GUIDELINE
Recommendations on screening for depression in adults

RESEARCH
Risk of suicide after a concussion

REVIEW
Neuromodulation for treatment-refractory major depressive disorder

PRACTICE
Repetitive transcranial magnetic stimulation for depression

NOVEMBER 2016
PRISTIQ is indicated for the symptomatic relief of major depressive disorder.

Choose PRISTIQ:
demonstrated improvements in functional outcomes: work, family life and social life (secondary endpoints).

PRISTIQ 50 mg demonstrated significant improvements in functional outcomes from baseline vs. placebo, as measured by the Sheehan Disability Scale (SDS).^1

- **Work score:** PRISTIQ -2.9 (n=156), placebo -2.2 (n=148), p=0.01.
- **Family life score:** PRISTIQ -3.0 (n=163), placebo -2.2 (n=160), p=0.002.
- **Social life score:** PRISTIQ -3.2 (n=163), placebo -2.3 (n=160), p=0.003.

The SDS measures the functional impairment that depressive symptoms have on a patient’s family life, social life and work. A decrease in SDS score represents improved functional outcomes.\(^2\)

Clinical Use:
- PRISTIQ is not indicated for use in children under the age of 18
- The short-term efficacy of PRISTIQ has been demonstrated in placebo-controlled trials of up to 8 weeks
- The efficacy of PRISTIQ in maintaining an antidepressant response for up to 26 weeks, following response during 20 weeks of acute, open-label treatment, was demonstrated in a placebo-controlled trial

Contraindications:
- Concomitant use with monoamine oxidase inhibitors (MAOIs) or within the preceeding 14 days
- Hypersensitivity to venlafaxine hydrochloride

Most Serious Warnings and Precautions:
- Behavioural and emotional changes, including self-harm: SSRIs and other newer antidepressants may be associated with:
  - Behavioural and emotional changes including an increased risk of suicidal ideation and behaviour
  - Severe agitation-type adverse events coupled with self-harm or harm to others
  - Suicidal ideation and behavior; rigorous monitoring
- **Discontinuation symptoms:** should not be discontinued abruptly. Gradual dose reduction is recommended

Other Relevant Warnings and Precautions:
- Concomitant use with venlafaxine not recommended
- Allergic reactions such as rash, hives or a related allergic phenomenon
- Bone fracture risk with SSRIs/SNRIs
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- Increases in blood pressure and heart rate (measurement prior to and regularly during treatment)
- Increases cholesterol and triglycerides (consider measurement during treatment)
- Hypotension or Syndrome of Inappropriate Antidiuretic Hormone (SIADH) with SSRIs/SNRIs
- Potential for GI obstruction
- Abnormal bleeding SSRIs/SNRIs
- Interstitial lung disease and eosinophilic pneumonitis with venlafaxine
- Seizures
- Narrow angle glaucoma
- Mania/hypomania
- Serotonin syndrome or neuroleptic malignant syndrome-like reactions

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EDITORIAL

Depression deserves better treatment
Kirsten Patrick

COMMENTARY

Should assisted dying for psychiatric disorders be legalized in Canada?
Scott Y.H. Kim and Trudo Lemmens

Why screening for depression in primary care is impractical
Roger C. Bland and David L. Streiner

RESEARCH in CMAJ

Risk of suicide after a concussion
Michael Fralick, Deva Thiruchelvam, Homer C. Tien, and Donald A. Redelmeier

Relation between place of residence and postpartum depression
Simone N. Vigod, Lesley A. Tarasoff, Barbara Bryja, Cindy-Lee Dennis, Mark H. Yudin, and Lori E. Ross

The diagnosis of depression and its treatment in Canadian primary care practices: an epidemiological study
Sabrina T. Wong, Donna Manca, David Barber, Rachael Morkem, Shahriar Khan, Jyoti Kotecha, Tyler Williamson, Richard Birtwhistle, and Scott Patten

Screening for depression: a systematic review and meta-analysis

GUIDELINES

Recommendations on screening for depression in adults
Canadian Task Force on Preventive Health Care, Michel Joffres, Alejandra Jaramillo, James Dickinson, Gabriela Lewin, Kevin Pottie, Elizabeth Shaw, Sarah Connor Gorber, and Marcello Tonelli

REVIEW

Neuromodulation for treatment-refractory major depressive disorder
Nir Lipsman, Tejas Sankar, Jonathan Downar, Sidney H. Kennedy, Andres M. Lozano, and Peter Giacobbe

PRACTICE

Repetitive transcranial magnetic stimulation: an emerging treatment for medication-resistant depression
Jonathan Downar, Daniel M. Blumberger, and Zafiris J. Daskalakis

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Brought to you by an unrestricted educational grant from Pfizer Canada.
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In major depressive disorder, her doctor calls it “demonstrated improved functional outcomes”

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Depression deserves better treatment

Kirsten Patrick MBBCh DA

Public perceptions about depression are rife with bafflement and false beliefs. Just look at the public reaction on digital media to the recent suicide of Robin Williams. I was surprised to encounter repeatedly the opinion that depression is a failing ("get a better attitude," "be positive") and is easily fixed with the right quality of religious faith. The majority wondered, "Why did he suffer alone?" Why, indeed. Why do so many? Why do we persist in stigmatizing and neglecting depression despite its high prevalence?

Based on disability-adjusted life-years, unipolar depressive disorder is ranked ninth in the most recent estimates from the World Health Organization (WHO) Global Burden of Disease 2010 study. On a global scale, its burden is greater than that of diabetes or tuberculosis. TB and malaria, with lesser global burden, get official WHO global public health "days." Not depression.

In high-income countries, only ischemic heart disease and stroke cause more disability than unipolar depression. If the amount of money donated to various charities is a way of gauging the relative importance attributed to medical causes, then depression goes down the list like a lead balloon: in Canada, when ranked by donation amount, not one mental-health charity cracks the top-10 list.

The burden of depression arises not just from the high cost of treating this condition, but also from the reduced functional ability of those affected, which leads to their reduced productivity. Effects on children and other loved ones can also be enduring and serious. Patients with chronic depression are at increased risk of comorbid illness, and incident depression also frequently complicates chronic physical conditions. Furthermore, depression affects younger people as frequently as it does older people, and it tends to recur throughout a person’s life.

The fact that we don’t have widely accessible and effective treatments for depression is a serious problem. Recent evidence suggests that antidepressants alone don’t work much better than placebo for many people. Behavioural therapies, particularly cognitive behavioural therapy, are moderately effective with effects that endure, but they are frequently difficult to access, rely on properly trained personnel for delivery, take time to work and have high attrition rates. Exercise is consistently shown to be effective in both treating and preventing depression, but motivation is a barrier in those for whom performing simple personal functions may be difficult. Creative interventions that use physical activity in group settings with buddy support can help, with the added bonus of mandated social interaction. Neurmodulation treatments were reviewed in CMAJ last year. Electroconvulsive therapy, itself highly stigmatized, is one, but there are other promising neurmodulatory interventions with evident short- to medium-term effectiveness. Unfortunately, few can access these treatments in Canada and the cost-effectiveness of using them in the Canadian setting has not been investigated. A combination of approaches — and ideally a tailored approach — may work best. Patients are discovering this for themselves and are sharing their experiences on online forums and blogs. However, policy lags behind.

We are not alone in asking why mental illness is such a low priority worldwide, in spite of coordinated efforts to destigmatize mental illness in recent years. The concept of “no health without mental health” has gained wide traction among health professionals worldwide, yet progress in improving identification of depressed patients and ensuring swift access to the right treatment has been slow. Mitigating the effects of depression on those close to the affected person continues to receive scant attention.

In Canada, we need to stop treating depression as a Cinderella disease. We need to fund research that can make a difference to people with depression. The federal government must make a commitment to improving mental-health infrastructure nationwide. Health practitioners ought to be able to connect patients identified as depressed with adequate support and appropriate treatment without delay. Community programs can play an important role in filling the support and treatment-delay gaps, and these programs should be boosted. We need to scale up training for behavioural therapists. Exercise interventions are cheap to run and effective, but they are currently underused and require funding support. Most neuromodulatory therapies are still classified as experimental; facilities and trained staff are rare, and relative expense is high. Yet, we should not limit these effective treatments to those whose depression is intractable and prolonged. Although substantial resources are needed, the high cost of depression to individuals, families and society justifies the expense. But such resources will only receive priority if we all decide to pay more positive attention to depression.

References


Competing interests: See www.cmaj.ca/site/misc/cmaj_staff.xhtml

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Should assisted dying for psychiatric disorders be legalized in Canada?

Scott Y.H. Kim MD PhD, Trudo Lemmens LLM DCL

The Supreme Court of Canada ruled in Carter v. Canada¹ that competent, consenting adults whose suffering is due to a “grievous and irremediable” medical condition should have access to some form of medical assistance in dying and invited Parliament to develop a regulatory regime along these “parameters.” The Parliamentary Special Joint Committee on Physician-Assisted Dying suggested that the “grievous and irremediable” criterion includes nonterminal medical conditions, including psychiatric disorders.² The federal government’s Bill C-14, on the other hand, defined “grievous and irremediable” as an “advanced state of irreversible decline in capabilities” in a person for whom “natural death has become reasonably foreseeable.”³ The Senate ultimately passed the bill, despite initially voting to remove the requirement for reasonably foreseeable death.⁴ The new law does not discriminate among people near death based on their disorder or disability, psychiatric or otherwise; however, assisted dying because of a psychiatric disorder would not fulfill the access criteria. The passing of the bill may not, however, put to rest the debate over whether psychiatric disorders could qualify as eligible conditions for assisted dying, and the government has indicated it will be studying the issue.

Arguments for including mental illness as an eligible condition for assisted dying almost always focus on severe depression. The assumption is that doctors can accurately determine medical futility and decisional capacity, with the implication that no ineligible person would receive assisted death. However, evidence suggests this focus is too narrow and fails to consider real threats to patients with mental illness.

If assisted dying is legalized for patients with psychiatric conditions, it will not be just for severe, refractory depression. In Belgium and the Netherlands, medical assistance in dying has been provided to people with chronic schizophrenia, posttraumatic stress disorder, severe eating disorders, autism, personality disorders and even prolonged grief.⁵,⁶ Women are more than twice as likely as men to request⁷ and receive⁸ assisted dying for psychiatric disorders, but we do not know why. Most people who request it for such reasons have characteristics that compromise their ability to cope with adversity, including personality disorders and social disconnection.⁹ Discussions, much less evidence-based guidance, of how to evaluate people who request assisted dying because of prolonged grief, autism, schizophrenia or personality disorders are lacking.

Furthermore, the key eligibility criterion of “irremediable” condition is inherently vague and unreliable, even when applied to the types of severe cases usually mentioned by those who advocate for including psychiatric disorders in the legislation for assisted dying. Consider a patient who has been suffering from chronic depression for 20 years, has tried more than a dozen different medications as well as electroconvulsive therapy and is currently in a depressive episode that has lasted several years. Based on published cases in Belgium⁵ and the Netherlands,⁶ such a patient would likely be deemed to meet the “irremediable” criterion. However, evidence suggests that most such patients can achieve remission if given high-quality treatment.⁷

The Parliamentary Special Joint Committee on Physician-Assisted Dying’s recommendation that “irremediable … does not require the patient to undertake treatments that are not acceptable to the individual” could be particularly consequential for patients with psychiatric conditions. It is one thing for a patient with a terminal illness to

**Key points**

- There is a gap between the idealized basis upon which medical assistance in dying is advocated for patients with psychiatric conditions and the reality of its practice.
- Specifically, the assumption that only patients with true irremediable depressive disorders would have access to assisted dying — after careful assessment of their decision-making capacity based on rigorous thresholds — is not supported by evidence.
- Because of the necessarily broad criteria used to regulate assisted dying, legalizing the practice for psychiatric conditions will likely place already vulnerable patients at risk of premature death.
refuse a last-ditch effort, but quite another to set aside a core clinical imperative in psychiatric treatment: compassionately and skillfully helping patients even through periods of sustained suffering during which people often lose the will to live and despair about whether things will get better. A review of 66 case summaries of euthanasia published by Dutch regional euthanasia review committees found that most patients who received assisted dying for a psychiatric condition were deemed to have met the criterion while refusing recommended treatments; many likely did not receive all indicated treatments. In fact, judgments of medical futility vary between physicians; in the Netherlands study, physicians disagreed about medical futility in almost a quarter of the cases. In a case series, a psychiatrist assessed 100 consecutive cases of Belgian patients with psychiatric conditions who requested assisted dying; all 100 patients were deemed have “no prospect of improvement” due to “treatment resistance,” which suggests vagueness of the applied criterion.

