Evidence based review of escitalopram in treating major depressive disorder in primary care

Thomas R. Einarson

The study aimed to summarize clinical data for escitalopram in the treatment of major depressive disorder in primary care. Medline, Embase and Cochrane databases were searched for randomized controlled trials of escitalopram (10–20 mg/day for 8 weeks) versus other antidepressants in therapeutic doses or placebo. Patients were required to have had moderate/severe depression, with Montgomery–Åsberg Depression Rating Scale (MADRS) scores recorded at baseline and 8 weeks. Outcomes examined were remission rates (MADRS $\leq$ 12) and response rates ($\geq$ 50% decrease from baseline in MADRS at week 8). Data were combined using a random effects meta-analytic model. Of the 15 studies identified, 11 were rejected (five not primary care, four duplicate reports, one lacked 8-week MADRS scores, one not depression) and four were accepted (n=1472 patients). The four studies had nine arms, four for escitalopram (n=654), two for citalopram (n=333), one for venlafaxine-XR (n=142) and two for placebo (n=343). Remission rates for escitalopram were superior to placebo (48.7% versus 37.6%, P=0.003) and citalopram (52.8% versus 43.5%, P=0.003) but similar to venlafaxine-XR (P=0.97). Response rates were superior to placebo (48.7% versus 43.1%, P<0.001) and citalopram (62.5% versus 49.5%, P=0.001) but not venlafaxine-XR (P=0.52). Adverse events were comparable among active drugs (P<0.05). Remission rates for escitalopram were superior to placebo (48.7% versus 37.6%, P=0.003) and citalopram (52.8% versus 43.5%, P=0.003) but similar to venlafaxine-XR (P=0.97). Response rates were superior to placebo (48.7% versus 43.1%, P<0.001) and citalopram (62.5% versus 49.5%, P=0.001) but not venlafaxine-XR (P=0.52). Adverse events were comparable among active drugs (P>0.05). Remission and response rates of escitalopram in primary care are clinically superior to placebo and citalopram, but similar to venlafaxine-XR. Further head-to-head trials are warranted to verify these findings. A pharmacoeconomic analysis is also required to determine whether these clinical advantages for the patients translate into economic advantages for the health care system. *Int Clin Psychopharmacol* 19:305–310 © 2004 Lippincott Williams & Wilkins.

International Clinical Psychopharmacology 2004, **19**:305–310

Keywords: Citalopram, escitalopram, major depressive disorder, remission, response

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Received 31 March 2004 **Accepted** 6 July 2004

Introduction

Major depressive disorder is a major health problem in primary care, affecting approximately 10% of the poupla-tion at any given time (Lépine *et al.*, 1997; Kessler *et al.*, 2003). The consequences of the disease can be substantial, in terms of morbidity (Wells *et al.*, 1989), mortality (Zheng *et al.*, 1997) and economic impact (Kind and Sorenson, 1993). Not all patients respond to pharmacotherapy and research continues for newer and improved therapies.

Escitalopram (Cipralex®, Lexapro®) is a selective serotonin reuptake inhibitor (SSRI). It is the *S*-enantiomer of citalopram, and appears to have clinical advantages over citalopram (Montgomery *et al.*, 2001; Auquier *et al.*, 2003; Gorman *et al.*, 2002). The efficacy of escitalopram in treatment of major depressive disorder has been established in randomized controlled trials (Waugh and Goa, 2003).

Reviews of the efficacy of escitalopram have been conducted for mixed populations (Auquier *et al.*, 2003; Gorman *et al.*, 2002; Waugh and Goa, 2003), but none has focused on primary care. Differences in treatment patterns and in outcomes have been found between primary care and other, more intensive settings, such as secondary or tertiary care (Einarson *et al.*, 1997). It has even been suggested that patients with major depressive disorder in primary care have a different aetiology and natural history compared to secondary care patients (Suh and Gallo, 1997; Arya, 1999), although this view has not been widely accepted. Nonetheless, these patients constitute an important subgroup that warrants examination. However, in their systematic review and meta-analysis, MacGillivray *et al.* (2003) concluded that 'evidence on the relative efficacy of selective serotonin reuptake inhibitors and tricyclic antidepressants in primary care is sparse and of variable quality'.

0268-1315 © 2004 Lippincott Williams & Wilkins DOI: 10.1097/01.yic.0000139342.22133.77

Therefore, there is a need to examine this clinical area. The aim of the present study was to examine the efficacy of escitalopram in treating major depressive disorder in primary care.

Methods

The population of interest was primary care adult patients ($\geq$ 18 years of age), either male or female, who had been diagnosed with major depressive disorder using any standard criteria. For the purposes of this research, the definition of primary care presented by MacGillivray *et al.* (2003) was used. They included patients treated by primary care practitioners (i.e. either general or family practitioners) in a primary care (ambulatory) setting. Specialists such as psychiatrists were excluded, as were hospitals and both secondary and tertiary care settings.

