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Efficacy of escitalopram in the treatment of social anxiety disorder: A meta-analysis *versus* placebo

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Abstract
Escitalopram is the most selective of the serotonin reuptake inhibitor (SSRI) antidepressants. We conducted a meta-analysis of placebo-controlled studies where escitalopram was used to treat patients with social anxiety disorder (SAD). Data from all randomised, double-blind placebo-controlled studies in SAD with escitalopram from both specialist settings and general practice were used. Patients met the DSM-IV criteria for SAD, were ≥ 18 years old, and had a Liebowitz Social Anxiety Scale (LSAS) ≥ 60. The primary outcome measure was the estimated treatment difference in LSAS total score at Week 12. Secondary outcome measures included the estimated treatment difference in the Clinical Global Impression-Severity (CGI-S) score at Week 12. A total of 1598 patients from 3 randomised controlled trials were included in the analyses. Escitalopram ($n=1061$) was superior to placebo ($n=537$), with an estimated treatment difference on the LSAS of -9.2 points (95%CI: [-14.4; -4.0], $p<0.01$) (escitalopram 5 mg/day), -4.6 points (95%CI: [-8.1; -1.0], $p<0.01$) (escitalopram 10 mg/day), -10.1 points (95%CI: [-13.7; -6.5], $p<0.01$) (escitalopram 20 mg/day) and -7.3 points (95%CI: [-12.3; -2.2], $p<0.01$) (escitalopram 10-20 mg/day). For the CGI-S, the corresponding values were -0.55 points (95%CI: [-0.79; -0.31], $p<0.01$) (escitalopram 5 mg/day), -0.26 points (95%CI: [-0.42; -0.10], $p<0.01$) (escitalopram 10 mg/day), -0.48 points (95%CI: [-0.64; -0.31], $p<0.01$) (escitalopram 20 mg/day) and -0.29 points (95%CI: [-0.51; -0.07], $p<0.05$) (escitalopram 10-20 mg/day). The withdrawal rate due to adverse events was 7.2% for

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escitalopram, compared with 4.3% for placebo ($p<0.05$). In this meta-analysis, all doses of escitalopram showed significant superiority in efficacy *versus* placebo in the treatment of patients with SAD.

1. Introduction

Social anxiety disorder (SAD) is typically a long-term medical condition with an estimated 1-year prevalence of 1.1–4.4% (Wittchen et al., 2011) or around 4.5% (Kessler et al., 2005), and a lifetime prevalence of 12.1% (Kessler et al., 2005) with an onset of symptoms typically in adolescence. This leads to significant functional impairment, including occupational, academic, and social dysfunction (de Menezes et al., 2011). SAD comprises social interaction fears, observation fears and public speaking fears. Early treatment is recommended, given the prolonged course of the disease and the low rate of spontaneous remission (Baldwin et al., 2014; Nagata et al., 2015).

Escitalopram is the most selective of the serotonin reuptake inhibitor (SSRI) antidepressants (Owens et al., 2001) and its efficacy has been demonstrated in SAD and other indications in both primary care and specialist settings (Kennedy et al., 2009). The efficacy of escitalopram, together with its good tolerability (Baldwin et al., 2007), suggests a favourable benefit-risk ratio.

To investigate the efficacy of the approved doses of escitalopram, the present analysis examined data from three randomised, double-blind placebo-controlled SAD studies. Meta-analysis is a method to synthesise data from several clinical studies providing they have similar trial designs, rating scales, duration, and patient selection criteria. When patient-level data are not available a meta-analysis uses the study as the unit of observation to produce a weighted average of trial results. The authors searched for all published and unpublished randomised placebo-controlled studies in SAD up to October 2015 involving escitalopram.

2. Experimental procedures

In this meta-analysis of published studies of the escitalopram treatment of patients with SAD, an attempt was made to identify all randomised, double blind placebo-controlled studies, regardless of patient numbers or treatment length.

2.1. Sources of data and criteria for review

Multiple computer searches using MEDLINE (1966-Oct 2015), EMBASE (1998–2015), and the Cochrane Collaboration (1980-Oct 2015) were conducted. The authors specified the keywords, including escitalopram, placebo, randomized controlled trials, and social anxiety disorder. Additional studies in any language were sought in reference lists of retrieved articles. Unpublished trials were identified through the Controlled Trials database and the National Institute of Health's Computer Retrieval of Information on Scientific Projects (CRISP) service (1972–2015). In addition, the following clinical trial registration sites were searched: www.lundbecktrials.com, www.forestclinicaltrials.com, www.japic.or.jp, www.clinicaltrials.gov, www.clinicaltrialresults.org, www.ifpma.org/clinicaltrials and www.controlled-trials.com. Results from all three of these studies have already been published (Lader et al., 2004; Kasper et al., 2005; Asakura et al., 2016a).

