalopram absorption is not influenced by food intake [13]. The compound is 80% bound to plasma proteins and extensively distributed to body compartments (volume of distribution [V_d]: 12–26 l/kg). Interconversion of R-citalopram and its metabolite to escitalopram and its metabolites does not occur [13]. The half-life of R-citalopram is longer than S-citalopram, so the metabolism and elimination of R-citalopram from the body takes place at a slower rate than that of escitalopram. In some people, the plasma concentration of R-citalopram is up to four-times higher that of escitalopram. It is not possible to predict the ratio of escitalopram and R-citalopram in a specific person [15]. All pharmacokinetic studies in humans have shown clearance of the S-enantiomer to be higher by 6–15% when it is given without R-citalopram, leading to slightly lower plasma concentrations of escitalopram. This difference becomes apparent at high doses (30 mg escitalopram vs 60 mg escitalopram) and leads to the conclusion of nonbioequivalence at this dose level [Data on file].

Escitalopram is metabolized via the cytochrome P450 (CYP450) isozymes CYP450 3A4 (35%), 2C19 (37%) and 2D6 (28%) to S-demethylcitalopram (S-DCT). However, ritonavir, a potent inhibitor of 3A4, does not affect the pharmacokinetics of escitalopram [16]. S-DCT is further metabolized to S-didemethylcitalopram [17]. Data obtained on synaptosomes *in vitro* show that S-DCT is ten times less effective as an inhibitor of serotonin reuptake than escitalopram, but preserves its selectivity for serotonin [3,18]. If the effect of serotonin reuptake inhibition by citalopram is set to 1, then escitalopram has a value of 2, S-DCT 0.4 and S-didemethylcitalopram 0.1. The S-DCT serum level is half that of the maternal compound, and its penetration into the brain is low, so that this metabolite does not contribute to the clinical effect of escitalopram. Based on tests with racemic citalopram, other pharmacologically inactive metabolites are known, such as derivatives of propionic acid via metabolism by monoaminoxidase [19], and N-oxides and glucuronides [20].

The formation of S-DCT is reduced by approximately 60% by ketoconazole (3A4 inhibitor), by approximately 80% by chinidine (2D6 inhibitor) and by omeprazole (2C19 inhibitor) [21,17]. Slow 2C19 but not 2D6 metabolizers have higher escitalopram plasma concentrations. S-DCT is biodegraded via 2D6 to didemethylcitalopram. Escitalopram and S-DCT are only weak CYP450 isoenzyme 2D6 inhibitors, while didemethylcitalopram is a weak inhibitor of 2C9 and 2C19 (Figure 3) [17,22]. The inhibitory capacity of didemethylcitalopram has no clinical relevance, because this metabolite reaches only low plasma concentrations compared with the maternal compound.

Escitalopram and its metabolites are eliminated mainly in urine, and to a lesser extent in stools [16,23]. The elimination half-time of escitalopram is 27–33 h; its plasma clearance after

oral administration is approximately 0.6 l/min. The pharmacokinetics of escitalopram are linear at a usual dosage regime. The elimination half-time of escitalopram is prolonged to approximately 39 h and the clearance is decreased to 0.35 l/min in persons over 65 years of age. For these patients, initial treatment with half the usually recommended dose and a lower maximum dose should be considered. While in mild renal dysfunction the daily dose does not need to be adjusted, in patients with mild or moderate hepatic impairment an initial dose of 5 mg daily for the first 2 weeks of treatment is recommended. Depending on individual patient response, the dose may be increased to 10 mg daily [24].

Animal models of depression & anxiety

The antidepressant efficacy of escitalopram has been demonstrated in the forced swimming test in mice [2], in the test with chronic mild stress in rats [25,26], and in the test of assertive behavior in rodents [27]. Escitalopram was more effective than other SSRIs in the forced swimming test, while the R-enantiomer was not at all active. In the test of assertive behavior, escitalopram was more than twice as effective as citalopram. In models of chronic mild stress and assertive behavior, the onset of escitalopram effect was faster than that of citalopram.

The anxiolytic efficacy of escitalopram has been demonstrated using a model with a black and white illuminated box (a test of generalized anxiety [2]), ultrasound vocalizations after painful stimuli (panic anxiety test [2]) as well as by stimulation of a dorsal periaqueductal grey [28]. In general, escitalopram was more than twice as effective as citalopram in animal models of anxiety and depression, while R-citalopram was minimally effective or inefficacious [2].

In humans, unlike rodents, the R-enantiomer is metabolized more slowly than the S-enantiomer [29], resulting in an on average twofold higher plasma concentration of the R-enantiomer than the S-enantiomer after dosing with racemic citalopram [30]. This was taken into consideration in the design of the nonclinical studies in rodents, where experiments were conducted with citalopram (ratio 1:1 of R- and S-enantiomer) and combinations of R- and S-citalopram in ratios of 2:1 and 4:1 to mimic the range of plasma exposures measured in humans treated with citalopram. The results of these studies have consistently shown qualitative and quantitative differences between escitalopram and citalopram.

Nonclinical *in vivo* studies have consistently shown superior efficacy and a shorter time to effect for escitalopram compared with citalopram. The differences have been observed in a broad range of nonclinical *in vivo* studies predictive of clinical efficacy, and these differences increase as the R-:S-citalopram ratio increases from 1:1 to 2:1 to 4:1. Escitalopram is superior to corresponding doses of citalopram in all *in vivo* studies conducted [2,10,31].

Even at doses higher than are used in humans, escitalopram and its metabolites did not exert any damaging effects in animal tests for acute and chronic toxicity [32].

Clinical trials

Depressive disorders

The efficacy of escitalopram has been tested in comparison with placebo, citalopram, venlafaxine, paroxetine, sertraline, bupropion and duloxetine. Its prophylactic efficacy has been shown in long-term studies. So far, escitalopram has not been tested in the treatment of depressed inpatients.

