# A comparative review of escitalopram, paroxetine, and sertraline: are they all alike?

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**It is known that newer antidepressants, such as the selective serotonin reuptake inhibitors (SSRIs), provide advantages in tolerability over antidepressants such as the tricyclics. However, even within the SSRI class, differences in efficacy or tolerability exist between the individual drugs. Among the three most widely prescribed SSRIs are paroxetine, sertraline, and escitalopram. Escitalopram is commonly referred to as an SSRI, but also has well-documented allosteric properties, and thus can be further classed as an allosteric serotonin reuptake inhibitor. All three antidepressants are efficacious compared with placebo, but there is evidence that escitalopram is more effective than a range of other antidepressants. There are no direct data to regard either paroxetine or sertraline as a superior antidepressant. Escitalopram is superior compared with paroxetine, which has a less favorable tolerability profile. Paroxetine is associated with cholinergic muscarinic antagonism and potent inhibition of CYP2D6, and sertraline has moderate drug interaction issues in comparison with escitalopram. Overall, as an allosteric serotonin reuptake inhibitor that is somewhat different from classical SSRIs, escitalopram is the first choice judged by combined efficacy and tolerability, and nonclinical data have offered possible mechanisms through which escitalopram could be more efficacious, based on its interaction with orthosteric and allosteric binding sites at the serotonin transporter. *Int Clin Psychopharmacol* 29:185–196 © 2014 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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## Introduction

Major depressive disorder (MDD) is among the most prevalent disabling diseases, affecting millions of people around the world. Pharmacotherapy for depression has evolved over the past 30 years. Initially, the main treatments were the tricyclic antidepressants and the monoamine oxidases. Newer antidepressants were approved for use from the late 1980s to the late 2000s, including the selective serotonin (5-HT) reuptake inhibitors (SSRIs) and the serotonin and norepinephrine (NE) reuptake inhibitors (SNRIs). Paroxetine and sertraline were among the first SSRIs to be approved for clinical use and have been available since the beginning of the 1990s (Grimsley and Jann, 1992; Johnson, 1992). Escitalopram, the *S*-enantiomer of the racemic SSRI citalopram, is the newest marketed SSRI, introduced in 2002. In general, newer antidepressants are better tolerated than the tricyclic antidepressants and monoamine oxidases owing in part to the reduced side effect burden (Gillman, 2007). Numerous direct comparisons in randomized double-blind, controlled clinical studies, pooled analyses, meta-analyses, and reviews have been published comparing the clinical efficacy and tolerability of antidepressants. The SSRIs share the same mechanistic target, the serotonin transporter (SERT), which is responsible for 5-HT uptake into serotonergic neurons (Blakely *et al.*, 1991). Inhibition of 5-HT uptake by an SSRI results in higher extracellular levels of 5-HT and this is considered the basis of their antidepressant activity, although the exact antidepressant mechanism has yet to be elucidated. On the basis of its unique pharmacological characteristics, escitalopram is further classified as an allosteric serotonin reuptake inhibitor (ASRI), as described in the Canadian Network for Mood and Anxiety Treatments (CANMAT) clinical guidelines (Lam *et al.*, 2009; Nutt and Feetam, 2010).

According to the classical definition of an SSRI, the selectivity for inhibition of 5-HT uptake is defined relative to the ability of a given drug to inhibit the reuptake of norepinephrine, and SSRIs are often referred to as one drug class based on this definition. However, there is published evidence from preclinical in-vitro and in-vivo pharmacology studies (e.g. Sanchez and Meier, 1997) and clinical efficacy studies (Montgomery *et al.*, 2007; Rao, 2007; Kasper *et al.*, 2009b; Montgomery and Moller, 2009) that would support meaningful differences among SSRIs in their effects. Furthermore, the literature often provides within-discipline comparisons of drugs. This paper reviews potential differences between the clinical, clinical pharmacology, and nonclinical properties of the three most widely prescribed SSRIs, escitalopram, paroxetine, and sertraline, and discusses the potential link between the mechanistic data obtained in nonclinical settings and from clinical trials.

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## Clinical efficacy and tolerability

Data from placebo-controlled and/or head-to-head comparisons of the ASRI escitalopram versus the SSRIs sertraline and paroxetine are listed in Table 1 and are described below.

### Efficacy: clinical studies with escitalopram and paroxetine

A relapse prevention study of 325 patients conducted with escitalopram and paroxetine included 8 weeks of initial treatment, followed by a 19-week maintenance treatment period and finally a 1–2 week tapered discontinuation period (Baldwin *et al.*, 2006). Overall, withdrawal of patients for lack of efficacy (normally referred to as relapses) was significantly less common on escitalopram than paroxetine (Baldwin *et al.*, 2006). In addition, the paroxetine treatment showed a higher rate of discontinuation symptoms, such as feeling tense, confusion, and nausea, than the escitalopram treatment (Baldwin *et al.*, 2007b).

In a 24-week study with severely depressed patients, escitalopram was more effective than paroxetine at 24 weeks and at 8 weeks at a clinically relevant level as judged by the Montgomery–Åsberg Depression Rating Scale (MADRS) difference of two points as well as by the remitter analysis (Boulenger *et al.*, 2006). In a post-hoc analysis of this study of patients with a high level of anxiety, identified as those with a baseline Hamilton Anxiety Rating Scale (HAM-A) score greater than 20 ($n = 280$) using analysis of covariance, escitalopram treatment showed a significantly greater improvement in both anxiety symptoms (HAM-A score) and depression symptoms (MADRS score) than paroxetine treatment (Boulenger *et al.*, 2010). In this study, the overall rate of withdrawal of patients in the paroxetine group was significantly higher than in the escitalopram group (Boulenger *et al.*, 2010).

In a pooled analysis of two studies, it was shown that at 6 months escitalopram was significantly more effective and had significantly fewer withdrawals than paroxetine (Kasper *et al.*, 2009a). A review found that escitalopram was significantly more effective than citalopram, paroxetine, and duloxetine at a clinically relevant level as judged by the strict criteria of responder analysis difference of 10% or two or more points difference on the MADRS (Montgomery and Moller, 2009). The response rate for escitalopram (74%) was also significantly higher with escitalopram than for these comparators (63%) (Montgomery and Moller, 2009). For long-term treatment, escitalopram ($n = 394$) showed a greater mean treatment difference from baseline than paroxetine ($n = 383$) on the MADRS and Clinical Global Impression (CGI) scores in post-hoc analysis of two trials (Kasper *et al.*, 2009a). In addition, in the subgroup of severely depressed patients, escitalopram demonstrated a significantly greater improvement in efficacy than paroxetine (Kasper *et al.*, 2009a).

