Escitalopram: A Second-Generation SSRI

By Michael J. Owens, PhD, and Jerrold F. Rosenbaum, MD

ABSTRACT

Serotonin (5-hydroxytryptamine, 5-HT) has long been suspected to play a role in the etiology of depression, and modern neurochemical techniques have confirmed this suspicion. Furthermore, all drugs known to be selective (a relative term) serotonin transporter (SERT) inhibitors are effective antidepressants. Of the selective serotonin reuptake inhibitors (SSRIs) approved in a number of countries for use in depression, panic disorder, and obsessive-compulsive disorder, citalopram is the most selective. Citalopram has been used worldwide to treat an estimated 35 million patients, with an excellent safety record. Citalopram is a racemic drug, and its effects on serotonin transport are thought to reside in the S*-enantiomer, known as* (S)*-citalopram or escitalopram. Escitalopram is the most selective SSRI yet developed. Its receptor binding properties and activity in preclinical animal models of depression predict that escitalopram would be effective in the treatment of depression, with approximately twice the potency of the racemate. The pivotal clinical trials of escitalopram not only support this conclusion, but also suggest escitalopram possesses advantages over citalopram in terms of both efficacy and safety. In conclusion, escitalopram is a promising candidate for use as a first-line antidepressant.*

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SEROTONIN AND THE SERT

Initially designated "enteramine" in 1946 because of its isolation from enterochromaffin cells of the gastrointestinal mucosa as well as other tissues (eg, amphibian skin and octopus salivary glands), serotonin (5-HT) has been of considerable interest to both psychiatrists and pharmacologists ever since its chemical characterization and complete synthesis in 1948 and 1951, respectively. Soon after its chemical identification, the structural similarities between 5-HT and LSD led to the logical speculation that substances related to 5-HT might cause mental aberrations. Coincidentally, physicians working in sanitariums for tuberculosis patients noted that iproniazid, an antitubercular drug (and monoamine oxidase inhibitor), improved mood in many individuals. Moreover, in the early 1950s it became evident that reserpine, an antihypertensive agent that depletes monoamine stores, including 5-HT, frequently produced depression as an unwanted side effect.

At that time it was still unknown whether 5-HT was endogenous to the brain. Both bioassay and spectrophotofluorometric methods developed in the 1950s soon revealed that 5-HT was indeed enriched in certain areas of mammalian brain. However, the groundbreaking histofluorescence studies of Dahlstrom and Fuxe in the mid-1960s using the Falk-Hillarp method enabled visualization of monoamine-containing pathways within the central nervous system (CNS). This arguably marked the beginning of modern neuropsychopharmacology: the hypothesis that alterations in serotonin neurotransmission are important in the pathophysiology and treatment of psychiatric illnesses originated almost 40 years ago.

In this regard, we recall a speculation by Emil Kraepelin,[1] the father of modern psychiatric nosology:

> "On the other hand, and this seems to be a distinct advantage of this 'pharmacopsychology,' we might be able to learn from the specific effect of a given drug on a specific psychic symptom something about the true nature of this symptom."
> – Emil Kraepelin, 1892

More than 100 years later, this insightful statement remains a logical avenue for research into the neurobiological basis of neuropsychiatric disorders, particularly in light of the array of techniques that have become available in the past 25 years. These techniques have confirmed the role of 5-HT in the pathophysiology of depression.

The primary mechanism by which the action of serotonergic neurons is terminated is via transport of 5-HT back into the serotonergic neuron and away from the area in and around the synapse. This effect is produced by a presynaptic protein known as a serotonin transporter (SERT), which reduces concentrations of 5-HT near the synapse to levels that do not maintain postsynaptic receptor activation. Tricyclic antidepressants (such as imipramine) and the SSRIs bind to the SERT and inhibit the uptake of 5-HT, suggesting the importance of the transporter for depression.