Placebo-controlled studies

In six double-blind, placebo-controlled studies, 2279 depressed patients (Diagnostic and Statistical Manual of Mental Disorders [DSM]-IV) were randomized and treated with escitalopram (10–20 mg/day) or a comparator for 8 weeks after a 1 week placebo period (Table 2) [33–38]. Only patients with Montgomery-Asberg Depression Rating Scale (MADRS) total score 22 or higher were eligible for these studies. Escitalopram was more efficient than placebo (approximately 57% responders vs 42%). Escitalopram differed from placebo already within the first 1–2 weeks of the treatment. In the clinical comparison of Wade *et al.*, escitalopram was superior to placebo (47 vs 34%) in the number of patients who achieved remission (MADRS ≤ 12) [33]. All items of the MADRS scale were significantly more reduced by escitalopram than by placebo except loss of appetite and lassitude. Escitalopram was also superior to placebo in long-term (12 months) treatment [39].

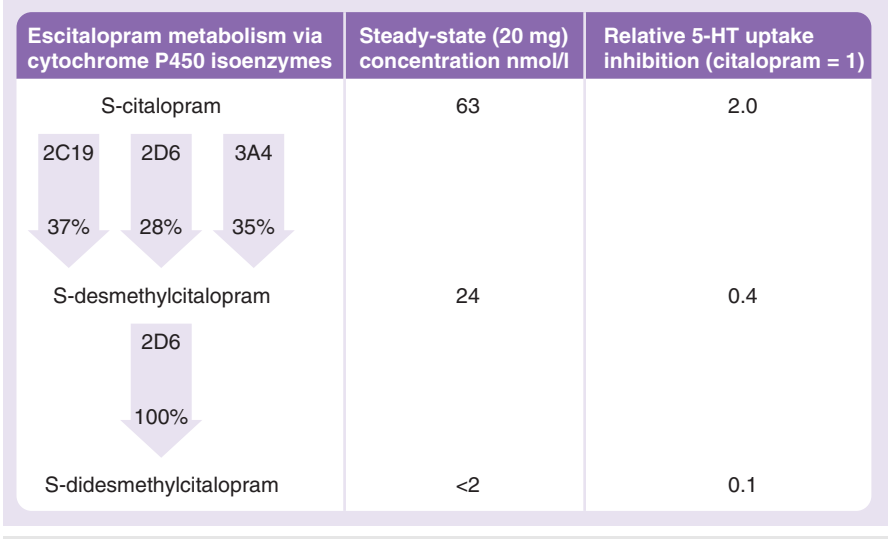

Figure 3. Biodegradation of escitalopram.
Based on [111].

Table 2. Escitalopram in the treatment of depression: comparison with placebo, citalopram and sertraline.

Study	n, setting and baseline	Duration (weeks)	Drug and dose (mg/day)	Results (response = MADRS ≤ 50%)	% responders or change at week 8	Ref.
Burke *et al*. (2002)	491 Outpatient MADRS ≥ 22	8	S-citalopram 10 S-citalopram 20 Citalopram 40 Placebo	S-citalopram = citalopram > placebo	50 51 46 28	[35]
Lepola *et al*. (2003)	469 Outpatient MADRS ≥ 22	8	S-citalopram 10–20 Citalopram 20–40 Placebo	S-citalopram ≥ citalopram > placebo Onset in 1 week	64	[34]
Wade *et al*. (2002)	380 Outpatient MADRS 22–40	8	S-citalopram 10 Placebo	S-citalopram > placebo Onset in 1–2 weeks	55 47	[33]
Ninan *et al*. (2003)	247 Outpatient MADRS ≥ 22	8	S-citalopram 10–20 Placebo	S-citalopram = placebo	-13.3 ± 0.9 -10 ± 0.9	[37]
Alexopoulos *et al*. (2004)	398 Outpatient MADRS ≥ 22	8	S-citalopram 10–20 Sertraline 50–200 Placebo	S-citalopram = sertraline > placebo	-15.75 ± 0.94 -16.73 ± 0.94 -12.38 ± 0.93	[36]
Rapaport *et al*. (2004)	300 Outpatient MADRS ≥ 22	8	S-citalopram 10–20 Citalopram 20–40 Placebo	S-citalopram = placebo	-12.9 ± 0.9 -11.2 ± 0.9	[38]
Total of six studies	2279	8	S-citalopram 10–20 Citalopram 20–40 Sertraline 50–200 Placebo	S-citalopram = citalopram = sertraline > placebo		

MADRS: Montgomery and Åsberg Depression Rating Scale.

Comparison with citalopram

In Table 2, there are six studies comparing escitalopram with citalopram. Of all the treated patients, more improved after escitalopram (10–20 mg/day) than after citalopram (20–40 mg/day) treatment. Results of comparative escitalopram/citalopram studies were pooled and analyzed [40]. Escitalopram (10–20 mg/day) was given to 520 depressed patients, citalopram (20–40 mg/day) to 403 patients and placebo to 398 patients. Patients with an initial MADRS total score of at least 22 were eligible for the trials. The average baseline MADRS total score in the three studies included was approximately 29. Both active antidepressants, escitalopram and citalopram, were superior to placebo. With escitalopram, the difference from placebo was significant from the first week of treatment, while with citalopram it was significant from 6–8 weeks (Figure 4). The response rate (MADRS ≤ 50%) was higher in the escitalopram and citalopram groups than in the placebo group (59 vs 53 vs 41% respectively). Similar results were obtained using clinical global impression (CGI) and confirmed in later analyses [41]. The difference between escitalopram and placebo, and between escitalopram and citalopram became greater the more severely depressed the patients were at baseline [40,42,43]. Moreover, in one study, mean per-patient costs for the escitalopram group compared with the citalopram group were 41% lower (EUR€96 vs 163; $p < 0.05$) from a healthcare perspective, mainly due to lower hospitalization rates [44].

