Clinical and Functional Benefits of Escitalopram for the Treatment of Major Depressive Disorder in Primary Care: A Canadian Naturalistic Investigation in Depression (NAVIGADE)

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There is growing awareness and concern for the health, social, and economic toll exacted by mental illness. Worldwide, unipolar major depression is second only to ischemic heart disease as a leading cause of disability[1] and is the leading cause of non-fatal burden of disease, accounting for almost 12% of years lived with disability[2]. Major depressive disorder (MDD) is associated with substantial functional impairment including loss of work productivity, increased risk of job loss or job turnover, and unemployment.[3-7] Greater symptom severity is associated with a greater reduction in health-related quality of life[8,9] and greater work impairment.[3]

Depression and Impairment in the Canadian Workplace

Depression is prevalent in Canada and has a profound impact on daily and workplace functioning. According to the 2002 Canadian Community Health Survey (CCHS), more than one million Canadian adults (aged 18 years or older) experienced a major depressive episode during the year prior to their survey interview and more than 70% of these were employed.[10] In a further analysis of the CCHS data, Gilmour and Patten[11] found that depressed workers reported an average of 32 days during the past year during which their symptoms caused an inability to work or to carry out normal activities. More than half (53%) of workers reported that depressive symptoms cause at least "moderate" interference with work, whereas approximately 20% of workers reported interference to be "very severe." Compared to workers with no history of depression, those who suffered a depressive episode in the past year were nearly three times more likely to report a reduction in

TABLE I **Baseline Symptom Severity**

MADRS scores		CGI-S scores	
MADRS < 25 (mild)	16.5% of subjects	CGI-S < 4	6.4% of subjects
MADRS ≥ 25 < 30 (moderate)	28.1% of subjects	CGI-S = 4 (moderately ill)	57.3% of subjects
MADRS ≥ 30 (severe)	55.4% of subjects	CGI-S ≥ 5 (markedly, severely, or extremely ill)	36.3% of subjects
Mean MADRS (± SD)	30.7 ± 5.2	Mean CGI-S	4.3 ± 0.7

MADRS = Montgomery-Åsberg Depression Rating Scale; CGI-S = Clinical Global Impression of Severity.

work activities due to long-term health conditions. The estimated total economic cost of depression and distress (including direct costs for healthcare services and indirect costs associated with disability and unemployment) to the Canadian economy has been estimated at $14.4 billion annually.[11,12]

Depression is Treated in Primary Care

In Canada, primary-care physicians are the vanguard in treating depression. In a recent survey of Canadian patients Vasiliadis and colleagues[13] reported that only 55.7% of respondents with depression used any health services; most commonly, respondents sought the services of a general practitioner or family physician. In an analysis of administrative-medical-service-use data from British Columbia, Bilsker and colleagues[14] found that 92% of patients diagnosed with depression were treated exclusively by their primary-care physician.