Stanley and colleagues[2] documented a reduction in the number of [^{3}H]-imipramine binding sites in the frontal cortex and hypothalamus of depressed suicide victims. Similarly, Perry and colleagues[3] reported a reduction in [^{3}H]-imipramine binding sites in postmortem hippocampus and occipital cortex of depressed patients. Although all its receptor interactions were not clearly understood at the time, [^{3}H]-imipramine is now known to label the SERT. This finding has been confirmed in brain tissue obtained from depressed subjects and suicide victims using the more selective ligands, [^{3}H]-citalopram and [^{3}H]-cyanoimipramine, respectively.[4] These findings provide further evidence for an alteration in neuronal 5-HT uptake mechanisms in depression, although they have not been universally replicated.[5,6]

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Antidepressant binding sites on platelets have served as a useful peripheral model, avoiding the inherent difficulties in obtaining post mortem brain tissue from large numbers of well-characterized patients and matched controls. Fortunately, platelet 5-HT transporters share many of the same properties as those of serotonergic nerve terminals, including embryological ancestry, biochemistry, identical SERT sequences, and others (Table 1).[6]

Beginning in the early 1980s, several groups reported decreased [^{3}H]-imipramine binding in platelets from drug-free depressed patients. These results, which have subsequently been replicated in many (but not all) studies, have become one of the more consistent findings in the biology of affective illness.[6-8] These findings are also observed in some more recent studies using very selective SERT ligands such as [^{3}H]-paroxetine or [^{3}H]-citalopram. This finding of reduced platelet SERT binding appears relatively specific for depressive disorders, but does not consistently correlate with symptom severity, post-dexamethasone serum cortisol concentrations, treatment effectiveness, or treatment outcome. In addition, preclinical studies in laboratory animals have not found a correlation between brain and platelet SERT number or response to changes in CNS serotonin neurotransmission or a hyperglucocorticoid state.[9]

Therefore, although the utility of SERT labeling at present is not particularly useful in identifying appropriate treatment strategies or monitoring outcome, the findings of decreased SERT numbers appear to be a relatively consistent finding in depressive disorders.

SELECTIVITY, POTENCY, AFFINITY, AND RECEPTOR BINDING

Affinity is the measure of how potent a drug is at binding to a site (for example, a receptor or transporter). This is fixed for a given drug at a given receptor and is denoted as the dissociation constant (K_d) or inhibition constant (K_i) depending upon how the data were generated, and represents the concentration of drug necessary to occupy 50% of the available receptors. In physical terms, affinity is a function of how well the three-dimensional structure of the receptor and the drug fit together. One can easily imagine how different stereoisomers, which have non-superimposable three-dimensional structures, can differ in affinity at any given binding site. Very few processes can alter measures of affinity.

Measuring a drug's affinity using saturation binding analysis requires that the drug be radiolabeled. Few drugs are available as such. More commonly, the affinity of a drug is determined using competition analysis, in which the drug

TABLE 1. COMPARISON BETWEEN PLATELETS AND SEROTONIN NEURONS

	Platelets	Neurons
Active transport for serotonin	+	+
SERT molecule	+	+
Subcellular storage of serotonin	+	+
Vesicular SERT (reserpine sensitive)	+	+
5-HT$_{2A}$ receptors	+	+
MAO type B	+	+
Embryonically derived from neural crest tissue	+	+
Neuron-specific enolase	+	+
Biosynthesis of serotonin	-	+

SERT=serotonin transporter; MAO=monoamine oxidase.

