Antidepressant Efficacy of Escitalopram in Major Depressive Disorder

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30.1 Introduction

Escitalopram is a selective serotonin reuptake inhibitor (SSRI) that selectively binds to the human serotonin transporter (SERT). This activity inhibits serotonin (5-HT) reuptake and increases the amount of serotonin in synaptic clefts, which results in antidepressant action.

Racemic citalopram (RS-citalopram), an SSRI widely used in patients with major depressive disorder (MDD), possesses both an active S-enantiomer and clinically inactive R-enantiomer [1, 2]. Escitalopram was produced by isolating the active S-enantiomer from RS-citalopram. In vitro and in vivo studies have shown that escitalopram inhibited the serotonin transporter protein more potently than citalopram [2–4]. For example, in vivo electrophysiological data indicated that escitalopram was four times more potent than citalopram in reducing the firing activity of presumed serotonergic neurons in the dorsal raphe nucleus of rat brain [5]. In November 2011, escitalopram was approved in 100 countries in Europe, North America, and other regions. Escitalopram is indicated for generalized anxiety disorder, social anxiety disorder, obsessive-compulsive disorder, panic disorder, premenstrual dysphoric disorder, and MDD [6].

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30.2 Pharmacological Profile

30.2.1 Pharmacodynamic Profile

Escitalopram has a highly selective, dose-dependent, inhibitory effect on SERT. Its antidepressant action arises from its inhibition of serotonin reuptake into presynaptic nerve ending, which enhances serotonin activity in the central nervous system [1, 7]. Radioligand binding assays revealed that escitalopram showed particularly high selectivity for SERT compared to citalopram and several other SSRIs [7–9]. Escitalopram is "the most typical SSRI" of the SSRI agents, because it has virtually no binding affinity for other transporters [7, 9].

Escitalopram binds to two different sites of SERTs. It binds to the high-affinity binding site (primary site) of SERT, which controls serotonin reuptake in nerve endings, and it binds to the low-affinity binding site (allosteric site), which induces structural changes in SERT. The latter (allosteric action) is thought to stabilize and prolong binding of escitalopram to the primary site [3, 10–12].

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30.2.2 Pharmacokinetic Profile

The half-life of receptor occupancy for escitalopram was calculated to be approximately 130 h, much longer than the half-life of the plasma concentration, which was approximately 30 h [13]. An allosteric action may be involved in this prolonged occupancy. Escitalopram is metabolized in the liver, mainly by cytochrome P-450 (CYP) 2C19 and also by CYP3A4 and CYP2D6. Escitalopram inhibits liver metabolic enzymes, but primarily only CYP2D6 [14], with minimal inhibition of the other enzymes; the IC_{50} for CYP2D6 was higher than its effective blood concentration. In this regard, its interactions with other drugs would presumably be minimal.

30.3 Clinical Efficacy

30.3.1 Comparison with Placebo

In a placebo-controlled study [15], patients with MDD received escitalopram at a dose of 10 mg/day, and a control group was given placebo. After 8 weeks of therapy, the total Montgomery-Asberg Depression Rating Scale (MADRS) score changed by −16.3 in the escitalopram group and −13.6 in the placebo group. Thus, escitalopram had significantly greater efficacy than placebo. The total MADRS score of the escitalopram group began to show significant improvement compared to that of the placebo group by the second week of therapy. This demonstrated its fast-acting property. In addition, the remission rate (the percentage of patients with a total MADRS score of 12 or less) was significantly higher in the escitalopram group than in the placebo group. Thus, the initial therapeutic dose (10 mg/day) was demonstrated to be effective. Likewise, in other studies [15, 16], escitalopram 10 or 20 mg/day was more effective than placebo in the treatment of MDD. Reduction in MADRS scores, the primary endpoint, was greater with escitalopram than with placebo as week 1 [16] or 2 [15] and was maintained throughout treatment. Furthermore, Clinical Global Impression-Improvement (CGI-I) and Clinical Global Impression-Severity (CGI-S) scores were reported [15] and support the MADRS score findings: escitalopram produced significant lower CGI-I scores from week 1 and CGI-S scores from week 3 than placebo and this continued throughout treatment.

