Research Article

ESCITALOPRAM IN THE TREATMENT OF MAJOR DEPRESSIVE DISORDER IN PRIMARY-CARE SETTINGS: AN OPEN-LABEL TRIAL

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Background: *The present trial was designed to assess the efficacy and safety of escitalopram prescribed to patients seeking treatment of major depressive disorder (MDD) in a Canadian primary-care setting.* **Methods:** *Investigators (mainly primary-care physicians) enrolled patients with MDD from their daily practice. Patients were treated with escitalopram (flexible dose 10–20 mg/day) for up to 24 weeks. Efficacy assessments included the Montgomery–Asberg Depression Rating Scale (MADRS), the Clinical Global Impression-Improvement and -Severity scales (CGI-I, CGI-S), the Patient Global Evaluation (PGE), and the Medical Outcome Study 36-item Short Form (SF-36).* **Results:** *Out of the 647 patients enrolled, 461 (71%) completed 24 weeks of treatment. The most common reason for discontinuation was adverse events (10%). The mean MADRS score decreased from 30.7 at baseline to 10.9 at the end of 24 weeks (last observation carried forward, LOCF). Remission (MADRS $\leq$ 12) was achieved by 65.5% of patients (LOCF). Symptom improvements were confirmed by global ratings of improvement made by physicians (CGI-I) as well as patients PGE. There was improvement on all dimensions of the SF-36, suggesting an overall improvement in quality of life.* **Conclusions:** *Escitalopram was well tolerated, safe, and efficacious. Escitalopram can be used with confidence to treat patients with MDD in Canadian primary-care settings. Depression and Anxiety 25:E173–E181, 2008.*

Key words: *depression; antidepressant; selective serotonin reuptake inhibitor; Canada; primary care*

INTRODUCTION

Depression is one of the most common conditions managed by primary-care physicians; it is estimated that between 5 and 14% of patients presenting to their primary-care physician suffer from major depressive disorder [MDD].[1–5] This likely represents a fraction of the true prevalence of MDD, because community and health-care surveys conducted in Europe, the United States, and Canada provide evidence that only about half (51.8–57%) of the individuals with depression seek help and of those who do, most consult a primary-care physician.[6–8] In a recent analysis of administrative data from the Canadian province of British Columbia, Bilsker et al.[9] found that 92% of patients diagnosed with depression were treated exclusively by their primary-care physician.

The efficacy and tolerability of escitalopram in MDD have been extensively evaluated in primary-care settings.[10–13] Nevertheless, there is concern that

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clinical efficacy trials fail to provide data that are relevant to real-world clinical practice.[14–16] This concern stems, in large part, from the recognition that clinical efficacy trials are designed to satisfy regulatory requirements and are conducted under conditions that are far removed from those seen in usual practice.[17–19] For instance, efficacy trials are commonly conducted by clinical research specialists, include highly selected patients, restrict treatment choices, and entail substantial deviations from usual practice. Consequently, there is increasing interest and demand for clinical trials that include a heterogeneous group of patients that are conducted under the conditions of usual daily practice.[20–22]

This 24-week study was carried out to assess clinical outcomes, tolerability, safety and quality of life (QoL) in patients with MDD treated with escitalopram in a primary-care setting. To obtain a representative sample of primary-care patients, there were few exclusion criteria. Escitalopram was prescribed in accordance with the Canadian labeling to a heterogeneous group of patients diagnosed with MDD.

METHODS

PATIENTS

Potential investigators were identified primarily by referral from local expert psychiatrists. One hundred and nine primary-care physicians working in 84 clinics across Canada participated in the study. In attempting to obtain a representative sample of primary-care physicians, investigators were not required to have previous clinical research experience to be selected for this study. The trial was conducted in accordance with International Conference on Harmonisation–Good Clinical Practice (ICH–GCP) guidelines, the Declaration of Helsinki, and Canadian regulatory requirements. All potential investigators and investigative sites were subject to a qualification visit by a trained Clinical Research Associate. An appropriate level training on ICH–GCP guidelines was provided to all investigators. Investigators with minimal clinical trial experience were provided with supplemental training. The study protocol, patient information sheet, informed consent form, and each investigator were subject to approval by an independent ethics review board. All investigators were subject to regular monitoring for GCP compliance.