### Efficacy: clinical studies with escitalopram and sertraline

In an 8-week head-to-head comparison study, escitalopram and sertraline showed similar efficacy, response rates (75 vs. 70%), and rates of withdrawn patients due to adverse events (2 vs. 4%) (Ventura *et al.*, 2007). However, this study may have underestimated the efficacy of escitalopram due to the bias of allowing sertraline to be flexibly dosed compared with the low fixed dose of escitalopram at 10 mg/day. In a placebo-controlled trial of flexibly dosed escitalopram and sertraline in MDD patients, both drugs were well tolerated with similar treatment response (60 and 62%, respectively) and remission rates (46 and 46%, respectively) as compared with placebo (42% response, and 27% remission) after 8 weeks of treatment (Alexopoulos *et al.*, 2004).

### Efficacy: clinical studies with sertraline and paroxetine

In a 24-week MDD study of continuation therapy ($n = 353$ patients), sertraline and paroxetine showed a similar very low recurrence rate, as assessed by the MADRS, the CGI, and the Battelle Quality of Life Questionnaire (Aberg-Wistedt *et al.*, 2000). In another MDD study, the subgroup with at least moderate depressive severity and high anxiety ($n = 108$) at baseline, treatment with paroxetine, sertraline, or fluoxetine for 10–16 weeks resulted in similar outcomes, as measured by improvement in Hamilton Depression Rating Scale (HAM-D) scores, response rates, and remission (Fava *et al.*, 2000b). The efficacies of paroxetine and sertraline were also compared in a head-to-head study (fluoxetine was also included in the study; $n = 284$ depressed patients) (Fava *et al.*, 2002). After 10–16 weeks of treatment, improvement in depression and insomnia symptoms was similar for all three groups, as measured by the HAM-D (Fava *et al.*, 2002). It should be noted that these two studies seem underpowered for a valid conclusion, and the study duration may not be ideal for observing either acute effects or long-term efficacy.

### Efficacy: meta-analyses

Overall, escitalopram, sertraline, and paroxetine are all efficacious as compared with placebo, as found in the meta-analysis of 35 trials reported from 1980 to 2011 involving 142 drug–placebo comparisons, which showed computed relative response rate ratios to placebo of 1.33, 1.33, and 1.44, respectively (Undurraga and Baldessarini, 2012). Escitalopram has been compared with other antidepressants including paroxetine and sertraline extensively in meta-analyses. Based on an analysis of 10 studies involving a total of 2687 MDD patients up to 2004, escitalopram was found to have significantly higher overall treatment effect (estimated difference in treatment effect of 1.07 points), response rate (odds ratio 1.29), and

**Table 1 Summary of data from clinical studies and meta-analyses comparing the efficacy and tolerability profiles of escitalopram, paroxetine, and sertraline**

| Trial/meta-analysis objectives | Indication and participants (*n*) | Drugs involved (and placebo where available)[a] | Duration | Results | | | |
|---|---|---|---|---|---|---|---|
| | | | | Escitalopram | Paroxetine | Sertraline | References |
| Efficacy and tolerability | MDD (325) | Escitalopram 10–20 mg and paroxetine 20–40 mg | 8 weeks, then 19 weeks maintenance, then 1–2 weeks withdrawal | Similar efficacy overall for escitalopram and paroxetine groups; but in severely depressed patients, escitalopram showed superiority | Higher withdrawal rate due to lack of efficacy; more discontinuation symptoms | – | Baldwin *et al.* (2006) |
| Efficacy | Severe MDD (459) | Escitalopram 20 mg and paroxetine 40 mg | 24 weeks | Escitalopram group showed greater improvement and greater remission rate (75% vs. 67%) than paroxetine group | Higher withdrawal rate than escitalopram (32 vs. 19%); higher withdrawal rate due to adverse events than escitalopram (16 vs. 8%) | – | Boulenger *et al.* (2006) |
| Improvement on depression and anxiety scores (post-hoc analysis) | MDD with anxiety (286) | Escitalopram 20 mg and paroxetine 40 mg | 24 weeks | For both scores, escitalopram greater than paroxetine ($P<0.05$) | See comparator | – | Boulenger *et al.* (2010) |
| Efficacy and tolerability | MDD (212) | Escitalopram 10 mg and sertraline 50–200 mg | 8 weeks | Escitalopram and sertraline groups showed similar efficacy and tolerability | – | See comparator | Ventura *et al.* (2007) |
| Efficacy and tolerability | MDD (403) | Escitalopram 10–20 mg and sertraline 50–200 mg | 8 weeks | Escitalopram and sertraline showed similar treatment responses) and remission | – | See comparator | Alexopoulos *et al.* (2004) |
| Efficacy, and sexual dysfunction | MDD (353) | Paroxetine 20–40 mg and sertraline 50–150 mg | 24 weeks | – | Efficacy: similar for paroxetine and sertraline; sertraline is associated with a greater libido decrease | See comparator | Aberg-Wistedt *et al.* (2000) |
| Improvement on depression and anxiety scores | MDD with anxiety (286) | Paroxetine 20–60 mg sertraline 50–200 mg | 10–16 weeks | – | For both scores, paroxetine similar to sertraline | For both scores, paroxetine similar to sertraline | Fava *et al.* (2000b) |
| Improvement on depression scores and baseline insomnia | MDD (284, with 125 having insomnia) | Paroxetine 20–60 mg and sertraline 50–200 | 10–16 weeks | – | Improvement in both depression scores and insomnia similar for paroxetine and sertraline | Improvement in both depression scores and insomnia similar for paroxetine and sertraline | Fava *et al.* (2002) |
| Efficacy and tolerability (meta-analysis) | MDD in 59 studies | Sertraline and paroxetine | – | – | Efficacy: sertraline similar to paroxetine; tolerability: sertraline greater than paroxetine, but sertraline is associated with higher rate of diarrhea | See comparator | Cipriani *et al.* (2010) |
| Weight gain | MDD (284) | Paroxetine and sertraline | 26–32 weeks | – | Paroxetine is associated with higher rate of weight gain than sertraline | See comparator | Fava *et al.* (2000a) |
| Discontinuation symptoms (pooled analysis of five studies) | MDD, SAD, GAD (1750) | Escitalopram and paroxetine | – | Escitalopram showed significantly lower rate of discontinuation symptoms than paroxetine in MDD ($P<0.05$), SAD ($P<0.05$) and GAD ($P<0.001$) | See comparator | – | Baldwin *et al.* (2007a) |
| Tolerability (perspective follow-up study) | MDD (1251) | Sertraline and paroxetine | – | – | Tolerability: sertraline (14%) is associated with higher rate of diarrhea than paroxetine and other SSRIs (7%) ($P<0.05$) | – | Meijer *et al.* (2002) |
| Sexual dysfunction (meta-analysis) | MDD | Escitalopram paroxetine sertraline other antidepressants | Mostly 4–12 weeks | – | Total rate of treatment-emergent sexual dysfunction ~70% | Total rate of treatment-emergent sexual dysfunction ~80% | Serretti and Chiesa, (2009) |
| Blood BDNF levels | MDD | – | – | Decreased blood BDNF levels predict treatment response | – | – | Wolkowitz *et al.* (2011) |
| Blood BDNF levels | – | – | – | – | Decreased blood BDNF levels, increased with treatment | Decreased blood BDNF levels, increased with treatment | Yoshimura *et al.* (2010) and Yasui-Furukori *et al.* (2011) |

Data are based on review of published clinical studies and analyses, which include results from direct comparisons of compounds within the same studies, as well as those in which the compared compounds were in different studies, but the primary measurements overlapped.