A further concern is that some patients who request assisted dying because of a psychiatric illness may not meet the criteria for mental capacity. Although psychiatric diagnoses should not be equated with incapacity, some conditions (e.g., psychotic illnesses, neurocognitive disorders, severe depression, anorexia nervosa and intellectual disability) may increase the risk of incapacity. Evaluating capacity involves applying broad criteria to complex clinical situations. In a survey of consultant psychiatrists, most reported that they find assessment of decision-making capacity to be a challenging task, and training in capacity evaluations was seen as suboptimal. To minimize bias and error, especially when the consequence could be premature death, assessments of decision-making capacity need to include rigorous thresholds with carefully articulated justifications. Evidence, however, indicates that this is not necessarily the case. In our review of 66 case summaries in the Netherlands (unpublished data), the capacity determination in most cases was reported as a simple global judgment of capacity, even for patients with disorders that increase the risk of incapacity. In 8 of the 66 cases, physicians disagreed about the patient’s capacity status. In the case series from Belgium, the psychiatrist deemed all 100 patients who requested assisted dying for psychiatric conditions (14 of whom had psychotic disorders) “capable,” which raises the question of whether a rigorous threshold for capacity was used.

Importantly, the Parliamentary Special Joint Committee also recommended that a prior review system by a panel or judge be prohibited, and it suggested that a retrospective review system would be sufficient. However, it is worth noting that the Belgian and Dutch euthanasia review bodies almost never find that doctors have breached the due care criteria; the Belgian review commission found that only 1 out of more than 10,000 reported euthanasia cases failed to meet the criteria. It seems improbable that doctors virtually never make a mistake when it comes to eligibility evaluations for assisted dying; it is more likely that broad and vague criteria make it difficult to hold doctors accountable.

In a survey of health care professionals and members of the general public in the Netherlands, only 28% of the public and 1 out of 3 health professionals approved of it for patients with psychiatric disorders. Because the Parliamentary Special Joint Committee recommends that, eventually, competent mature minors should be eligible for assisted dying, even those with a psychiatric condition (a practice that even the liberal Belgian regime forbids), it is conceivable that without clear wording in Bill C-14, young people struggling with psychological issues could be eligible for assisted dying.

We believe there is a serious gap between the idealized basis upon which assisted dying for patients with psychiatric conditions is advocated and the reality of its practice, as reflected in evidence from Belgium and the Netherlands. A policy for access to assisted dying by nonterminally ill patients with psychiatric conditions will put many vulnerable and stigmatized people at risk. Perhaps those who advocate for extending access to people with psychiatric disorders may be willing to tolerate a number of potentially avoidable premature deaths as acceptable because access to assisted dying is felt to be so important in principle. However, that argument must be made explicit and debated publicly.

References
Commentary


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In its latest set of guidelines, the Canadian Task Force on Preventive Health Care presents clear and comprehensive conclusions on screening for depression in adults. The document replaces the task force’s 2005 guidelines, which recommended screening adults in the general population for depression in primary care settings that have integrated systems to manage treatment. That approach is no longer recommended.

The current guidelines focus on screening in primary care settings, because it already seems to be well accepted that screening the general population outside the treatment setting is not recommended. This focus is most appropriate, because most people with depression will receive treatment in primary care, many solely in primary care.

Unfortunately, the task force does not state how it defines “screening.” In practice, this may mean asking as few as 2 questions, as is recommended in the National Institute for Health and Clinical Excellence (NICE) guidelines (the so-called “Whooley questions”). Clearly, responses to these questions would not be diagnostic and would serve only as clues to investigate further.

Alternatively, clinicians can screen patients for depression using a more comprehensive assessment tool, such as the 9-item Patient Health Questionnaire (PHQ-9). However, this questionnaire has more of the characteristics of a diagnostic instrument rather than a screening tool. Further, as a diagnostic instrument for major depression, the PHQ-9 or similar tools may miss patients with minor depression, dysthymia, recurrent brief depression or bereavement, or depression associated with a major medical condition, substance use or an organic mental state, unless there is further inquiry.

In addition, because comorbidity is common in depression, there may be considerable distress and morbidity from contemporaneous subthreshold disorders that may not be detected by a screening instrument. Comorbidity is also an important driver of treatment seeking.

Depression is a disorder defined by its symptoms. If the DSM-IV-TR (Diagnostic and Statistical Manual of Mental Disorders, fourth edition, text revision) is followed, the diagnosis is categorical; that is, one either has it or one does not. But what about the person who is only a single symptom short of meeting the criteria for such a categorical diagnosis? In this situation, comorbidity is likely to be an important determinant of the actual diagnosis and the treatment plan, which supports the need for assessing distress rather than a specific diagnosis.

In the current set of guidelines, the task force defines major depressive episode according to the DSM-IV-TR criteria. However, only the “A” criteria are used, not the “B, C, D or E” criteria, and the categories of depressive disorders mentioned earlier are not included. By screening for a single disorder such as depression, one may miss other diagnoses such as anxiety, which is more frequent than depression and commonly associated with it. If screening is to be done, perhaps a better case could be made for the use of screening instruments such as the Kessler Psychological Distress Scale (K10) or the General Health Questionnaire, which are designed to detect levels of mental distress that should lead to further inquiry to establish a more definitive diagnosis.

The task force mentions in passing some of the problems caused by false-positive diagnoses, but it does not address the magnitude of erroneous diagnoses. If we use the 12-month prevalence of 5% for depression reported in the guideline and the K10 tool’s sensitivity of 71% and specificity of 90%, the false-positive rate will be nearly 73%. Given that family physicians and mental health workers have difficulty dealing

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### Key points

- There is little evidence of sufficient quality to guide practitioners about what type of screening, if any, to use to detect depression in adults in primary care settings.
- The number of false-positive screens with current assessment tools is too high, and the follow-up required to rule them out too time-consuming, to justify routine screening for depression in primary care practices.
- If false-positive screens are not ruled out, patients are at increased risk of receiving the wrong diagnosis and inappropriate treatment.
with their existing caseloads, it is not feasible to ask them to follow up everyone identified by a screening instrument, when only about one-quarter will actually have depression.

The K10 tool is used to screen for a variety of disorders, not just depression. Therefore, even if we use the average of the prevalence rates for those disorders (including depression) among men and women (17.3%), then the false-positive rate drops to 40% — much better, but still too high to justify use of the tool for screening in a primary care setting. Use of a simpler screening method, such as the Whooley questions, is likely to lead to even higher false-positive rates. These points argue strongly against any form of routine screening.

There is no question, as the task force amply illustrates, that depression constitutes a major public health problem. Although milder cases may require only watchful waiting rather than treatment, about 15% of people with major depression go on to a chronic course, with much residual disability. Family physicians have been criticized for failing to recognize depression. However, studies have shown that many missed cases are those of milder depression, which often remits spontaneously, and that patients with milder forms of depression may experience adverse effects and other complications if the depression is treated. Family physicians have also been criticized for not treating depression even when it is diagnosed. In certain situations, however, a physician may decide not to treat after an assessment of the patient’s social circumstances and situation.

The task force is correct in drawing attention to the lack of evidence in some areas and suggesting that there is little evidence to guide practitioners about what type of screening, if any, to use. In this type of report, which is based on synthesizing and grading the available information, recommendations can be made only when there is sufficient evidence. This leaves areas where recommendations for screening cannot be made, at least for the time being. Clinicians and program managers thus do not have scientific evidence to support routine screening for depression and will need to make decisions based on their experience and practical knowledge.

References

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Suicide is a leading cause of death in both military and community settings. During 2010, 3951 suicide deaths occurred in Canada and 38,364 in the United States. The frequency of attempted suicide is about 25 times higher, and the financial costs in the US equate to about US$40 billion annually. The losses from suicide in Canada are comparable to those in other countries when adjusted for population size. Suicide deaths can be devastating to surviving family and friends. Suicide in the community is almost always related to a psychiatric illness (e.g., depression, substance abuse), whereas suicide in the military is sometimes linked to a concussion from combat injury.

Concussion is the most common brain injury in young adults and is defined as a transient disturbance of mental function caused by acute trauma. About 4 million concussion cases occur in the US each year, equivalent to a rate of about 1 per 1000 adults annually; direct Canadian data are not available. The majority lead to self-limited symptoms, and only a small proportion have a protracted course. However, the frequency of depression after concussion can be high, and traumatic brain injury in the military has been associated with subsequent suicide. Severe head trauma resulting in admission to hospital has also been associated with an increased risk of suicide, whereas mild concussion in ambulatory adults is an uncertain risk factor.

The aim of this study was to determine whether concussion was associated with an increased long-term risk of suicide and, if so, whether the day of the concussion (weekend v. weekday) could be used to identify patients at further increased risk. The severity and mechanism of injury may differ by day of the week because recreational injuries are more common on weekends and occupational injuries are more common on weekdays. The risk of a second concussion, use of protective safeguards, propensity to seek care, subsequent oversight, sense of responsibility and other nuances may also differ for concussions acquired from weekend recreation rather than weekday work.

**Background:** Head injuries have been associated with subsequent suicide among military personnel, but outcomes after a concussion in the community are uncertain. We assessed the long-term risk of suicide after concussions occurring on weekends or weekdays in the community.

**Methods:** We performed a longitudinal cohort analysis of adults with diagnosis of a concussion in Ontario, Canada, from Apr. 1, 1992, to Mar. 31, 2012 (a 20-yr period), excluding severe cases that resulted in hospital admission. The primary outcome was the long-term risk of suicide after a weekend or weekday concussion.

**Results:** We identified 235,110 patients with a concussion. Their mean age was 41 years, 52% were men, and most (86%) lived in an urban location. A total of 667 subsequent suicides occurred over a median follow-up of 9.3 years, equivalent to 31 deaths per 100,000 patients annually or 3 times the population norm. Weekend concussions were associated with a one-third further increased risk of suicide compared with weekday concussions (relative risk 1.36, 95% confidence interval 1.14-1.64). The increased risk applied regardless of patients’ demographic characteristics, was independent of past psychiatric conditions, became accentuated with time and exceeded the risk among military personnel. Half of these patients had visited a physician in the last week of life.

**Interpretation:** Adults with a diagnosis of concussion had an increased long-term risk of suicide, particularly after concussions on weekends. Greater attention to the long-term care of patients after a concussion in the community might save lives because deaths from suicide can be prevented.
care on weekends may also be limited because of shortfalls in staffing.32

Methods

Patient selection
We conducted a longitudinal cohort analysis of adults with a diagnosis of a concussion in Ontario, Canada, from Apr. 1, 1992, to Mar. 31, 2012 (20 yr), based on vital statistics data available through the Office of the Registrar General database.55 Ontario is Canada’s most populous province, with 12 259 564 individuals in 2003 (study midpoint).34 During the study period, the annual suicide rate in Ontario was about 9 per 100 000,35 somewhat lower than the global suicide rate of 11 per 100 00036 and the rate among former military personnel of 14 per 100 000.37,38 During the study period, Ontario health insurance covered primary, emergency and hospital care with no out-of-pocket costs to patients.39,40 The project was approved by the Research Ethics Board of Sunnybrook Health Sciences Centre; the approval included a waiver of the need for informed consent.

We identified patients with a diagnosis of a concussion by screening physician claims data using the International Classification of Diseases, 9th revision (ICD-9) diagnostic criteria for concussion (code 850) from the Ontario Health Insurance Plan database.41,42 This code has been validated with high specificity (99%) and mid-range sensitivity (22%–76%).43–45 Patients who were admitted to hospital immediately or within 2 days of injury were excluded because such cases tend to reflect severe brain injury (a known risk factor for suicide) and do not represent ambulatory patients with concussion.46,47 Patients under 17 years of age were excluded because most suicide deaths occur in adults.48,49 Otherwise, the selection criteria were fully comprehensive and included all patients seeking care whose diagnosis was made by a physician.

Data collection
We distinguished each case as a weekend concussion (midnight Friday to midnight Sunday) or a weekday concussion (remaining 5 days and nights of the week).50 Differentiating a weekend from a weekday concussion was based on the date of medical care, which closely corresponds to the date of injury.51,52 For patients with multiple concussions, we used the date of the first concussion, such that each person was counted once in the analyses; repeat concussions were tracked for separate secondary analyses. Further data on duration of amnesia, loss of consciousness, mechanism of injury, severity of symptoms, delays in seeking care and standardized concussion assessment scores were not available.53 Similarly, information was not available on cases that did not lead to medical attention or on whether day of the week was an imperfect proxy for concussion circumstances.