Patients were accepted if they had moderate to severe depression, i.e. baseline scores $\leq$ 18 and $\geq$ 40 on the Montgomery–Åsberg Depression Rating Scale (MADRS). The focus was restricted to primary care patients because our group has previously found differences in severity, treatments and outcomes for those individuals who are managed by specialists (e.g. psychiatrists) or in different settings such as the hospital (Einarson *et al.*, 1997). This approach was taken recently by MacGillivray *et al.* (2003).

Only randomized controlled trials were included. The drug of interest was escitalopram, administered in doses of 10–20 mg daily. Acceptable comparators included other antidepressants in standard therapeutic doses or placebo. Treatments must have been given for a minimum of 8 weeks. For the analysis, patients must have had at least one dose of drug and a valid MADRS measurement at approximately 8 weeks after starting treatment.

Outcomes must have been measured after 6–8 weeks of treatment, and included remission rate (numbers of patients with post treatment MADRS score $\leq$ 12), response rate (numbers of patients whose MADRS score decreased by $\geq$ 50%) and adverse event rates. With respect to adverse events, the proportions of patients who reported at least one event were calculated, regardless of causality. In addition, adverse events that were reported for all drugs in at least one study were identified and quantified. The Medline, Embase and Cochrane databases (1995 to present) were searched. References were searched for further articles, published abstracts, conference proceedings, etc. When published data were not retrievable, or could not be extracted from published articles, the manufacturer (H. Lundbeck A/S, Copenhagen, Denmark) provided the (raw) data.

Data were combined using a random effects model, weighting studies by sample size and by between-study variance (Cochran, 1954). Heterogeneity of effects was examined using the chi-square test. If more than one study reported incidences of the same adverse event, they were combined in a random effects meta-analytic model to determine overall rates (Einarson, 1997). Outputs were clinical rates weighted by sample size, and also incorporating between-study variance.

Results

The initial search identified 15 articles, of which 11 were rejected. Five included patients who were not treated in primary care (Burke *et al.*, 2002; Rapaport *et al.*, 2002; Bielski *et al.*, 2003; Ninan *et al.*, 2003; Rapaport *et al.*, 2004); four were duplicate reports (Wade *et al.*, 2002a, 2002b; Bothmer *et al.*, 2003; Colonna *et al.*, 2004); in one, MADRS was not measured at 8 weeks (Montgomery *et al.*, 2001); and one did not deal with depression (Stahl *et al.*, 2003).

That left four studies with 1472 patients (Colonna, 2002; Wade *et al.*, 2002c; Lepola *et al.*, 2003). Table 1 provides clinical and demographic details of the studies, included patients and drugs. Patients had no differences in any parameters across drugs within or between studies. The majority were females (average proportion in each study = 73 ± 3%), with an average age of 44 ± 3 years, and all were recruited from Europe or Canada.

The four studies had a total of nine arms: four for escitalopram (n = 654), two for citalopram (n = 333), one for venlafaxine-XR (n = 142) and two for placebo (n = 343). Table 2 indicates the disposition of patients in each trial. There were no significant differences in overall withdrawal rates among the four comparators (chi squared = 1.75, d.f. = 3, P = 0.63), or in rates of patients who completed 8 weeks of treatment (chi squared = 1.53, d.f. = 3, P = 0.68).

Clinical results are shown in Table 3. All homogeneity tests were non-significant, suggesting that it was appropriate to pool the data. In terms of remission, escitalopram was both clinically (difference = 11%) and statistically (P = 0.003) superior to placebo and citalopram (difference = 9.3%, P = 0.017). The number-needed-to-treat (NNT) was 9.0 compared to placebo and 10.8 with citalopram. In other words, for every nine additional patients treated with placebo (or 11 with citalopram), there will be one more patient in remission. With respect to response rates, escitalopram was similarly superior to placebo (difference = 15%, P < 0.001) and citalopram (difference = 13%, P = 0.001). The NNTs of 6.7 and 7.8 were slightly lower that with remissions. Rates did not differ from venlafaxine-XR in either response or remission after 8 weeks of treatment.