BDNF, brain-derived neurotrophic factor; GAD, generalized anxiety disorder; MDD, major depressive disorder; SAD, social anxiety disorder; SSRI, selective serotonin reuptake inhibitor.

[a]Only escitalopram, paroxetine, and sertraline are listed.

remission rate (odds ratio 1.21) compared with all comparators including paroxetine and sertraline (Kennedy *et al.*, 2006). In a follow-up meta-analysis comparing escitalopram with active controls including SSRIs (citalopram, fluoxetine, paroxetine, sertraline) and SNRIs (venlafaxine, duloxetine) involving 4549 patients in 16 randomized controlled trials, escitalopram was again found to be significantly more effective than comparators in treatment effect (measured as change from baseline in MADRS total score), as well as in the rates of response and remission (Kennedy *et al.*, 2009). The results suggest the overall superior efficacy of escitalopram compared with paroxetine and sertraline as well as other SSRIs and SNRIs, though the superiority to other SSRIs was to the largest degree between escitalopram and citalopram (Kennedy *et al.*, 2009), a difference that has been well established (Montgomery *et al.*, 2011). In a recent meta-analysis of 10 antidepressants including paroxetine and sertraline for their remission rates, escitalopram was reported to have the most favorable treatment effect, with a remission probability of 0.47 after an 8- to 12-week treatment (Ramsberg *et al.*, 2012). Another indirect (rather than using pooled raw data) meta-analysis of 12 newer-generation antidepressants involved in 117 randomized controlled trials concluded that the odds ratios on efficacy (escitalopram vs. paroxetine, 1.3; sertraline vs. paroxetine, 1.2) and tolerability (escitalopram vs. paroxetine, 1.3; sertraline vs. paroxetine, 1.25) profiles significantly favored escitalopram and sertraline compared with those of paroxetine (Cipriani *et al.*, 2009). Meta-analyses for sertraline or paroxetine, however, did not find any superiority to each other or to escitalopram on efficacy (Thase *et al.*, 2005; Cipriani *et al.*, 2010). In the meta-analysis based on results reported from 234 studies between 1980 and 2011, Gartlehner *et al.* (2011) also found similar response rates for paroxetine and sertraline (odds ratio 1.02). In addition, a statistically significant odds ratio (1.49) for escitalopram compared with citalopram and numerical advantages for escitalopram in comparison with paroxetine (odds ratio 0.78) and sertraline (odds ratio 0.8) in treatment response rate were reported.

In general, results from individual well-designed and adequately powered randomized controlled trials should have priority in both scientific and regulatory settings, whereas meta-analyses are always *post hoc* and regarded as carrying less weight. An antidepressant is considered superior in efficacy if there are two or more double-blind studies where it is significantly better on the primary efficacy measure than a marketed antidepressant under conditions of fair comparison. Escitalopram has met this criterion with seven studies, but neither sertraline nor paroxetine was able to rely on a single study and therefore cannot be considered superior (Montgomery *et al.*, 2007). For example, when the efficacies of the newer drugs were compared, escitalopram (23.7%) ranked higher than sertraline (20.3%) (Cipriani *et al.*, 2009).

**Tolerability: escitalopram, paroxetine, and sertraline**

A comprehensive literature search of randomized controlled clinical studies found that about 60% of patients experienced at least one adverse event during treatment with an antidepressant. Overall, the newer-generation antidepressants had similar tolerability profiles, with the types of adverse events usually including diarrhea, dizziness, dry mouth, fatigue, headache, nausea, sexual dysfunction, sweating, tremor, and weight gain (Cipriani *et al.*, 2010). As concluded by a meta-analysis reviewing 117 randomized controlled trials involving 25 928 participants and 12 newer-generation antidepressants, escitalopram and sertraline showed a superior profile of tolerability, with significantly fewer discontinuations of patients than other antidepressants, including paroxetine (Cipriani *et al.*, 2009). In addition, a meta-analysis showed a considerably higher incidence of treatment-emergent sexual dysfunction for sertraline ($\sim$80%) than for escitalopram ($\sim$40%) (Serretti and Chiesa, 2009). This is in agreement with escitalopram having the highest cumulative probability of being among the four best treatments in terms of acceptability in a recent review: escitalopram (27.6%), sertraline (21.3%), and paroxetine (0.2%) (Cipriani *et al.*, 2009).

Compared with other SSRIs, a higher incidence of adverse effects was indicated for paroxetine treatment, including sedation, constipation, sexual dysfunction, discontinuation syndrome, weight gain, and congenital malformations, in a review of head-to-head studies (Marks *et al.*, 2008). A review of tolerability based on data from randomized controlled clinical trials involving about 4000 patients with short-term and long-term treatments indicated that paroxetine was associated with significantly higher incidence of adverse events related to sexual dysfunction, as well as more discontinuation symptoms, than escitalopram (Baldwin *et al.*, 2007b). In general, these findings are consistent with a recent review on the overall profile of paroxetine (Gibiino and Serretti, 2012).

On the basis of a head-to-head comparative study of MDD patients ($n = 284$) treated with sertraline or paroxetine, the paroxetine group showed a significantly higher weight gain (measured as the proportion of patients with a weight increase of >7% from baseline) than the sertraline group (Fava *et al.*, 2000a). A pooled analysis of five studies in MDD, social anxiety disorder, and generalized anxiety disorder patients showed that discontinuation of escitalopram treatment resulted in significantly lower rates of discontinuation symptoms than paroxetine and venlafaxine XR in MDD ($P < 0.05$), and also showed lower rates than paroxetine in social anxiety disorder ($P < 0.05$) and generalized anxiety disorder ($P < 0.001$) (Baldwin *et al.*, 2007a). Diarrhea is another common adverse event worth noting for antidepressants. In an earlier study, in which 659 patients were randomized to treatment with sertraline and 592 patients to other SSRIs (paroxetine, fluoxetine or

fluvoxamine), the rates of other adverse events were similar for all four drugs, but the incidence of diarrhea was higher with sertraline (14%) than with the other SSRIs (7%) (Meijer *et al.*, 2002). Consistent with this, a recent meta-analysis found that sertraline was indeed associated with a higher incidence of diarrhea than comparator drugs (including paroxetine) (Cipriani *et al.*, 2010). The review by Gartlehner *et al.*, (2011) further supports these differences by showing that paroxetine had a higher incidence of sexual dysfunction compared with escitalopram and sertraline, and sertraline was associated with higher incidence of diarrhea than paroxetine (average rates 16 vs. 8%).