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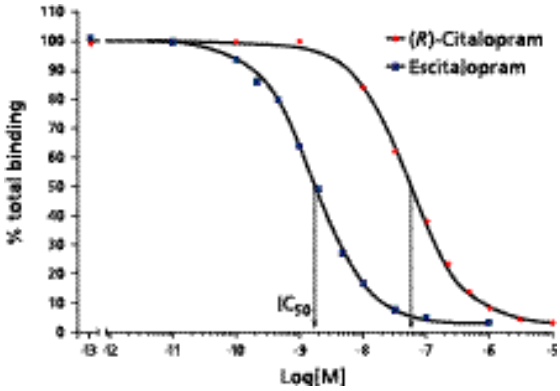

FIGURE 1. ANALYSIS OF COMPETITION BINDING DATA

Increasing amounts of competing drug (eg, individual enantiomers of citalopram) displace a radioactive tracer drug from the SERT. IC_{50} represents the concentration of drug that inhibits specific binding by 50%. The K_i (inhibition constant) or affinity can be calculated from the IC_{50} using the following equation: $K_i=[IC_{50}]/(1+([\text{tracer drug}]/[K_d \text{ radioactive drug}]))$.

SERT=serotonin transporter; K_i=inhibition constant; K_d=dissociation constant.

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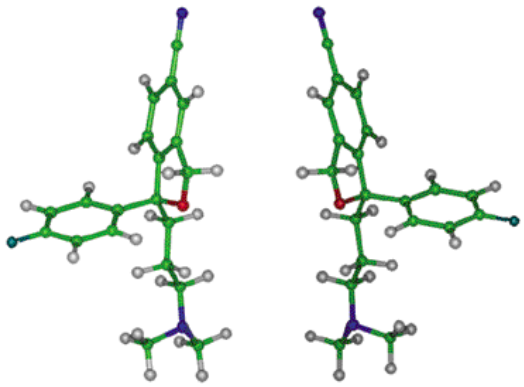

FIGURE 2. CHEMICAL STRUCTURES OF ESCITALOPRAM ([*S*]-CITALOPRAM) AND (*R*)-CITALOPRAM

Figure provided by Connie Sánchez (H. Lundbeck, Copenhagen).

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is added in increasing concentrations to a preparation containing a trace amount of a radioactive drug that shares a common binding site. At low concentrations, very little radioactive drug is displaced by the drug of interest. However, as the drug concentration is gradually increased, the radioactive drug is displaced from the common binding site in a sigmoidal manner on a semi-log scale (Figure 1). Drugs with a high affinity have smaller K_d values; they fit the binding site so well that less drug is necessary to bind to 50% of sites. For every drug, there will be a concentration that displaces/inhibits 50% of the radioactive drug's ability to bind (IC_{50}). This value depends upon the particular radioactive drug that is being used, thus the IC_{50} for a given drug is dependent upon the assay conditions. However, this value can be converted to an inhibition constant (K_i) with the equation:

$$K_i=[IC_{50}]/(1+([\text{tracer drug}]/[K_d \text{ radioactive drug}]))$$

Selectivity is determined by comparing the affinity of a given drug at different binding sites. The selectivity of a drug can be predictive of the likelihood of its therapeutic and side-effect potential. For example, if a new compound had a high affinity for the SERT, one would predict that it would be an effective antidepressant. However, if the compound also had a high affinity for muscarinic and histaminergic receptors, it would likely cause dry mouth and sedation, respectively. Thus, a highly selective SERT inhibitor without affinity at these other sites associated with side effects is theoretically preferred.

ESCITALOPRAM—PRECLINICAL PHARMACOLOGY

Single isomers of the SSRIs citalopram and fluoxetine have been in clinical development for the treatment of depression and other psychiatric disorders. For citalopram (Figure 2), this has been motivated by the finding that its actions on the SERT reside largely in the *S*-enantiomer

TABLE 2. AFFINITY (K_i, nmol/L) OF ANTIDEPRESSANTS FOR BINDING OR INHIBITING MONOAMINE TRANSPORTERS AND RECEPTORS[14]