The official demographic registry provided data on patient age, sex and home location (urban or rural).34 Socioeconomic status was based on neighbourhood income quintile and was determined through the validated Statistics Canada algorithm.54–56 The health care services databases provided data on hospital admissions, outpatient contacts and diagnoses in the previous year.57,58 Prior psychiatric conditions (schizophrenia, depression, bipolar disorder, suicide attempt, anxiety, substance abuse) were determined from physician diagnostic data for the full year before injury.59 The available databases contained no information on social stress, life events, employment status, race or ethnicity, sexual orientation, immigration status, borderline personality disorder, childhood abuse, eating disorders, suicidal ideation, novel biomarkers or other suicide risks.60–62

Outcome identification
We determined the cause of death from official death certificates encompassing definite or probable suicide, as investigated by the responsible coroner. All coroners were licensed physicians in Ontario, and suicidal death investigations have an interrater agreement of about 70% in this setting.63 We identified definite cases of suicide by ICD-9 codes (E950–E959) or International Statistical Classification of Diseases and Related Health Problems, 10th revision (ICD-10)64 codes (X60–X84) and probable cases of suicide by ICD-9 codes (E980–E987, E989) or ICD-10 codes (Y10–Y32, Y34), as validated in past research.65 The database for death certificates has been validated previously and is the official source for vital statistics reporting, as well as the authoritative file for population-based analyses of suicides.59,66,67

For each case, we recorded the forensic certainty and mechanism of suicide from the death certificate. We calculated age at death and elapsed time from index concussion from the same source, coded to the exact day. Similarly, we recorded the time since the last visit with a physician by linking to the physician care database. We also recorded the reason for the last visit, classified as a psychiatric, neurologic, medical or miscellaneous diagnosis along with the physician’s specialty.68 The available databases did not have information on pathology reports, toxicology reports, psychological scores, presence of a suicide note, litigation involvement, seniority of the investigating coroner or findings from a psychiatric autopsy.59
Statistical analysis
In the prespecified primary analysis, we assessed cumulative incidence rates (accounting for censoring and deaths) to estimate the probability of suicide after concussions on weekends and weekdays (Appendix 1, sections 1–5, available at www.cmaj.calookup/suppl/doi:10.1503/cmaj.150790/-/DC1). Absolute risks were calculated as deaths per 100 000 persons annually and were also compared with the prevailing suicide rate in the population during the same period.\(^7\) Cause-specific proportional hazards regression was applied to further quantify differences in suicide risk between the 2 groups before and after adjustment for baseline differences in demographic characteristics, psychiatric diagnoses and history of suicide attempts. All reported p values were 2-tailed and were calculated with exact 95% confidence intervals (CIs).

We developed additional statistical models with time-dependent covariables to evaluate patients who had multiple concussions over time (Appendix 1, section 7). For this approach, we applied an accumulating step function so that each concussion was considered a new event and the observed dose–response gradient correlated a patient’s total number of concussions with his or her overall risk of suicide. A 4-week interval was required to identify a subsequent diagnosis as a new concussion (an interval that was defined a priori, because symptoms typically resolve within 1 week and a variable period of rest is recommended afterward).\(^7\) We used the same step function to distinguish each additional concussion according to weekend or weekday occurrence.

Results
A total of 235 110 patients had a diagnosis of a concussion during the 20-year study period. Patient characteristics are detailed in Table 1. About half of the patients were men, the mean age was 41 years, and most were living in an urban location. Most of the patients had no formal medical imaging, additional diagnosed fracture, prior psychiatric diagnosis, prior hospital admission or prior suicide attempt. The baseline frequency of depression and other measured characteristics was not clinically significantly different between those injured on weekends and those injured on weekdays. Anxiety disorder, the single most common prior psychiatric diagnosis, was slightly less frequent among patients injured on weekends. The distribution of characteristics of both groups was generally stable over time.

A total of 667 suicide deaths occurred over a median follow-up of 9.3 years, equivalent to 31 deaths per 100 000 patients annually. Those with a concussion occurring on weekdays

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Weekend n = 39 940</th>
<th>Weekday n = 195 170</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 29</td>
<td>16 088 (40)</td>
<td>67 793 (35)</td>
</tr>
<tr>
<td>30–44</td>
<td>9 493 (24)</td>
<td>50 390 (26)</td>
</tr>
<tr>
<td>45–59</td>
<td>6 051 (15)</td>
<td>35 727 (18)</td>
</tr>
<tr>
<td>≥ 60</td>
<td>8 308 (21)</td>
<td>41 260 (21)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>22 380 (56)</td>
<td>98 922 (51)</td>
</tr>
<tr>
<td>Female</td>
<td>17 560 (44)</td>
<td>96 248 (49)</td>
</tr>
<tr>
<td>Income quintile</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Highest</td>
<td>7 141 (18)</td>
<td>37 700 (19)</td>
</tr>
<tr>
<td>Next to highest</td>
<td>7 500 (19)</td>
<td>38 148 (20)</td>
</tr>
<tr>
<td>Middle</td>
<td>7 799 (20)</td>
<td>38 209 (20)</td>
</tr>
<tr>
<td>Next to lowest</td>
<td>8 266 (21)</td>
<td>38 973 (20)</td>
</tr>
<tr>
<td>Lowest*</td>
<td>9 234 (23)</td>
<td>42 140 (22)</td>
</tr>
<tr>
<td>Home location</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urban</td>
<td>34 038 (85)</td>
<td>167 975 (86)</td>
</tr>
<tr>
<td>Rural*</td>
<td>5 902 (15)</td>
<td>27 195 (14)</td>
</tr>
<tr>
<td>Date of enrolment†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Remote</td>
<td>18 874 (47)</td>
<td>87 386 (45)</td>
</tr>
<tr>
<td>Recent</td>
<td>21 066 (53)</td>
<td>107 784 (55)</td>
</tr>
<tr>
<td>Initial imaging</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skull radiography</td>
<td>2 728 (7)</td>
<td>10 678 (5)</td>
</tr>
<tr>
<td>Computed tomography</td>
<td>7 364 (18)</td>
<td>22 269 (11)</td>
</tr>
<tr>
<td>Magnetic resonance imaging</td>
<td>189 (&lt;1)</td>
<td>1 654 (1)</td>
</tr>
<tr>
<td>Any fracture‡</td>
<td>830 (2)</td>
<td>2 234 (1)</td>
</tr>
<tr>
<td>Prior diagnosis§</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>336 (1)</td>
<td>1 362 (1)</td>
</tr>
<tr>
<td>Depression</td>
<td>1 707 (4)</td>
<td>8 515 (4)</td>
</tr>
<tr>
<td>Bipolar disorder</td>
<td>603 (2)</td>
<td>2 720 (1)</td>
</tr>
<tr>
<td>Substance abuse</td>
<td>1 554 (4)</td>
<td>6 646 (3)</td>
</tr>
<tr>
<td>Anxiety disorder</td>
<td>8 223 (21)</td>
<td>44 003 (23)</td>
</tr>
<tr>
<td>Any condition¶</td>
<td>9 734 (24)</td>
<td>51 181 (26)</td>
</tr>
<tr>
<td>Prior hospital admission§</td>
<td>1 491 (4)</td>
<td>8 157 (4)</td>
</tr>
<tr>
<td>Prior suicide attempt§</td>
<td>56 (&lt;1)</td>
<td>200 (&lt;1)</td>
</tr>
</tbody>
</table>

*Includes missing values.
‡Any bone (codes 800–829; International Classification of Diseases and Related Health Problems, 9th revision*).§Assessed during the year before concussion.
¶Any of the specified psychiatric diagnoses listed above.
accounted for 519 suicides, 1 804 520 patient-years of follow-up and an absolute suicide risk of 29 per 100 000 annually or 3 times the population norm. Those with a concussion occurring on weekends accounted for 148 suicides, 377 115 patient-years of follow-up and an absolute suicide risk of 39 per 100 000 annually or 4 times the population norm. The difference between the 2 groups was equivalent to a one-third increase in suicide risk after a weekend concussion relative to a weekday concussion. Time profiles indicated that the increased suicide risk was distributed evenly over years, with accumulating long-term differences (Figure 1).

The increased risk of suicide after concussions on weekends was evident in comparisons with each individual day of the week (Figure 2). Similarly, all patient subgroups showed an absolute suicide risk above the population norm, all had a further increase in risk after concussions on weekends relative to weekdays, and the findings persisted during both remote and recent eras (Appendix 1, section 6). Patients with a prior suicide attempt had the highest absolute risk and also a further increase after a weekend concussion. Patients with no prior suicide attempt, psychiatric diagnosis or hospital admission (n = 168 188) had an absolute risk more than twice the population norm and also a further increase after a weekend concussion.

Several other baseline factors were additional independent predictors of the long-term risk of suicide. As expected, suicide risk was associated with male sex, low socioeconomic status and prior psychiatric diagnosis (Table 2). A prior suicide attempt was the single most powerful predictor. Also as expected, a prior diagnosis of substance abuse was another powerful predictor, whereas a diagnosed fracture was not a significant predictor of suicide risk. Each specific psychiatric condition was associated with an increased risk, and no significant anomalies were apparent in analyses that explored post hoc pairwise product interaction terms. Adjustment for all predictors yielded a one-quarter increase in risk of suicide after a weekend concussion (relative risk 1.27, 95% CI 1.06–1.53).

The observed association between concussion and risk of suicide was accentuated in time-dependent statistical models accounting for additional concussions. A total of 24 746 patients had 2 or more concussions and accounted for 205 575 patient-years of follow-up, with 76 suicide deaths. The median interval between consecutive concussions was 214 (interquartile range 69–1018) days. Overall, each additional concussion was associated with a further increase in suicide risk (estimate 1.30, 95% CI 1.12–1.50). Analyzing all concussions in all patients yielded a one-third increase in suicide risk after a concussion on a weekend compared with weekdays (estimate 1.35, 95% CI 1.12–1.63).

We found no significant differences in suicide characteristics after a concussion on a weekend.
compared with a weekday. The mean time from concussion to suicide was 5.7 years (Table 3). In accordance with legal criteria, three-quarters of the cases were determined as definite suicide and the remainder as probable suicide. Poisoning was the most common mechanism, accounting for almost half of the cases in both groups. Asphyxiation was the second most common mechanism, accounting for about a third of the cases in both groups. Most of the patients had visited a physician in the month before death, primary care physicians accounted for the majority of these visits, and a psychiatric disorder was the responsible diagnosis for a minority of the visits.

**Interpretation**

We studied data for about a quarter million adults to assess the risk of suicide after a concussion. We found that the long-term risk of suicide among those with a concussion was 3 times the population norm and was even higher if the concussion occurred on a weekend. The increased risk applied regardless of demographic characteristics, was independent of past psychiatric conditions, became accentuated with time, followed a dose–response gradient and was not as high as the risk associated with past suicide attempts. About half of the patients had visited a physician in the last week of life, typically for a diagnosis unrelated to mental illness. The absolute risk was equal to about 470 suicide deaths that might not have occurred if the prevailing risks had matched the population norm (Appendix 1, section 9).

Our findings are congruent with the results of past studies indicating that suicide attempts are the single most important long-term predictor of subsequent risk of suicide.72,75 Additional long-term predictors confirmed in this analysis included male sex, low socioeconomic status and prior psychiatric history.72,75 Past studies have cautioned that individual risk factors have low accuracy for predicting individual events.76,77 No past study, to our knowledge, has focused on concussions and tested the potential difference between weekends and weekdays. Moreover, the increased long-term risk of suicide observed in this study persisted among those who had no psychiatric risk factors and was distinctly larger than among patients after an ankle sprain (Appendix 1, section 8).

Our findings also support past research on differing theories of suicide.78–80 Past studies have suggested that a concussion can cause lasting deficits through changes in physiology (e.g., disrupted serotonin pathways), mood (e.g., post-traumatic stress disorder) or behaviour (e.g., disinhibition with impulsivity).81–84 Cognitive dissonance could also lead patients and clinicians to attribute injuries after weekend recreation to misadventure, whereas injuries following weekday occupation might be attributed to the employer.85–87 With hindsight, a difference in activity restriction or cognitive dissonance might arise if the injury event was self-initiated88,89 Further research is needed to address these issues; in the interim, our findings suggest that a history of concussion may be relevant when assessing a patient’s suicide risk.