Table 1 Description of accepted studies

Author	Location	Mean age ± SD	Females (%)	Diagnostic criteria	Drug	Dosing	Average dose (mg)	Scales used	Baseline scores ± SD
Colonna *et al.* (2002)	Austria	46 ± 12	73	DSM-IV	Escitalopram	10 mg/day × 24 weeks	10	MADRS	29.5 ± 4.3
				MADRS ≥ 22				CGI-S	4.16
	Belgium Denmark France Germany Norway Sweden	46 ± 11	76		Citalopram	20 mg/day × 24 weeks	20	MADRS CGI-S	30.2 ± 4.7 4.33
Lepola *et al.* (2003)	Belgium	43 ± 11	74.8	DSM-IV	Escitalopram	10 mg/day, doubled at week	14.0	MADRS	29.0 ± 4.3
				MADRS 22–40		4 or week 6 if needed; treated 8 weeks		CGI-S	4.34
	Canada	44 ± 11	69.4		Citalopram	20 mg/day, doubled at week	28.4	MADRS	29.2 ± 4.2
	Finland France Norway					4 or week 6 if needed; treated 8 weeks		CGI-S	4.30
	Sweden	43 ± 12	72.1		Placebo	Once a day, doubled at week	NA	MADRS	28.7 ± 4.0
	Switzerland UK					4 or week 6 if needed; treated 8 weeks		CGI-S	4.22
Montgomery *et al.* (2004)	Denmark	49 ± 15	73	DSM-IV	Escitalopram	10 or 20 mg, titrated;	12.1	MADRS	28.7 ± 5.0
				MADRS >18		treated 8 weeks		CGI-S	4.5
	Finland Germany Ireland Spain Switzerland UK	47 ± 14	71		Venlafaxine-XR	75 or 150 mg, titrated; treated 8 weeks	92.5	MADRS CGI-S	29.0 ± 5.4 4.4
Wade *et al.* (2002c)	Canada	41 ± 11	73.8	DSM-IV	Escitalopram	10 mg/day × 8 weeks	10	MADRS	29.2 ± 4.2
	Estonia France			MADRS 22–40				CGI-S	4.38
	Netherlands UK	40 ± 12	77.8		Placebo	Once a day × 8 weeks	NA	MADRS CGI-S	28.7 ± 3.7 4.37

CGI-S, Clinical Global Impression–Severity; DSM, Diagnostic and Statistical Manual; MADRS, Montgomery–Åsberg Depression Rating Scale.

Table 2 Disposition of patients in accepted trials

Author	Drug	Enrolled	Withdrawals				Completed 8 weeks	Evaluable dropouts	Total evaluable
			Total	ADRs	LOE	Other			
Colonna *et al.* (2002)	Escitalopram	175	31	10	2	19	144	21	165
	Citalopram	182	47	18	3	26	135	39	174
Lepola *et al.* (2003)	Escitalopram	155	9	4	0	5	146	9	155
	Citalopram	160	8	6	1	1	152	7	159
	Placebo	154	15	4	5	6	139	15	154
Montgomery *et al.* (2004)	Escitalopram	148	21	12		9[a]	125	21	146
	Venlafaxine-XR	145	19	16		3[a]	124	18	142
Wade *et al.* (2002c)	Escitalopram	191	31	9	7	15	160	28	188
	Placebo	189	29	2	13	14	160	29	189

ADR, Adverse drug reaction; LOE, lack of efficacy. [a]Reported only total and ADR dropouts.

Rates of adverse events and the proportions of patients reporting them are shown in Table 4. The majority of patients in all studies (meta-analytic average = 57.8%) reported at least one event. However, the rates were similar across the drugs studied. Statistically, event rates for active drugs rates were higher than those for placebo ($P = 0.005$), but did not differ between active drugs ($P = 0.06$).

Discussion

Previous research has shown escitalopram to be clinically superior to placebo in the general population

Table 3 Rates of remission and response to escitalopram and its comparators in head-to-head randomized controlled trials

		Comparator 1			Comparator 2					Homogeneity of effects	
Outcome	Studies	Drug	Patients	Rate (%)	Drug	Patients	Rate (%)	P^*	NNT (95% CI)	Chi-square	*P*
Remission	2	Escitalopram	343	48.7	Placebo	343	37.6	0.003	9.0 (5.4–26.8)	0.16	0.691
	2	Escitalopram	320	52.8	Citalopram	333	43.5	0.017	10.8 (5.9–59.8)	0.01	0.904
	1	Escitalopram	146	69.9	Venlafaxine-XR	142	69.7	0.970	691.1	NA	NA
Response	2	Escitalopram	343	58.1	Placebo	343	43.1	<0.001	6.7 (4.4–13.4)	0.30	0.584
	2	Escitalopram	320	62.5	Citalopram	328	49.5	0.001	7.8 (4.8–20.1)	1.10	0.294
	1	Escitalopram	146	77.4	Venlafaxine-XR	142	79.6	0.524	NA	NA	NA

*P-value for the difference between groups. NA, Not applicable.