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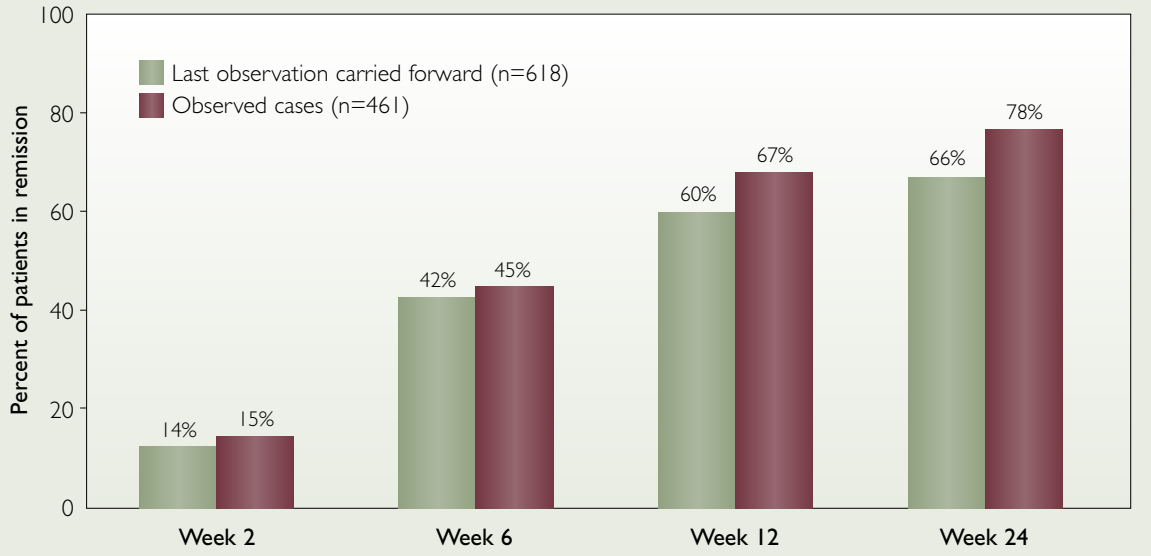
Randomized controlled trials (RCTs) represent the gold standard in evaluating antidepressant efficacy. However, despite the critical role of primary-care physicians in treating depression, clinical trials with antidepressants are most commonly conducted in specialist settings. Furthermore, RCTs are widely recognized for employing methods and restrictions that are not reflective of real-world clinical practice.[15-20] Consequently, there are limited data available to primary-care physicians in guiding evidence-based treatment decisions.

Escitalopram is a selective serotonin reuptake inhibitor (SSRI) with the additional property of allosterically modifying the serotonin transporter, the effect of which is to enhance its own binding to the transporter and enhance serotonin reuptake blockade.[21,22] A number of RCTs conducted in primary-care settings provide evidence that escitalopram is effective in the symptomatic treatment of major depressive disorder.[23-26] Further to these trials, an exclusively Canadian trial (Naturalistic Investigation in Depression, or NAVIGADE) was conducted in order to evaluate the effectiveness of escitalopram in treating MDD in a naturalistic primary-care setting.

Naturalistic Investigation in Depression: NAVIGADE

The NAVIGADE trial[27] was conducted in primary-care clinics across Canada with general practitioners or family physicians as investigators. To our knowledge, it is the first exclusively

FIGURE 1 **Remission Rates Over 24 Weeks of Treatment**



Remission = MADRS total score ≤ 12

Canadian study focused on identifying MDD patients, delivering antidepressant treatment, and evaluating its effectiveness in everyday primary-care practice. Although there were few criteria for inclusion, potential participants were required to be adults (18 years of age or older), to have a primary diagnosis of MDD (according to DSM-IV criteria) and to have a minimum score of 19 on the Montgomery-Åsberg Depression Rating Scale (MADRS).[28]

Patient characteristics: working age with moderate to severe depression. There were 641 patients (65% women) treated with escitalopram in the NAVIGADE study. The mean age of patients was 43 years, with a standard deviation of 14 years. This age range is similar to the range of depressed workers described in the CCHS (25 to 64 years).

Depression severity at baseline was assessed using the MADRS and the Clinical Global Impression of Severity (CGI-S) scale.[29] The MADRS is scored on the basis of a semi-structured interview comprised of 10 items focused on the core symptoms of depression. The CGI-S is a single-item scale in which the physician is asked to rate the global severity of the patient's illness, taking into consideration factors such as overall functioning and health status.

Regardless of the scale used, the majority of primary-care patients could be characterized as suffering from moderate or severe depression (baseline severity scores are shown in Table 1). More than 80% of patients had a baseline MADRS score ≥ 25, the threshold for moderate severity,[30] and more than half (55%) of patients had a baseline score of ≥ 30, indicative of severe depression.[31] When sever-