In the two initial clinical studies of escitalopram that included citalopram as an active reference, escitalopram was consistently numerically better than citalopram on multiple efficacy parameters [34,35]. These initial observations were confirmed by pooled analyses conducted after finalization of the studies, which showed statically significant superiority for escitalopram compared with citalopram [41], particularly in patients with severe depression [40].

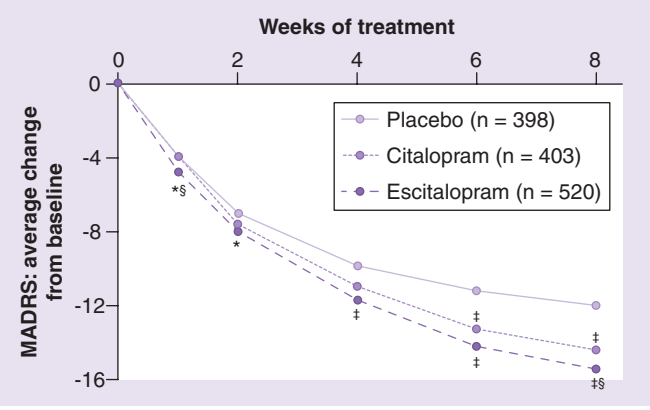

Figure 4. Escitalopram and citalopram in comparison with placebo in the treatment of depression.
*$p < 0.05$ vs placebo; ‡$p < 0.001$ vs placebo; §$p < 0.05$ vs citalopram.
Gorman *et al.* (2002)

The statistically significant superior efficacy of escitalopram compared with citalopram seen in the pooled analyses was prospectively investigated in two randomized, double-blind head-to-head studies [45,46]. Moore *et al.* compared fixed doses of escitalopram (20 mg/day) with citalopram (40 mg/day) over 8 weeks in outpatients with major depressive disorder (MDD; baseline MADRS score ≥ 30) in a double-blind, randomized clinical trial in which general practitioners and psychiatrists participated [45]. Of 138 and 142 patients who were randomized to escitalopram and citalopram, respectively, six and 15 withdrew prematurely ($p = 0.05$). The MADRS score decreased more in the escitalopram than in the citalopram arm (-22.4 ± 12.9 vs -20.3 ± 12.7; $p < 0.05$). There were more treatment responders with escitalopram (76.1%) than with citalopram (61.3%; $p < 0.01$). Adjusted remitter rates were 56.1 and 43.6%, respectively ($p < 0.05$).

Yevtushenko *et al.* compared fixed doses of escitalopram (20 mg/day) with citalopram (20 and 40 mg/day) over 6 weeks in outpatients with MDD (mean baseline MADRS score of 35) in a double-blind, randomized clinical trial [46]. The MADRS score decreased more in the escitalopram 20 mg than in the citalopram 40 mg arm (-28.7 vs -25.2; $p < 0.001$). There were more treatment responders with escitalopram (95.4%) than with citalopram (83.3%; $p<0.001$). Adjusted remitter rates were 89.8 and 50.9%, respectively ($p<0.001$). The differences in the treatment effect (differences of 2.1 [45] and 3.5 MADRS points [46]) and response rates (absolute differences of 14.8 and 12.1 percentage points, respectively) between escitalopram and citalopram are both statistically significant and clinically relevant. The results of these studies are consistent with the differences seen with 'real life' patients in a naturalistic nonrandomized study reported by Lancon *et al.*, in which 127 patients with a mean MADRS score of approximately 38 were treated for 8 weeks with either escitalopram 20 mg or citalopram 40 mg [47]. Escitalopram reduced the mean MADRS total score at week 8 compared with citalopram (-23.5 vs -17.5; $p < 0.001$).

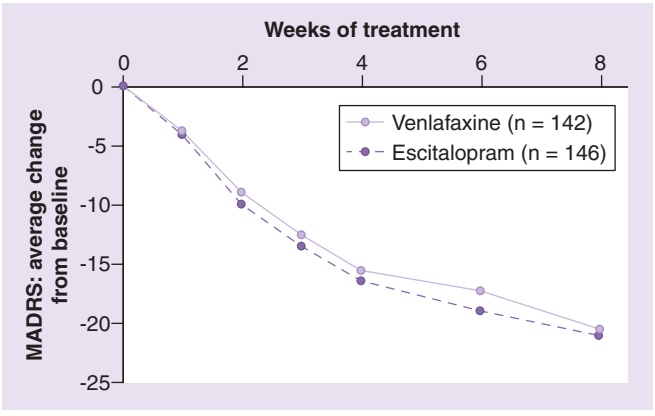

Figure 5. Head-to-head comparison of escitalopram with venlafaxine.
MADRS: Montgomery–Asberg Depression Rating Scale.
Montgomery *et al.* 2002

Escitalopram-treated patients were more likely to respond to treatment (79.4 vs 44.0%; $p < 0.001$) and remission rates were also in favor of escitalopram (56.9 vs 11.2%; $p < 0.001$).

