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 ≤ 12) and response rates (≥ 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 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.

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

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Introduction

Major depressive disorder is a major health problem in primary care, affecting approximately 10% of the population 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’.
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 (≥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 ≤18 and ≥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 ≤12), response rate (numbers of patients whose MADRS score decreased by ≥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 study. 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 than with remissions. Rates did not differ from venlafaxine-XR in either response or remission after 8 weeks of treatment.
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...
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 individuals 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 found previously in 324 patients.

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

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Comparator 1</th>
<th>Comparator 2</th>
<th>Homogeneity of effects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Drug</td>
<td>Patients</td>
<td>Rate (%)</td>
</tr>
<tr>
<td>Remission</td>
<td>Escitalopram</td>
<td>343</td>
<td>48.7</td>
</tr>
<tr>
<td></td>
<td>320</td>
<td>52.8</td>
<td>Citalopram</td>
</tr>
<tr>
<td></td>
<td>146</td>
<td>69.9</td>
<td>Venlafaxine-XR</td>
</tr>
<tr>
<td>Response</td>
<td>Escitalopram</td>
<td>343</td>
<td>58.1</td>
</tr>
<tr>
<td></td>
<td>320</td>
<td>62.5</td>
<td>Citalopram</td>
</tr>
<tr>
<td></td>
<td>146</td>
<td>77.4</td>
<td>Venlafaxine-XR</td>
</tr>
</tbody>
</table>

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

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

<table>
<thead>
<tr>
<th>Drug</th>
<th>Author</th>
<th>n</th>
<th>With ADRs (%)</th>
<th>Nausea (%)</th>
<th>Rhinitis (%)</th>
<th>Headache (%)</th>
<th>Pain (%)</th>
<th>Sweating (%)</th>
<th>Diarrhoea (%)</th>
<th>Insomnia (%)</th>
<th>Somnolence (%)</th>
<th>Mouth (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Escitalopram</td>
<td>Colonna et al. (2002)</td>
<td>175</td>
<td>62.9</td>
<td>16.0</td>
<td>9.7</td>
<td>6.9</td>
<td>6.3</td>
<td>1.1</td>
<td>1.1</td>
<td>1.1</td>
<td>1.1</td>
<td>1.1</td>
</tr>
<tr>
<td></td>
<td>Lepola et al. (2003)</td>
<td>155</td>
<td>69.7</td>
<td>17.4</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>7.7</td>
<td>6.5</td>
<td>6.5</td>
<td>5.2</td>
<td>4.5</td>
</tr>
<tr>
<td></td>
<td>Montgomery et al. (2004)</td>
<td>148</td>
<td>66.9</td>
<td>16.9</td>
<td>–</td>
<td>12.8</td>
<td>6.1</td>
<td>6.8</td>
<td>8.1</td>
<td>7.4</td>
<td>6.1</td>
<td>3.4</td>
</tr>
<tr>
<td></td>
<td>Wade et al. (2002c)</td>
<td>191</td>
<td>58.6</td>
<td>8.9</td>
<td>–</td>
<td>12.0</td>
<td>2.1</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Overall</td>
<td>669</td>
<td>64.4</td>
<td>17.6</td>
<td>–</td>
<td>12.9</td>
<td>4.5</td>
<td>5.8</td>
<td>5.8</td>
<td>7.0</td>
<td>3.8</td>
<td>7.0</td>
</tr>
<tr>
<td>Citalopram</td>
<td>Colonna et al. (2002)</td>
<td>192</td>
<td>72.0</td>
<td>9.9</td>
<td>6.6</td>
<td>8.8</td>
<td>8.2</td>
<td>6.8</td>
<td>6.8</td>
<td>6.6</td>
<td>6.6</td>
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</tr>
<tr>
<td></td>
<td>Lepola et al. (2003)</td>
<td>160</td>
<td>65.0</td>
<td>14.4</td>
<td>6.9</td>
<td>–</td>
<td>–</td>
<td>5.6</td>
<td>7.5</td>
<td>4.4</td>
<td>3.1</td>
<td>7.5</td>
</tr>
<tr>
<td></td>
<td>Overall</td>
<td>342</td>
<td>68.7</td>
<td>11.8</td>
<td>6.7</td>
<td>–</td>
<td>–</td>
<td>6.1</td>
<td>7.0</td>
<td>5.8</td>
<td>5.8</td>
<td>3.8</td>
</tr>
<tr>
<td>Venlafaxine-XR</td>
<td>Montgomery et al. (2004)</td>
<td>145</td>
<td>71.0</td>
<td>26.2</td>
<td>–</td>
<td>8.3</td>
<td>6.2</td>
<td>12.4</td>
<td>6.2</td>
<td>9.7</td>
<td>3.4</td>
<td>6.9</td>
</tr>
<tr>
<td>Placebo</td>
<td>Lepola et al. (2003)</td>
<td>154</td>
<td>59.7</td>
<td>9.1</td>
<td>5.8</td>
<td>–</td>
<td>–</td>
<td>1.9</td>
<td>3.2</td>
<td>1.9</td>
<td>1.3</td>
<td>1.3</td>
</tr>
<tr>
<td></td>
<td>Wade et al. (2002c)</td>
<td>189</td>
<td>55.6</td>
<td>3.7</td>
<td>–</td>
<td>10.1</td>
<td>5.3</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Overall</td>
<td>343</td>
<td>57.5</td>
<td>6.1</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
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<td>–</td>
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</tbody>
</table>

ADR, Adverse drug reaction.
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 (Einaron 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 pharmaeconomics analysis is required to determine whether these clinical advantages for the patients translate into economic advantages for health care systems.

**Acknowledgements**

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**References**