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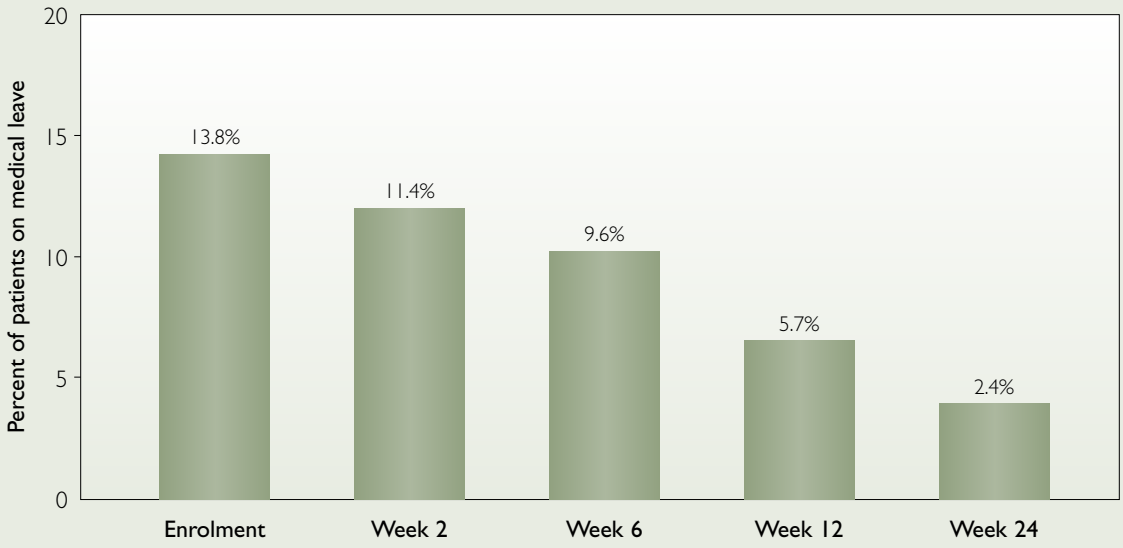
FIGURE 2 Work Status (Medical Leave Due to Depression)



ity was rated using the CGI-S scale, more than 90% of patients were rated moderately ill or worse, with more than one third of patients rated as markedly ill or worse, indicating an important level of severity and global dysfunction among primary-care patients presenting with depression.

Adherence to treatment. 71% of patients enrolled in the study completed 24 weeks of treatment. The most common reason for discontinuation was adverse events (10%). Less than 4% of patients discontinued due to lack of efficacy or non-adherence to treatment.

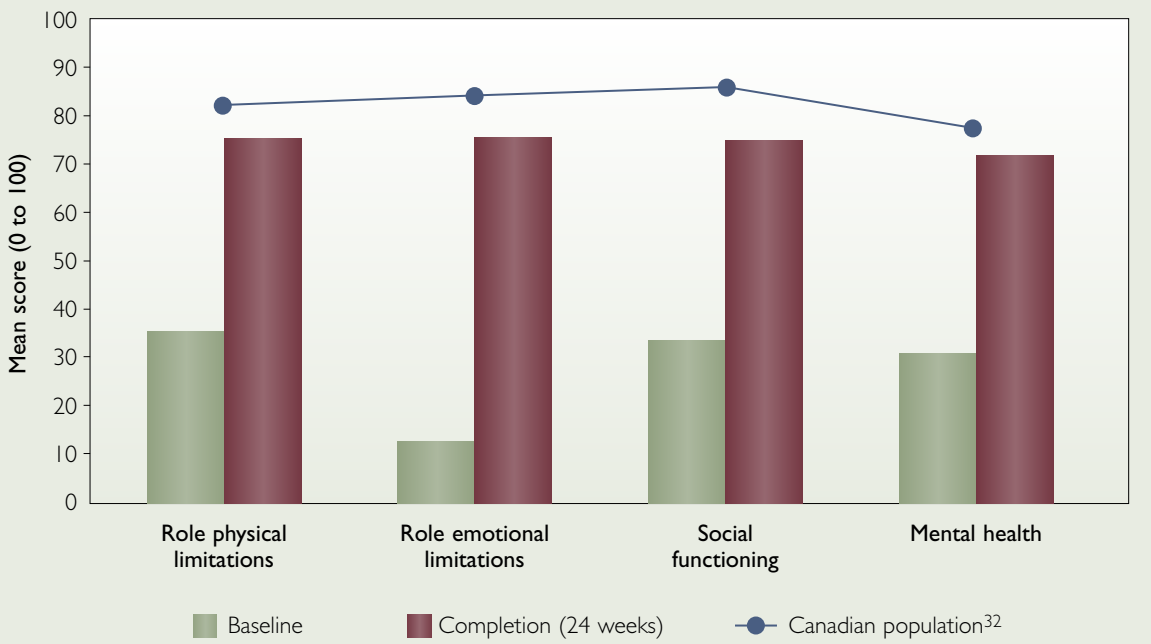
To our knowledge, [the NAVIGADE trial] is the first exclusively Canadian study focused on identifying MDD patients, delivering antidepressant treatment, and evaluating its effectiveness in everyday primary-care practice.