Patients were men or women (aged 18 years or older) with a primary diagnosis of MDD according to the DSM-IV criteria, confirmed using the Mini International Neuropsychiatric Interview (MINI) sections A1–A3.[23] Patients were required to have a minimum score of 19 on the Montgomery–Åsberg Depression Rating Scale [MADRS][24] at baseline. Patient enrolment was conducted according to the ICH–GCP guidelines. Patients were informed that escitalopram and other treatment options were available outside of participating in the study. All participating patients were provided with written information on the study and study medication and provided written informed consent.

To obtain a representative sample of primary-care patients, enrolment was open to adult patients regardless of medical co-morbidity. The limited exclusion criteria included patients with mania or bipolar disorder, psychotic disorder, cognitive disorder or dementia, as well as alcohol or drug abuse, or dependence within 3 months before the baseline visit. Patients with a co-morbid anxiety disorder were permitted, as long as MDD was judged to be the primary diagnosis. Patients who had been previously non-responsive or intolerant to escitalopram or citalopram were excluded, as were patients who had not responded to two previous adequate trials with other antidepressants and patients with serious suicidal risk (as judged by the investigator or scoring ≥ 4 on Item 10 of the MADRS). Patients who were pregnant or breast-feeding were excluded. Patients were not permitted to participate in any other clinical trials. Disallowed concomitant medications included those specified in the Canadian labeling. Furthermore, concomitant antidepressants, St. John's Wort, *S*-adenosylmethionine (SAMe), or electroconvulsive therapy (within the past 12 months) were disallowed, as were antipsychotics and sibutramine. Short half-life hypnotics (anxiolytics) were allowed *p.r.n.* in the evening for the treatment of insomnia.

STUDY DESIGN

This was a 24-week open-label flexible-dose study. Escitalopram treatment was initiated at the baseline visit or the next day. The starting dose was 10 mg/day (single oral dose), which could be increased to 20 mg/day based on the investigator's judgment of the patient's clinical response. There were five face-to-face contacts between the investigator and the patient including the baseline visit and follow-up visits after 2, 6, 12, and 24 weeks of treatment. Patients who did not complete 24 weeks of treatment were asked to attend an early-withdrawal visit. In addition, a telephone contact was scheduled at the end of the 1st week of treatment to obtain information on adverse events and any changes in concomitant medications. Additional non-study visits could be scheduled at the physician's discretion.

ASSESSMENTS

The primary efficacy assessment was the MADRS. Investigators or clinical research staff were trained and certified before being allowed to provide MADRS ratings. Training involved individuals providing their independent ratings of a videotaped MADRS interview of a depressed patient conducted by an experienced clinician. Acceptable ratings for each item and for total score were established *a priori* and had to be met before allowing an investigator or research staff member to provide ratings for this study. Supplemental training was provided if necessary.

The primary outcome measure was changed from baseline on MADRS total score at endpoint (after 24 weeks of treatment or early discontinuation). MADRS score of ≥ 30 was used to define patients as *severely* depressed.[25] Secondary efficacy outcome measures based on MADRS ratings were response and remitter rates. Response was defined as $\geq 50\%$ reduction in MADRS total score from baseline. Remission was defined in the protocol as a MADRS score ≤ 12. Furthermore, an exploratory assessment was conducted with remission defined as a MADRS score ≤ 10. Additional secondary efficacy assessments included the physician-rated Clinical Global Impression-Severity (CGI-S) and the Clinical Global Impression-Improvement (CGI-I) scales.[26] Patient-rated assessments included the Patient Global Evaluation [PGE],[26] which is an analogue of the CGI-I used to assess the patient's global perception of improvement. Patient-rated QoL was also assessed using the Medical Outcome Study 36-item Short Form [SF-36],[27] which was completed at the baseline and final study visits.