2.2. Patients

Patients were randomly assigned to double-blind treatment at the daily dosages shown in Table 1. Eligible patients fulfilled the DSM-IV criteria for a primary diagnosis of generalised SAD and were at least 18 years old. Patients were required to have a baseline LSAS score ≥ 70 (Lader et al., 2004; Kasper et al., 2005) or an LSAS-J ≥ 60 (the LSAS-J is the Japanese translation of the LSAS) and a Clinical Global Impression-Severity (CGI-S) score ≥ 4 (Kasper et al., 2005; Asakura et al., 2016a). Patients were excluded if their baseline Montgomery

Table 1 Overview of studies included in the meta-analysis.

Study no. (reference)	Duration	Design	ESC dose	Baseline LSAS	ΔLSAS[a]	FAS (*n*)
1 Lader et al. (2004)	24 weeks[b]	Fixed	5 mg	94.3	−38.7	166
			10 mg	92.4	−34.6	163
			20 mg	94.0	−39.8	164
		PBO	-	96.0	−29.5	165
2 Kasper et al. (2005)	12 weeks	Flexible	10-20 mg	96.3	−34.5	177
		PBO	-	95.4	−27.2	176
3 Asakura et al. (2016a)	12 weeks	Fixed	10 mg	94.5	−26.9	198
			20 mg	93.4	−32.6	193
		PBO	-	95.3	−23.1	196

ESC: escitalopram; LOCF: last observation carried forward; LSAS: Liebowitz Social Anxiety Scale; PBO: placebo, FAS: full analysis set.
[a]Change from baseline to primary endpoint (ANCOVA, LOCF, FAS).
[b]Data from primary endpoint at Week 12.

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Table 2 Baseline characteristics of the APTS population in the meta-analysis.

	Lader et al. (2004)		Kasper et al. (2005)		Asakura et al. (2016a)	
	Placebo	**Escitalopram 5, 10 & 20 mg**	**Placebo**	**Escitalopram 10-20 mg**	**Placebo**	**Escitalopram 10 & 20 mg**
Patients (*n*)	166	504	177	181	196	391
Age[a]	37±12	37±11	36±11	39±11	33±10	33±10
Men (%)	81 (48.8%)	233 (46.2%)	94 (53.1%)	101 (56%)	87 (44.4%)	173 (44.2%)
Caucasian (%)	100	99.7	91.6	90.6	0	0
Japanese (%)	0	0	0	0	100	100
Age of SAD onset (years)[a]	18±8	17±8	15±8	15±9	19±10	19±9
Duration of disorder (years)[a]	19±13	20±12	21±12	24±13	14±11	14±10
LSAS total score[a]	96.0±14.4	93.6±14.4	95.4±16.4	96.3±17.4	95.3±18.5	94.0±18.0
CGI-S total score[a]	4.8±0.8	4.8±0.7	4.8±0.7	4.8±0.7	4.8±0.8	4.9±0.8
MADRS total score[a]	7.6±4.8	7.0±4.4	7.5±4.4	7.6±4.5	3.6±4.0	3.8±3.9

[a]mean±SD. APTS: all patients treated set; CGI-S: Clinical Global Impression-Severity, LSAS: Liebowitz Social Anxiety Scale, MADRS: Montgomery Åsberg Depression Rating Scale SAD: social anxiety disorder, SD: standard deviation.

Åsberg Depression Rating Scale (MADRS) (Montgomery and Åsberg, 1979) total score was ≥18 (Lader et al., 2004), MADRS >19 (Kasper et al., 2005), or MADRS ≥15 (Asakura et al., 2016a). Patients with a serious concomitant illness or a recent history of alcohol or drug abuse were excluded from study participation. Clinically significant abnormalities on the baseline physical examination, electrocardiogram, or laboratory tests were also criteria for exclusion from study participation (Lader et al., 2004; Kasper et al., 2005). Patients who had a known hypersensitivity to citalopram or escitalopram (Asakura et al., 2016a) had taken disallowed recent or concomitant medication were also excluded. Patients were excluded if they had been diagnosed with another psychiatric disorder (mania, bipolar disorder, schizophrenia, or any other psychotic disorder); if they were considered to be at significant risk of suicide; if they were unlikely to be able to comply with the protocol; or if they had any disorder that might interfere with study treatment or impair treatment compliance.

2.3. Variables

The primary efficacy variable in each of the 3 studies was the LSAS. The primary outcome endpoint of this meta-analysis was the estimated difference to placebo in the LSAS total score at Week 12. A secondary outcome measure was the estimated difference to placebo in the CGI-S score at Week 12 and response to treatment (CGI-I score ≤2).

2.4. Statistical analyses

Meta-analyses were carried out by dose on three endpoints: change from baseline to Week 12 on the symptom-specific LSAS scale (the primary analysis in all three studies); change from baseline on the Clinical Global Impression- Severity scale (CGI-S); as well as on the binary endpoint response (CGI-I score ≤2). The treatment effects and standard errors based on the pre-defined adjusted analyses reported by dose were used as inputs to the meta-analyses for the continuous endpoint, while the raw unadjusted prevalences were used for the binary response endpoint. Treatment estimates and confidence intervals are shown in tables and in forest plots with pooled estimates by dose groups. Study-specific treatment effects were analysed and tested for heterogeneity using chi-squared tests, in order to check if the fixed-effect model was adequate or if random-effect models had to be used. The study-specific treatment effect test was not statistically significant and the pooled analyses were thus all conducted using fixed-effect models. These analyses used the statistical summary data from each published study based on a modified intent-to-treat analysis (the full-analysis set [FAS], using the last observation carried forward (LOCF) method for missing data.