30.3.2 Comparison with SSRIs

Six randomized, double-blind, controlled studies [16–21] compared escitalopram and citalopram. Escitalopram was administered to patients with MDD for 4–8 weeks at 10–20 mg/day. All six studies [16–21] showed that the efficacy of escitalopram was equivalent to or greater than that of citalopram. Details of these studies are as follows. In the study of Burke et al. [16] ($N=491$; randomly assigned to placebo, escitalopram, 10 mg/day, 20 mg/day or citalopram, 40 mg/day), escitalopram (10 mg/day) was at least as effective as citalopram (40 mg/day) at endpoint. In the study of Lepola et al. [17], by week 8, significantly more patients had responded to treatment with escitalopram ($N=155$) than with citalopram ($N=160$). In the study of Lalit et al. [18], response rates at the end of 2 weeks were 58 % for escitalopram (10 mg/day) ($N=69$) and 49 % for citalopram ($N=74$) (20 mg/day). Response rates at the end of 4 weeks were 90 % for escitalopram (10–20 mg/day) and 86 % for citalopram (20–40 mg/day). The remission rates at the end of 4 weeks were 74 % for escitalopram and 65 % for citalopram. Additionally, there were lesser dropouts and lesser requirement for dose escalation in escitalopram than in citalopram. In the study of Moore et al. [19], MADRS score decreased more in the escitalopram ($N=138$) than in the citalopram arm ($N=142$). There were more treatment responders with escitalopram (76.1 %) than with citalopram (61.3 %), and adjusted remitter rates were 56.1 % and 43.6 %, respectively. In the study of Yevtushenko et al. [21] ($N=322$; randomly assigned to escitalopram, 10 mg/day or citalopram, 10–20 mg/day), at study end, the mean change from baseline in MADRS total score was significantly greater in the escitalopram arm than in the 10 and 20 mg/day citalopram

arms. Changes in the CGI-S and CGI-I scores and the rates of response and remission were significantly greater in the escitalopram group compared with those in the citalopram 10- and 20-mg/day groups. On the other hand, in the study of Ou et al. [20] ($N=240$, randomly assigned to escitalopram, 10–20 mg/day or citalopram, 20–40 mg/day), no significant differences were found in the change in the total Hamilton Depression Rating Scale (HAM-D17) score between the two groups.

The meta-analysis of Montgomery et al. [22] comparing escitalopram and citalopram supported these controlled studies: escitalopram was significantly more effective than citalopram in overall treatment effect, with an estimated mean treatment difference of 1.7 points at week 8 on the MADRS and in responder rate (8.3 percentage points) and remitter rate (17.6 percentage points) analyses, corresponding to number-needed-to-treat (NNT) values of 11.9 for response and 5.7 for remission. The overall odds ratios were 1.44 for response and 1.86 for remission, in favor of escitalopram. However, Trkulja [23] reported that MADRS reduction was greater with escitalopram, but 95 % confidence intervals (CI) around the mean difference were entirely or largely below 2 scale points (minimally important difference), and CI around the effect size (ES) was below 0.32 ("small") at all-time points. Risk of response was higher with escitalopram at week 8 (relative risk, 1.14; 95 % CI, 1.04–1.26), but number needed to treat was 14 (95 % CI, 7–111). All 95 % CIs around the mean difference and ES of CGI-S reduction at week 8 were below 0.32 points and the limit of "small," respectively. The report concluded that the claims about clinically relevant superiority of escitalopram over citalopram in short-to-medium-term treatment of MDD are not supported by evidence.

A long-term, double-blind, controlled study compared paroxetine to escitalopram given for 24 weeks to patients with severe disease [24]. In that study, escitalopram at 20 mg/day showed better efficacy than paroxetine at 40 mg/day. The total MADRS score changed by −25.2 in patients given escitalopram and by −23.1 in those given paroxetine. Thus, the outcome was significantly better for the escitalopram group, with an intergroup difference of 2.12. Furthermore, the HAM-D17 total score changed by −16.9 and −15.0 in the two groups, respectively; again this showed a significantly better outcomes for the escitalopram group than for the paroxetine group. In addition, the remission rate (percentage of patients with a total MADRS score of 12 or lower) was significantly higher (75.0 %) in the escitalopram group than in the paroxetine group (66.8 %). On the other hand, another study [25] that compared variable doses of escitalopram (10–20 mg/day) and paroxetine (20–40 mg/day) revealed equivalent efficacy in the two groups at week (end of acute treatment), although significantly more patients withdrew from the paroxetine group (34 %) than from the escitalopram group (21 %), and significantly more paroxetine patients withdrew due to lack of efficacy. In severely depressed patients (baseline MADRS total score ≥30), escitalopram was superior to paroxetine at week 27 (end of maintenance treatment).