**Limitations**

An alternative interpretation of our findings is unmeasured confounding. A concussion might indicate a latent predisposition toward suicide before the injury or worsening neurodegenerative deficits that precipitated the injury.90,91 Exploring these mechanisms is difficult because of the fallibility of gauging comorbid illness, concussion severity, chronic traumatic encephalopathy, long-term risk of suicide and the exact time of a concussion.92 Such mechanisms might fully explain our findings, including the observed increased risk that expanded for years after injury, did not change the mechanism of suicide and occurred despite medical care (Appendix 1, section 10). Regardless of interpretation, these findings sug-

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**Table 2: Long-term predictors of suicide after concussion**

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Univariable analysis†</th>
<th>Multivariable analysis‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weekend concussion</td>
<td>1.36 (1.14–1.64)</td>
<td>1.27 (1.06–1.53)</td>
</tr>
<tr>
<td>Age, per yr older</td>
<td>1.00 (1.00–1.00)</td>
<td>NA</td>
</tr>
<tr>
<td>Sex, male</td>
<td>2.28 (1.92–2.70)</td>
<td>2.47 (2.08–2.94)</td>
</tr>
<tr>
<td>Income, low</td>
<td>1.68 (1.33–2.13)</td>
<td>1.30 (1.02–1.65)</td>
</tr>
<tr>
<td>Home, rural</td>
<td>0.97 (0.78–1.20)</td>
<td>NA</td>
</tr>
<tr>
<td>Enrolment, recent§</td>
<td>0.96 (0.95–0.98)</td>
<td>0.96 (0.94–0.97)</td>
</tr>
<tr>
<td>Imaging¶</td>
<td>1.38 (1.15–1.66)</td>
<td>1.31 (1.09–1.57)</td>
</tr>
<tr>
<td>Fracture</td>
<td>1.09 (0.59–2.04)</td>
<td>NA</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>10.78 (7.89–14.73)</td>
<td>2.38 (1.68–3.37)</td>
</tr>
<tr>
<td>Depression</td>
<td>4.32 (3.49–5.35)</td>
<td>1.65 (1.30–2.11)</td>
</tr>
<tr>
<td>Bipolar disorder</td>
<td>7.03 (5.31–9.32)</td>
<td>1.96 (1.43–2.68)</td>
</tr>
<tr>
<td>Substance abuse</td>
<td>8.43 (7.04–10.10)</td>
<td>3.60 (2.94–4.41)</td>
</tr>
<tr>
<td>Anxiety disorder</td>
<td>3.98 (3.42–4.64)</td>
<td>3.04 (2.57–3.60)</td>
</tr>
<tr>
<td>Prior hospital admission</td>
<td>2.28 (1.53–3.40)</td>
<td>1.40 (0.89–2.21)</td>
</tr>
<tr>
<td>Prior suicide attempt</td>
<td>38.83 (23.94–62.99)</td>
<td>5.65 (3.26–9.81)</td>
</tr>
</tbody>
</table>

Note: CI = confidence interval, NA = not applicable, RR = relative risk.
*Results from proportional hazards analysis, with weekdays defined as referent.
†Basic comparison with no adjustments for other baseline differences.
‡Adjusted comparison accounting for other baseline differences in demographic characteristics, psychiatric diagnoses and history of suicide attempts.
§“Recent” denotes years 2002–2012 (years 1992–2001 denoted as “remote”).
¶Includes skull radiography, computed tomography and magnetic resonance imaging.

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gest that an association between concussion and suicide is not confined to the military.

Our study also highlights the modest ability of any one factor to predict suicide because most patients do not die from suicide (Appendix 1, section 11). Furthermore, studies of suicide are prone to detection bias because social stigma leads analyses to underestimate total counts.93,94 Each case is different, such that mathematical models are fallible through a lack of myriad relevant data, such as alcohol consumption and suicidal ideation.95 Long-term predictions and generalizability are also problematic because of the network of intervening factors and shifting definitions of concussion.17,96-97 Some patients with concussion receive care that may mitigate the risk of suicide, such as antidepressant medication;98,99 however, our study lacked data on such care, which remains a topic for future research.

**Conclusion**

Concussion differs in 3 important ways from other risk factors for suicide. First, concussions are sometimes preventable through adequate training, the minimizing of distractions, avoidance of alcohol, use of protective gear and other safety basics.100 Second, concussions are easily neglected under a popular belief that the neurologic symptoms have an obvious cause, will resolve quickly, leave nothing visible on medical imaging and do not require follow-up.101,102 Third, concussions are rarely deemed relevant for consideration by psychiatrists or other physicians when eliciting a patient’s history.103,104 Greater attention to the long-term implications of a concussion in community settings might save lives because deaths from suicide can be prevented.105,106

**Table 3: Distinguishing circumstances of suicide**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Timing of concussion; no. (%) of suicide deaths*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Weekend n = 148</td>
</tr>
<tr>
<td></td>
<td>Weekday n = 519</td>
</tr>
<tr>
<td>Determination of death as definite suicide</td>
<td>107 (72)</td>
</tr>
<tr>
<td></td>
<td>393 (76)</td>
</tr>
<tr>
<td>Time since concussion, yr, mean ± SD</td>
<td>5.6 ± 4.5</td>
</tr>
<tr>
<td></td>
<td>5.8 ± 4.8</td>
</tr>
<tr>
<td>Age at death, yr, mean ± SD</td>
<td>43.6 ± 14.1</td>
</tr>
<tr>
<td></td>
<td>44.1 ± 14.1</td>
</tr>
<tr>
<td>Mechanism of death</td>
<td></td>
</tr>
<tr>
<td>Poisoning</td>
<td>66 (45)</td>
</tr>
<tr>
<td></td>
<td>227 (44)</td>
</tr>
<tr>
<td>Asphyxiation†</td>
<td>51 (34)</td>
</tr>
<tr>
<td></td>
<td>158 (30)</td>
</tr>
<tr>
<td>Violence‡</td>
<td>18 (12)</td>
</tr>
<tr>
<td></td>
<td>80 (15)</td>
</tr>
<tr>
<td>Jumping</td>
<td>8 (5)</td>
</tr>
<tr>
<td></td>
<td>39 (8)</td>
</tr>
<tr>
<td>Other</td>
<td>5 (3)</td>
</tr>
<tr>
<td></td>
<td>15 (3)</td>
</tr>
<tr>
<td>Recent physician visit</td>
<td></td>
</tr>
<tr>
<td>&lt; 1 wk</td>
<td>75 (51)</td>
</tr>
<tr>
<td></td>
<td>240 (46)</td>
</tr>
<tr>
<td>&lt; 1 mo</td>
<td>114 (77)</td>
</tr>
<tr>
<td></td>
<td>370 (71)</td>
</tr>
<tr>
<td>&lt; 1 yr</td>
<td>142 (96)</td>
</tr>
<tr>
<td></td>
<td>494 (95)</td>
</tr>
<tr>
<td>Physician specialty</td>
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</tr>
<tr>
<td>Psychiatry</td>
<td>12 (8)</td>
</tr>
<tr>
<td></td>
<td>55 (11)</td>
</tr>
<tr>
<td>Neurology§</td>
<td>7 (5)</td>
</tr>
<tr>
<td></td>
<td>16 (3)</td>
</tr>
<tr>
<td>Internal medicine</td>
<td>16 (11)</td>
</tr>
<tr>
<td></td>
<td>38 (7)</td>
</tr>
<tr>
<td>Family medicine</td>
<td>90 (61)</td>
</tr>
<tr>
<td></td>
<td>334 (64)</td>
</tr>
<tr>
<td>Other¶</td>
<td>17 (11)</td>
</tr>
<tr>
<td></td>
<td>51 (10)</td>
</tr>
<tr>
<td>Recent diagnosis</td>
<td></td>
</tr>
<tr>
<td>Psychiatric**</td>
<td>40 (27)</td>
</tr>
<tr>
<td></td>
<td>166 (32)</td>
</tr>
<tr>
<td>Neurologic††</td>
<td>4 (3)</td>
</tr>
<tr>
<td></td>
<td>25 (5)</td>
</tr>
<tr>
<td>Medical††</td>
<td>40 (27)</td>
</tr>
<tr>
<td></td>
<td>139 (27)</td>
</tr>
<tr>
<td>Miscellaneous§§</td>
<td>64 (43)</td>
</tr>
<tr>
<td></td>
<td>189 (36)</td>
</tr>
</tbody>
</table>

Note: SD = standard deviation.
*Unless indicated otherwise.
†Asphyxiation includes hanging, strangulation, drowning and suffocation.
‡Violence includes firearms, explosives, crashes and stabbings.
§Includes neurosurgery, anesthesiology, ophthalmology and otorhinolaryngology.
¶Includes surgery, obstetrics, gynecology and medical imaging.
**Codes 295 to 316 (International Classification of Diseases and Related Health Problems, 9th revision†† ICD-9).
††ICD-9 codes 290 to 389, except psychiatric.
‡‡ICD-9 codes 051 to 779, except psychiatric or neurologic.
§§ICD-9 codes 780 to 999 or missing.

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Postpartum depression is an internationally recognized health concern for women and their families. Depression during the perinatal period is associated with serious negative consequences for both mother and baby, particularly if the depression is untreated. Outcomes among women include impaired functioning, poor quality of life and death. Outcomes for infants include developmental delay, poor growth, malnutrition and illness. Numerous risk factors for postpartum depression have been identified; low levels of social support and history of depression are among the variables most consistently associated with postpartum depression. However, previous reports are inconsistent as to whether geographical size or location is associated with the risk of postpartum depression. In Canada, about 30% of the population lives in rural or remote areas, a large proportion live in several large urban areas, and the remainder live in smaller urban settings. To design appropriate supports and services for the prevention and treatment of postpartum depression among Canadian women, it is important to identify and target geographical variation in the risk of postpartum depression.

Our primary objective was to compare the risk of postpartum depression among Canadian women living in rural and urban areas. Our secondary objective was to identify factors that could explain any associations between place of residence and risk of postpartum depression. We used multiple definitions of rural and urban locations to more accurately reflect differences between communities and to account for the level of social and occupational connectivity of smaller areas to more urban areas.

Methods

Study design
We used a population-based Canadian survey of women who had recently given birth (the Mater...
Community Experiences Survey); this survey was performed by the Public Health Agency of Canada and the Canadian Perinatal Surveillance System. This national cross-sectional survey collected information on key perinatal health indicators from recent mothers in all provinces and territories using the 2006 Canadian Census sampling frame. Sampling was stratified by province or territory to ensure adequate sample size in specific groups, and certain vulnerable groups and low population-density regions were oversampled to ensure adequate sample size for the analysis of those groups. A simple random sample without replacement was drawn from each stratum. Mothers living on First Nations reserves and in collective dwellings were excluded from the sampling frame. The response rate was high (78%), and the responses were collected (primarily by telephone) by use of computer-assisted interviews with women who had a singleton birth between Feb. 15 and May 15, 2006, in the provinces and between Nov. 1, 2005, and Feb. 1, 2006, in the territories. The included mothers were all over the age of 15 years and were living with their child at the time of the interview. The response rate was 78% (6421/8244 women contacted), representing about 76 500 Canadian women (after applying survey weights).

For the present study, Health Canada’s Science Advisory Board and Research Ethics Board and the Federal Privacy Commissioner reviewed the research protocol, and approval was received from Statistics Canada’s Policy Committee before implementation. We accessed the data through an application process to the Social Sciences and Humanities Council of Canada. Our study was also approved by the Research Ethics Board at the Centre for Addiction and Mental Health in Toronto, Ontario.

**Exposure definitions**

Our definitions of rural and urban areas were based on a Canadian framework for defining rurality advanced by Statistics Canada. This framework uses strategies that capitalize on potential differences between communities, not only in terms of population size, but also in terms of social and occupational connectivity with larger centres.

We used 3 methods to define rural and urban areas: population size and density; population size of an area’s urban core (areas with < 10 000 people living in an urban core were considered rural and small town); and the proportion of individuals in rural areas who commute to larger urban centres (classified into strong, moderate and weak metropolitan-influenced zones).

We defined rural populations as those outside settlements of 1000 or more people or outside areas with a population density of 400 or more inhabitants per square kilometre. We further classified remaining women as living in semi-rural (population < 30 000), semiurban (population 30 000–499 999) or urban (population ≥ 500 000) areas.