For all efficacy measures, point estimates were expressed with their 95% confidence intervals (95% CI). The number needed to treat (NNT) is the inverse of the difference in the proportion of patients responding to treatment between escitalopram and placebo rounded up to the nearest integer. Similarly, the limits of the NNT confidence intervals are the inverted limits of the confidence intervals of the difference in proportions. Statistical analyses were performed using SAS software, and all statistical tests were two-sided. The alpha risk was set to 5%. Disposition, safety and tolerability data are presented for each study.

3. Results

A total of 1615 patients comprised the treated population of the three studies [escitalopram (*n*=1076) and placebo (*n*=539)] and 1598 (98.9%) were included in the intent-to-treat (ITT) analysis of the efficacy [escitalopram (*n*=1061) and placebo (*n*=537)]. There was an approximately 1:1 distribution of men (44.8%) and women (55.2%). The patients had a mean age of 36 years and an onset of SAD at approximately 18 years of age, with a mean duration of about 18 years. The mean LSAS total score at baseline was 95.1, with a mean CGI-S of 4.8 (indicating that the patients were markedly ill) and a low level of depressive symptoms (mean MADRS total score of 6.1). All studies were randomised without stratification, and baseline scores were not statistically significantly different between treatment groups (Table 2).

3.1. Efficacy at end of 12 weeks of double-blind treatment

The overall difference in treatment effect was in favour of escitalopram *versus* placebo at all doses, with an estimated

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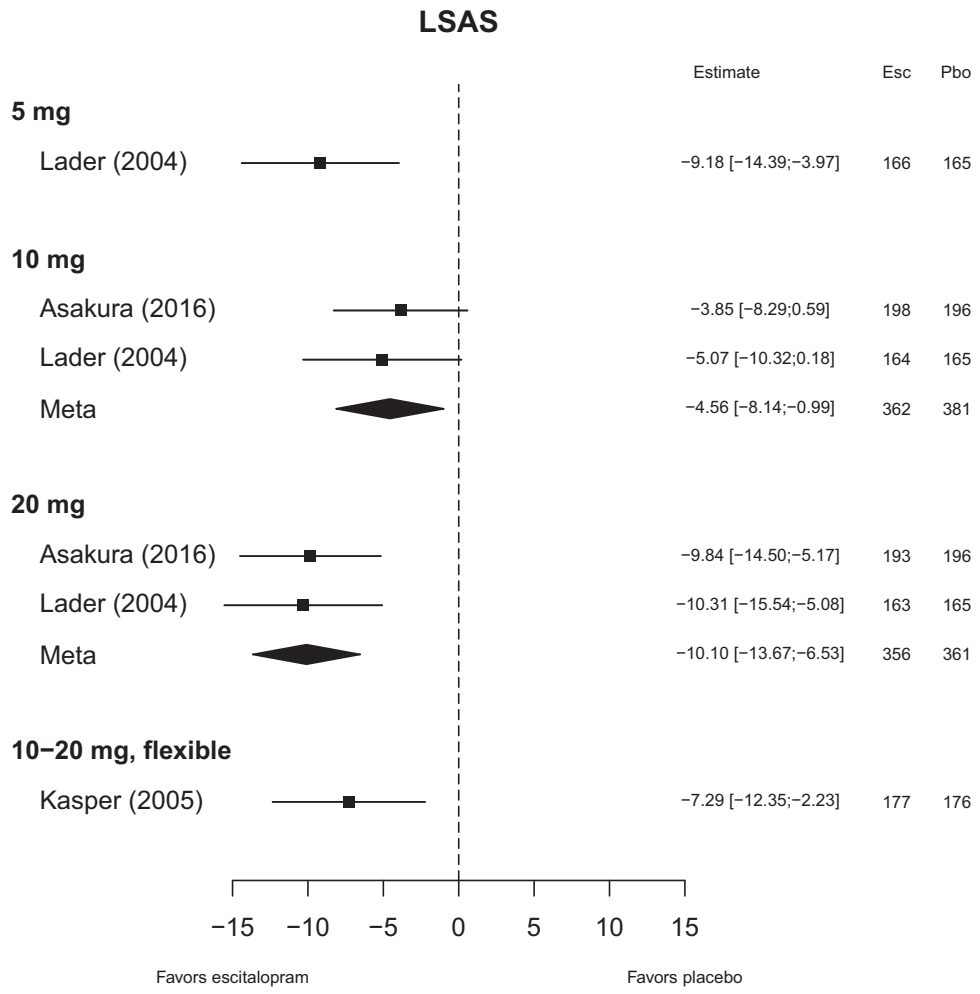