Transporter Binding	SERT [^{3}H]-citalopram human	NET [^{3}H]-nisoxetine human	DAT [^{125}I]-RTI-55 human
Escitalopram	1.1±0.1	7,841±998	27,410±3,106
(*R*)-citalopram	36±5	12,270±906	18,720±2,740
Citalopram	1.6±0.1	6,190±818	16,540±3,795
(*R*)-fluoxetine	1.4±0.1	410±59	3,097±268
Fluoxetine	1.1±0.01	599±99	3,764±106
Paroxetine	0.10±0.01	45±3	268±8
Sertraline	0.26±0.02	714±37	22±1
Fluvoxamine	2.3±0.2	1,427±141	16,790±2,202

Uptake Inhibition	SERT [^{3}H]-5-HT human	NET [^{3}H]-NE human	DAT [^{3}H]-dopamine human
Escitalopram	2.5±0.4	6,514±423	>100,000
(*R*)-citalopram	67±8	6,243±945	>100,000
Citalopram	9.6±0.5	5,029±126	>100,000
(*R*)-fluoxetine	13±3	686±89	4,974±549
Fluoxetine	5.7±0.6	574±29	5,960±989
Paroxetine	0.34±0.03	156±29	963±113
Sertraline	2.8±0.8	925±98	315±40
Fluvoxamine	11±1	1,119±136	32,240±7,959

Receptor Binding	5-HT$_{2C}$ [^{3}H]-mesulergine porcine	α_1 [^{3}H]-prazosin human	Muscarinic$_1$ [^{3}H]-NMS human	Histamine$_1$ [^{3}H]-pyrilamine guinea pig
Escitalopram	2,531±324	3,870±441	1,242±72	1,973±152
(*R*)-citalopram	1,804±163	559±57	2,438±90	181±5
Citalopram	2,051±62	1,211±160	1,430±105	283±18
(*R*)-fluoxetine	64±14	1,528±74	998±18	812±38
Fluoxetine	72±1	3,171±390	702±48	1,548±102
Paroxetine	9,034±451	2,741±193	72±3	23,740±1,167
Sertraline	2,298±27	188±23	427±45	6,578±771
Fluvoxamine	5,786±515	1,288±131	31,200±9,626	29,250±7,269

K_i=inhibition constant; SERT=serotonin transporter; NET=norepinephrine transporter; DAT=dopamine transporter.

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[(*S*)-citalopram or escitalopram]. In contrast, both enantiomers of fluoxetine contribute to its biological activity[10,11]—the *R*-enantiomer having preferable pharmacokinetics. However, development of (*R*)-fluoxetine has ceased because of cardiac adverse effects at high doses.[12]

The initial observation that escitalopram is responsible for the SSRI activity of citalopram was reported by Hyttel and colleagues.[13] In rat brain synaptosomes, escitalopram demonstrated greater potency in inhibiting 5-HT uptake than citalopram; (*R*)-citalopram was 167 times less potent than escitalopram. Neither the racemate, nor either isomer, had substantial effect on noradrenergic or dopaminergic uptake. This pharmacological evidence was confirmed in whole animals. Escitalopram was at least as potent as citalopram in potentiating "serotonin" behaviors (such as head weaving, tremor, and hind limb abduction) in mice loaded with the serotonin precursor l-5-HTP.

In a recent study in cells expressing human serotonin transporters, escitalopram was found to be the most SERT-selective drug compared with other SSRIs.[13] Table 2 lists the affinities (K_i, nmol/L) of various antidepressants for selected transporters and receptors. Additionally, Table 2 presents the K_i of antidepressants for uptake inhibition. Escitalopram is the most SERT-selective compound tested and is ~30-fold more potent than (*R*)-citalopram in receptor binding. All compounds tested were SERT selective, though paroxetine, sertraline, fluoxetine, and (*R*)-fluoxetine are moderately potent at other transporters and receptors as well. Paroxetine and sertraline bind potently to the SERT, but they both also possess moderate affinity (<50 nmol/L) for the human norepinephrine transporter (NET) and dopamine transporter (DAT), and exhibit submicromolar affinities for muscarinic M_1 and α_1-adrenergic receptors, respectively. Furthermore, both (*R*)-fluoxetine and fluoxetine possess moderate affinities for the 5-HT_{2C} receptor. (*R*)-citalopram and citalopram possess moderate affinities for histaminergic H_1 receptors.