Escitalopram treatment and symptom improvement. After 24 weeks of treatment, the mean MADRS score decreased by 19.8 points (from 30.7 to 10.9). When compared to baseline, decreases were statistically significant from week two onward ($t = 45.17$, $p < 0.001$). Similar improvements were seen on the CGI-S scale, which decreased from a mean baseline score of 4.3 to 2.2 at endpoint.

Remission rates at each visit for the last observation carried forward (LOCF) and observed cases (OC) datasets are shown in Figure 1. Remission (as defined in the protocol as a MADRS score ≤ 12) was achieved by 65.5% of patients (95% CI, 61.6% to 69.3%) treated. More than three quarters (78%) of those who completed 24 weeks of treatment achieved remission (95% CI, 73.6% to 81.4%). There were 405 remitters and 358 remitters in the LOCF and OC datasets, respectively. The higher number of remitters in the LOCF dataset indicates that, among patients who did not complete the study, there were 47 remitters.

Work status: medical leave from work due to depression. Patients' work status was documented at each study visit. At the time of enrolment, 84 patients (13.8%) were placed on, or were

FIGURE 3 **Functional Subscales of the SF-36® at Baseline and Completion**



already on, medical leave due to their depressive symptoms. The number of patients on medical leave due to depression decreased at each trial visit (Figure 2). After 24 weeks, there were 19 patients on leave.

Functional outcomes: SF-36®. Health-related quality of life (HRQOL) was assessed using the Medical Outcomes Study 36-Item Short Form (SF-36®).[9] This is a patient-rated questionnaire with eight subscales: four subscales are used to assess physical health (physical function, role physical limitations, bodily pain, general health) and four subscales to assess mental health (role emotional limitations, mental health, social functioning, vitality). There are three subscales that reflect functional disability: the two role-limitation subscales (role physical limitations and role emotional limitations) assess problems with work or daily activities. In addition, the social-functioning subscale is used to assess interference with social activities due to physical or emotional problems.

Patients completed the SF-36® at baseline and at the final visit. At baseline, all subscale scores fell well below published normative scores obtained from random sample of 9,423 Canadians.[32] At the final visit, there were statistically significant improvements on all subscales (Student's t-test, $p < 0.001$). Final scores on all dimensions were within 88% of Canadian norms.

71% of patients enrolled in the study completed 24 weeks of treatment. The most common reason for discontinuation was adverse events (10%). Less than 4% of patients discontinued due to lack of efficacy or non-adherence to treatment.

Figure 3 shows the mean scores on the two functional "role-limitation" subscales, the social functioning subscale, and the mental health sub-

scale which is relevant for assessing patient-rated symptoms related to depression. Among the physical-health subscales, patients scored lowest on role physical limitations and, among the mental-health subscales, patients scored lowest on role emotional limitations, suggesting that overall, patients experienced considerable functional limitations. At completion, the mean scores of both of these scales were within 90% of Canadian norms.