In an 8-week double-blind randomized comparative study [26] with escitalopram (10 mg/day fixed-dose) or sertraline (50–200 mg/day flexible dose), no difference in efficacy was observed for either treatment. The mean changes from baseline to endpoint in MADRS scores were −19.1 and −18.4 for the escitalopram and sertraline groups, respectively, with response rates of 75 % and 70 % for escitalopram- and sertraline-treated patients, respectively. Both treatments were generally well tolerated. Consistent with these findings, a meta-analysis by Cipriani et al. [27] and comments by Patrick et al. in a related paper [28] advocated escitalopram and sertraline as the two "best" drugs in terms of efficacy and acceptability.

30.3.3 Comparison with SNRIs

In a double-blind, controlled study [29] of escitalopram (10–20 mg/day) vs. duloxetine (60 mg/day) for 8 weeks, the changes in the total MADRS scores were −18.0 ± 9.4 and −15.9 ± 10.3, respectively. This result showed that escitalopram was significantly superior to duloxetine. In another long-term, double-blind, controlled study [30] of

escitalopram (20 mg/day) vs. duloxetine (60 mg/day) for 24 weeks, the total MADRS score improved significantly to a greater extent in the escitalopram group than in the duloxetine group at week 8. This trend persisted until week 24.

Escitalopram has also shown equivalent or superior efficacy to that of venlafaxine extended release (XR) and better tolerated [31, 32]. In an 8-week double-blind randomized parallel-group trial [31], there were no significant differences in measures of efficacy between the two antidepressants, although tolerability measures favored escitalopram over venlafaxine XR. Another 8-week double-blind randomized parallel-group trial indicated that the efficacy of escitalopram was similar to venlafaxine XR; this was based on the mean change from baseline to week 8 in MADRS total score. However, escitalopram-treated patients achieved a sustained remission significantly faster than venlafaxine-treated patients. There were higher incidences of nausea, constipation, and increased sweating in the venlafaxine-treated patients, and significantly more of these patients had discontinuation symptoms when treatment was completed at week 8.

30.3.4 Relapse and Recurrence Prevention Study

An MDD relapse prevention study [33] was carried out in another group of patients aged 65 and older. Escitalopram was administered at a dose of 10 mg or 20 mg/day for 12 weeks. Patients that reached remissions (a total MADRS score of 12 or lower) were allocated to receive either escitalopram at 10 mg or 20 mg/day or placebo. The two groups were followed to determine the relapse rate. The cumulative non-relapse rate remained high in the escitalopram group but decreased over time in the placebo group. At the end of study, relapses were observed in only 9 % of the escitalopram group and 33 % of the placebo group; thus, the relapse rate was significantly lower in the escitalopram group.

An MDD recurrence prevention study [34] examined recurrences after 16 weeks of continuous therapy with escitalopram. Patients given escitalopram at a fixed dose of 10 mg or 20 mg/day were compared to controls given placebo for 52 weeks of maintenance therapy. Time to recurrence was significantly longer in patients who received maintenance treatment with escitalopram compared with patients switched to placebo, and MDD recurrence was 27 % in the escitalopram group significantly lower than the 65 % observed in the placebo group (Table 30.1).

30.4 Tolerability

Patients with MDD generally exhibited favorable tolerance to escitalopram, regardless of whether they received short-term or long-term therapy. Adverse events were typically mild and temporary [35]. The most frequent adverse events that occurred during escitalopram therapy included insomnia, nausea, excessive sweating, fatigue/somnolence, dysspermatism, and decreased libido [36].

30.4.1 Comparison with SSRIs or SNRIs

Escitalopram was compared to other SSRIs or SNRIs in a meta-analysis of patient data from 16 double-blind, controlled studies [37]. When attention was focused on adverse events that occurred at a frequency of 5 % or more, escitalopram showed significantly lower frequencies of diarrhea and dry mouth and the presence of more than one adverse event compared to the other SSRIs. Escitalopram was also associated with significantly lower frequencies of nausea, insomnia, dry mouth, vertigo, excessive sweating, constipation, and vomiting than the SNRIs.