The functional aspect of SERT binding was also examined in studies of uptake inhibition. The potency of escitalopram in the functional assays was approximately four times that of citalopram (Table 2).[14] By either relative binding or uptake inhibition, escitalopram is the most selective compound, compared with the other SSRI antidepressants (Figure 3).

Escitalopram has also been studied in animal models that are predictive of antidepressant efficacy, such as the chronic mild stress model. In this well-validated model,[15] rats exposed to 3 weeks of a chronic mild stress (eg, noise, overcrowding, mild foot shock, etc.) reduce their voluntary intake of a sucrose solution compared to control (non-stressed) rats. This has been likened to anhedonia, a hallmark symptom of major depression. Treatment with both citalopram (10 mg/kg/day) and escitalopram (5 mg/kg/day) was effective in reversing the reduction in sucrose intake; however, escitalopram demonstrated a faster time to onset of action than citalopram.[16] This is consistent with other chronic mild stress studies that have shown that the onset of action with escitalopram is more rapid than that seen with tricyclic antidepressants as well.[17] Compared to citalopram, escitalopram was approximately 5 times as effective in reducing aggressive behavior in rats,[18] another model predictive of antidepressant-like activity.

In animal models of anxiety (footshock-induced ultrasonic vocalization and lit/unlit areas of a box), escitalopram produced potent anxiolytic-like effects in rats compared to (*R*)-citalopram, which was inactive or showed only weak activity, suggesting that escitalopram accounts for citalopram's anxiolytic activity.[19]

Escitalopram, like citalopram, is biotransformed to its principal demethylated metabolite by three distinct human cytochrome P450 (CYP) hepatic enzymes, CYP 3A4, CYP 2C19, and CYP 2D6 in parallel. Escitalopram is a negligible inhibitor of CYP 1A2, 2C9, 2C19, 2E1, and 3A, and only weakly inhibited CYP 2D6. Thus escitalopram, biotransformed by 3 CYP isoforms in parallel, is unlikely to be affected by drug interactions and unlikely to cause clinically important drug interactions via CYP inhibition.[20]

ESCITALOPRAM—CLINICAL EFFICACY

These preclinical data provided the rationale for the clinical development of escitalopram and made several specific predictions as to how it could perform in humans. Efficacy in clinical trials was anticipated by the observation that the *S*-enantiomer had greater potency as an SSRI than that of the racemate.

Burke and colleagues[21,22] have recently reported on the first large-scale clinical study with escitalopram. This was a randomized, double-blind, fixed-dose study in which moderately to severely depressed patients received

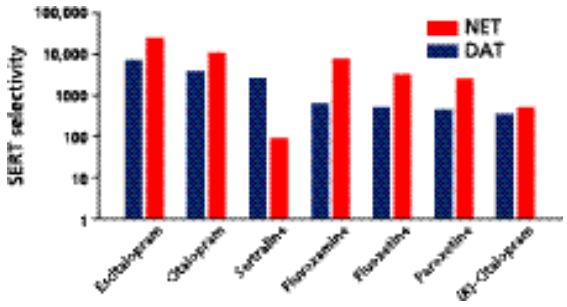

FIGURE 3. SERT SELECTIVITY USING BINDING DATA

Relative selectivity of several antidepressants for the SERT versus the NET or DAT. The K_i for the NET or DAT is divided by the K_i for the SERT and results in a unitless value in which 1 equals equipotency for both transporters. Values >1 represent relatively greater SERT selectivity. Note that the Y-axis is logarithmic.

SERT=serotonin transporter; K_i=inhibition constant; NET=norepinephrine transporter; DAT=dopamine transporter.