Table 4 Summary of rates of adverse events reported in accepted studies

			Patients				Back					Dry
Drug	Author	*n*	With ADRs (%)	Nausea (%)	Rhinitis (%)	Headache (%)	Pain (%)	Sweating (%)	Diarrhoea (%)	Insomnia (%)	Somnolence (%)	Mouth (%)
Escitalopram	Colonna *et al.* (2002)	175	62.9	16.0	9.7	6.9	6.3	1.1	1.1	1.1	1.1	1.1
	Lepola *et al.* (2003)	155	69.7	17.4	–	–	–	7.7	6.5	6.5	5.2	4.5
	Montgomery *et al.* (2004)	148	66.9	16.9	–	12.8	6.1	6.8	8.1	7.4	6.1	3.4
	Wade *et al.* (2002c)	191	58.6	8.9	–	12.0	2.1	–	–	–	–	–
	Overall	669	64.4	17.6	–	12.9	4.5	5.8	5.8	7.0	3.8	7.0
Citalopram	Colonna *et al.* (2002)	182	72.0	9.9	6.6	8.8	8.2	6.6	6.6	6.6	6.6	6.6
	Lepola *et al.* (2003)	160	65.0	14.4	6.9	–	–	5.6	7.5	4.4	3.1	7.5
	Overall	342	68.7	11.8	6.7	–	–	6.1	7.0	5.8	5.8	3.8
Venlafaxine-XR	Montgomery *et al.* (2004)	145	71.0	26.2	–	8.3	6.2	12.4	6.2	9.7	3.4	6.9
Placebo	Lepola *et al.* (2003)	154	59.7	9.1	5.8	–	–	1.9	3.2	1.9	1.3	1.3
	Wade *et al.* (2002c)	189	55.6	3.7	–	10.1	5.3	–	–	–	–	–
	Overall	343	57.5	6.1	–	–	–	–	–	–	–	–

ADR, Adverse drug reaction.

(Montgomery *et al.*, 2001; Burke *et al.*, 2002; Waugh and Goa, 2003). This meta-analysis supports the efficacy of escitalopram in the population of primary care patients. Similarly, it confirms that escitalopram also has clinical advantages over its racemate, citalopram, in these patients. Consequently, primary care practitioners may welcome this innovative pharmacotherapy, which offers clinical advantages to the psychotherapeutic armamentarium.

It is important that patient populations are separated because their clinical courses and responses to treatment can differ substantially. It is to be expected that patients treated by a psychiatrist, or who must be treated in an institution, would have more severe symptoms or would respond less well than those indiviuduals in primary care. For example, in a previous study performed by this author, it was found that SSRIs had a success rate for outpatients that was 26% higher than that for inpatients (Einarson *et al.*, 1995).

The rates found in the present study are comparable to those found in another meta-analysis (Einarson *et al.*, 1999). For example, the response rate for venlafaxine-XR of 79.6% in 142 patients is similar to the 73.7% found previously in 324 patients.

The success rates found here, both for remission and response, were clinically relevant and statistically significant. That was true against both placebo and citalopram. In addition, the NNT was quite low for escitalopram versus placebo and citalopram, respectively, ranging from 6.7 to 10.8. This means that one extra success is obtained when 7–11 (i.e. the numbers are rounded up) more patients are treated with escitalopram. These values compare favourably to those

presented by Sackett *et al.* (2000) in their definitive textbook.

The differences in success rates often can translate into economic advantages. Drugs that truly have a higher success rate result in a lower utilization of healthcare resources, including fewer visits to the physician or psychiatrist, fewer titrations or switching of medications, as well as fewer and shortened hospitalizations. The final result is a lower overall cost and a more efficient use of healthcare resources (Einarson *et al.*, 1995, 1997).

Limitations

This analysis is limited due to the small number of studies that have been published to date. As a result, the precision of estimate is limited. Nonetheless, there are still data for almost 1500 patients, which provide for reasonable estimates. More studies are required to make the results more robust.

Only three studies could be found where escitalopram was compared directly with other active antidepressants. Other than citalopram and venlafaxine-XR, no other antidepressants have been studied in direct head-to-head comparisons. Therefore, the results may apply only to the drugs studied. There is a need for further comparisons to determine whether other advantages or disadvantages may exist.

Conclusions

With respect to remission rates and response rates in primary care, escitalopram is clinically superior to citalopram and placebo, but similar to venlafaxine-XR. Further head-to-head trials are warranted to extend these findings to other antidepressants. A pharmacoeconomic analysis is required to determine whether these clinical advantages for the patients translate into economic advantages for health care systems.

Acknowledgements

Michiel Hemels at H. Lundbeck A/S, Paris is thanked for help in providing the raw data. This study was funded by H. Lundbeck A/S, who also paid for T.R.E. to present pharmacoeconomic results for this drug at a symposium in Madrid in March 2004. T.R.E. has previously conducted similar work for the competing drugs venlafaxine and venlafaxine-XR (Efexor®, Effexor®).

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