30.4.2 Discontinuation Symptoms

Discontinuation symptoms typically occur at the end of treatment with antidepressant drugs. A detailed study [38] compared discontinuation symptoms in patients with MDD during the post-therapy observation period after 27 weeks of

Table 30.1 Summary of clinical and safety outcomes of escitalopram treatment of major depressive disorder as reported by randomized controlled trials

Study	Study design	Subjects (N)	Dose (mg/day)	Clinical outcomes	Safety outcomes
Wade et al. [15]	8-week double-blind placebo-controlled trial	MDD (380)	Escitalopram 10 (fixed doses)	MADRS score changed by −16.3 in the escitalopram group and −13.6 in the placebo group	Well tolerated in all patients. Nausea episodes significantly increased in the escitalopram group than in the placebo group
Burke et al. [16]	8-week randomized double-blind placebo-controlled fixed-dose multicenter trial	MDD (49)	Escitalopram 10, 20; citalopram 40 (fixed doses)	Escitalopram (10, 20 mg/day) produced significant improvement at study endpoint relative to placebo Escitalopram (10 mg/day) was as effective as citalopram (40 mg/day) at study endpoint	Discontinuation due to adverse events for the escitalopram (10 mg/day) group was not different from those for the placebo group, and no difference between the escitalopram (20 mg/day) and citalopram (40 mg/day) groups was noted
Lepola et al. [17]	8-week randomized double-blind placebo-controlled trial	Moderate to severely depressed patients ($n=469$)	Escitalopram 10–20; citalopram 20–40 (flexible doses)	Significantly more patients responded to escitalopram than to citalopram or the placebo	Escitalopram was as well tolerated as citalopram. Both escitalopram and citalopram had placebo-level adverse event withdrawal rates
Lalit et al. [18]	4-week randomized double-blind parallel-group controlled multicentric trial	MDD (214)	Citalopram 20–40; escitalopram 10–20; sertraline 50–150 (flexible doses)	Response rates after 2 weeks were 58 % for escitalopram (10 mg/day) and 49 % for citalopram (20 mg/day) Response rates after 4 weeks were 90 % for escitalopram (10–20 mg/day) and 86 % for citalopram (20–40 mg/day). Remission rates after 4 weeks were 74 % for escitalopram and 65 % for citalopram	There were fewer dropouts in the escitalopram group than in the citalopram group
Moore et al. [19]	8-week double-blind randomized trial	MDD (280)	Escitalopram 20; citalopram 40 (fixed doses)	MADRS score decreased more in the escitalopram group than in the citalopram group There were more treatment responders with escitalopram (76.1 %) than with citalopram (61.3 %). Adjusted remission rates were 56.1 % and 43.6 %, respectively	Tolerability was similar in both groups

(continued)

Table 30.1 (continued)

Study	Study design	Subjects (N)	Dose (mg/day)	Clinical outcomes	Safety outcomes
Yevtushenko et al. [21]	6-week prospective randomized double-blind active control trial	MDD (322)	Escitalopram 10; citalopram 10, 20 (fixed doses)	Mean change in MADRS was significantly greater in the escitalopram group than in the 10 and 20 mg/day citalopram groups	Prevalence of adverse events was significantly lower with escitalopram than with citalopram. Nausea and headache were the most frequently reported adverse events
				Changes in CGI-S and CGI-I and response and remission rates were significantly greater in the escitalopram group than in the citalopram 10 and 20 mg/day groups	
Ou et al. [20]	6-week double-blind trial	MDD (240)	Escitalopram 10–20; citalopram 20–40 (flexible doses)	No significant differences were found between the two groups for changes in the HAM-D17 total score	No significant differences were found between the two groups for adverse events
Boulenger et al. [24]	24-week long-term double-blind controlled trial	MDD (459)	Escitalopram 20; paroxetine 40 (flexible doses)	Escitalopram (20 mg/day) showed better efficacy than paroxetine (40 mg/day). The total MADRS score changed by −25.2 in escitalopram group and by −23.1 in paroxetine group	Withdrawal rate due to adverse events was significantly lower for escitalopram (8 %) than for paroxetine (16 %). There were no significant differences in the incidence of adverse events during treatment. HAMD-17 total score change indicated significantly better outcomes for escitalopram (−16.9) than for paroxetine (−15.0). The remission rate was significantly higher (75.0 %) with escitalopram than in paroxetine (66.8 %)
Baldwin et al. [25]	27-week double-blind randomized parallel-group trial	MDD (323)	Escitalopram 10–20; paroxetine 20–40 (8-week flexible-dose acute period followed by 19-week fixed-dose maintenance period)	Equivalent efficacy was found in both groups at week 8	Paroxetine demonstrated significantly more discontinuation symptoms relative to escitalopram based on DESS scores
				Significantly more paroxetine-treated (34 %) than escitalopram-treated patients (21 %) withdrew from the study. Significantly more paroxetine-treated patients withdrew due to lack of efficacy at week 27	
				In severely depressed patients, escitalopram was superior to paroxetine at week 27	