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placebo, escitalopram (10 or 20 mg/day), or citalopram (40 mg/day) for 8 weeks. As shown in Table 3, all three active treatment arms were significantly better than placebo on measures of antidepressant response at 8 weeks (for escitalopram, on all depression measures, significant separation from placebo occurred within the first 2 weeks). Of particular interest, escitalopram 10 mg/day produced at least as much improvement on key depression measures as citalopram 40 mg/day, and there were trends for the superiority of 20 mg/day escitalopram over 40 mg/day citalopram. In addition, subject withdrawals due to adverse events for escitalopram 10 mg/day did not differ from that of placebo (Figure 4).[23]

The other pivotal studies of escitalopram have also demonstrated its efficacy and tolerability in depressed outpatients. In addition to the report of Burke and colleagues,[21,22] two other randomized, double-blind, placebo-controlled, 8-week trials have shown that escitalopram at doses of 10–20 mg/day significantly improves depressive symptoms compared with placebo after 1–2 weeks of treatment in outpatients.[23]

The results from the chronic mild stress experiments discussed above predict the possibility of a faster onset of antidepressant action in clinical trials for escitalopram relative to citalopram, and this, in fact, has been observed in human subjects. For example, in one pivotal trial, the first 4 weeks of double-blind treatment used fixed doses of escitalopram (10 mg/day) and citalopram (20 mg/day—this a dose that provides 10 mg/day of escitalopram). Escitalopram (10 mg/day) produced a significantly superior response on the Montgomery Asberg Depression Rating Scale (MADRS) compared with placebo after 1 week of treatment, an effect that was maintained at every study visit thereafter. By comparison, citalopram (20 mg/day) did not produce a statistically significant effect on MADRS scores until after 4 weeks of treatment.[16]

SAFETY COMPARISON OF ESCITALOPRAM AND CITALOPRAM

The above clinical trial data suggest that escitalopram may possess some efficacy advantages over citalopram. As reviewed elsewhere in this supplement (Hutt pp. 14-22, Gal pp. 8-13), a single isomer can have a different safety and efficacy profile than the parent racemic compound. To compare what is known about the safety profiles of the two drugs, we examined the comprehensive safety database of all acute (up to 8-week duration) trials of citalopram in depression and the safety data from the acute (8-week duration) clinical trial experience with escitalopram for depression.

Many of the studies included in the citalopram safety database were performed prior to its approval in the United States; however, more recent trial data, such as the comparator arms from the escitalopram trials, are also available. In total, 1,471 patients have received citalopram at doses of 10–80 mg/day (more than 90% having received no more than 60 mg/day, and most patients receiving 40 mg/day or less). A total of 715 patients have received escitalopram (10–20 mg/day) in clinical trials. A total of 1,038 patients received placebo treatment in these studies.

As shown in Table 4, the most common adverse events for both drugs are those that are commonly associated with SSRIs, such as nausea and insomnia. However, the incidence for most of these events was lower for escitalopram-treated patients. It is notable that the incidence of somnolence is lower for escitalopram than for citalopram. This is consistent with the low to moderate affinity of (*R*)-citalopram for histaminergic receptors, which is absent in escitalopram. Although rates of spontaneously reported ejaculation disorders were similarly low for both drugs, and lower than rates of patient-reported ejaculation disorders from most modern studies of SSRIs (which tend to be well over 10%[24]) these rates have to be viewed with some circumspection given the lack of systematic assessment. This comparison is also reassuring in that the additional selectivity of escitalopram over citalopram for the SERT does not accentuate any "serotonin" adverse events.