Figure 1 Estimated treatment difference in the Liebowitz Social Anxiety Scale (LSAS) total score at Week 12 (primary analysis) for all 3 studies shown with 95% confidence intervals. All of the tests for heterogeneity within dose are non-significant ($p>0.05$), so the analysis is based on a fixed effects model. Negative values are in favour of escitalopram, while positive values are in favour of placebo. Patient numbers are shown for escitalopram (Esc) and placebo (Pbo).

treatment difference to placebo on the LSAS of −9.2 points (95% CI: [−14.4; −4.0], $p<0.01$) (escitalopram 5 mg/day), −4.6 points (95%CI: [−8.1; −1.0], $p<0.01$) (escitalopram 10 mg/day), −10.1 points (95% CI: [−13.7; −6.5], $p<0.01$) (escitalopram 20 mg/day) and −7.29 points (95% CI: [−12.3; −2.2], $p<0.01$) (escitalopram 10-20 mg/day) (Figure 1). For the CGI-S, the corresponding values were −0.55 points (95% CI: [−0.79; −0.31], $p<0.01$) (escitalopram 5 mg/day), −0.26 points (95%CI: [−0.42; −0.10], $p<0.01$) (escitalopram 10 mg/day), −0.48 points (95%CI: [−0.64; −0.31], $p<0.01$) (escitalopram 20 mg/day) and −0.29 points (95% CI: [−0.51; −0.07], $p<0.05$) (escitalopram 10-20 mg/day) (Figure 2).

3.2. Efficacy at end of 24 weeks of double-blind treatment

In one study (Lader et al., 2004) although the pre-defined endpoint was at Week 12, patients were in double-blind treatment for 24 weeks. At the end of this period, the estimated treatment difference to placebo on the LSAS was −10.5 points (95% CI: [−16.3; −4.7], $p<0.001$) (escitalopram 5 mg/day), −7.45 points (95% CI: [−13.3; −1.5], $p<0.05$) (escitalopram 10 mg/day), and −15.1 points (95% CI: [−20.9; −9.2], $p<0.001$) (escitalopram 20 mg/day). For the CGI-S, the corresponding values were −0.42 points (95% CI: [−0.71; −0.14], $p<0.01$) (escitalopram 5 mg/day), −0.47 points (95% CI: [−0.76; −0.17], $p<0.01$) (escitalopram 10 mg/day), −0.88 points (95% CI: [−1.17; −0.60], $p<0.001$) (escitalopram 20 mg/day).

3.3. Response to treatment at week 12

The estimated treatment difference in response (CGI-I score ≤ 2) at Week 12 is shown in Figure 3. For each treatment arm in each study, the response rates were 41.2% (placebo) and 60.8% (escitalopram 5 mg), 37.8% (placebo) and 48.0% (escitalopram 10 mg), 41.2% (placebo) and 54.9% (escitalopram 10 mg), 37.8% (placebo) and 54.9% (escitalopram 20 mg), 41.2% (placebo) and 62.0% (escitalopram 20 mg) and 38.6% (placebo) and 54.2% (escitalopram 10-20 mg). The difference to placebo was significant for all escitalopram doses in each of the three studies, and ranged from 10.2% to 20.8%. The number-needed-to-treat (NNT) for