Comparison with other SSRIs

Escitalopram (20 mg/day; n = 232) was significantly more effective than paroxetine (40 mg/day; n = 227) in a long-term (24 weeks) double-blind controlled study in patients with severe depression (MADRS ≥ 30) [48]. Another multicenter trial was conducted to compare the efficacy and tolerability of a fixed dose of escitalopram 10 mg/day with sertraline optimally dosed within its recommended dose range (50–200 mg/day) for the treatment of MDD [49]. Depressed patients (DSM-IV; baseline MADRS 22) aged 18–80 years were randomly assigned to 8 weeks of double-blind treatment with escitalopram (10 mg/day) or sertraline (50–200 mg/day) following a 1-week single-blind placebo lead-in period. Sertraline was initiated at 50 mg/day, and could be increased by 50 mg/day at weekly intervals based on clinical need and tolerability at the lower dose level. The blindness was maintained with matching double-blind placebo capsules for the escitalopram group. Change from baseline to end point in MADRS total score (last observation carried forward [LOCF]) was the primary efficacy measure. At week 8, the mean sertraline dosage was 144 mg/day (median: 150 mg/day). Mean changes from baseline to end point in MADRS scores were -19.1 and -18.4 for the escitalopram and sertraline groups, respectively. At end point, 75 and 70% of escitalopram- and sertraline-treated patients, respectively, were responders (≥50% improvement from baseline in MADRS). Both treatments were well tolerated; 2 and 4% of patients prematurely discontinued escitalopram and sertraline treatment, respectively, owing to adverse events. No significant differences in efficacy were observed for the two compounds [49].

Comparison with venlafaxine

Montgomery *et al.* tested antidepressant efficacy of escitalopram compared with venlafaxine [50]. A total of 293 outpatients aged 18–85 years with a diagnosis of mood disorder according to DSM-IV and with baseline MADRS greater than or equal to 18 were included in the double-blind trial. After an initial placebo interval, they were treated either with escitalopram (10–20 mg/day) or venlafaxine XR (75–150 mg/day) for 8 weeks. Escitalopram was as effective as venlafaxine XR (88% responders; scales used: MADRS, Hamilton Depression Scale [HAMD], CGI), but its onset of action was earlier by 4.6 days ($p < 0.05$). The decrease of MADRS total score was comparable after both drugs (Figure 5). Dropouts for adverse effects included 8% of patients on escitalopram and 11% receiving venlafaxine XR. Escitalopram was better tolerated than venlafaxine XR and was associated with nausea (17 vs 27%), sweating (6 vs 12.5%) and constipation (1.2 vs 5.8%). After 8 weeks the treatment was abruptly stopped and withdrawal symptoms occurred to a lesser extent with escitalopram than venlafaxine XR (15 vs 31%). The noninferiority of escitalopram to venlafaxine XR and the better

tolerance were confirmed in a study with higher doses (escitalopram 20 mg/day vs venlafaxine XR 225 mg/day) [51,52] as well as in a large meta-analysis [53]. Another (indirect) analysis also led to the conclusion that escitalopram is noninferior to venlafaxine XR [54].

Comparison with bupropion

To compare the antidepressant efficacy and the effects on sexual functioning of bupropion XL and escitalopram, outpatients with moderate-to-severe DSM-IV-defined major depression and normal sexual functioning were randomly assigned to receive bupropion XL (300–450 mg/day; n = 276), escitalopram (10–20 mg/day; n = 281), or placebo (n = 273) for up to 8 weeks in two identically designed, randomized, double-blind, parallel-group studies [55]. Data were analyzed prospectively for each study, and pooled data were analyzed retrospectively. While bupropion XL did not significantly differ from placebo on HAMD-17 total score in either study, escitalopram showed statistical superiority to placebo in one of the two studies and in the pooled data. However, bupropion XL was not significantly inferior to escitalopram with respect to mean change in HAMD-17 total score, response or remission rates, and percentage of patients much or very much improved on CGI scores at week 8 [55]. In both individual studies and the pooled dataset, the incidence of orgasm dysfunction at week 8 (primary end point) and the incidence of worsened sexual functioning at the end of the treatment period were statistically significantly lower with bupropion XL than with escitalopram ($p < 0.05$), not statistically different between bupropion XL and placebo ($p \geq 0.067$), and significantly higher with escitalopram than with placebo ($p \leq 0.001$). The respective percentages of patients with worsened sexual functioning at the end of the treatment period in either study and the pooled dataset were 18, 22 and 20% with bupropion XL; 37, 34 and 36% with escitalopram; and 14, 16 and 15% with placebo. A recent meta-analysis of randomized controlled trials with bupropion XL concluded that there did not appear to be any statistically detectable difference in the rapidity of antidepressant effect between bupropion XL and escitalopram [56].

Comparison with duloxetine

The goal of a noninferiority study [57] was to compare the speed of onset of antidepressant efficacy for duloxetine (a dual serotonin and norepinephrine reuptake inhibitor) and escitalopram in a randomized, double-blind, placebo- and active comparator-controlled trial. Patients meeting DSM-IV criteria for MDD received duloxetine 60 mg/day (n = 273), escitalopram 10 mg/day (n = 274) or placebo (n = 137) for 8 weeks. The study was designed to test the hypothesis that the percentage of duloxetine-treated patients achieving onset criteria at week 2 was not inferior to that in the escitalopram group. Onset of efficacy was defined as a 20% decrease from baseline on the HAMD-17. Probabilities of meeting onset criteria at week 2 for duloxetine- and escitalopram-treated patients were 42.6 versus 35.2%, respectively (95% confidence interval: $p = 0.097$). Both drugs showed significant improvement compared with placebo ($p \leq 0.05$) on the primary efficacy measure (Maier subscale) at week 1 and end point (week 8). No differences were found between duloxetine, escitalopram and placebo rates of remission or response at 8 weeks. Adverse events that occurred significantly more frequently among duloxetine-treated patients when compared with those receiving escitalopram were nausea, dry mouth, vomiting, yawning and irritability. The rate of discontinuation owing to adverse events did not differ significantly between treatment groups, although escitalopram (10 mg) was better tolerated than duloxetine (60 mg). Also, another study did not find any differences in efficacy between the two medicines [58]. Side effects occurred somewhat earlier during the treatment in the duloxetine group. Escitalopram was superior to duloxetine in acute treatment, and at least as efficacious and better tolerated in long-term treatment of MDD in studies by Khan *et al.* [59] and Wade *et al.* [60].