Discussion

The objective of this naturalistic study was to assess escitalopram in the treatment of MDD under conditions that reflect—as closely as possible—those of a Canadian primary-care clinic. Investigative sites represented urban, sub-urban, and rural areas across Canada, investigators were not required to be clinical-research experts, and there were limited inclusion and exclusion criteria. Nevertheless, NAVIGADE was not designed as a national epidemiologic survey and the study objectives may have biased the selection of patients. With this caveat in mind, it is likely NAVIGADE patients are a fair representation of those seen in every-day clinical practice and that the data have heuristic value for primary-care physicians.

Despite their level of illness, it is clear from the present results that many patients with moderate to severe depression and clinically important levels of disability can be successfully treated with escitalopram in primary care.

The majority of patients treated in NAVIGADE could be described as suffering from moderate to severe depression. At the time of entry into the study, more than half of patients had a MADRS score greater than 30, more than one third were considered to be markedly ill, there were striking deficits on HRQOL, and more than one in 10 patients were on medical leave due to depression. Whereas it may be commonly held that patients treated in primary care experience less severe and a more transient course of illness than those treated by psychiatrists,[33-35] data from the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study indicate that MDD patients vary little in terms of severity between primary- and specialty-care settings[36] and that identical remission rates can be achieved regardless of treatment setting.[37] Although direct comparisons between STAR*D and the present study should be made with caution, it is noteworthy that the majority of patients in both trials suffered from moderate to severe depression.[38] Overall, these results highlight the important first-line role of primary-care physicians in treating patients with a serious level of illness or impairment.

Despite their level of illness, it is clear from the present results that many patients with moderate to severe depression and clinically important levels of disability can be successfully treated with escitalopram in primary care. Mitigating the loss of function in depressed patients typically focuses on managing depressive symptoms; it is a widely held opinion[39] that when remission is reached, day-to-day functioning returns to premorbid levels. In NAVIGADE, approximately two thirds (66%) of patients who started treatment with escitalopram achieved remission. For patients who completed 24 weeks of treatment, the probability of achieving remission was 78%. Evidence that escitalopram can help patients return to normal levels of daily function is provided by the significant improvements on the patient-rated SF-36® and by the reduction in the number of patients on medical leave due to depression at each study visit. On the SF-36® the relatively low mean baseline scores on the physical and emotional role-limitation subscales indicate a general and substantial reduction in daily functioning. After 24 weeks of treatment, the

mean score on each of the role-limitation scales was within 90% the Canadian norm. Social functioning was also reduced at baseline and returned to within 88% of the Canadian norm after 24 weeks.

Adherence to antidepressant treatment has been shown to reduce the incidence of short-term disability.[40] In an analysis of data from Canadian financial and insurance companies, Dewa and colleagues[41] found that the use of antidepressants within 30 days of a disability episode decreased the length of the episode by 24 days, and that patients who used one antidepressant were more likely to return to work than those who switched antidepressants (who were more likely to leave their employment). The NAVIGADE study provides evidence of high adherence rates to escitalopram. Nearly three quarters (71%) of patients enrolled in the study completed 24 weeks of treatment with escitalopram. This adherence rate is substantially better than what would be predicted based on naturalistic studies of adherence to antidepressant treatment, which generally show discontinuation rates around 50% within six months.[42-44]

Conclusions

Escitalopram was effective and well tolerated when used in conditions closely reflecting everyday primary-care practice. These data are in agreement with the efficacy of escitalopram observed in RCTs showing high remission rates and improvement in global function as rated by physicians (CGI-S), as rated by patients (SF-36®) and as objectively measured by the number of patients on medical leave due to depression. Furthermore, 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 critical to consolidating remission, achieving long-term recovery, reducing the risk of prolonged disability, and regaining daily functioning, the present results suggest that escitalopram should be considered among the first-line choices of antidepressants used in primary care.

Evidence that escitalopram can help patients return to normal levels of daily function is provided by the significant improvements on the patient-rated SF-36® and by the reduction in the number of patients on medical leave due to depression at each study visit.

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