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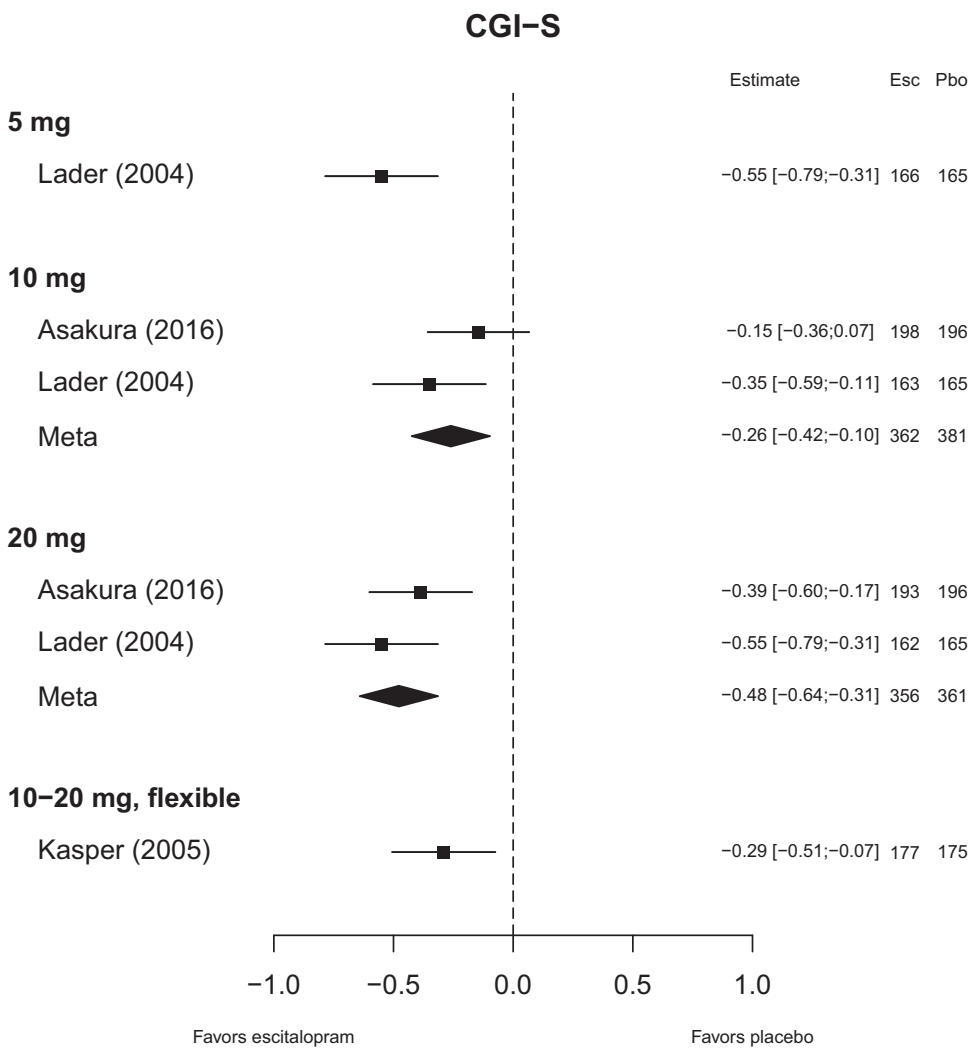

Figure 2 Estimated treatment difference in the Clinical Global Impression-Severity (CGI-S) total score at Week 12 for all 3 studies shown with 95% confidence intervals. All of the tests for heterogeneity within dose are non-significant ($p > 0.05$), so the analysis is based on a fixed effects model. Negative values are in favour of escitalopram, while positive values are in favour of placebo. Patient numbers are shown for escitalopram (Esc) and placebo (Pbo).

response to treatment ranged from 5 to 10 for the individual studies, with values of 6 (escitalopram 5 mg/day), 9 (escitalopram 10 mg/day) and 6 (escitalopram 20 mg/day) in the meta-analysis.

3.4. Withdrawal rates

The total withdrawal rate was 17.3% for all escitalopram doses, compared with 17.1% for placebo. Withdrawal rates for different escitalopram doses were as follows: 17.4% *versus* 23.5% (5 mg *versus* placebo), 16.2% *versus* 16.6% (10 mg *versus* placebo) and 16.8% *versus* 16.6% (20 mg *versus* placebo). The withdrawal rate due to adverse events was 8.1% for all escitalopram doses *versus* 4.6% for placebo: withdrawal rates due to adverse events for different escitalopram doses were as follows: 4.8% *versus* 6.0% (5 mg *versus* placebo), 7.9% *versus* 4.7% (10 mg *versus* placebo) and 9.4% *versus* 4.7% (20 mg *versus* placebo). In the flexible dose study, the overall withdrawal rate was 19.9% *versus* 18.1% (10–20 mg *versus* placebo) and the withdrawal rate due to adverse events was 8.8% *versus* 4.5% (10–20 mg *versus* placebo).

4. Discussion

This meta-analysis involved patients with social anxiety disorder from Europe, North America and Japan who took part in one of 3 double-blind randomised clinical trials involving escitalopram. The principal finding in this meta-analysis is that escitalopram consistently demonstrated greater efficacy compared to placebo, as assessed by the LSAS and the CGI, on a series of endpoint comparisons involving change in scores from baseline and response rates.

What is the clinical relevance of these results? Reductions in LSAS scores of at least 20–30% from baseline have been defined as clinically significant (Hansen et al., 2008). In this meta-analysis, the mean decrease from baseline was 41.0% (escitalopram 5 mg), 33.0% (escitalopram 10 mg), and 38.6% (escitalopram 20 mg) *versus* 27.8% for placebo (Table 1). This compared with a mean decrease from baseline in the