## Mechanisms related to efficacy and tolerability

### Clinical pharmacokinetics

Some basic pharmacokinetic and pharmacodynamic properties of escitalopram, paroxetine, and sertraline are compared in Table 2. In general, the three antidepressants produce good absorption, distribution, and clearance profiles at their therapeutic doses. Escitalopram is approved at clinical dosages of 10 and 20 mg (with 5 mg in certain subpopulations or as starting dose), and when taken orally reaches $T_{max}$ in 5 h, is 56% protein bound, and reaches steady-state concentration in the blood within 1–2 weeks (Sogaard *et al.*, 2005; Rao, 2007; Spina *et al.*, 2012). Paroxetine is approved at clinical dosages of 12.5, 25, 37.5, and 50 mg daily, and when taken orally reaches $T_{max}$ in 6–10 h, is 95% protein bound, and reaches steady-state concentration in the blood within two weeks (Hiemke and Hartter, 2000; Bourin *et al.*, 2001). Sertraline is approved at higher clinical dosages, that is with 50 mg daily up to 200 mg daily for certain subpopulations, and when taken orally sertraline reaches $T_{max}$ in 5–9 h, is highly protein bound (99%), and reaches steady-state concentration in the blood within 1 week (Hiemke and Hartter, 2000; MacQueen *et al.*, 2001; DeVane *et al.*, 2002). Frequently, treatment with sertraline or paroxetine needs to be titrated by the physician to obtain the optimal dose for the individual patient.

Aspects of drug–drug interactions provide clinically relevant differences between escitalopram, paroxetine, and sertraline (Hiemke and Hartter, 2000). The three cytochrome P450 (CYP) isoenzymes, CYP1A2, CYP2D6, and CYP3A4, are responsible for the metabolism of most drugs; thus, drugs with inhibitory activities at any of the three CYPs may be prone to drug–drug interactions. Escitalopram is metabolized in parallel by at least two CYP enzymes, CYP3A4 and CYP2C19 (and to a lesser extent by CYP2D6), and has little inhibitory action against other CYP enzymes or P-glycoprotein (Rao, 2007), thus having a low potential for drug–drug interactions. As shown in Table 2, paroxetine is a potent inhibitor of CYP2D6 and is the SSRI most likely to cause drug–drug interactions (Richelson, 2001). Sertraline can inhibit CYP2C9/19 and CYP2D6 but to a lesser degree than paroxetine, and thus has a lower likelihood of causing drug–drug interactions (Richelson, 2001). Thus, escitalopram may be superior to paroxetine and sertraline in this regard.

### Pharmacological mechanisms related to clinical efficacy and tolerability

The primary target mediating the therapeutic actions of escitalopram, paroxetine, and sertraline is the SERT, and all three drugs have very high affinity at the SERT (Table 3). Paroxetine has the highest affinity at the SERT, whereas escitalopram has the highest degree of

**Table 2 The pharmacokinetic and pharmacodynamic properties of escitalopram, paroxetine, and sertraline**

| | Escitalopram | Paroxetine | Sertraline |
|---|---|---|---|
| Pharmacokinetics | | | |
| Dosage (mg) | 5, 10, 20 | 12.5, 25, 37.5, 50 | 25, 50, 100 |
| $C_{max}$ (ng/ml) | – | 2.0, 5.5, 9.0, 12.5 | 20–55 |
| $T_{max}$ (h) | 5 | 6–10 | 5–9 |
| AUC (ng h/ml) | – | 121, 261, 338, 540 | – |
| Elimination $t_{½}$ (h) | 27–33 | 15–20 | 27 |
| Protein binding | 56% | 95% | 99% |
| Time to steady state | 1–2 weeks | 2 weeks | 1 week |
| Steady state $C_{max}$ (ng/ml) | – | 30 (at 25 mg daily) | – |
| Steady state $C_{min}$ (ng/ml) | – | 20 (at 25 mg daily) | – |
| Metabolizing enzyme | CYP3A4, CYP2C19 | CYP2D6 | CYP2C9/19 |
| Drug–drug interaction | Low potential, CYP2D6 inhibition (*in vivo* only) | Potent CYP2D6 inhibition | Low potential, CYP2C9/19 and CYP2D6 inhibition |
| References | Sogaard *et al.* (2005), Rao (2007), and Spina *et al.*, 2012 | Hiemke and Hartter (2000) and Bourin *et al.* (2001) | Hiemke and Hartter (2000), MacQueen *et al.* (2001) and DeVane *et al.* (2002) |
| Pharmacodynamics | | | |
| SERT occupancy | 82% (in midbrain at 20 mg/day for 10 days; [$^{123}$I]ADAM SPECT imaging) | 85% (in striatum at 20 mg/day for 4 weeks; [$^{11}$C]DASB PET imaging) | 85% (in striatum at 50–100 mg/day for 4 weeks; [$^{11}$C]DASB PET imaging) |
| References | Kasper *et al.* (2009b) | Meyer *et al.* (2004) and Gibiino and Serretti (2012) | Meyer *et al.* (2004) |

Data are based on published results with references indicated.
AUC, area under the curve; SERT, serotonin transporter.