Dose response

There is an ongoing debate in the literature as to whether a dose–response relationship exists for SSRIs. For escitalopram, there is some evidence from studies in anxiety disorders that higher doses performed better than lower doses. However, for depression this has not been directly studied. A pooled analysis of the database in depression, however, showed that after 8 weeks of treatment, escitalopram 10 mg was superior to placebo, with a standardized effect size above 0.40 for patients with moderate depression (baseline MADRS scores between 22 and 29), but not for those with severe depression (baseline MADRS score of at least 30). By contrast, escitalopram 20 mg was superior to placebo, with a standardized effect size of 0.40 for patients with severe depression, but not for those with moderate depression. This led the authors to conclude that escitalopram 10 mg is optimal for patients with moderate depression (according to their baseline MADRS scores) while escitalopram 20 mg is effective treatment for patients with severe depression [61].

Anxiety in depressive disorders

During initial clinical trials, escitalopram has been shown to influence favorably not only depressive symptoms but also anxiety (assessed using the Hamilton rating scale for anxiety [HAMA]) compared with placebo. This effect was more pronounced on 20 than on 10 mg/day [33,34].

In three studies with a total of 853 patients the change in the MADRS item 'inner tension' was compared after escitalopram, citalopram and placebo [62]. Both antidepressants were superior to placebo, but onset of action of escitalopram was earlier than that of citalopram (second vs fourth week of treatment). This was confirmed in later analyses [63]. In addition, patients with comorbid anxiety have been described by Olié *et al.*, who assessed the efficacy and tolerability of escitalopram in patients with depression, with or without comorbid anxiety [64]. Escitalopram was administered over a 12-week treatment

period to 790 depressed patients (649 completed), including 482 patients with at least one concomitant anxiety disorder. At baseline, the mean MADRS total score was 31.5 and decreased to 12.4 at end point (LOCF). The MADRS score decreased by 20.5 points in patients with no anxiety disorder and by 18.3 points in patients with at least one concomitant anxiety disorder. The mean HAMA total score at baseline was 25.6, and decreased to 10.8 at end point (LOCF). The HAMA score decreased by 13.8 points in patients with no anxiety disorder and by 15.5 points in patients with at least one anxiety disorder. Adverse events were reported by 246 patients (31%): nausea in 65 patients (8%) and headache in 38 patients (5%). A total of 61 patients (8%) discontinued treatment owing to adverse events. In summary, over a 12-week treatment period, escitalopram was well tolerated and efficacious in reducing symptoms of depression in patients with or without comorbid anxiety.

Depression relapse prevention

Rapaport *et al.* enrolled 274 depressed patients who responded (MADRS ≤ 12) to initial open-label 8 weeks escitalopram administration in a double-blind, placebo-controlled relapse prevention study [38]. The prevention study lasted 36 weeks. Relapse was defined as an increase of MADRS global score to 22 or more. For patients with escitalopram prophylaxis (10–20 mg/day), the relapse rate was 26% compared with 40% for placebo ($p = 0.013$), and their time to relapse was significantly longer (Figure 6). The authors suggested escitalopram decreased the risk of a new episode by 44%. Recently, Gorwood *et al.* confirmed escitalopram was effective in preventing relapse of major depression in elderly patients with depression and was well tolerated as continuation treatment [65]. A total of 405 patients who were aged 65 years or older with a primary diagnosis of MDD and a MADRS total score of 22 or more received escitalopram 10 or 20 mg per day open-label for 12 weeks. Remitters (MADRS ≤ 12) were randomized to 24-week double-blind treatment with escitalopram or placebo. The primary efficacy parameter was the time to relapse, defined as either an increase in MADRS total score of 22 or more, or lack of efficacy as judged by the investigator. Initially, 305 patients achieved remission and were randomly assigned to treatment with escitalopram (n = 152) or placebo (n = 153). The risk of relapse was 4.4-times higher for placebo than for escitalopram-treated patients. Escitalopram was well tolerated (the overall withdrawal rate was 7.2% for escitalopram and 8.5% for placebo during the double-blind period). The results are in agreement with conclusions of Kornstein *et al.*, who examined the efficacy of maintenance escitalopram treatment in preventing depression recurrence in patients who responded to acute SSRI therapy [66]. Maintenance treatment with escitalopram was well tolerated and significantly reduced the risk for recurrence of depression.

Anxiety disorders

Escitalopram is also approved in the EU for the treatment of anxiety disorders, such as PD, GAD, OCD and SAD. Table 3 summarizes the first three studies. All patients were diagnosed according to DSM-IV. In the first study, escitalopram not only better prevented panic attacks, but also reduced anticipatory anxiety, phobic avoidance behavior and improved quality of life (QoL) in comparison with placebo [67]. The onset of action was observed in the fourth week of treatment. Escitalopram was as well tolerated as placebo. A total of 6% of patients using escitalopram and 8% on placebo dropped out of the study because of side effects. In both groups, 10–15% of patients complained of headache, insomnia, nausea and fatigue. A recent study confirmed the favorable effect of escitalopram on QoL in patients suffering from panic disorder [68].

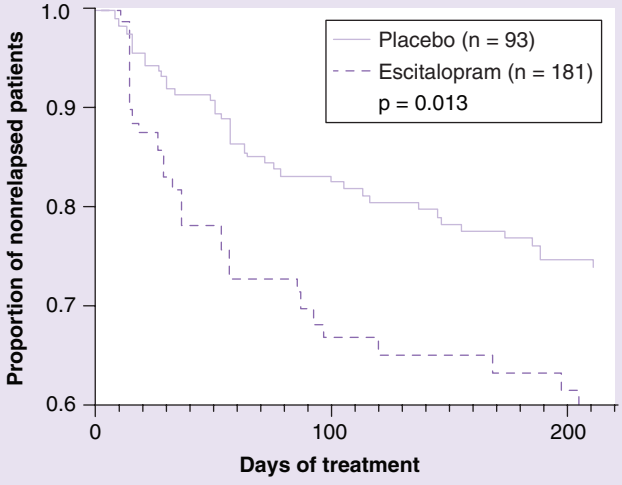

Figure 6. Time to relapse.