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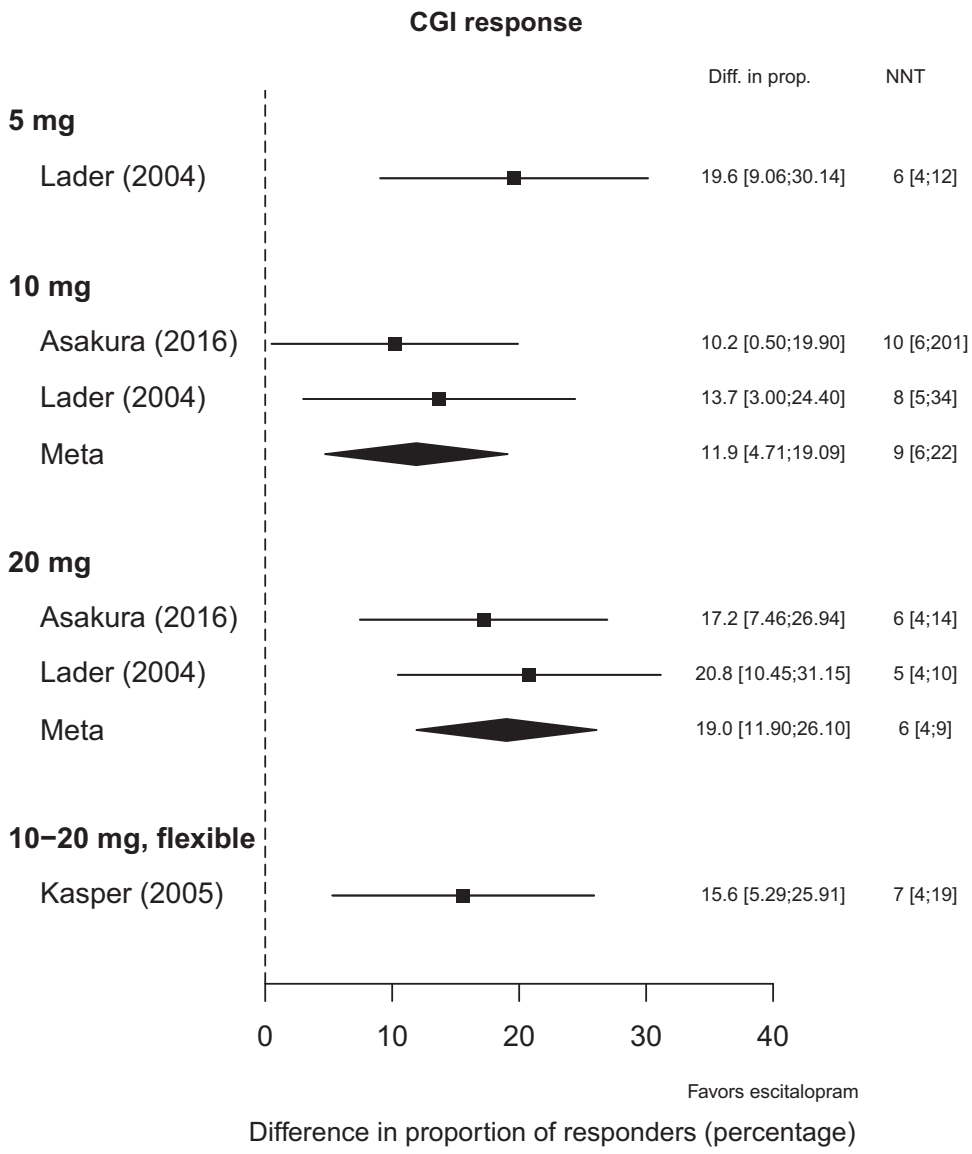

Figure 3 Estimated treatment difference in the proportion of patients responding to treatment at Week 12 for all 3 studies, based on a Clinical Global Impression-Improvement (CGI-I) of 1 or 2 (with 95% confidence intervals). The number-needed-to-treat (NNT) is the inverse of the difference between escitalopram and placebo in the proportion of patients responding to treatment, rounded up to the nearest integer.

LSAS-J of 33.3% *versus* 24.4% for placebo in a 10-week SAD study with fluvoxamine (150–300 mg) (n=273) in Japan (Asakura et al., 2007).

The estimated treatment differences for escitalopram, ranging from 4 to 10 points on the LSAS, are statistically significant for all three doses (Figure 1). The response rates were 37.8–41.2% for placebo (n=537), which was remarkably consistent between studies, and 48.0–62.0% for escitalopram (n=1061), depending on dose. This corresponds to a difference to placebo in response rates of over 16%, considered to be a clinically meaningful difference in studies in patients with major depression undergoing antidepressant treatment (Melander et al., 2008).

In the 12-week open-label phase of a relapse prevention study with escitalopram 10–20 mg (n=517), LSAS scores improved by −46.6 points, from 94.8 at baseline to 48.2 (observed cases) (Montgomery et al., 2005). In the open-label phase of this study, 70% of the patients had their dose increased to escitalopram 20 mg by Week 12. After randomisation, both escitalopram doses showed significantly lower relapse rates compared to their corresponding placebo group. The mean dose at Week 12 in the flexibly-dosed study of Kasper et al., 2005 was 17.6 mg, indicating that 76% of patients had increased their dose to 20 mg/day escitalopram.