**Table 3 The in-vitro pharmacological profiles of escitalopram, paroxetine, and sertraline**

| $K_i$ (nmol/l) | Escitalopram | Paroxetine | Sertraline |
|---|---|---|---|
| SERT | 0.8–1.1 | 0.07–0.2 | 0.2–0.4 |
| SERT selectivity, compared with nearest target | >1000 | >200 | >60 |
| Allosteric at SERT | Yes | Yes (weak) | No |
| Other targets | | | |
| DAT | 27400 | 490 | 25 |
| NET | 7800 | 40–85 | 420–820 |
| $M_1$, muscarinic | 1240 | 72 | 430 |
| 5-$HT_{1A}$ | >1000 | 21200 | 3700 |
| 5-$HT_{2A}$ | >1000 | 6300 | 2200 |
| 5-$HT_{2C}$ | 2500 | 9000 | 2300 |
| $H_1$, histaminergic | 2000 | 13700–23700 | 5000–6600 |
| $\alpha_1$, adrenergic | 3900 | 1000–2700 | 36–190 |
| $\alpha_2$, adrenergic | >1000 | 3900 | 480 |
| $D_2$, dopamine | >1000 | 7700 | 11000 |
| References | Bolden-Watson and Richelson (1993), Owens *et al.* (1997, 2001), Tatsumi *et al.* (1997), Bourin *et al.* (2001), Richelson (2001), Sanchez *et al.* (2002, 2003), Chen *et al.* (2005a, 2005b), and Zhong *et al.* (2009) | | |

The in-vitro pharmacological profiles of escitalopram, paroxetine, and sertraline at human targets are compared.
Data are based on published results with references indicated.
SERT, serotonin transporter.

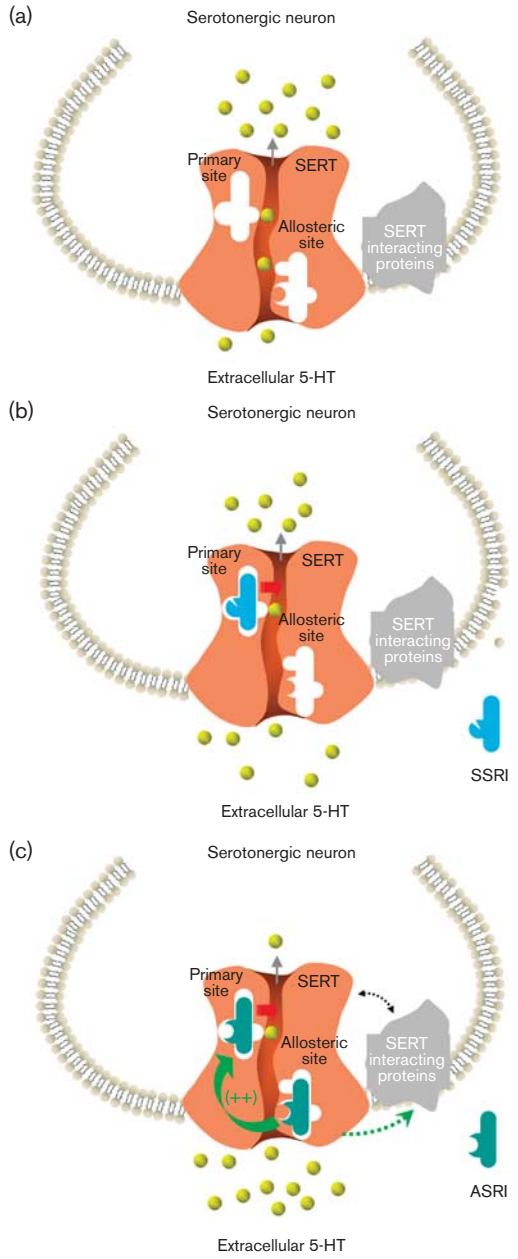
selectivity (i.e. >1000-fold relative to a large number of receptors and neurotransmitter transporters) as compared with paroxetine (> 200-fold) and sertraline (> 60-fold). In the clinical imaging studies mentioned above, the three antidepressants all bind to SERT at their therapeutic doses in humans, with occupancy of ~80%.

The clinical trial data, in head-to-head comparisons and in meta-analyses and as described in literature reviews, have shown higher efficacy for escitalopram and sertraline treatment of depression than paroxetine, with data also showing that escitalopram is associated with higher efficacy compared with other SSRIs. The efficacy of escitalopram may at least in part be ascribed to its actions at allosteric sites of the SERT (Chen *et al.*, 2005a, 2005b; Sanchez, 2006; Nutt and Feetam, 2010; Zhong *et al.*, 2009, 2012a, 2012b). The SERT has two types of binding site, the orthosteric binding site (also referred to as the primary site) to which escitalopram and other SSRIs bind, resulting in inhibition of its uptake function, and one or more allosteric sites (Chen *et al.*, 2005a, 2005b; Sanchez, 2006). Many studies have led to the thorough characterization of the allosteric mechanism of escitalopram (Wennogle and Meyerson, 1982; Plenge and Mellerup, 1997; Chen *et al.*, 2005a, 2005b), although other compounds have also been reported to have allosteric activities at the SERT but are less well characterized (Nandi *et al.*, 2004; Nightingale *et al.*, 2005; Boos *et al.*, 2006).

In binding experiments with the SERT, the allosteric activity of escitalopram is characterized by its ability to prolong its own dissociation kinetics (Chen *et al.*, 2005a, 2005b; Sanchez, 2006). By binding to both the orthosteric and allosteric binding sites, escitalopram elicits a more complete and sustained inhibition of 5-HT uptake, leading to higher extracellular 5-HT levels *in vivo* and faster 5-$HT_{1A}$ autoreceptor desensitization, as reviewed previously (Sanchez *et al.*, 2004, 2006). Additional elucidation of this mechanism includes in-vitro as well as in-vivo studies demonstrating that specific mutations in the SERT disrupt the allosteric effect of escitalopram, and that *R*-citalopram, a less active enantiomer of citalopram (citalopram is also an antidepressant), inhibits the efficacy of escitalopram (Zhong *et al.*, 2012a, 2012b). This makes escitalopram the only SERT-related antidepressant that shows dual allosteric and chiral advantages (El Mansari *et al.*, 2007; Nutt and Feetam, 2010; Zhong *et al.*, 2012a, 2012b). Thus, even though escitalopram was derived from the SSRI citalopram, it is further referred as an ASRI (Lam *et al.*, 2009; Zhong *et al.*, 2012a, 2012b), and these molecular interactions are depicted in Fig. 1. As noted in Table 3, paroxetine is also allosteric, but its allosteric effect is weaker (Chen *et al.*, 2005b; Sanchez, 2006). In comparison, sertraline and many other antidepressants (e.g. fluoxetine, duloxetine, and venlafaxine) do not have allosteric activities at the SERT (Fig. 1b) (Chen *et al.*, 2005a, 2005b).