Physicians were asked to list any relevant current medical illness for each patient. Safety and tolerability were evaluated by adverse event reporting. All adverse event reports (either spontaneously reported by the patient or elicited by the investigator through non-specific questioning) were recorded and the investigator assessed the relationship between the event and the study medication.

STATISTICAL ANALYSES

Efficacy analyses were conducted on the modified "intent-to-treat" (ITT) set, which included all patients who took at least one dose of escitalopram and had at least one post-baseline efficacy assessment. Change in score from baseline to endpoint was analyzed using Student's paired *t* test. For patients who did not complete 24 weeks of treatment, missing data were imputed using the method of last observation carried forward (LOCF).

Safety analyses were based on the all-patients-treated set, which consisted of all patients who took at least one dose of escitalopram.

RESULTS

PATIENT CHARACTERISTICS

Six hundred and forty-seven patients, including 415 women (65%), were enrolled in the trial. The mean age was 43.4 years ($SD = 14.2$) and there were 43 patients older than 65 years. Treatment was documented for adult outpatients suffering from a depressive disorder (as diagnosed by the treating physician using the MINI). Patient disposition is detailed in Table 1. Briefly, the safety population consisted of 641 patients who received at least one dose of escitalopram, whereas the modified ITT population consisted of 618 patients who received escitalopram and had at least one post-baseline efficacy assessment. Nearly three quarters (71%) of patients completed 24 weeks of escitalopram treatment.

The distribution of symptom severity ratings at baseline is given in Table 2. The mean baseline MADRS score was 30.7. More than 80% of patients had a baseline MADRS score ≥ 25 with 55% having a baseline MADRS total score ≥ 30. According to the CGI-S ratings, the majority of patients were considered to be moderately ill (score of 4) with more than one third (36.3%) being rated as markedly ill or worse (score of ≥ 5).

Table 3 lists the medical conditions and concomitant medications that were reported in more than 5% of patients. Hypertension was the most commonly reported co-morbid condition (16%) followed by insomnia (12%). With the exception of sex hormones (primarily oral contraceptives), which were used by 12% of patients or previous antidepressant treatment (reported by 7% of patients), all of the most common medications could be ascribed to one of the common medication conditions.

Anxiety was listed as a current medical condition in 28 (4%) of patients. Specific diagnoses for co-morbid anxiety disorders were rare (generalized anxiety disorder reported for five patients, panic attack for four patients, and one patient with obsessive–compulsive disorder). The most commonly reported concomitant medications were benzodiazepines and sedative hypnotics, which were used by 18% of patients for the treatment of insomnia.

TABLE 1. Patient disposition

	n (%)
Patients enrolled	647
Safety population	641
Modified ITT population	618 (96)
Patients complete	459 (71)
Patients withdrawn	188 (29)
Reasons for withdrawal	
Adverse event	65 (10)
Lost to follow-up	40 (6.2)
Lack of efficacy	23 (3.6)
Withdrawal of consent	22 (3.4)
Non-adherence to medication	21 (3.3)
Protocol violation	9 (1.4)
Other	8 (1.3)

ITT, intent to treat.
Percentages are based on number of enrolled patients ($n = 647$).

TREATMENT AND EXPOSURE

The mean daily dose of escitalopram at the last assessment was 14.3 ± 5.1 mg/day. The majority of patients (54%) received a dose of 10 mg/day, whereas 44% of patients received 20 mg/day. A small percentage of patients were treated with a daily dose of 5 mg (1.5%) or 15 mg (0.5%). For patients who discontinued treatment for any reason ($n = 188$), the mean number of days until discontinuation was 88.8 (median: 82 days). For patients who discontinued due to adverse events ($n = 65$), the mean number of days to discontinuation was 61.1 (median: 35 days).