There are also open-label studies in SAD with escitalopram. In a large (n=158) open-label flexible-dose study (10–20 mg/day) in Japan (Asakura et al., submitted for publication), 81.0% of patients completed 52 weeks of treatment. LSAS-J scores improved from 95.3 at baseline to 49.9 (FAS, OC) at Week 52 and (56.3 at last assessment (LOCF, FAS]), with 68.4% of patients increasing their dose from 10 to 20 mg/day. In a small (n=29) 12-week open-label study with escitalopram 10–20 mg in patients with

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treatment-resistant SAD, LSAS scores reduced by 29.2 points, from 62.4 at baseline to 33.2 (mixed model repeated measures) (Pallanti and Quercioli, 2006). In another small ($n=14$) 12-week open-label study with escitalopram 10–20 mg in patients with SAD, LSAS scores reduced by 25.8 points, from 83.6 at baseline to 57.8 (Warwick et al., 2012), with a significantly greater improvement in patients with an A10/A10 genotype, which is associated with increased expression of the dopamine transporter. In the third small 12-week open-label study with escitalopram 10–30 mg in patients with SAD ($n=39$) and fear of blushing, LSAS scores reduced by 24.2 points, from 76.8 at baseline to 52.6, and 20 of 28 patients (71.4%) responded (CGI-I ≤ 2, FAS, OC) to treatment (Pelissolo and Moukheiber, 2013). And in a 12-week open-label study with escitalopram 10–20 mg in children with SAD, 13 of 20 patients (65.0%) responded (CGI-I ≤ 2) to treatment (Isolan et al., 2007). In spite of the possibility of expectation effects in these open-label studies (Bandelow et al., 2015), the mean improvement from baseline is similar in magnitude to those found in the randomised controlled trials included in this meta-analysis (Table 1).

In a comparison of pharmacological and psychological treatments based on the difference between pre-post and treated *versus* control effect sizes, medications have been associated with a significantly higher average pre-post effect size than psychotherapies (Bandelow et al., 2015). The choice of a pharmacotherapy should be made on the basis of efficacy as well as on possible side effects, contra-indications and interactions (Baldwin et al., 2014). The total withdrawal rate for patients treated with escitalopram in the three SAD studies included in this meta-analysis was at placebo level, while the adverse event withdrawal rate for all escitalopram doses was 4.8–9.4% *versus* placebo (4.5-6.0%).

A limitation of this meta-analysis is the small number of randomised controlled studies, all of which were sponsored by the manufacturer of escitalopram. As a result of regulatory and safety requirements, patients with another psychiatric disorder were excluded, as were those with depressive symptoms. Very few patients with an ethnicity other than Caucasian or Japanese were treated in these studies. Thus, these patients may not be representative of those seen in actual clinical practice.

In conclusion, in this meta-analysis all doses of escitalopram (5, 10 and 20 mg/day) had significantly greater efficacy *versus* placebo, as assessed by the LSAS and the CGI on a series of endpoint comparisons involving change in efficacy scores from baseline and response rates. Given its favourable tolerability profile based on withdrawals due to adverse events, these results suggest that escitalopram has a good benefit-risk ratio.

Contributors

K. Larsen conceived the design and methodology and conducted the systematic review and meta-analysis. Prof. Baldwin wrote the first draught of the manuscript. All authors contributed to and have approved the final manuscript.

Role of funding source

The studies in this meta-analysis were sponsored by H. Lundbeck A/S, the manufacturer of escitalopram, and the Mochida Pharmaceutical Company. Lundbeck and Mochida were involved in the design, analysis and interpretation of data, and in the decision to submit the paper for publication.

Conflict of interest

Prof. Baldwin has received honoraria for educational presentations from H. Lundbeck A/S, and has acted as a paid consultant to Eli Lilly, Lundbeck, Pfizer and Servier, and currently holds research grants (on behalf of his employer) from Lundbeck and Pfizer. He has accepted paid speaking engagements in industry-supported satellite symposia or other meetings hosted by GlaxoSmithKline, Eli Lilly, Lundbeck, Pfizer and Servier. L.C. Dr. Asakura and Dr. Koyama report no potential conflict of interest in this work. T. Hayano and A. Hagino are employees of the Mochida Pharmaceutical Co., Ltd. Dr. Reines and K. Larsen are employees of H Lundbeck A/S.

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References

Asakura, S., Hayano, T., Hagino, A., Koyama, T., 2016a. A randomized, double-blind, placebo-controlled study of escitalopram in patients with social anxiety disorder in Japan. Curr. Med. Res. Opin. http://dx.doi.org/10.1185/03007995.2016.1146663.

Asakura, S., Hayano, T., Hagino, A., Koyama, T., 2016b. Long-term administration of escitalopram in patients with social anxiety disorder in Japan. Neuropsychiatric Disease Treat. submitted for publication.

Asakura, S., Tajima, O., Koyama, T., 2007. Fluvoxamine treatment of generalized social anxiety disorder in Japan: a randomized double-blind, placebo-controlled study. Int. J. Neuropsychopharmacol. 10, 263–274.

Baldwin, D.S., Reines, E.H., Guiton, C., Weiller, E., 2007. Escitalopram therapy for major depression and anxiety disorders. Ann. Pharmacother. 41, 1583–1592.