Ventura et al. [26]	8-week randomized double-blind multicenter parallel-group trial	MDD (212)	Escitalopram 10 (fixed doses); sertraline; 50–200 (flexible doses)	No differences in efficacy were observed for escitalopram and sertraline treatments	Both treatments were generally well tolerated
Khan et al. [29]	8-week randomized double-blind multicenter parallel-group trial	MDD (278)	Escitalopram 10–20 (fixed at 10 for the first 4 weeks followed by flexible doses), duloxetine; 60 (fixed doses)	A significantly greater proportion of escitalopram-treated patients than that of duloxetine-treated patients completed the 8-week study (87 % vs. 69 %). At week 8, escitalopram treatment resulted in significantly greater improvement than duloxetine treatment	Significantly fewer escitalopram-treated patients discontinued because of adverse events than duloxetine-treated patients (2 % vs. 13 %)
Wade et al. [30]	24-week double-blind randomized parallel-group trial	MDD (294)	Escitalopram 20; duloxetine 60 (fixed doses)	MADRS score improvement was significantly better in the escitalopram group than in the duloxetine group at week 8. This trend persisted until week 24	Withdrawal rate due to adverse events was lower for escitalopram (9 %) than for duloxetine (17 %), and significantly more patients treated with duloxetine reported insomnia (12.6 % vs. 4.9 %, respectively) and constipation (8.6 % vs. 2.8 %, respectively)
Gorwood et al. [33]	12-week open-label trial followed by a 24-week randomized double-blind placebo-controlled trial	MDD (305)	Escitalopram 10, 20 (fixed doses).	Significantly fewer escitalopram-treated patients (9 %) than placebo-treated patients (33 %) relapsed	Escitalopram was well tolerated with 53 patients (13 %) withdrawn as a result of adverse events during the open-label phase, and 3 (2 %) escitalopram-treated patients and 6 (4 %) placebo-treated patients were withdrawn as a result of adverse events during the double-blind treatment phase (not significant)
Kornstein et al. [34]	16-week open-label trial followed by 52-week randomized, double-blind placebo-controlled trial	MDD (139)	Escitalopram 10, 20 (fixed doses)	Time to recurrence was significantly longer in patients who received maintenance treatment with escitalopram than in patients switched to placebo	Long-term escitalopram treatment was well tolerated
				MDD recurrence was 27 % in the escitalopram group, which was significantly lower than the 65 % observed in the placebo group	

therapy with escitalopram (20 mg/day) or paroxetine (40 mg/day). Discontinuation symptoms were evaluated in terms of the Discontinuation Emergent Signs and Symptoms (DESS) score. During the observation period, the drug doses were gradually decreased over 1–3 weeks, followed by 1 week of alternate-day dosing and, subsequently, 1–3 weeks of placebo. The escitalopram group exhibited smaller changes in the total DESS score and significantly less frequent discontinuation symptoms compared to the paroxetine group, both at the end of alternate-day dosing and after 1 week of placebo administration. On the other hand, it has been reported that an antidepressant withdrawal syndrome may induce manic states in patients treated for major depression, even in the absence of a history of bipolar disorder [39–42], and there has been a case report of a young woman with unipolar depression who developed a manic state after abrupt discontinuation of low-dose escitalopram [43]. This manic state remitted when escitalopram was reintroduced within a week after the interruption of treatment [43]. Therefore, careful observation should be performed when discontinuing escitalopram, although escitalopram induces less discontinuation symptoms compared with other SSRIs.