RESPONSE TO TREATMENT

The mean MADRS score decreased from 30.7 to 10.9 after 24 weeks of treatment (modified ITT; LOCF); a mean decrease of 19.8 points (Fig. 1). When compared to baseline MADRS score, significant improvements were seen from 2 weeks onward ($t = 45.17$, $P < .001$). Similar improvements were seen on the CGI-S, which decreased from a mean baseline score of 4.3 to 2.2 at endpoint.

Remission rates at each visit and endpoint (LOCF) are shown in Figure 2. Remission (as defined in the protocol as a MADRS score ≤ 12) was achieved by 65.5% (LOCF) of patients (95% CI: 61.6–69.3%) at last assessment. For the observed case (OC) analysis, 44.5% of patients had achieved remission after 6 weeks, 66.7% after 12 weeks, and 77.7% at 24 weeks (95% CI: 73.6–81.4%). When remission was defined as a MADRS ≤ 10, the remission rate after 12 weeks of treatment was 51.8% (OC). By endpoint, 59.2% (OC) of patients met this remission criterion (95% CI: 55.2–63.1%).

Progressive improvements in MADRS score and remission rate were mirrored by improvements in global ratings of improvement, as judged either by the investigators' CGI-I scores or by the patients' self-rating on the PGE. As can be seen in Figure 3, there was a close correspondence between the number of

TABLE 2. Distribution of baseline symptom severity

MADRS scores	*n* (%)	CGI-S scores	*n* (%)
MADRS < 25	106 (16.5)	CGI-S < 4	41 (6.4)
MADRS ≥ 25 < 30	180 (28.1)	CGI-S = 4 (*moderately ill*)	367 (57.0)
MADRS ≥ 30 < 35	187 (29.2)	CGI-S = 5 (*markedly ill*)	213 (33.3)
MADRS ≥ 35	168 (26.2)	CGI-S = 6 or 7[a]	19.0 (3)
Mean MADRS (± *SD*)	30.7 ± 5.2[b]	Mean CGI-S	4.3 ± 0.7[b]

MADRS, Montgomery–Åsberg Depression Rating Scale; CGI-S, Clinical Global Impression-Improvement and -Severity scales.
Percentages are based on the number of patients who met all inclusion criteria and for whom baseline MADRS was recorded ($n = 641$).
[a]CGI-S score: 6 = "Severely ill"; 7 = "Among the most extremely ill".
[b]Standard deviation.

TABLE 3. Most common (≥ 5%) medical conditions and concomitant medications

Medical condition (system organ class)		Concomitant medication	
Endocrine			
Hypothyroidism	9%	Thyroid therapy (primarily synthroid)	9%
Gastrointestinal			
Gastresophageal reflux disease	6%	Acid-related disorders, usually proton pump inhibitors	8%
Irritable bowel syndrome	5%		
Psychiatric			
Insomnia	12%	Benzodiazepines and sedative hypnotics	18%
Metabolic and nutritional			
Hypercholesterolemia	9%	Serum lipid reducing agents, usually statins	10%
Hyperlipidemia	6%		
Obesity	6%		
Musculoskeletal and connective tissue			
Back pain	8%	Analgesics	13%
Osteoarthritis	7%	Anti-inflammatory and antirheumatics	13%
Nervous system			
Migraine	7%		
Headache	5%		
Respiratory			
Asthma	10%	Obstructive airway diseases (for asthma), usually β-2 adrenoceptor agonists or other adrenergic	10%
Vascular			
Hypertension	16%	Agents acting on the rennin–angiotensin system	11%
		Beta-blockers	6%
		Diuretics	5%
		Anti-thrombotic agents (excluding heparin)	10%