In our secondary analyses, we used additional definitions from Statistics Canada that better reflect the degree of connectivity of small towns to larger urban settings in a way that is not captured by population size alone. In this definition, individuals living within census metropolitan areas and census agglomerations are considered to be living in a “larger urban centre.” In Canada, a census metropolitan area has a total population of 100 000 or more people, with 50 000 or more in the urban core, and a census agglomeration has an urban core of 10 000 or more people. Both include neighbouring towns and municipalities where 50% or more of the workforce commutes to the urban core.

Individuals living outside census metropolitan areas and census agglomerations are classified as living in “rural and small town” areas.

To separate the women with the most potential for social isolation from those with less potential for isolation, we further divided women living in rural and small town areas by “metropolitan-influenced zone.” These zones indicate the percentage of residents who commute to larger urban centres. The zones are designated as strong (≥ 30% of residents commute to an urban core), moderate (5%–29%), weak (> 0%, but < 5%) or no (0%) metropolitan influence.

**Outcome measures**

Our primary outcome was postpartum depression, as measured by use of the 10-item Edinburgh Postnatal Depression Scale, which was administered to all survey respondents. This is the most widely used screening questionnaire for postpartum depression, and it has good discriminant validity. The risk of postpartum depression (as confirmed by clinical diagnosis) is increased more than 10 times among women who score ≥ 13 points.

**Covariates**

The Maternity Experiences Survey contains information about sociodemographic and medical characteristics and health service use. The variables of interest were age, parity, marital status, socioeconomic status, education status, country of birth (Canadian born v. non-Canadian born), recent immigration (within 5 yr), distance travelled to give birth, history of depression, life stressors, abuse, social support during pregnancy and the postpartum period, substance and alcohol use,
type of antenatal care provider, and complications during pregnancy, delivery and the perinatal period (e.g., cesarean section, preterm birth, birth weight, stay in the neonatal intensive care unit).

**Statistical analysis**
The data were analyzed using SAS version 9.3 at the Toronto Region Statistics Canada Research Data Centre. We used population weights supplied by Statistics Canada to weight all estimates to represent the population at the time of the survey. To account for the complex cluster-sample design of the survey, we used a weighted bootstrapping resampling procedure to calculate the coefficients of variation for the estimates. We did not report estimates for which the coefficients of variation were greater than 33.3%, because this indicates a high likelihood of bias in the esti-

| Table 1: Baseline characteristics of 6126 new mothers who completed the Maternity Experiences Survey, by location |
|------------------|------------------|------------------|------------------|
| Characteristic                             | Rural n = 1362   | Semirural n = 1225 | Semiurban n = 2187 | Urban n = 1352 |
| Maternal age, yr, mean (95% CI)            | 29.7 (29.5–30.0) | 29.5 (29.2–29.8)  | 29.5 (29.3–29.7)  | 31.1 (31.0–31.3) |
| Parity, primiparous                        | 39.6 (37.0–42.2) | 40.8 (37.9–43.6)  | 49.4 (46.9–51.9)  | 47.0 (45.5–48.6) |
| Marital status, married or common-law       | 92.7 (91.2–94.2) | 91.0 (89.4–92.6)  | 88.6 (87.0–90.3)  | 93.2 (92.2–94.2) |
| Born in Canada                             | 89.0 (87.0–91.0) | 88.1 (86.0–90.2)  | 87.2 (85.3–89.2)  | 61.9 (59.9–63.9) |
| Household income†                          |                   |                   |                   |                   |
| Lowest                                      | 10.5 (8.85–12.2) | 9.9 (8.12–11.6)   | 12.0 (10.1–13.8)  | 11.2 (9.82–12.5)  |
| Lower-middle                                | 23.9 (21.4–26.3) | 18.8 (16.4–21.3)  | 21.5 (19.2–23.8)  | 20.5 (18.7–22.3)  |
| Upper-middle                                | 37.6 (34.7–40.5) | 36.9 (33.9–40.0)  | 36.6 (33.9–39.3)  | 30.9 (28.9–32.9)  |
| Highest                                     | 28.0 (25.2–30.8) | 34.4 (31.4–37.4)  | 29.9 (27.3–32.5)  | 37.4 (35.5–39.4)  |
| Education level                             |                   |                   |                   |                   |
| Less than high school                       | 8.82 (7.3–10.4)  | 9.87 (8.10–11.6)  | 7.79 (6.42–9.16)  | 5.94 (4.98–6.90)  |
| High school                                 | 15.5 (13.4–17.6) | 16.2 (13.9–18.4)  | 15.1 (13.0–17.1)  | 10.8 (9.53–12.0)  |
| Some postsecondary                         | 19.0 (16.7–21.2) | 16.2 (14.0–18.3)  | 16.9 (14.9–19.0)  | 13.9 (12.5–15.4)  |
| Postsecondary                               | 56.8 (53.8–59.7) | 57.8 (54.8–60.8)  | 60.2 (57.5–62.9)  | 69.4 (67.5–71.2)  |
| History of depression                       | 16.4 (14.1–18.6) | 16.4 (14.2–18.6)  | 18.7 (16.6–20.9)  | 13.5 (12.0–14.9)  |
| Maternal health, excellent or very good     | 73.3 (70.7–75.8) | 73.1 (70.4–74.8)  | 75.1 (72.7–77.5)  | 70.7 (68.8–72.6)  |
| Stress                                      |                   |                   |                   |                   |
| No. of life stressors in last 2 yr, mean (95% CI) | 1.25 (1.17–1.34) | 1.37 (1.27–1.46)  | 1.38 (1.30–1.47)  | 1.19 (1.13–1.25)  |
| Abuse in last 2 yr                          | 9.82 (8.21–11.4) | 12.6 (10.6–14.5)  | 13.1 (11.3–14.9)  | 9.94 (8.79–11.1)  |
| Labour and delivery complications           | 14.3 (12.2–16.4) | 14.4 (12.3–16.5)  | 14.6 (12.7–16.6)  | 14.9 (13.4–16.3)  |
| Preterm birth                               | 6.06 (4.62–7.50) | 6.49 (4.90–8.08)  | 6.67 (2.30–8.04)  | 6.15 (5.13–7.18)  |
| Infant in NICU                              | 10.8 (8.98–12.5) | 11.0 (9.06–12.8)  | 14.8 (12.8–16.8)  | 13.0 (11.6–14.4)  |
| Social support                              |                   |                   |                   |                   |
| Pregnancy                                   |                   |                   |                   |                   |
| None or a little of the time                | 4.52 (3.28–5.76) | 4.05 (2.82–5.28)  | 3.52 (2.54–4.51)  | 6.21 (5.18–7.24)  |
| Some of the time                            | 6.65 (5.21–8.10) | 6.87 (5.29–8.46)  | 6.25 (4.91–7.59)  | 9.21 (8.00–10.4)  |
| Most of the time                            | 27.9 (25.2–30.6) | 30.0 (27.1–32.9)  | 27.4 (24.9–29.9)  | 31.4 (29.5–33.4)  |
| All of the time                             | 60.9 (58.0–63.8) | 59.1 (56.0–62.1)  | 62.8 (60.1–65.5)  | 53.1 (51.1–55.2)  |
| Postpartum                                  |                   |                   |                   |                   |
| None or a little of the time                | 4.51 (3.32–5.70) | 5.34 (3.89–6.79)  | 4.82 (3.67–5.96)  | 6.53 (5.50–7.55)  |
| Some of the time                            | 9.48 (7.74–11.2) | 8.51 (6.84–10.2)  | 8.42 (6.82–10.0)  | 12.2 (10.8–13.6)  |
| Most of the time                            | 31.8 (29.0–34.5) | 33.4 (30.5–36.3)  | 31.2 (28.6–33.9)  | 34.1 (32.1–36.1)  |
| All of the time                             | 54.3 (51.4–57.1) | 52.8 (49.7–55.9)  | 55.5 (52.8–58.3)  | 47.2 (45.1–49.3)  |

Note: CI = confidence interval, NICU = neonatal intensive care unit.
*Unless otherwise stated.
†Household income is reported by quartile.
We calculated the weighted prevalence of postpartum depression (score ≥ 13 on the Edinburgh Postnatal Depression Scale) for the entire population and subsequently for the exposure groups using each definition of rurality. We described and compared the prevalence of postpartum depression among women living in rural, semirural, semiurban and urban areas. We then generated adjusted odds ratios (ORs) and 95% confidence intervals (CIs) using the urban group as the referent category. We adjusted the multivariable models for known risk factors of postpartum depression (history of depression, life stressors, interpersonal abuse, social support and maternal self-reported health), as well as for covariates for which clinically significant differences were observed between groups for potential prognostic variables.

In our secondary analysis, we compared the prevalence of postpartum depression among women living in rural and small town areas to the prevalence among women living in large urban centres. Among women who lived in rural and small town areas, we compared the prevalence of postpartum depression between women living in areas designated as having strong, moderate, weak and no metropolitan influence.

Results

The weighted prevalence of postpartum depression in the overall sample was 7.47% (95% CI 6.76%–8.17%), and the weighted mean score on the Edinburgh Postnatal Depression Scale was 5.27 (95% CI 5.16–5.39). Descriptive characteristics are shown in Table 1. Compared with women in the urban group, women in the other groups were slightly younger, more likely to be born in Canada and less likely to receive their obstetrical care from an obstetrician (v. family practitioner) (data not shown). Compared with women who lived in urban areas, women in the other groups were less likely to have postsecondary education and to be in the highest income quintile. Over 50% of women in the rural group and 44% of women in the semirural group indicated that they had to travel outside of their community to give birth (v. 11% of semiurban and 15% of urban women). Women in urban areas reported lower rates of depression history and fewer stressful life events compared with women in the other groups. However, a smaller proportion of women in urban areas reported that they were in excellent or very good health, and they were less likely to report adequate social support during pregnancy and the postpartum period.

The prevalence of postpartum depression varied depending on urban, semiurban, semirural and rural area, as did the mean score on the Edinburgh Postnatal Depression Scale. Women in the urban group were at higher risk of postpartum depression than women in the other groups (Table 2). When we compared women in the

<table>
<thead>
<tr>
<th>Table 2: Postpartum depression among 6126 new mothers who completed the Maternity Experiences Survey, by score on the Edinburgh Postnatal Depression Scale*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristic</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td>Location‡</td>
</tr>
<tr>
<td>Rural, n = 1362</td>
</tr>
<tr>
<td>Semirural, n = 1225</td>
</tr>
<tr>
<td>Semiurban, n = 2187</td>
</tr>
<tr>
<td>Urban, n = 1352</td>
</tr>
<tr>
<td>Census metropolitan and census agglomeration areas</td>
</tr>
<tr>
<td>Rural and small town, n = 1248</td>
</tr>
<tr>
<td>Large urban centre n = 4878</td>
</tr>
<tr>
<td>Rural and small-town areas, by metropolitan influence</td>
</tr>
<tr>
<td>Strong, n = 316</td>
</tr>
<tr>
<td>Moderate, n = 444</td>
</tr>
<tr>
<td>Weak, n = 440</td>
</tr>
<tr>
<td>None, n = 48</td>
</tr>
</tbody>
</table>

Note: CI = confidence interval, EPDS = Edinburgh Postnatal Depression Scale, NR = not reportable.

* Differences between groups were evaluated using χ² tests for categorical variables and independent t test or analysis of variance (ANOVA) for continuous variables.

†EPDS ≥ 13 represents likelihood that a woman has postpartum depression.

‡p < 0.05 for differences between groups for both EPDS ≥ 13 and EPDS mean score.
rural and small town group with those living in larger urban centres, women in the latter group had nonsignificantly higher prevalence of postpartum depression and mean score on the Edinburgh Postnatal Depression Scale (Table 2).

There were no statistically significant differences in the prevalence of postpartum depression among women living in rural areas when we examined prevalence by level of influence from a metropolitan zone. There was a nonsignificant gradient in which the prevalence was highest among women in areas with weak metropolitan influence. There was a slightly lower prevalence among women in moderate zones, and prevalence was lowest among women in strong metropolitan-influenced zones (5.50%, 95% CI 2.94–8.06). The mean scores on the Edinburgh Postnatal Depression Scale followed similar trends (Table 2).

