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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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