patients who achieved responder status (≥ 50% reduction from baseline in MADRS score) or the number of patients who achieved a rating of 1 or 2 (*very much improved* or *much improved*) on the CGI-I or the PGE (Fig. 3). At endpoint (LOCF), 72.5% of patients were responders [95% CI: 68.8–76.0%], whereas 73.1 and 74.1% of patients were rated *very much improved* or *much improved* on the CGI-I or PGE, respectively. There was a significant correlation between the number of MADRS responders and the number of patients scoring 1 or 2 on the CGI-I (Spearman's rank-order correlation coefficient $\rho = 0.76$ at endpoint, LOCF). Similarly, there was a significant correlation between investigator-rated and patient-rated improvements (Spearman's rank-order correlation coefficient between CGI-I and PGE $\rho = 0.8$, $P < .0001$ at endpoint, LOCF). For the OC analysis, 85% of patients [95% CI: 81.7–88.4%] met the MADRS criterion for response at endpoint, whereas 86% of patients received a CGI-I or PGE rating or *very much improved* or *much improved*.

The SF-36 was completed by patients at baseline and the final visit. Scores for patients who completed 24 weeks of treatment are summarized in Table 4. Improvements ranged from an increase of 12.7 points in the *physical functioning* dimension to an increase of

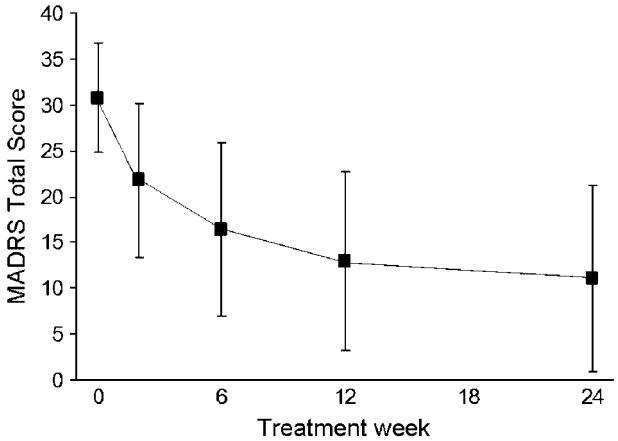

Figure 1. MADRS mean total score for the modified ITT (LOCF) data set ($n = 618$). Vertical bars represent standard deviations.

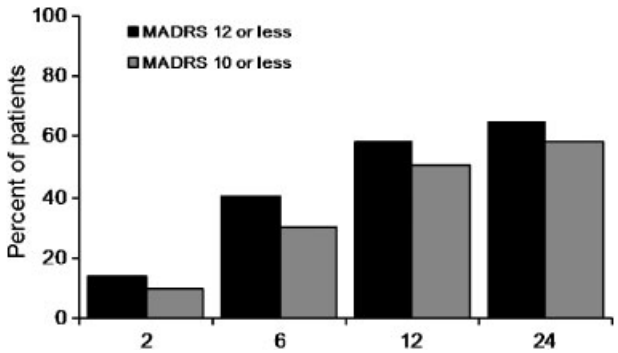

Figure 2. Percentage of patients in the modified ITT (LOCF) data set ($n = 618$) who achieved remission. The protocol-defined criterion for remission was MADRS ≤ 12. Exploratory analyses included defining remission as a mean MADRS ≤ 10.

63.0 points on *role emotional limitations*. Improvements on all eight dimensions as well as the Mental Health and Physical Health sub-scales were statistically significant ($P < .0001$, see Table 4 for t values).

There were 111 patients on sick leave at the time they entered the trial, of which 84 (13.1%; based on safety data set, $n = 641$) were on sick leave specifically due to depression. The number of patients on sick leave due to depression decreased at each trial visit. After 2 weeks, there were 66 patients (10.3%) on leave due to depression and by endpoint, there were 11 patients (1.7%) on sick leave.