After adjusting for known predictors of postpartum depression and possible prognostic variables (parity, country of origin, household income) for which we found clinically significant differences, we were able to explain the higher risk among urban women, but not for the lower-risk women in the semiurban group, who remained at significantly lower risk of postpartum depression than women in the urban group (OR 0.60, 95% CI 0.42–0.84) (Table 3).

**Interpretation**

We found that Canadian women who lived in large urban areas (i.e., population > 500 000 inhabitants) were at higher risk of postpartum depression than women living in other areas. The risk factors for postpartum depression (including history of depression, social support and immigration status) that were unequally distributed across geographic regions accounted for most of the variance in the rates of postpartum depression. Combining women in large urban areas with those who lived outside rural and small town areas obscured differences in the rates of postpartum depression across geographic regions, suggesting that more sophisticated definitions of urbanicity are required for research in this area.

The overall prevalence of postpartum depression of 7.47% in this study is lower than the traditionally reported rates in developed countries (about 13%). However, most of the studies included in the systematic review involved selected populations with many risk factors for postpartum depression (e.g., high prevalence of single mothers, low socioeconomic status), which would potentially inflate the prevalence estimates. Only 3 of the studies in the systematic review included comparison groups of women living in nonrural areas; the results of these studies were more con-

![Table 3: Multivariable model for the relationship between population area size and postpartum depression (EPDS ≥ 13)](image)

Note: CI = confidence interval, EPDS = Edinburgh Postnatal Depression Scale, ref = reference. *All variables were adjusted for all covariates in the model. We included variables that are known predictors of postpartum depression (history of depression, life stressors in past 2 yr, interpersonal abuse in last 2 yr, social support, maternal self-reported health) or those for which there were major differences between groups for possible prognostic variables (parity, country of origin, household income). Hosmer–Lemeshow for goodness of fit of the multivariable model $X^2 = 8.43, p = 0.4$. All variance inflation factors < 1.30.
sistent with the results of the current study. Two studies found no significant differences in the risk of depression at 6–8 weeks postpartum.10,21 In the third study, Australian women from non-metropolitan areas (n = 213) had significantly lower odds (OR 0.54, 95% CI 0.33–0.90) of depression at 8–9 months postpartum than did women living in metropolitan areas (n = 535).21 These results are not surprising, because outcomes can change depending on the definition of the rural exposure group.

Limitations

As with most population-based surveys, the potential limitations include the self-reported nature of the data, as well as the potential for a sampling bias of healthy respondents (with telephone access). The sampling frame excluded women living on First Nations Reserves or in group dwellings. Although the psychometric properties and predictive validity of the Edinburgh Postnatal Depression Scale as a measure of postpartum depression have been well-established, diagnostic confirmation for postpartum depression was not available.

Because of the cross-sectional nature of the data, we can only hypothesize about causal pathways to explain the observed variability in postpartum depression across regions of different population size.

We were limited to the variables collected in the survey. Certain elements important to social support and social capital such as marital discord and access to supportive resources may not have been captured by the 4-item social support scale. This may explain why we were unable to account for all of the observed variability in the risk of postpartum depression across geographic regions.

Conclusion

Our study helps to clarify the relation between place of residence and risk of postpartum depression in Canada. Our findings suggest that women in urban areas with a large population were at increased risk of postpartum depression compared with women in other regions. Geographical differences in the distribution of important risk factors for postpartum depression, such as immigration status, interpersonal violence, self-perceived health and social support, account for much of this variance.

Supports and services targeted toward increasing connections for isolated women in large urban centres may need to be increased in Canada. Considering the substantial negative effect of postpartum depression, such interventions could have broad-reaching social and public health impact. Other countries might also benefit from studying the levels of perceived social support across regions, particularly in cases where geographical variation in the rates of postpartum depression is observed. Further, our results show that careful consideration of the definitions of rurality and urbanicity is essential because of the way the results depend on how geographical exposure is defined.

References


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**Contributors:** Simone Vigod, Lori Ross and Cindy-Lee Dennis contributed to the conception of the study, and all of the authors contributed to the study’s design. Simone Vigod and Lori Ross led the statistical analysis. Lesley Tarasoff, Simone Vigod and Lori Ross prepared the first draft of the manuscript. All of the authors critically revised the manuscript for important intellectual content and approved the final version submitted for publication.

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Using Canadian Primary Care Sentinel Surveillance Network data to examine depression in patients with a diagnosis of Parkinson disease: a retrospective cohort study

Kimberly Rose P. Singian RN MSN, Morgan Price MD PhD, Vicky Bungay RN PhD, Sabrina T. Wong RN PhD

Abstract

Background: Parkinson disease is a complex neurodegenerative disorder, and a comorbidity of depression is common. We aimed to describe demographic and health characteristics of patients with Parkinson disease and examine sex differences in antidepressant prescriptions for those with comorbid depression using electronic medical records.

Methods: We analyzed Canadian Primary Care Sentinel Surveillance Network data for patients 18 years and older with a diagnosis of Parkinson disease who had at least 1 primary care encounter between Sep. 30, 2012, and Sep. 30, 2014. We used regression modelling to determine sex differences in antidepressant prescriptions. An advisory group of clinicians helped determine the common list of medications and interpreted the results.

Results: We identified a total of 1815 patients (54.9% male) with Parkinson disease during the study period. The mean age of patients was 74.6 years. Most (82.0%) lived in urban areas. Patients had a mean number of 15.5 primary care encounters over the 2-year study period. Almost 40% of patients had a concurrent diagnosis of depression. More than half of the patients had received a depression diagnosis within 1 year of their Parkinson diagnosis. Eight out of every 10 patients had a prescription for at least 1 medication for depression, the most frequently prescribed being selective serotonin reuptake inhibitors (SSRIs). No sex differences were found in the number or type of medications.

Interpretation: Our findings support Canadian Parkinson Guidelines for Routine Screening of Comorbid Depression, but more evidence and decision-support tools are needed to examine the efficacy of antidepressants and assist clinicians in evaluating the frequent SSRI prescriptions in this population.

Parkinson disease is the second most common neurodegenerative disorder worldwide after Alzheimer disease.\(^1\) It has an estimated prevalence rate ranging from 57 to 230 per 100,000 and an incidence rate ranging from 1.5 to 26 per 100,000 per year.\(^2,3\) The epidemiologic estimates increase with age and differ by sex; men have a 1.46 times higher incidence rate than women.\(^2,4\) Parkinson Society Canada reported that there are about 100,000 people with the condition across Canada.\(^5\) Parkinson disease is characterized by the degeneration of dopamine-producing cells in the brain,\(^1\) resulting in motor symptoms including rest tremor, rigidity, bradykinesia and postural instability, in addition to nonmotor symptoms including depression, anxiety, cognitive decline, pain, fatigue, insomnia, constipation and urinary urgency.\(^6,4\)

Many people with Parkinson disease receive their diagnosis and have their care managed in primary care.\(^9\) Available diagnostic tools are better at detecting motor symptoms than nonmotor symptoms, such as depression.\(^7\) Treatment has primarily focused on dopaminergic replacement therapy to address motor symptoms.\(^10\) Yet, past work suggests that the co-occurrence of a diagnosis of depression occurs in up to half of patients with Parkinson disease, which can exacerbate motor symptoms and negatively affect quality of life.\(^11-13\) Canadian guidelines on Parkinson disease suggest that clinicians assess for comorbid depression and tailor its management to co-existing therapy, which may include the tricyclic

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amitriptyline. Previous work using American Veteran Affairs data examined simultaneous treatment of Parkinson disease and depression. Yet, there remains limited knowledge as to how these 2 chronic conditions are treated in Canadian primary care or the patient characteristics of those with both Parkinson disease and depression.

This study aimed to describe the demographic and health characteristics of those with a diagnosis of Parkinson disease in Canadian primary care. In addition, we examined sex differences in the number and type of pharmacologic treatments for depression among those with comorbid depression. We hypothesize that there are higher rates of medication use for depression among women than among men with concurrent diagnoses of Parkinson disease and depression. Existing studies on depression treatments in general have shown that women are more likely to have higher rates of medication use for treating depression given the higher prevalence of both depression diagnosis and use of primary care among women.

Methods

This retrospective cohort included a pan-Canadian sample of patients, aged 18 years and older, with a diagnosis of Parkinson disease. All patients had at least 1 primary care encounter with a participating Canadian Primary Care Sentinel Surveillance Network practice between Sept. 30, 2012, and Sep. 30, 2014.

Data source

Electronic medical record data from the pan-Canadian Primary Care Sentinel Surveillance Network were used. The network consists of 11 practice-based research networks across Canada (as of January 2016). Deidentified patient data (demographic characteristics [e.g., age, sex], chronic conditions [hypertension, osteoarthritis, diabetes, chronic obstructive pulmonary disease, depression, dementia, epilepsy and Parkinson disease], encounters, encounter diagnoses, billing, laboratory results, medications, allergies, physical signs [e.g., blood pressure], medical procedures, referrals, risk factors [e.g., smoking status] and vaccines) are extracted from the electronic medical records held by family physicians and nurse practitioners who voluntarily agree to be sentinels in the network.

As of January 2016, the Canadian Primary Care Sentinel Surveillance Network contains more than 800 participating sentinels and represents about 1 000 000 patients. All networks received ethical approval from their institutions and Health Canada.

The Canadian Primary Care Sentinel Surveillance Network represents a similar geographic distribution to the 2010 National Physician Survey. A recent cross-sectional study found that the network physicians were more likely to be female, less than 45 years of age and in academic practice when compared with the 2013 National Physician Survey. At the time of this study, there were more than 600 000 patients in network who were systematically older but reasonably similar to the age distribution of 2011 Canadian Census.

Diagnoses of Parkinson disease and depression

All case definitions for the chronic conditions were based on diagnostic code descriptions (International Statistical Classification of Diseases and Related Health Problems, 9th revision codes), free text searches within the problem list, billing and encounter diagnoses, laboratory results and medication history.

The previously validated case definition for Parkinson disease was used and included paralysis agitans and parkinsonism. Tremor, Wolf–Parkinson–White syndrome and “suspected” or “possible” variants were excluded. The diagnosis of Parkinson disease in the Canadian Primary Care Sentinel Surveillance Network has 98.8% sensitivity, 99.0% specificity, 82.0% positive predictive value and 99.9% negative predictive value.

The case definition for depression included episodic mood disorders, depressive disorder, bipolar, manic affective disorder, manic episodes, mild depression (not simply clinical depression); exclusions were anxiety disorders, alcohol or drug-induced mental disorders, schizophrenic disorders, delusional disorders, nonorganic psychoses, pervasive developmental disorders or other intellectual disabilities. The depression case definition has 81.1% sensitivity, 94.8% specificity, 79.6% positive predictive value and 95.2% negative predictive value.

Data collection

Data were obtained from the Canadian Primary Care Sentinel Surveillance Network through a data access request. We used a 2-year period because it is the recommended number of years needed to define a primary care practice population. We recruited an advisory group of 5 voluntary primary care physicians in British Columbia and Alberta. The advisory group helped determine the common list of medications for depression. Upon completing data analyses, key informant telephone interviews were conducted to assist with interpretation. Participants were offered Can$20 as a token of appreciation. Interviews were recorded, summarized and synthesized. Procedures were approved by the University of British Columbia Behavioural Ethics Board.

Key variables

Demographic characteristics included sex, current age, age at diagnosis, duration of Parkinson disease, number of encounters with a primary care provider in a 1-year and 2-year period and geographic residence. Health characteristics included body mass index (BMI), smoking status and number and type of comorbidities. In addition, we examined age at diagnosis and duration of depression. Data collected on pharmacologic treatments for depression included number and type of medications prescribed in a 2-year period. Appendix 1 (available at www.cmajopen.ca/content/4/3/E417/suppl/DC1) shows the types of medications for depression commonly used in primary care. Benzodiazepines and related hypnosedatives were added because these can be prescribed for treating symptoms of depression, including insomnia and agitation. We used the World Health Organization’s Ana-
Data analysis
To detect sex differences in the number and type of pharmacologic treatments for depression, a power calculation was conducted using G*Power29 for a medium effect size (51 patients per group [male, female]). All analyses were carried out using R Studio (version 3.1.2). Descriptive statistics included percentages, means and standard deviations to determine frequency distributions and assess heterogeneity.10 We examined correlations between the following variables: age, number of comorbidities, number of encounters and the dependent variables of interest. Neither age nor number of comorbidities were significant; thus, they were excluded from the regression modelling. Inferential statistics provided a method for drawing tentative conclusions about a population from a sample.30 A t test was used to test sex differences between means and a χ2 test was used to compare sex differences in proportions. Poisson and logistic regression modelling were used to test sex differences in the number and type of pharmacologic treatments for depression, as rate and odds ratios (ORs), respectively, while controlling for the number of encounters with a primary care provider in a 2-year period. The number of encounters was a covariate that used a log-2 scale to account for outliers influencing the regression models.