In the second study, escitalopram was significantly superior to placebo in the treatment of GAD assessed using both anxiety scales (HAMA and the Hospital Anxiety and Depression Scale), general severity assessment according to CGI, and QoL [69]. Escitalopram superiority reached statistical significance in fourth and eighth week of treatment. Here escitalopram was also well tolerated. The most frequent side effects reported were headache, impaired ejaculation, nausea, insomnia, somnolence, diarrhea and dry mouth.

In the third study, escitalopram in the dose 10–20 mg/day was better than placebo in the 12-week-long treatment of patients with SAD [70]. Escitalopram was better in elimination of phobic symptoms and avoidance behavior (Liebowitz scale for Social Anxiety), in CGI and in working and social but not family functioning (Sheehan Disability Scale). According to CGI-1, 54% patients on escitalopram and 39% on placebo were kept with no or minimum symptoms of mental disorders ($p = 0.001$). Nausea (22%), fatigue (14%) and somnolence (10%) belonged to the most frequently reported side effects.

In addition to studies with escitalopram in the treatment of GAD mentioned above, Goodman *et al.* [71] and Stein *et al.* [72] came to similar conclusions in their analyses.

Table 3. Escitalopram in the treatment of anxiety disorders: first three studies.

Study	n (outpatients)	Duration (weeks)	Drugs and dose (mg/day)	Results	Ref.
Panic disorder					
Stahl *et al*. (2002)	247	10	S-citalopram 5–20 Placebo	S-citalopram > placebo No attacks 50 vs 39% Onset fourth week	[109]
Generalized anxiety disorder					
Davidson *et al*. (2004)	315	8	S-citalopram 10–20 Placebo	S-citalopram > placebo Response rate 68 vs 31%	[69]
Social phobia					
Kasper *et al*. (2002)	358	12	S-citalopram 10–20 Placebo	S-citalopram > placebo LSAS, CGI 54 vs 39%	[110]
Total of three studies	920	8–12	S-citalopram 5–20 Placebo	S-citalopram > placebo	

CGI: Clinical global impression; LSAS: Liebowitz Social Anxiety Scale.

In more recent studies, the efficacy of escitalopram in PD (older patients in community setting – Rampello *et al*. [73]), GAD [74–77], SAD [70,78,79] (for reveiw, see [80]) and OCD [81] has been repeatedly confirmed. In the latter study, escitalopram 20 mg/day was noninferior to paroxetine 40 mg/day and more effective than placebo. The authors concluded that given that escitalopram 20 mg/day was associated with an earlier onset, higher response and remission rates, improved functioning, and better tolerability than the reference drug, escitalopram deserves to be considered as one of the first-line agents in the pharmacotherapy of OCD for longer term treatment periods.

To examine the efficacy of escitalopram in the prevention of relapse in patients with OCD, Fineberg *et al*. treated 468 patients with OCD for 16 weeks with open-label escitalopram (10 or 20 mg), after which the 320 responders (Yale-Brown Obsessive Compulsive Scale total score decrease ≥25%) were randomized to placebo or escitalopram for 24 weeks double-blind treatment [82]. The primary analysis (time to relapse) showed a significant advantage for escitalopram. The risk of relapse was 2.74-times higher for placebo compared with escitalopram. These results demonstrate that escitalopram is effective not only for long-term treatment but also for relapse prevention in OCD.

Indications

Escitalopram is indicated and registered for the treatment of depressive disorders including severe forms. Results from clinical studies have also shown a good efficacy of escitalopram in the treatment of anxiety disorders (PD, GAD, SAD and OCD). In most countries, escitalopram is also registered for the treatment of these anxiety disorders.

Contraindications

Hypersensitivity to the drug and the current use of monoamine oxidase inhibitors (MAOI) are contraindications for the use of escitalopram. Escitalopram is not indicated for the treatment of children under the age of 18 years. In cases where there are reasons to treat a child with escitalopram, the patients should be carefully followed-up for signs of suicide or hostile behavior, which, although questionable, have been reported in a higher rate in some clinical studies after treatment with SSRIs and serotonin–norepinephrine reuptake inhibitors. Caution is also recommended in patients suffering from epilepsy or diabetes, having mania or hypomania in their personal history (occurrence of mania is the reason to immediately stop treatment with escitalopram), and in patients with a risk of bleeding or who are taking medication that can increase such a risk. Suicidal patients should be carefully monitored.

Dosage

The recommended initial dose of escitalopram is 10 mg/day given once daily, either in the morning or evening, before or after a meal. If necessary, the dose can be increased to 20 mg/day. In older people and in patients with a liver dysfunction, an initial treatment with half the usually recommended dose and a lower maximum dose should be considered. In PD, a low initial dose of escitalopram (5 mg/day) with slow consequent titration is recommended (see later).

Side effects

The most frequent side effects during treatment with escitalopram are headache (~18%), nausea (~17%), insomnia (9%), fatigue (8%), diarrhea (8%), ejaculation impairment (9%), drowsiness (6%), dry mouth (6%), dizziness (6%), increased sweating (5%) and tiredness (5%) (Table 4) [83,84; see also Summary of Product Characteristic]. Based on the assessment of 1618 patients from various studies [84] the incidence of the most common adverse effects was not dose dependent, although a nonsignificant trend is seen for a higher incidence at the higher dose (10 vs 20 mg/day). The percentage of patients who withdrew from 8-week treatment owing to adverse effects was significantly

higher in paroxetine and venlafaxine groups than in escitalopram groups. The authors also analyzed the incidence of adverse effects from week 8 to week 24 in the six long-term studies. Only nasopharyngitis (escitalopram 3.2%; comparator 2.9%) and headache (escitalopram 2.5%; comparator 2.6%) had an incidence greater than or equal to 2%. In studies comparing escitalopram with bupropion XL [55], orgasm dysfunctions were more frequent in escitalopram groups (29–32%) than in bupropion XL (13–16%) or placebo (8–11%) groups, respectively. Mean changes in Changes in Sexual Functioning Questionnaire scores for all domains at week 8 were statistically significantly worse for escitalopram compared with bupropion XL ($p \leq 0.05$).