It is worth noting that for the SSRIs fluoxetine and paroxetine, enantiomers have also been studied. The different ability of escitalopram, paroxetine, and sertraline in increasing extracellular levels of 5-HT in relation to SERT occupancy in the rat brain has been demonstrated, which indicates that the allosteric property of escitalopram may translate to physiological conditions (Brennum *et al.*, 2004). As shown in Fig. 2, extracellular 5-HT levels were measured in the ventral hippocampus of freely moving rats by means of microdialysis, and related to occupancy at the SERT using [$^3$H]citalopram binding. At escitalopram, paroxetine, and sertraline doses of 0.5, 0.3, and 3.1 mg/kg, respectively, which corresponds to 88–92% SERT occupancy, the increase in extracellular 5-HT levels was the largest for escitalopram, followed by paroxetine and sertraline (Fig. 2a). From comparisons of the relationships between 5-HT level and SERT occupancy, it appears that escitalopram produces a higher extracellular 5-HT level than paroxetine and sertraline

**Fig. 1**



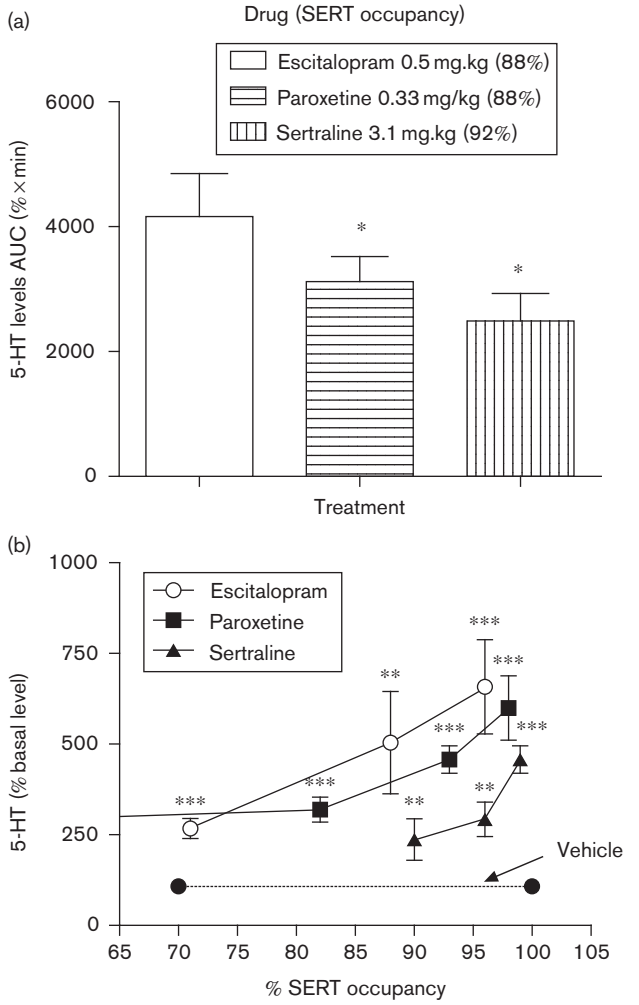

A putative model showing that escitalopram, paroxetine, and sertraline interact with the primary (orthosteric) and allosteric binding sites at the SERT leading to differential increases in extracellular 5-HT levels. In each diagram, the SERT is shown to be located at serotonergic neurons and to have the primary and allosteric binding sites. (a) In the absence of inhibitor drugs, the SERT performs its transport function, which removes extracellular 5-HT; (b) SSRIs such as sertraline are not able to bind to the allosteric site, and thus their action in increasing extracellular 5-HT levels is only mediated through the primary site; (c) ASRIs such as escitalopram bind to both the primary and the allosteric sites. Allosteric site binding enhances their binding to the primary site, resulting in more pronounced increases in extracellular 5-HT levels and potentially signaling through SERT-interacting proteins (SIPs) (Sanchez *et al.*, 2004; Zhong *et al.*, 2012a, 2012b). ASRI, allosteric serotonin reuptake inhibitor; SERT, serotonin transporter; SSRI, selective serotonin reuptake inhibitor. Drawing is based on previously published diagrams by Zhong *et al.* (2012a), with permission.

at the same SERT occupancy (Fig. 2b). For example, to achieve a 250% increase in extracellular levels of 5-HT, SERT occupancy needs to be 70, 83, and 95% for escitalopram, paroxetine, and sertraline, respectively (Fig. 2b). These differences do not reflect the in-vitro SERT inhibitory potency rank order (Table 3) and potentially support that there is an additional site of action (presumably an allosteric site) that mediates the more efficacious uptake inhibition by escitalopram, in addition to binding to the orthosteric site of the SERT.

In clinical studies, the level of SERT occupancy during chronic SSRI treatment studied by PET using the radioligand [$^{11}$C]*N*,*N*-dimethyl-2-(2-amino-4-cyanophenylthio) benzylamine ([$^{11}$C]DASB) suggested that a SERT occupancy of ~80% is necessary to achieve therapeutic effects of SSRI treatment and higher doses plateaued right above this range (Meyer *et al.*, 2004). Thus, at higher doses of SSRIs, such as sertraline and citalopram, a maximal of 85% occupancy was achieved (Voineskos *et al.*, 2007). Similar findings were seen with escitalopram using a selective radioligand 2-([2-([dimethylamino]methyl)phenyl]thio)-5-[$^{123}$I]-iodophenylamine ([$^{123}$I]ADAM) in single-photon emission computerized tomography studies, in which a maximal 82% SERT occupancy was identified (Kasper *et al.*, 2009b). Thus, due to the plateau in SERT occupancy seen for these antidepressants, higher doses are thought to be unable to further increase efficacy, but rather to incur additional side effects, which may contribute to higher discontinuation rates (Preskorn, 2012). On the basis of the above preclinical observations, it may be hypothesized that the increase in extracellular 5-HT induced by escitalopram might be higher in humans than for paroxetine and sertraline, even though there is an ~80% plateau of SERT occupancy.

Although it is clear that the primary target of escitalopram, paroxetine, and sertraline is the SERT, the precise cellular and physiological changes following uptake inhibition that mediate their antidepressant actions are poorly understood. It takes antidepressants, including the SSRIs, 1–2 weeks to produce their therapeutic effect, probably because slower neuroadaptive and neurochemical changes in the brain following the elevation of 5-HT levels are required for the therapeutic effect (Blier and de Montigny, 1999; Zhong *et al.*, 2012a). For example, the recovery of raphe 5-HT neuronal firing after the desensitization of 5-HT$_{1A}$ autoreceptors is thought to reflect the neuroadaptive process underlying the delayed onset of antidepressant action (Blier and de Montigny, 1999; El Mansari *et al.*, 2005). For escitalopram, it takes 2 weeks before 5-HT neuronal firing returns to control levels in rats, but for most SSRIs, it takes at least 3 weeks, suggesting a faster onset of action for escitalopram, possibly due to its action at the allosteric site (El Mansari *et al.*, 2005; Mnie-Filali *et al.*, 2007). This is consistent with the indication of escitalopram having a faster clinical onset than other SSRIs (Lepola *et al.*, 2004; Kasper *et al.*, 2006; Wade and Andersen, 2006).