Results
There were a total of 1815 patients, 996 men (54.9%) and 819 women (45.1%), with a diagnosis of Parkinson disease. The characteristics of these patients are shown in Table 1. The mean age of the patients was 74.6 years (standard deviation [SD] 12.4). On average, patients received their diagnosis at 71.3 years of age (SD 12.6). The mean number of encounters with a primary care provider was 15.5 over 2 years. Most patients (82.0%) lived in urban areas. The average BMI of patients was 26.7; 37.5% of those with a recorded BMI were overweight. About 55.3% of patients with a recorded smoking status had never smoked. Most patients with (83.6%) also had 1 or more of the chronic conditions recorded by surveillance network. The most frequent comorbidities were hypertension (64.1%), depression (38.1%) and osteoarthritis (37.7%). Men had significantly fewer diagnoses of depression and osteoarthritis than women.

Demographic and health characteristics
Among patients with comorbid depression, 51.0% were female. Although some received a diagnosis of depression before that of Parkinson disease, about 58.1% had a diagnosis of depression within 1 year of receiving their Parkinson diagnosis. The mean number of encounters with a primary care provider for patients with diagnoses of Parkinson disease and depression was higher than among patients with just a Parkinson disease diagnosis (8.5 v. 7.5 encounters in a 1-year period). Women with a diagnosis of Parkinson and those with diagnoses of Parkinson and depression had higher mean numbers of encounters with a primary care provider than men.

Table 2 describes the prescribed pharmacologic treatments for depression in patients with diagnoses of Parkinson disease and depression. The average number of medications for depression in patients with both diagnoses was 1.8 (SD 1.2). Amitriptyline, suggested as the first line of treatment by the Canadian guidelines,12 was prescribed to 4.5% of patients with both diagnoses. Most of the prescribed medications for depression were selective serotonin reuptake inhibitors (SSRIs), followed by benzodiazepines and related hypnosedatives (47.2%).

There were no significant differences for the number or type of prescribed medications for depression between men and women after controlling for the number of encounters with a primary care provider in a 2-year period (Tables 3 and 4).

Interpretation
We used primary care electronic medical record data to examine the characteristics and pharmacologic treatments of patients with a diagnosis of depression in a cohort of patients with a diagnosis of Parkinson disease. Patients with Parkinson disease represented 0.3% of the total patients in Canadian Primary Care Sentinel Surveillance Network during the study period. This prevalence is higher than the 0.2% estimate of patients with Parkinson disease in the 2010/2011 Canadian Community Health Survey.11 The mean age at diagnosis of in our cohort was older than the reported typical age of onset of 50–75 years old.2,3,6 The prevalence of comorbid depression was higher than the reported general lifetime prevalence of depression among Canadians aged 65 years and older (11%–20%).16 Our results are comparable to past work not completed in primary care, whereby depression is reported in up to 50% of patients with Parkinson disease.11–13 The sex difference in the prevalence of depression in our study is lower than in the Canadian population.12 It is possible that sex differences diminish with age,12 which may be reflective of the study’s older sample of patients.

The prevalence of prescribed antidepressants is comparable to what is reported for those with a diagnosis of depression in a study using Canadian Primary Care Sentinel Surveillance Network data from 2011 to 2012.18 We did not find women with Parkinson disease to have a statistically significant difference in the number or type of prescribed medications for depression compared with men. This result is somewhat surprising given the prevalence of depression diagnosis and use of primary care appear to be higher in women.16–18 The reasons for the lack of sex differences require more research. The most frequently prescribed type of antidepressant, SSRIs, is comparable to past American Veteran Affairs studies involving patients with Parkinson disease and depression.14,15 In addition, depression treatment in the general population shows a high prescribing average (68.0%) of SSRIs in Canadian primary care practices.18 Possible explanations for this high frequency might be the current general prescription trends and lower adverse effect profile compared with other antidepressants.15
Table 1: Characteristics of patients with Parkinson disease in the Canadian Primary Care Sentinel Surveillance Network

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Men, no. (%)*</th>
<th>Women, no. (%)*</th>
<th>Overall, no. (%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( n = 996 )</td>
<td>( n = 819 )</td>
<td>( n = 1815 )</td>
</tr>
<tr>
<td>Age,† mean ± SD</td>
<td>74.1 ± 11.8</td>
<td>75.1 ± 13.4</td>
<td>74.6 ± 12.4</td>
</tr>
<tr>
<td>14–50</td>
<td>29 (2.9)</td>
<td>44 (5.4)</td>
<td>73 (4.0)</td>
</tr>
<tr>
<td>51–60</td>
<td>94 (9.5)</td>
<td>55 (6.7)</td>
<td>149 (8.2)</td>
</tr>
<tr>
<td>61–70</td>
<td>208 (20.9)</td>
<td>156 (19.1)</td>
<td>364 (20.1)</td>
</tr>
<tr>
<td>71–80</td>
<td>341 (34.3)</td>
<td>237 (29.0)</td>
<td>578 (31.9)</td>
</tr>
<tr>
<td>81–90</td>
<td>282 (28.4)</td>
<td>258 (31.6)</td>
<td>540 (29.8)</td>
</tr>
<tr>
<td>&gt; 90</td>
<td>40 (4.0)</td>
<td>67 (8.2)</td>
<td>107 (5.9)</td>
</tr>
<tr>
<td>Age at diagnosis of Parkinson disease,† mean ± SD</td>
<td>70.9 ± 11.7</td>
<td>71.8 ± 12.6</td>
<td>71.3 ± 12.6</td>
</tr>
<tr>
<td>Duration of Parkinson disease, yr,† mean ± SD</td>
<td>3.3 ± 2.8</td>
<td>3.4 ± 2.8</td>
<td>3.3 ± 2.8</td>
</tr>
<tr>
<td>Encounters with a primary care provider, mean ± SD</td>
<td>7.2 ± 9.2</td>
<td>7.9 ± 10.1</td>
<td>7.5 ± 9.6</td>
</tr>
<tr>
<td>1-year period</td>
<td>14.7 ± 16.1</td>
<td>16.3 ± 17.3</td>
<td>15.5 ± 16.7</td>
</tr>
<tr>
<td>Residence type†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urban</td>
<td>780 (81.3)</td>
<td>653 (82.3)</td>
<td>1433 (82.0)</td>
</tr>
<tr>
<td>Rural</td>
<td>180 (18.8)</td>
<td>135 (17.1)</td>
<td>315 (18.0)</td>
</tr>
<tr>
<td>Body mass index†, mean ± SD</td>
<td>270 ± 4.8</td>
<td>26.2 ± 5.6</td>
<td>26.7 ± 5.2</td>
</tr>
<tr>
<td>Body mass index category</td>
<td>( n = 483 )</td>
<td>( n = 370 )</td>
<td>( n = 853 )</td>
</tr>
<tr>
<td>Normal (18–24)</td>
<td>144 (29.8)</td>
<td>144 (38.9)</td>
<td>288 (33.8)</td>
</tr>
<tr>
<td>Underweight (&lt; 18)</td>
<td>1 (0.2)</td>
<td>8 (2.2)</td>
<td>9 (1.1)</td>
</tr>
<tr>
<td>Overweight (25–29)</td>
<td>202 (41.8)</td>
<td>118 (31.9)</td>
<td>320 (37.5)</td>
</tr>
<tr>
<td>Obese (≥ 30)</td>
<td>136 (28.2)</td>
<td>100 (27.0)</td>
<td>236 (27.7)</td>
</tr>
<tr>
<td>Smoking status*</td>
<td>( n = 451 )</td>
<td>( n = 328 )</td>
<td>( n = 779 )</td>
</tr>
<tr>
<td>Never</td>
<td>223 (49.6)</td>
<td>208 (63.4)</td>
<td>431 (55.3)</td>
</tr>
<tr>
<td>Current</td>
<td>47 (10.4)</td>
<td>38 (11.6)</td>
<td>85 (10.9)</td>
</tr>
<tr>
<td>Past</td>
<td>181 (40.1)</td>
<td>82 (25.0)</td>
<td>263 (33.8)</td>
</tr>
<tr>
<td>No. of comorbidities‡, mean ± SD</td>
<td>1.7 ± 1.2</td>
<td>1.9 ± 1.3</td>
<td>1.8 ± 1.3</td>
</tr>
<tr>
<td>0</td>
<td>168 (16.9)</td>
<td>130 (15.9)</td>
<td>298 (16.4)</td>
</tr>
<tr>
<td>1</td>
<td>300 (30.1)</td>
<td>234 (28.6)</td>
<td>534 (29.4)</td>
</tr>
<tr>
<td>2</td>
<td>281 (28.2)</td>
<td>207 (25.3)</td>
<td>488 (26.9)</td>
</tr>
<tr>
<td>≥ 3</td>
<td>247 (24.8)</td>
<td>248 (30.3)</td>
<td>495 (27.3)</td>
</tr>
<tr>
<td>Type of comorbidity§</td>
<td>( n = 828 )</td>
<td>( n = 689 )</td>
<td>( n = 1517 )</td>
</tr>
<tr>
<td>Hypertension</td>
<td>520 (62.8)</td>
<td>453 (65.8)</td>
<td>973 (64.1)</td>
</tr>
<tr>
<td>Depression‡</td>
<td>283 (34.2)</td>
<td>295 (42.8)</td>
<td>578 (38.1)</td>
</tr>
<tr>
<td>Osteoarthritis‡</td>
<td>259 (31.3)</td>
<td>313 (45.4)</td>
<td>572 (37.7)</td>
</tr>
<tr>
<td>Dementia</td>
<td>245 (29.6)</td>
<td>194 (28.2)</td>
<td>439 (29.0)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>232 (19.6)</td>
<td>162 (33.7)</td>
<td>394 (26.0)</td>
</tr>
<tr>
<td>COPD†</td>
<td>146 (176)</td>
<td>78 (11.3)</td>
<td>224 (14.8)</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>26 (3.1)</td>
<td>28 (4.1)</td>
<td>54 (3.6)</td>
</tr>
</tbody>
</table>

Note: COPD = chronic obstructive pulmonary disease, SD = standard deviation.
*Unless otherwise specified.
†Missing data: age, age at diagnosis of Parkinson disease, duration of Parkinson disease and residence type had < 4.0% missing data; body mass index was missing for 53.0% of patients; smoking status was missing for 57.1%.
‡Significance by sex defined as \( p < 0.05 \) using \( t \) test and \( \chi^2 \) of independence test.
§Column percentage is > 100% because patients could have more than 1 chronic condition.
Using an advisory group allowed us to contextualize results on data contributed by sentinels in Canadian Primary Care Sentinel Surveillance Network. The advisory group suggested more work was needed to understand the efficacy of prescribing tricyclics as the first line of treatment for depression in patients with Parkinson disease. Past work on the use of SSRIs for depressive symptoms in patients with Parkinson disease remains debatable. Previous evidence suggests that SSRIs, such as paroxetine, may magnify the motor symptoms in Parkinson disease.\textsuperscript{33,34} More recent meta-analyses\textsuperscript{35,36} and the Canadian guidelines\textsuperscript{12} suggest that tricyclics might be more effective for this population. Discrepancies found between commonly prescribed SSRIs for depression and what is recommended by the Canadian guidelines\textsuperscript{12} might be the result of different factors.