Discrepant reports can also be partly explained by the fact that the incidence of some adverse effects after escitalopram treatment changes in time, usually decreasing. Very often, the dropout rate owing to side effects on escitalopram does not differ from that on placebo, and may be lower than on citalopram. No clinically notable changes in mean laboratory, vital signs or ECG values were observed [76,85]. In most studies, escitalopram did not cause a change in body weight or blood pressure. Gergel *et al.* found a minimal decrease in heart rate (by 2–3 beats/min) and clinically irrelevant QTc prolongation by 3.9 ms on average after escitalopram [85]. In some studies, however, a weight gain has been reported. In the open-label GAD study of Davidson *et al.*, the mean increase in weight from baseline was 3.0 lb after 24 weeks [76]. In the Pigott *et al.* study, mean change in weight was significantly higher for escitalopram compared with duloxetine (duloxetine: +0.61 kg; escitalopram: +1.83 kg; $p < 0.05$) [58]. However, the incidence of treatment-emergent abnormal weight gain (≥7% increase in weight from baseline) was similar between drugs and was significantly greater for both duloxetine and escitalopram compared with placebo.

Table 4. The most frequent side effects of escitalopram in placebo-controlled trials.

Side effect	Placebo (%; n = 2199)	Escitalopram (%; n = 2740)
Headache	16	18.5*
Nausea	8.5	17.7§
Insomnia	5	8.4§
Fatigue	3.4	8.1§
Diarrhea	4.9	7.7§
Dry mouth	4.6	6.8‡
Dizziness	4.5	6.1*
Somnolence	2.9	5.9§
Ejaculation delayed	0.6	5.4§
Sexual dysfunction (all)	2.1	10.3‡
Patients with adverse effects	63.1	72.7§
Withdrawn owing to adverse effects	2.8	7.3§

*$p < 0.05$; ‡$p < 0.01$; §$p < 0.001$; see also [Summary of Product Characteristic]. Modified from [84].

Rosenthal *et al.* described 46 depressed patients who discontinued treatment with citalopram, fluoxetine, sertraline or paroxetine because of adverse effects, and were then switched to escitalopram 10 mg and followed-up for a further 8 weeks [83]. A total of 85% of the patients completed the study. They tolerated treatment with escitalopram better than with other SSRIs, and the former side effects did not occur afterwards.

The incidence of the switch to mania was lower in patients receiving escitalopram (0.1%) than tricyclics and comparable to paroxetine or fluvoxamine. The side effects for sexual dysfunction, delayed ejaculation (9%), loss of libido (4%), impotency (3%) and anorgasmia (2%) most often occurred [86].

Very rarely, hyponatremia can occur during SSRI treatment as a consequence of inappropriate antidiuretic hormone secretion, particularly in older women [87]. Exceptionally, all SSRIs can cause subcutaneous bleeding (purpura and ecchimosis). Therefore, caution is recommended in concurrent treatment with drugs lowering the aggregability of thrombocytes (antiplatelet agents such as aspirin and clopidogrel) [88].

According to Baldwin *et al.*, there is no signal in the clinical trial database indicating that escitalopram might induce seizures [84].

An analysis of suicidal behavior in placebo-controlled escitalopram studies in depressive and anxiety disorders (n = 2277) has been published [89]. No completed suicide occurred among patients during treatment with escitalopram.

Initial intensification of anxiety can occur in some patients with PD at the beginning of treatment with escitalopram, so low initial doses of 5 mg/day are recommended with slow consequent titration after 2 weeks.

Although no teratogenicity was reported in animal trials, escitalopram has been labeled as category C according to the FDA, because there is a lack of experience of administration to humans during pregnancy. The manufacturer recommends high caution in administration during pregnancy and no administration during breast feeding [32].

Specific populations

Liver impairment

Although escitalopram has a slightly longer half-life in patients with hepatic impairment [24], this was not associated with a higher incidence or severity of adverse effects. So far, no sufficient data on the subpopulation of patients with renal impairment are available.

Elderly patients

In elderly patients with MDD, the tolerability of escitalopram was similar to that in the younger population (<65 years of age). Nausea was the only adverse effect that occurred significantly more frequently in the escitalopram group than in the placebo group (6.9 vs 1.7%; $p < 0.01$) [89].

Pregnancy

In a recent article, Baldwin *et al.* refer to 60 pregnancies reported in clinical trials with escitalopram as of June 2006 [84]. There were 17 abortions, ten of which were therapeutically induced with no reports of underlying abnormalities. In the remaining seven spontaneous abortions, two women reported use of concomitant medication with drugs in FDA pregnancy category D (ibuprofen and tetracycline). There was one case of premature placental separation 1 day prior to delivery; despite an immediate cesarean section, the infant developed fetal distress and died 3 days after birth. There was one case of congenital malformation out of the 60 reported clinical study pregnancies, which was trisomy 21 (Down syndrome) in a twin birth in a 37-year-old woman with pre-existing risk factors of age, previous use of oral contraceptives and an older child with developmental delays. Besides escitalopram, she concomitantly administered clonazepam (FDA pregnancy category D) and bupropion (FDA pregnancy category C). While escitalopram and clonazepam treatments were stopped approximately 1 month after the last menstrual period, bupropion therapy continued during pregnancy. Although the direct evidence is rather small, analysis of these data did not indicate an obvious risk of either spontaneous abortions or malformations after escitalopram exposure in pregnancy.