In conclusion, binding studies have indicated that escitalopram is the most selective SERT inhibitor among all of those that have been developed for the treatment of depres-

TABLE 3. END POINT VALUES FOR EFFICACY VARIABLES (CHANGE FROM BASELINE) IN FIXED-DOSE TRIAL OF ESCITALOPRAM[22]

Outcome Measure	Placebo (n=119)	Escitalopram 10 mg/day (n=125)	Escitalopram 20 mg/day (n=118)	Citalopram 40 mg/day (n=123)
MADRS	-9.4	-12.8*	-13.9*	-12.0†
HAMD	-7.6	-10.2†	-11.7*	-9.9†
CGI-I‡	3.0	2.5*	2.4*	2.6†
CGI-S	-0.8	-1.3*	-1.4*	-1.2†
HAMD depressed mood item	-0.9	-1.3*	-1.4†	-1.4*

* Significantly different from placebo, $P<.01$
† Significantly different from placebo, $P<.05$.
‡ Values represent scores after 8 weeks of treatment, not change from baseline.
MADRS=Montgomery Asberg Depression Rating Scale; HAMD=Hamilton Rating Scale for Depression; CGI-I=Clinical Global Impression-Improvement; CGI-S=Clinical Global Impression-Severity.

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sion.[14] From these binding data, it was also predicted that only half the dose of the drug would be needed compared with its racemate, citalopram. As animal models of antidepressant action suggested that escitalopram would not only be more potent, but perhaps faster acting than citalopram, the pivotal trials of escitalopram are supportive of these conclusions. Moreover, when the safety databases of the two drugs are compared with each other, there is evidence of an improved tolerability profile as well for the single isomer. Escitalopram, therefore, appears to be a promising candidate for use as a first-line SSRI antidepressant.

If future work with this molecule replicates or extends these findings, the development of escitalopram will have confirmed the hypothesis that single-isomer drug development is a scientifically meaningful and clinically useful enterprise. CNS

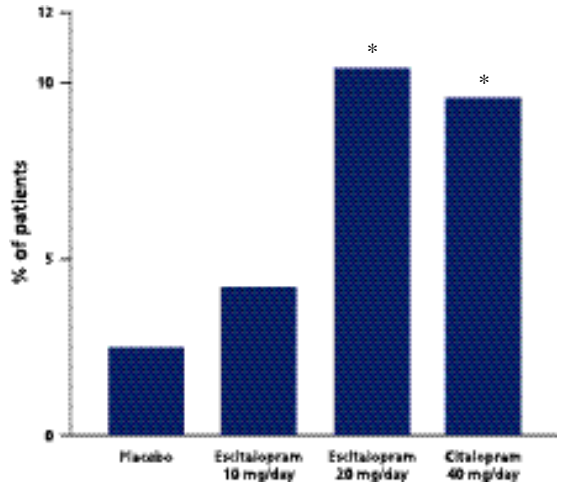

FIGURE 4. DISCONTINUATIONS[22]

Rates of discontinuation due to adverse events in a fixed-dose study. Escitalopram 10 mg/day did not differ from placebo (4.2% versus 2.5%; *P*=.5), and escitalopram 20 mg/day did not differ from citalopram 40 mg/day (10.4% versus 8.8%; *P*=.83).

*$P<.05$ versus placebo.[22]

Owens MJ, Rosenbaum JF. *CNS Spectrums*. Vol 7, No 4 (suppl 1). 2002.

TABLE 4. MOST COMMON ADVERSE EVENTS REPORTED IN ESCITALOPRAM AND CITALOPRAM DATABASES

	Placebo (n=1,038)	Escitalopram (n=715)	Citalopram (n=1,471)
Nausea	10%	15%	20%
Insomnia	8%	9%	13%
Mouth Dry	9%	6%	17%
Somnolence	5%	6%	14%
Diarrhea	5%	8%	9%
Dizziness	6%	5%	9%
Sweating	5%	5%	9%
Ejaculation Disorder*	1%	9%	7%
Fatigue	3%	5%	4%

*Percentages are relative to the number of male patients (placebo n=380; escitalopram n=225; citalopram n=584).

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