30.4.3 Suicidality

Suicidality was studied in a detailed meta-analysis [44] conducted on data from 34 placebo-controlled studies on SSRIs. That analysis included >40,000 patients, and approximately 2,600 had been treated with escitalopram. They found one instance of suicide, which occurred 6 days after treatment cessation. Another analysis of placebo-controlled studies [46] specifically included patients with MDD or anxiety disorders that used escitalopram. They reported no suicides during the first 2 weeks of treatment or during the entire period of escitalopram (<24 weeks), but one suicide occurred in the placebo group. Furthermore, there was no indication of increased risk of nonfatal self-harm or suicidal thoughts among patients that received escitalopram compared those that received placebo [45]. Rather, escitalopram reduced the MADRS item 10 ("suicidal thought") or HAM-D item 3 ("suicidal thought") scores to a significantly greater extent than placebo [16, 45, 46]. For an estimated >12 million patients with MDD and/or anxiety disorders treated with escitalopram, pharmacovigilance information revealed a suicide rate of 1.8 per 1 million patients; this rate was similar to that in patients treated with citalopram (2 per 1 million) and considerably lower than that in patients treated with tricyclic antidepressants (12 per 1 million) or monoamine oxidase inhibitors (MAOIs) (14 per 1 million) [45].

30.4.4 Sexual Dysfunction

A small, retrospective study [47] ($N=47$) indicated that two-thirds of patients with SSRI/SNRI-induced sexual dysfunction reported mild or marked improvements after switching to a regimen with escitalopram. However, several reports have suggested that escitalopram may be associated with increased sexual dysfunction in both men and women compared to bupropion or sertraline [48, 49].

30.4.5 QT Prolongation

The cardiovascular safety of antidepressants has been the subject of recent debate. Additionally, the prescribing information and recommended dosing for citalopram have been modified to address concerns about the risk of QTc prolongation [50, 51]. Cardiovascular effects of escitalopram were assessed in participants in double-blind randomized placebo-controlled studies [52]. Escitalopram-placebo differences in mean changes in ECG values were not clinically meaningful. The difference compared to placebo in systolic or diastolic blood pressure (BP) was not clinically or statistically significant. The mean differences when compared to placebo in the corrected QT [Fridericia's (QTcF)] interval were 3.5 ms (all escitalopram doses), 1.3 ms (escitalopram 10 mg), and 1.7 ms (escitalopram 20 mg,

$p = 0.2836$ for 10 vs. 20 mg). One out of 2,407 escitalopram patients had a QTcF interval >500 ms and a change from baseline of >60 ms. The incidence and types of cardiac-associated adverse events were similar among patients treated for 8–12 weeks with placebo (2.2 %) or escitalopram (1.9 %) as well as patients treated for 24 weeks with placebo (2.7 %) or escitalopram (2.3 %). These data demonstrate that escitalopram, like other SSRIs, has a statistically significant effect on heart rate and no clinically meaningful effect on ECG values or BP compared with the observed placebo-level incidence of cardiac-associated adverse events. However, caution is required in administering escitalopram to aged individuals, patients with liver dysfunction, patients with defective CYP2C19 activity, or patients that have received other drugs that confer a risk of QT prolongation [53, 54].

30.4.6 Overdosage

In a retrospective analysis [55] of 28 patients that underwent a supratherapeutic ingestion of escitalopram (5–300 mg), only one patient reported adverse events. That patient was admitted to a hospital for persistent lethargy, but the outcome was good. However, when escitalopram is taken at high doses or in polysubstance ingestions, CNS depression may occur. Patients ($N = 13$) that had taken escitalopram (mean dosage 126 mg) as a co-ingestant in polysubstance ingestions exhibited CNS depression (54 %), cardiovascular effects (54 %), and ECG changes (23 %) [56]. In a case report [57], after an overdose of escitalopram (100–200 mg), a 38-year-old man exhibited severe, prolonged serotonin syndrome and elevated serum escitalopram concentration.

30.4.7 Hyperglycemia

The exact mechanism responsible for the impairment of glucose control in patients taking SSRIs such as escitalopram is still unclear; however, there has been a case report on escitalopram-induced hyperglycemia in an 83-year-old female patient with diabetes [58], suggesting that escitalopram may cause the loss of glycemic control.