Child & adolescents

See 'Contraindications'.

Interactions

Escitalopram must not be combined with classical MAOI or with moclobemide and other serotonergic compounds (e.g., triptans) because of a risk of serotonin syndrome. Escitalopram cannot be administered earlier than 14 days after discontinuation of irreversible MAOI and 1–2 days after withdrawal of moclobemide. On the other hand, therapy with MAOI can be introduced 7 days after discontinuation of escitalopram [86,32]. No pharmacodynamic or pharmacokinetic interactions of escitalopram with alcohol were detected [90].

As stated above, escitalopram is a substrate and weak inhibitor of CYP450 isoenzymes 3A4, 2C19 and 2D6 [17]. There were no interactions found in the concomitant use of escitalopram and substrates of 1A2 (clozapine and theophylline), 2C9 (warfarin; prothrombin time was prolonged by only 5%), 2C19 (mephenytoine and imipramine), 2D6 (sparteine and imipramine, amitriptyline) and 3A4 (ritonavir) [91,92]. Nevertheless, the manufacturer recommends decreasing daily doses of escitalopram during concomitant use of 2D6 substrates with a narrow therapeutic range (e.g., flecainamide, propaphenone, metoprolol, desipramine, nortriptyline, clomipramine, risperidone, thioridazine and haloperidol) [32].

Inhibitors of CYP2C19, such as omeprazole, or general inhibitors of P450 (e.g., cimetidine) can increase plasma levels of escitalopram, so that in such combinations it may be necessary to lower the escitalopram daily dose.

Intoxication

There are reports of escitalopram overdose, with up to 600 mg reported without any harmful consequences. LoVecchio *et al.* conducted a retrospective chart review of isolated escitalopram ingestions reported to their regional poison center during 2003–2004 [93]. A total of 28 patients were included with an average age of 28.1 years (range 2–75) and an average amount of escitalopram ingested of 62.5 mg (range 5–300 mg). There were eight accidental ingestions and 20 intentional overdoses. Six of the eight accidental ingestions were observed at home with follow-up within 24 h, and no adverse outcomes were reported. The other two were observed in the emergency department and discharged home with no adverse events reported. A total of 19 of the intentional overdoses were observed in the department for approximately 4–6 h and discharged home or to an inpatient psychiatry ward. One of them showed persistent lethargy, but had a good outcome. Escitalopram toxicity can theoretically be life threatening, but no patients from the reported series had harmful adverse sequelae after accidental or intentional overdose. There is no specific antidote to treat escitalopram overdose. Stomach lavage and medical monitoring is recommended. Hemodialysis is ineffective [32,93,94].

Conclusion

In summary, escitalopram is at least as effective in the treatment of depression and anxiety as other SSRIs, as the extended-release formulation of the serotonin/noradrenaline reuptake inhibitor venlafaxine, and duloxetine, and may have cost–effectiveness and cost–utility advantages [95–98]. Compared with other antidepressants, escitalopram is generally better tolerated and its onset of action is relatively rapid. It seems to be an effective first-line option in the management of patients with major depression and various anxiety disorders.

Expert commentary

Escitalopram represents a promising option in the treatment of depression and anxiety. Its comparative advantage over other antidepressants in the clinical setting is based on the purity, selectivity, low interaction potential, benign side-effect profile and favorable pharmacokinetics of the drug. Renal dysfunction, concomitant treatments and older age belong to such special conditions. Escitalopram also exerts a faster onset of action than the majority of compared compounds. It has been shown that escitalopram is effective even in severe forms of depression, and its antidepressant and anxiolytic potential is not inferior to that of the most potent antidepressants (venlafaxine and duloxetine). The clinical success of escitalopram shows the perspective opened with new technology that enables modern pharmacology to exploit separately chiral enantiomers with the identical chemical formula. Only sexual dysfunction (orgasmic and ejaculation impairment), nausea, insomnia and drowsiness

were observed significantly more often after escitalopram than with placebo. More double-blind, head-to-head and controlled studies including the studies in hospital inpatients are needed to further assess the right position and perspective of this elegant drug compared with other antidepressants.

Five-year view

There are some questions remaining regarding the pharmacology and use of escitalopram that require further investigation. First, the paradox of equal antidepressant efficacy of such a selective monotransmitter compound and dual antidepressants such as venlafaxine and duloxetine should be elucidated, as well as the reason for the rapid onset of action. Second, more short- and long-term head-to-head comparator clinical studies are needed to establish the relative efficacy of escitalopram compared with other antidepressants. Third, although there is much literature on the pharmacoeconomics of escitalopram [99–108], pharmacoeconomic assessments in other healthcare systems are needed to estimate the relative cost–benefit advantage of this antidepressant. Fourth, the special suitability of escitalopram for defined subpopulations of patients (e.g., elderly, with somatic comorbidity) should be properly tested. Finally, the adequate combination of pharmacotherapy with escitalopram, psychotherapy and psychosocial interventions is worth establishing to optimize the treatment outcome.

Information resources

- www.lexapro.com
- www.cipralex.com/about_cipralex/product_monograph
- Clinical trial registries at: www.forestclinicaltrials.com and www.lundbecktrial.com.

Reviews, profiles & further reading

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Key issues

Escitalopram represents a promising option in the treatment of depression and anxiety; it:

- Is a highly selective serotonin reuptake inhibitor.
- Has a low drug–drug interaction potential.
- Is highly effective in depression and anxiety.
- Is effective in severe forms of depression.
- Has a rapid onset of action.
- Has a benign side-effect profile.
- Requires no dose adjustment in renal dysfunction and older age.
- More often causes the side-effects of sexual dysfunctions, nausea, insomnia, and drowsiness than with placebo.

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