TOLERABILITY

Overall, 77.2% of patients reported at least one adverse event; of those, 75% reported the event to be mild. The most commonly reported adverse events (occurring in $\geq 5\%$ of patients) are listed in Table 5. Adverse events led to treatment discontinuation in 65 patients (10%) who had received at least one dose of escitalopram. The only adverse event that led to discontinuation in more than 2% of patients was nausea (2.2%).

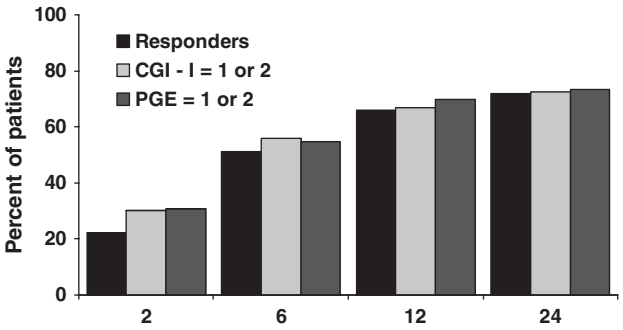

Figure 3. Percentage of patients in the modified ITT (LOCF) data set ($n = 618$) who achieved response (defined as a decrease of at least 50% in mean MADRS score from baseline) or who achieved a score of 1 (*very much improved*) or 2 (*much improved*) on the CGI - I or PGE.

Serious adverse events were reported for 19 patients (3%). For all but one patient, serious adverse events were judged by the investigator to be not related to escitalopram. This patient was hospitalized for depression within 2 weeks of starting escitalopram (10 mg/day). The patient had a history of grieving factors and recovered without sequelae.

DISCUSSION

This study provides evidence of a good response to treatment with escitalopram in a heterogeneous group of more than 600 primary-care patients and is, to our knowledge, the first Canadian semi-naturalistic study of the treatment of patients with MDD in primary care. Although the majority of depressed patients, including those with severe MDD, are treated in primary care, evaluation of patient outcomes within this setting is underrepresented in clinical research.

Nearly two thirds of patients (65%) in the efficacy population achieved remission (MADRS ≤ 12) at endpoint and more than half (60%) were in remission after 12 weeks (LOCF). Remission rates were higher in the OC analysis (67% at 12 weeks and 78% after 24 weeks) highlighting the importance of adherence to treatment. The 12-week remission rate is comparable to the 58% remission rate obtained in a 12-week naturalistic study of escitalopram conducted in French psychiatric centers.[28] The 24-week remission rate is similar to those reported in two long-term double-blind efficacy trials in which escitalopram-treated patients achieved remission at rates exceeding 70%.[10,29] These data, along with those from other long-term antidepressant trials, are consistent in showing that the majority of patients who achieve remission do so with acute treatment although some (as few as 10%) will achieve remission only over the long-term if treatment is maintained unchanged.[30–31]

TABLE 4. SF-36 scores for patients completing 24 weeks of treatment

Dimension	Baseline score	Final score	Difference	*t* value[a]
Physical function	71.4	84.1	12.7	11.7
Role physical limitations	36.6	75.3	38.9	17.7
Bodily pain	60.0	73.1	12.9	10.3
General health	52.1	69.2	16.9	16.8
Role emotional limitations	12.8	75.9	63.0	32.3
Social functioning	33.9	75.9	42.0	30.2
Mental health	30.7	71.5	40.8	37.5
Vitality	20.6	58.5	37.8	30.2
Physical health sub-scale	48.2	72.0	23.8	24.7
Mental health sub-scale	30.1	70.2	40.0	37.9

The possible range of scores on each dimension or sub-scale is from 0 to 100.
[a]Each *t* test was significant at a $P<.0001$.