30.5 Patient Acceptability

A meta-analysis by Cipriani et al. [27] reported on the efficacy and patient acceptability of 12 new antidepressant drugs. In that meta-analysis, patient acceptability was defined as the persistence observed in taking a drug during an 8-week therapy. Escitalopram and sertraline showed the best profile of acceptability, leading to significantly fewer discontinuations than did duloxetine, fluvoxamine, paroxetine, reboxetine, and venlafaxine. Especially, among those 12 drugs, escitalopram was associated with the highest rate for both efficacy and acceptability.

The rates of discontinuing therapy were analyzed among pooled data from double-blind, controlled studies of escitalopram vs. paroxetine [59] or duloxetine [60]. The pooled data for paroxetine was derived from two studies that treated patients for 24 [24] and 27 weeks [25]. The discontinuation rate at the end of the study period was significantly lower for patients on escitalopram (16.8 %) than for those on paroxetine (27.9 %). When the reason for discontinuing therapy was restricted to adverse events, the discontinuation rates remained significantly lower for escitalopram (6.6 %) than for paroxetine (11.7 %).

The pooled data for duloxetine were derived from two studies that treated patients for 8 [29] and 24 weeks [30]. The discontinuation rate at the end of the study period was significantly lower for escitalopram (12.9 %) than for duloxetine (24.6 %). When the reason for discontinuing therapy was restricted to adverse events, the discontinuation rates remained significantly lower for escitalopram (4.6 %) than for duloxetine (12.7 %). Thus, escitalopram was associated with high therapy continuity.

MDD has a relatively high likelihood of recurrence. Thus, high therapy continuity with escitalopram represents an advantage for patients with this disease. There may be several reasons for the high therapy continuity of escitalopram. First, it

has high efficacy and good tolerability, as shown in the clinical studies mentioned in Sects. 2 and 3 above. Thus, dropouts from escitalopram therapy due to insufficient efficacy or adverse events appeared to be limited. Furthermore, the demonstrated efficacy of escitalopram at an initial dose of 10 mg [15] could be detected in early therapeutic phase by patients [15, 30]. It was speculated that early signs of improvement most likely led to increased adherence, which, in turn, led to prevention of relapse [33] and recurrence [34].

The fact that escitalopram demonstrated preventive effects on relapse [33] and recurrence [34] represented major benefit to patients that desire to be reintegrated into society. For instance, for a company employee that wants to return to work, escitalopram may facilitate the return-to-work program, and thus, the patient would expect to return to work smoothly.

Conclusion

This review provided an overview of escitalopram focusing on its efficacy, tolerability, and patient acceptability in the management of MDD. In terms of efficacy, escitalopram was superior to placebo and equal to or better than paroxetine or other SSRIs and SNRIs. In addition, escitalopram exerted a stable antidepressive action. Escitalopram had high tolerability, because adverse events related to escitalopram therapy were generally mild and temporary. Moreover, discontinuous symptoms were apparently milder than those related to paroxetine therapy.

The meta- and pooled analyses [27] showed high patient acceptability of escitalopram, which indicated that patients found it easy to continue this antidepressant therapy. Therefore, escitalopram can be regarded as an antidepressant drug associated with high therapy continuity, and the high efficacy of escitalopram is in part based on improved adherence due to high tolerability. In addition, the high therapy continuity of escitalopram can be expected to prevent relapses and recurrences. A comparison with placebo demonstrated that escitalopram had preventive effects on both relapse and recurrence of MDD.

A review of Murdock et al. [7] discussed the positioning of escitalopram in the management of MDD. Preliminary studies have suggested that escitalopram was as effective as other SSRIs and venlafaxine XR (venlafaxine hydrochloride extended release); furthermore, escitalopram may provide the advantage of cost-effectiveness and cost utility. However, additional longer-term, comparative studies that evaluate specific efficacy, tolerability, health-related quality of life, and economic indices would be needed to determine definitively the position of escitalopram relative to other SSRIs and venlafaxine in the treatment of MDD. Nevertheless, available clinical and pharmacoeconomical data indicate that escitalopram is an effective first-line option in the management of patients with MDD.

Because MDD recurs readily, it is important to select antidepressant drugs that allow high therapy continuity for pharmacological treatments. The effects of escitalopram highlighted in this review indicated that it is an antidepressant drug appropriate for first-line therapy.

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