**Fig. 2**




Increase in extracellular levels of 5-HT by escitalopram, paroxetine, and sertraline in relation to SERT occupancy in the rat. The ability of escitalopram, paroxetine, and sertraline to increase 5-HT levels in rat prefrontal cortex via SERT inhibition is shown. Rats in the microdialysis experiments were anesthetized and the drugs were administered by the subcutaneous route. SERT occupancy was measured by in-vivo binding using [$^3$H]citalopram as radioligand. (a) Different 5-HT levels in the rat prefrontal cortex after treatment with escitalopram 0.5 mg/kg ($n=8$), paroxetine 0.33 mg/kg ($n=7$), and sertraline 3.1 mg/kg ($n=6$) to achieve 88–92% occupancies of the SERT. Data shown are averaged 5-HT levels by AUC (% × min); *$P<0.05$ compared with escitalopram. (b) Differential 5-HT level vs. SERT occupancy relationships for escitalopram, paroxetine, and sertraline. Data shown are averaged 5-HT levels as percentages of baseline; **$P<0.01$, ***$P<0.001$ compared with vehicle (Brennum *et al.*, 2004). AUC, area under the curve; SERT, serotonin transporter.

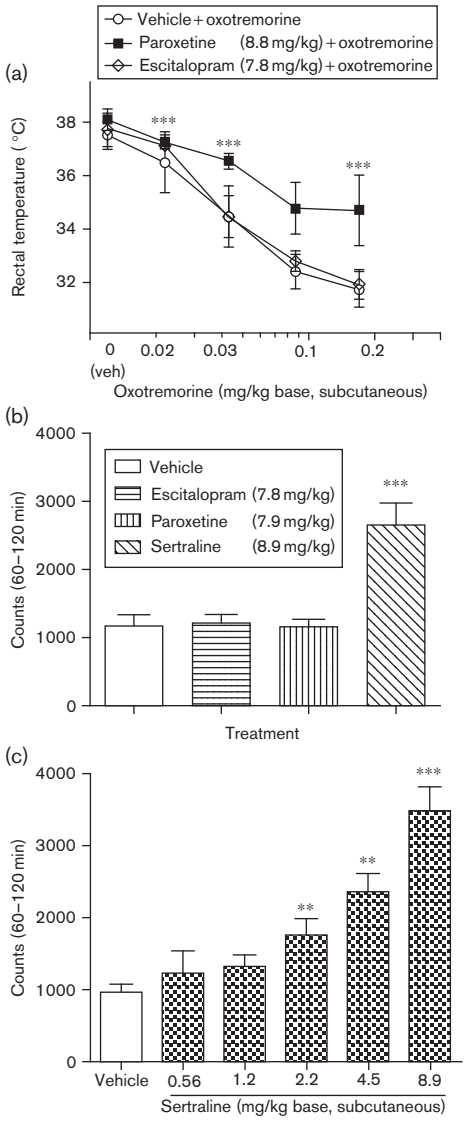
Among other neurochemical changes during antidepressant treatment, the neurotropin brain-derived neurotrophic factor (BDNF) was recently reviewed (Zhong *et al.*, 2012a). As a potential biomarker, BDNF shows decreased levels in the blood of depressed patients and this can predict treatment response for escitalopram, paroxetine, and sertraline (Yoshimura *et al.*, 2010; Wolkowitz *et al.*, 2011; Yasui-Furukori *et al.*, 2011). Thus, neurotropins such as BDNF might hold key insights associated with the neuroadaptive and neurochemical changes during antidepressant treatment, which may help differentiate the actions of SSRIs. Further studies in this area are warranted.

## Pharmacological mechanisms beyond SERT inhibition and putative functional relevance

Although it is believed that the therapeutic effects of escitalopram, paroxetine, and sertraline are mediated through their actions at the SERT, some side effects also can be explained by their off-target effects at other transporters and receptors (Richelson, 2001, 2003). The activities of escitalopram, paroxetine, and sertraline at some of these targets, such as the adrenergic α1, histamine $H_1$, and cholinergic muscarinic $M_1$ receptors, and the dopamine (DA) transporter (DAT), are listed in Table 3.

It is worth mentioning the antagonistic activity of paroxetine at cholinergic $M_1$ muscarinic receptors ($K_i$ = 72 nmol/l in comparison with $K_i$'s of 430 and 1240 nmol/l for sertraline and escitalopram), sertraline's DAT inhibitory activity ($K_i$ = 25 nmol/l in comparison with $K_i$'s of 490 and 27 400 nmol/l for paroxetine and escitalopram), and paroxetine's NE transporter (NET) inhibitory activity ($K_i$ = 40–85 nmol/l in comparison with $K_i$'s of 420–820 and 7800 nmol/l for sertraline and escitalopram) (Table 3). Potencies of this order of magnitude may be potentially meaningful at clinical exposure levels. Thus, commonly reported adverse effects of paroxetine are symptoms of sedation, constipation, and visual disturbance, which could be ascribed to anticholinergic activity (Pae and Patkar, 2007). Indeed, paroxetine has considerable potency for muscarinic receptors, allowing it to affect these receptors at the blood levels expected during treatment (Table 2). A study in mice, in which the anticholinergic effects of paroxetine were measured using oxotremorine-induced tremor, spontaneous defecation, and passive avoidance performance tests, also supports the notion of paroxetine having anticholinergic activity *in vivo* (Fujishiro *et al.*, 2002). It was found that paroxetine induced more anticholinergic effects than fluvoxamine (another SSRI), although its effects were lower than those of a tricyclic clomipramine, as expected (Fujishiro *et al.*, 2002). In a comparative study of escitalopram and paroxetine, the anticholinergic activity was assessed as blockade of hypothermia induced by the muscarinic agonist oxotremorine (Fig. 3a). Oxotremorine caused dose-dependent hypothermia, which was prevented by paroxetine but not escitalopram (Fig. 3a), demonstrating the anticholinergic activity of paroxetine. The role of dopamine reuptake inhibition (DAT activity) was also measured as stimulation of spontaneous locomotor activity (Fig. 3b and c). Sertraline produced a significant increase in the spontaneous locomotor activity compared with vehicle controls at doses close to those that produce 5-HT reuptake inhibition, that is, the minimal effective dose of 2.2 mg/kg corresponds to ~89% SERT occupancy