TABLE 5. Most common (≥5%) adverse events

Adverse event	*n* (%)
Nausea	140 (21.8)
Headache	112 (17.4)
Dizziness	61 (9.5)
Insomnia	61 (9.5)
Diarrhea	60 (9.4)
Fatigue	51 (8.0)
Dry mouth	40 (6.2)
Somnolence	33 (5.2)

Therefore, in keeping with published treatment guidelines, clinicians should consider more aggressive management for non-remitters once the treatment extends beyond the acute phase.[32, 33]

Although there are few naturalistic studies with which to provide clinical context to the present remission rates, it is noteworthy that the landmark Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial, reported remission rates of 28% after up to 14 weeks of treatment with citalopram.[21] Notwithstanding the different antidepressant medications used in these two studies, one obvious distinction is the assessment scales from which the remission criterion was derived: a MADRS score ≤12 was used in this study, whereas STAR*D defined remission as ≤7 on the 17-item Hamilton Depression Rating Scale. According to some analyses, a MADRS ≤10 or less represents a more conservative approximation of the Hamilton Depression Rating Scale criterion.[19] According to this criterion, more than 50% of escitalopram-treated patients had achieved remission by week 12 suggesting that remission rates with escitalopram are robust.

Monitoring patients' work status and obtaining subjective ratings on the SF-36 also provided a means to assess overall well-being and QoL. The final SF-36 scores were comparable to normative scores obtained from random samples of 9,423 Canadians[34]; on six of eight dimensions the final scores were within 90% of the Canadian norms (*physical function*, *role physical limitations*, *bodily pain*, *general health*, *role emotional limitations*, *mental health*), whereas the scores for *social functioning* and *vitality* were 88 and 89% of the Canadian norm. The number of patients on medical leave due to depressive illness decreased steadily over the course of the trial, indicating a resumption of normal daily activities. These results are consistent with those of Winkler et al.[35] who reported a significant reduction in days of sick leave after 3 months of treatment with escitalopram (compared to days of sick leave during the 3 months before treatment).

Nearly three quarters (71%) of the patients enrolled in the trial completed 24 weeks of treatment with escitalopram. The completion rate is similar to that of a long-term extension study with escitalopram, in which 74% of patients completed 12 months of open-label treatment in primary care.[36] An important difference between these two studies is that patients participating in the trial of Wade et al.[36] completed 8 weeks of double-blind treatment with escitalopram, citalopram, or placebo; the extension study therefore excludes patients who did not complete the acute treatment phase and may be considered biased toward favoring higher adherence rates. In this study, there was no lead-in or screening phase that could be used to select patients on the basis of previous adherence or response to treatment.

The adherence rate in this study is substantially better than what would be predicted based on studies of adherence to antidepressant treatment, which generally show higher discontinuation rates for an average length of treatment shorter than 6 months.[37] For instance, Katon et al.[1] showed that fewer than 40% of patients treated in primary care filled 6-months worth of antidepressant prescriptions. Furthermore, Lin et al.[38] reported that 44% of primary-care patients stopped taking antidepressants within the first

3 months of therapy. One limitation of these studies is that, by today's standards, there is an overrepresentation of tricyclic antidepressants, which carry an unfavorable tolerability profile compared to more modern antidepressants. In a more recent study, adherence to treatment with newer antidepressants in primary care yielded similar results, with more than 50% of patients discontinuing treatment over a 6-month period.[39] Similarly, in a 24-week double-blind study, withdrawal rates for paroxetine and mirtazapine exceeded 50%.[40] Insofar as non-adherence is an important risk factor for relapse,[41] the present results suggest that escitalopram is a good choice for initiating long-term antidepressant treatment.