Baldwin, D.S., Anderson, I.M., Nutt, D.J., Allgulander, C., Bandelow, B., den Boer, J.A., Christmas, D.M., Davies, S., Fineberg, N., Lidbetter, N., Malizia, A., McCrone, P., Nabarro, D., O'Neill, C., Scott, J., van der Wee, N., Wittchen, H.U., 2014. Evidence-based pharmacological treatment of anxiety disorders, post-traumatic stress disorder and obsessive-compulsive disorder: a revision of the 2005 guidelines from the British Association for Psychopharmacology. J. Psychopharmacol. 28, 403–439.

Bandelow, B., Reitt, M., Röver, C., Michaelis, S., Görlich, Y., Wedekind, D., 2015. Efficacy of treatments for anxiety disorders: a meta-analysis. Int. Clin. Psychopharmacol. 30, 183–192.

Hansen, R.A., Gaynes, B.N., Gartlehner, G., Moore, C.G., Tiwari, R., Lohr, K.N., 2008. Efficacy and tolerability of second-generation antidepressants in social anxiety disorder. Int. Clin. Psychopharmacol. 23, 170–179.

Isolan, L., Pheula, G., Salum Jr., G.A., Oswald, S., Rohde, L.A., Manfro, G.G., 2007. An open-label trial of escitalopram in children and adolescents with social anxiety disorder. J. Child Adolesc. Psychopharmacol. 17, 751–760.

Kasper, S., Stein, D., Loft, H., Nil, R., 2005. Escitalopram in the treatment of social anxiety disorder. Randomised, placebo-controlled, flexible-dosage study. Br. J. Psychiatry 186, 222–226.

Kennedy, S.H., Andersen, H.F., Thase, M.E., 2009. Escitalopram in the treatment of major depressive disorder: a meta-analysis. Curr. Med. Res. Opin. 25, 161–175.

Kessler, R.C., Demler, O., Frank, R.G., Olfson, M., Pincus, H.A., Walters, E.E., Wang, P., Wells, K.B., Zaslavsky, A.M., 2005. Prevalence and treatment of mental disorders, 1990 to 2003. N. Engl. J. Med. 352, 2515–2523.

Lader, M., Stender, K., Burger, V., Nil, R., 2004. Efficacy and tolerability of escitalopram in 12- and 24-week treatment of social anxiety disorder: randomised, double-blind, placebo-controlled, fixed-dose study. Depress. Anxiety 19, 241–248.

de Menezes, G.B., Coutinho, E.S., Fontenelle, L.F., Vigne, P., Figueira, I., Versiani, M., 2011. Second-generation antidepressants in social anxiety disorder: meta-analysis of controlled clinical trials. Psychopharmacology 215, 1–11.

Melander, H., Salmonson, T., Abadie, E., van Zwieten-Boot, B., 2008. A regulatory apologia - a review of placebo-controlled studies in regulatory submissions of new-generation antidepressants. Eur. Neuropsychopharmacol. 18, 623–627.

Montgomery, S.A., Åsberg, M., 1979. A new depression scale designed to be sensitive to change. Br. J. Psychiatry 134, 382–389.

Montgomery, S.A., Nil, R., Durr-Pal, N., Loft, H., Boulenger, J.P., 2005. A 24-week randomized, double-blind, placebo-controlled study of escitalopram for the prevention of generalized social anxiety disorder. J. Clin. Psychiatry 66, 1270–1278.

Nagata, T., Suzuki, F., Teo, A.R., 2015. Generalized social anxiety disorder: a still-neglected anxiety disorder 3 decades since Liebowitz's review, Psychiatry Clin. Neurosci. http://dx.doi.org/10.1111/pcn.12327.

Pallanti, S., Quercioli, L., 2006. Resistant social anxiety disorder response to escitalopram. Clin. Pract. Epidemol. Ment. Health 2, 35.

Pelissolo, A., Moukheiber, A., 2013. Open-label treatment with escitalopram in patients with social anxiety disorder and fear of blushing. J. Clin. Psychopharmacol. 33, 695–698.

Owens, M.J., Knight, D.L., Nemeroff, C.B., 2001. Second-generation SSRIs: human monoamine transporter binding profile of escitalopram and R-fluoxetine. Biol. Psychiatry 50, 345–350.

Warwick, J.M., Carey, P.D., Cassimjee, N., Lochner, C., Hemmings, S., Moolman-Smook, H., Beetge, E., Dupont, P., Stein, D.J., 2012. Dopamine transporter binding in social anxiety disorder: the effect of treatment with escitalopram. Metab. Brain Dis. 27, 151–158.

Wittchen, H.U., Jacobi, F., Rehm, J., Gustavsson, A., Svensson, M., Jönsson, B., Olesen, J., Allgulander, C., Alonso, J., Faravelli, C., Fratiglioni, L., Jennum, P., Lieb, R., Maercker, A., van Os, J., Preisig, M., Salvador-Carulla, L., Simon, R., Steinhausen, H.C., 2011. The size and burden of mental disorders and other disorders of the brain in Europe 2010. Eur. Neuropsychopharmacol. 21, 655–679.

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