**Fig. 3**




In-vivo measurements of the effects of escitalopram, paroxetine, and sertraline on muscarinic cholinergic and DAT activities in mice. The anticholinergic and DAT-inhibiting effects of escitalopram, paroxetine, and sertraline are shown in oxotremorine-induced hypothermia (a) and spontaneous locomotor activity (b, c) in mice. (a) The role of muscarinic cholinergic antagonism is assessed as antagonism of hypothermia induced by the muscarinic agonist oxotremorine. The test was conducted at room temperature and started at 11 a.m. Drug or vehicle was injected subcutaneously 30 min before oxotremorine. The rectal temperature was measured before drug and oxotremorine administration and after 30 min. Data were analyzed by analysis of variance; ***$P<0.001$ compared with vehicle + oxotremorine. (b) The role of dopamine reuptake inhibition by a single dose of escitalopram, paroxetine, or sertraline was assessed as stimulation of spontaneous locomotor activity. The test was conducted in cages equipped with infrared light sources and photocells and the number of light beam interruptions was used as measure of locomotor activity. The mice were placed individually in the test cages and were habituated for 30 min before administration of drug. The accumulated number of light beam interruptions recorded 60–120 min after drug administration was used as the measure of drug effect; ***$P<0.001$ compared with vehicle. (c) Multiple doses of sertraline were assessed for stimulation of spontaneous locomotor activity as in (b). Data were analyzed by analysis of variance; **$P<0.01$, ***$P<0.001$ compared with vehicle (Sanchez, 2002).

in mice (Sanchez, 2002; Larsen *et al.*, 2004), whereas paroxetine and escitalopram were devoid of this effect, even at much higher doses (Fig. 3b and c). In line with these behavioral observations, Kitaichi *et al.* (2010) reported that sertraline, unlike paroxetine and fluvoxamine, increases extracellular DA in nucleus accumbens and striatum in freely moving rats (Kitaichi *et al.*, 2010). It is difficult to predict the functional net effect of this combined SERT and DAT inhibition, as there is a high degree of functional connectivity between the monoaminergic neurotransmitter systems, but sertraline may potentially differ from an SSRI that is devoid of DAT inhibition. Thus, in the dorsal raphe nucleus, activation of dopaminergic $D_2$ receptors increases whereas activation of serotonergic 5-$HT_{1A}$ receptors decreases the activity of 5-HT neurons. In the ventral tegmental area, activation of $D_2$ receptors or 5-$HT_{2C}$ receptors decreases the activity of DA neurons (Alex and Pehek, 2007).

NE reuptake inhibition was assessed as antagonism of tetrabenazine-induced ptosis in mice, and paroxetine showed NE reuptake-inhibiting activity at doses close to those that produced 5-HT reuptake inhibition (Sanchez, 2002). Tetrabenazine is a monoamine-depleting agent producing immobility and ptosis. The latter effect is mediated by alpha adrenoceptors and has been shown to be reversed by compounds with NE reuptake inhibitory activities (Arnt *et al.*, 1985). Despite inhibiting NET activities, paroxetine is still grouped in the class of SSRIs, as no clinical data support any comparable or superior SNRI features with paroxetine. In contrast, even though escitalopram does not have any noticeable activity on the NET, it seems to have advantages when compared with SNRIs in the treatment of MDD patients. For example, escitalopram was found to be associated with significantly lower duration of sick leave compared with duloxetine during treatment (Wade *et al.*, 2008), and it may also have a better efficacy and tolerability profile than the SNRIs venlafaxine and duloxetine as second-step treatment for MDD (Lam *et al.*, 2010).

Extrapyramidal side effects (EPS) have been discussed in association with SSRI treatment. A literature review of 89 cases of EPS associated with antidepressant treatment, including tremor, akathisia, dystonia, dyskinesia, and tardive dyskinesia, suggests relatively low occurrence rates for escitalopram (7%) and sertraline (10%) in comparison with other antidepressants (Madhusoodanan *et al.*, 2010). Direct comparison analyses in clinical trials do not indicate a risk of EPS for escitalopram or sertraline (Baldwin *et al.*, 2007b; Ventura *et al.*, 2007; Cipriani *et al.*, 2010). The exact mechanism for development of EPS is not fully understood, although it is generally accepted that dysfunction in dopaminergic transmission of the nigrostriatal pathway plays a key role (Glazer, 2000; Tuppurainen *et al.*, 2010). Reduced DA transmission in the form of DA receptor blockade by antipsychotic treatment in schizophrenia is frequently manifested by

the side effects of EPS and hyperprolactinemia, since dopamine exerts a potent and tonic inhibition of prolactin secretion under normal conditions (Kane, 2011). In a study of 159 patients on different medications, 27 cases (17%) of hyperprolactinemia were reported after SSRI treatment, and the occurrence was the highest for sertraline followed by paroxetine and other antidepressants (Petit *et al.*, 2003). However, a more recent review of spontaneous reports suggested that paroxetine, but not sertraline or escitalopram, was associated with a higher risk of hyperprolactinemia (Trenque *et al.*, 2011). An earlier analysis with the identification of 61 spontaneous reports concluded that SSRI use seems to be only moderately associated with EPS compared with other antidepressants, and suggests that patients with an already compromised dopaminergic function may be more susceptible (Schillevoort *et al.*, 2002).

### Conclusion

Escitalopram, paroxetine, and sertraline have well-established efficacy and tolerability profiles based on decades of clinical use as some of the most widely prescribed antidepressants. Although these antidepressants belong to the same general class (SSRIs) and all have demonstrated therapeutic efficacy, differences exist with respect to efficacy and tolerability, as shown by head-to-head comparisons and meta-analyses. There are studies demonstrating the superiority of escitalopram compared with paroxetine as well as a combined group of various SSRIs including paroxetine and sertraline. Paroxetine's cholinergic muscarinic antagonism and potent inhibition of CYP2D6 may have an impact on its tolerability. Although sertraline has moderate drug–drug interaction issues, its DAT inhibitory properties may result in a different pharmacodynamic profile. Therefore, when compared with paroxetine and sertraline, escitalopram as an ASRI different from classical SSRIs consistently shows advantages in efficacy and tolerability profiles, and nonclinical data have offered possible mechanisms through which escitalopram could be more efficacious based on its interaction with orthosteric and allosteric binding sites at the SERT.

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### Conflicts of interest

Connie Sanchez and Elin H. Reines are full-time employees of H. Lundbeck A/S. Stuart A. Montgomery has received consulting fees or honoraria from AstraZeneca, Bionevia, Bristol–Myers Squibb, GlaxoSmithKline, Johnson & Johnson, Lilly, H. Lundbeck A/S, Merck & Co. Inc., M's Science, Merz Pharmaceuticals, Neurim Pharmaceuticals, Otsuka, Pfizer Inc., Pierre Fabre, Roche Pharmaceuticals, Sanofi-Aventis, Sepracor Inc., Servier Laboratories, Synosis, Takeda, Theracos, Transcept, UBC, Xytis, and Wyeth.

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