Escitalopram (10–20 mg/day) was well tolerated. These results are particularly relevant when considering this heterogeneous population of primary-care patients. Overall, 10% of patients withdrew from the study due to adverse events and although co-morbid medical conditions and concomitant medications were frequently listed, the general adverse event profile was comparable to that seen in randomized controlled trials with escitalopram of similar duration.[10, 29] In this study, as in most clinical trials, the documentation of adverse event relies heavily on the patients' spontaneous reports. An exception in this study is that a telephone interview (to assess any potential safety or tolerability issues) was scheduled after patients had completed the 1st week of treatment. This interview afforded patients the specific opportunity to report any adverse events associated with start of treatment. Nevertheless, the overall incidence of the most frequently reported adverse events (nausea, headache) is similar to the incidence reported in randomized controlled trials.[29, 36]

This semi-naturalistic study provides an important opportunity to explore symptom severity among patients presenting spontaneously to a physician for treatment of depressive symptoms and who are identified as suffering from MDD. The symptom severity of patients who spontaneously seek treatment for depression has not been well characterized despite the practical value of such characterization for clinical research and the potential heuristic value for clinical practice.

Among the present patients, 55% had a baseline MADRS score of 30 or more. Although no single rating scale or cutoff score is universally accepted for delineating grades of depressive symptom severity,[25] suggested a total score of 28–30 as a criterion for severe depression given that this score would most likely represent a clear cut loss of function. If a score of 30 on the MADRS is accepted as a reasonable criterion for severe depression, then over half of patients in this study can be described as severely depressed. These data suggest that primary-care physicians commonly treat severely depressed patients. Although the efficacy of escitalopram in the treatment of severe depression (patients with baseline MADRS score ≥ 30) has been demonstrated in clinical trials[42–44] the present results suggest that escitalopram is also effective for severe depression treated in real-world clinical practice.

There was a good correlation between improvements in the MADRS score and improvements on physicians' and patients' ratings of improvement. At endpoint, just more than 70% of patients (LOCF) were MADRS responders and a similar proportion was judged to be *much improved* or *very much improved* according to patients' ratings on the PGE or physician's rating on the CGI-I. The correspondence between these three measures signals that improvements in depressive symptoms were clinically meaningful, apparent to physicians, and relevant to patients.

An important limitation of the present trial is its open-label design. Because of this, it is difficult to establish the degree to which clinical improvements were due to escitalopram treatment, the natural course of MDD, or non-specific benefits of participation in a clinical trial (i.e., validation of symptoms, frequent contacts with a physician). With respect to the latter, scheduled visits in this study were less frequent than are generally seen in randomized controlled efficacy trials, in which visits may be scheduled once every 1–4 weeks. This study was designed to more closely resemble the frequency of physician–patient contacts in everyday clinical practice. As such, there were three scheduled face-to-face visits over the first 6 weeks of treatment and only two scheduled visits from week 6–24. Consequently, any non-specific therapeutic benefits of regular physician contacts can be expected to more closely reflect those that are inherent in day-to-day practice.

Another limitation is that investigators were not asked to conduct a complete psychiatric diagnostic interview (such as the full MINI) on trial patients. Such a detailed assessment is beyond usual primary-care practice and an epidemiological survey of psychiatric co-morbidity among MDD patients was not an objective of the present trial. Although investigators were asked to document relevant co-morbid conditions and medical history, it is noteworthy that anxiety was listed as a concurrent illness in only 4% of patients and few specific anxiety disorder were diagnosed (none were co-morbid in at a frequency of 1% or greater). These rates of co-morbid anxiety or anxiety disorders are considerably lower than those reported in other naturalistic studies[28, 45] or epidemiological surveys,[46–48] but is consistent with the 3.4% rate of psychiatric co-morbidity reported in the large German study[49].

CONCLUSIONS

Escitalopram was effective, well tolerated, and safe in the treatment of MDD in a heterogeneous population of primary-care patients. To the extent that this patient sample represents the patients seen in day-to-day primary-care practice, the data support a close corre-

spondence between the efficacy of escitalopram observed in randomized controlled trials and the effectiveness of escitalopram in real-world clinical practice. The adherence rate (71% of completers) was beyond what could be predicted from naturalistic primary-care studies of adherence. As adherence to antidepressant treatment is paramount to achieving long-term recovery, the present results suggest that escitalopram should be considered among the first-line choices of antidepressant used in primary care.

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