<p>| Table 2: Recorded medications for depression in patients with diagnoses of both Parkinson disease and depression in the Canadian Primary Care Sentinel Surveillance Network |
|---------------------------------|---------------------------------|---------------------------------|</p>
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Men, no. (%)*</th>
<th>Women, no. (%)*</th>
<th>Overall, no. (%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>\textit{n = 283}</td>
<td>\textit{n = 295}</td>
<td>\textit{n = 578}</td>
</tr>
<tr>
<td>Age at diagnosis of depression, yr, mean ± SD</td>
<td>71.8 ± 11.9</td>
<td>72.0 ± 12.3</td>
<td>71.9 ± 12.1</td>
</tr>
<tr>
<td>Diagnosed before Parkinson disease</td>
<td>121 (42.8)</td>
<td>121 (41.0)</td>
<td>242 (41.9)</td>
</tr>
<tr>
<td>Diagnosed after Parkinson disease</td>
<td>162 (57.2)</td>
<td>174 (58.9)</td>
<td>336 (58.1)</td>
</tr>
<tr>
<td>Duration of depression, yr, mean ± SD</td>
<td>5.0 ± 3.1</td>
<td>4.8 ± 3.2</td>
<td>4.9 ± 3.2</td>
</tr>
<tr>
<td>Encounters with a primary care provider, mean ± SD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-year period</td>
<td>8.3 ± 9.1</td>
<td>8.6 ± 8.5</td>
<td>8.5 ± 8.8</td>
</tr>
<tr>
<td>2-year period</td>
<td>17.2 ± 16.5</td>
<td>17.7 ± 15.6</td>
<td>17.5 ± 16.1</td>
</tr>
<tr>
<td>No. of medications for depression, mean ± SD</td>
<td>1.7 ± 1.2</td>
<td>1.9 ± 1.2</td>
<td>1.8 ± 1.2</td>
</tr>
<tr>
<td>0</td>
<td>44 (15.5)</td>
<td>36 (12.2)</td>
<td>80 (13.8)</td>
</tr>
<tr>
<td>1</td>
<td>76 (26.9)</td>
<td>91 (30.8)</td>
<td>167 (28.9)</td>
</tr>
<tr>
<td>2</td>
<td>96 (33.9)</td>
<td>82 (27.8)</td>
<td>178 (30.8)</td>
</tr>
<tr>
<td>≥ 3</td>
<td>67 (23.7)</td>
<td>86 (29.2)</td>
<td>153 (26.5)</td>
</tr>
<tr>
<td>Type of medication for depression</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Selective serotonin reuptake inhibitors</td>
<td>140 (49.5)</td>
<td>162 (54.9)</td>
<td>302 (52.2)</td>
</tr>
<tr>
<td>Benzodiazepines and related hypnosedatives</td>
<td>130 (45.9)</td>
<td>143 (48.5)</td>
<td>273 (47.2)</td>
</tr>
<tr>
<td>Atypical antipsychotic agents</td>
<td>86 (30.4)</td>
<td>97 (32.9)</td>
<td>183 (31.7)</td>
</tr>
<tr>
<td>Serotonin–norepinephrine reuptake inhibitors</td>
<td>45 (15.9)</td>
<td>54 (18.3)</td>
<td>99 (17.1)</td>
</tr>
<tr>
<td>Serotonin antagonist and reuptake inhibitors</td>
<td>44 (15.6)</td>
<td>31 (10.5)</td>
<td>75 (13.0)</td>
</tr>
<tr>
<td>Tricyclics and tetracyclics</td>
<td>21 (7.4)</td>
<td>36 (12.2)</td>
<td>57 (9.9)</td>
</tr>
<tr>
<td>Amitriptyline†</td>
<td>9 (3.2)</td>
<td>17 (6.0)</td>
<td>26 (4.5)</td>
</tr>
<tr>
<td>Bipolar medications</td>
<td>24 (8.5)</td>
<td>30 (10.2)</td>
<td>54 (9.3)</td>
</tr>
<tr>
<td>Monoamine oxidase inhibitors</td>
<td>5 (1.8)</td>
<td>4 (1.4)</td>
<td>9 (1.6)</td>
</tr>
<tr>
<td>No depression medication</td>
<td>44 (15.5)</td>
<td>36 (12.2)</td>
<td>(80) 13.8</td>
</tr>
</tbody>
</table>

Note: SD = standard deviation.
*Unless otherwise specified.
†Tricyclic recommended in Canadian guidelines on Parkinson disease.\textsuperscript{12}

| Table 3: Encounter-adjusted Poisson regression of the recorded number of medications for depression by sex in patients with diagnoses of Parkinson disease and depression |
|---------------------------------|---------------------------------|---------------------------------|
| Dependent variable*            | Sex (male reference = 1.00)     | No. of encounters with a primary care provider |
|                                | RR (95% CI)                     | p value                         | RR (95% CI)                     | p value |
| No. of medications             | 1.08 (0.95–1.22)                | 0.2                             | 1.11 (1.06–1.16)                | < 0.001* |

Note: 95% CI = confidence intervals (lower bound-upper bound), p value = probability value, RR = rate ratio.
*Sex served as the main independent variable and number of encounters with a primary care provider in a 2-year period served as a covariate using a log-2 scale in the regression model.
†Significance defined as $p < 0.05$.  

including low baseline knowledge among providers regarding management of motor and nonmotor symptoms of Parkinson disease,9,45 current prescription trends for depression15 and insufficient evidence on the efficacy of medications for patients with comorbid depression.12,35,36 Increased practice support and insufficient evidence on the efficacy of medications for patients with concurrent disease in the Canadian Primary Care Sentinel Surveillance Network allows examination of other chronic diseases, including a recent study on dementia.44 Each surveillance network case definition refers to lifetime prevalence of only 8 chronic diseases.13 Finally, we made assumptions as to our list of medications that would be prescribed for depressive symptoms.

### Conclusion

This study provides a description of the characteristics of patients with Parkinson disease and the pharmacologic treatments for depression among those with comorbid depression in Canadian primary care. Depression remains a common comorbidity, which is mostly treated by SSRIs despite guideline recommendations. Our findings highlight the need for more resources and decision-making tools to guide primary care providers in treating comorbid depression.

### Table 4: Encounter-adjusted logistic regressions for the recorded type of medications for depression by sex in patients with diagnoses of Parkinson disease and depression

<table>
<thead>
<tr>
<th>Dependent variable</th>
<th>Sex (male reference = 1.00)</th>
<th>No. of encounters with a primary care provider</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>p value</td>
</tr>
<tr>
<td>Selective serotonin reuptake inhibitors</td>
<td>1.25 (0.90–1.73)</td>
<td>0.2</td>
</tr>
<tr>
<td>Benzodiazepines and related hypnosedative</td>
<td>1.11 (0.80–1.54)</td>
<td>0.5</td>
</tr>
<tr>
<td>Atypical and antipsychotic agents</td>
<td>1.12 (0.79–1.59)</td>
<td>0.5</td>
</tr>
<tr>
<td>Serotonin–norephinephrine reuptake inhibitors</td>
<td>1.18 (0.77–1.83)</td>
<td>0.4</td>
</tr>
<tr>
<td>Serotonin antagonist and reuptake inhibitors</td>
<td>0.64 (0.39–1.04)</td>
<td>0.07</td>
</tr>
<tr>
<td>Tricyclics and tetracyclics</td>
<td>1.73 (0.99–3.10)</td>
<td>0.06</td>
</tr>
<tr>
<td>Bipolar medications</td>
<td>1.22 (0.69–2.16)</td>
<td>0.5</td>
</tr>
<tr>
<td>Monoamine oxidase inhibitors</td>
<td>0.76 (0.19–2.90)</td>
<td>0.7</td>
</tr>
</tbody>
</table>

Note: CI = confidence intervals, OR = odds ratio.
*Significance defined as p < 0.05.
Gender served as the main independent variable and the number of encounters with a primary care provider in a 2-year period served as a covariate using a log-2 scale in the regression model.
References


24. Menee V, Black C, Roos NP, et al. Defining practice populations for primary care: method and metrics. West Health Policy Centre for Health Policy and Evaluation, Department of Community Health Sciences, Faculty of Medicine, University of Manitoba; 2000.


Affiliations: School of Nursing (Singian, Bungay, Wong), Department of Family Practice (Price, Wong) and Centre for Health Services and Policy Research (Wong), University of British Columbia, Vancouver, BC.

Contributors: This retrospective cohort study is original, unpublished, and conducted by the principal investigator, Kimberly Rose Pineda Singian. Morgan Price, Victoria Bungay and Sabrina Wong served as coauthors and contributed substantially to the conception, design, analysis, and interpretation of data. The coauthors also provided critical feedback throughout the stages of the study, including the multiples drafts of all sections. All of the authors gave final approval of the version to be published and agreed to act as guarantors of the work.

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About 20 years ago, Anderson and colleagues1 pointed out that individual-level psychological distress, such as depression, in a population correlates highly with the mean population level of psychological distress.1 Depression has been found to significantly worsen individuals’ overall health status.2 Previous studies report that the prevalence of depression varied by patient characteristics, the number of chronic conditions and the presence of the following chronic conditions: hypertension, diabetes, chronic obstructive pulmonary disease, osteoarthritis, dementia, epilepsy and parkinsonism. We used regression models to examine whether patient characteristics and type of comorbidity were associated with a depression diagnosis.

The World Health Organization reports that unipolar depressive disorder is more common than traffic accidents, cerebrovascular disease and ischemic heart disease and therefore responsible for a greater decrease in disability-adjusted life years in middle- and high-income countries.7 Depression is so prevalent that it is considered a serious public health issue.2 The 12-month prevalence rate of the most common form of depression, major depressive disorder, ranges from 5% to 14%.2 A large collaborative study by the World Health Organization, which included 26 000 patients in 15 centres worldwide, found a point prevalence rate of 10.4% for depression as defined by the International Statistical Classification of Diseases and Related Health Problems, 10th revision.8 It is estimated that, over the course of a single year, 1 360 000 Canadians meet the
criteria for major depressive disorder alone, as defined by the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders. However, data from a large study are lacking on the prevalence of major depressive disorder or any form of depression in primary care in Canada.

Depression is most commonly diagnosed and treated in primary care. To determine the prevalence of depression among patients living in Canada, we used data from primary care electronic medical records collected for the purpose of surveillance of chronic conditions. The Canadian Primary Care Sentinel Surveillance Network is the first pan-Canadian, multidisease population health surveillance system. The purpose of this study was to describe the prevalence of a diagnosis of depression among men and women, patient characteristics, and the treatment (i.e., type and number of prescriptions) provided to these patients in a primary care setting in Canada.

Methods

Data source
The Canadian Primary Care Sentinel Surveillance Network consists of 10 practice-based research networks across Canada. The network contains data from almost 500 sentinel primary care providers (family physicians and nurse practitioners) and more than 600 000 patients. Although these providers are more likely to be younger and female than a general sample of primary care providers, patients included in this study are representative of those who visit primary care in Canada. Each consenting provider contributes de-identified patient data from the electronic medical records on a quarterly basis. Patients of consenting providers can decline to participate in the Canadian Primary Care Sentinel Surveillance Network (< 0.01% decline to participate) and their patient records are then excluded from this pan-Canadian clinical data repository. All practice-based research networks have received research ethics board approval from their institution as well as ethics approval from Health Canada for collecting this information. To optimize the quality, comparability and usefulness of data for research, each network’s data manager transforms the extracted data into a common database template. Various checks for completeness and validity are performed, and several algorithms are performed for identifying cases of chronic disease and for coding textual data into discrete categories. Once data processing is complete, each practice-based research network database is securely submitted to a central repository, where a national Canadian Primary Care Sentinel Surveillance Network database is constructed, checked and prepared for quarterly analysis and reporting.

Case definition for depression
The Canadian Primary Care Sentinel Surveillance Network developed and validated a case definition for the diagnosis of depression: episodic mood disorders, depressive disorder not elsewhere classified, bipolar, manic affective disorder, manic episodes, mild depression (not simply clinical depression). This definition uses a combination of codes from the International Classification of Diseases, 9th Revision (ICD-9), and free-text searches within the problem list, billing and encounter diagnoses and the medication history. Previous work on case validation, using a review of randomly sampled charts, has shown that the network’s diagnostic algorithm for depression performed adequately, with a sensitivity of 81.1% (95% confidence interval [CI] 77.2%–85.0%), a specificity of 94.8% (95% CI 93.7%–95.9%), a positive predictive value of 79.6% (95% CI 75.7%–83.6%) and a negative predictive value of 95.2% (95% CI 94.1%–96.3%). This definition was used to identify any instance of a diagnosis throughout the patient’s entire electronic medical record.

Inclusion criteria
All patients who visited their primary care provider between Jan. 1, 2011, and Dec. 31, 2012, were included in this study. We used a 2-year prevalence time frame because this is an accepted estimate of panel size in the primary care setting. A 12-month period will underestimate the panel size because

<table>
<thead>
<tr>
<th>Classification</th>
<th>Medication (generic name)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selective serotonin reuptake inhibitors</td>
<td>Citalopram, Escitalopram, Fluoxetine, Fluvoxamine, Paroxetine, Sertraline</td>
</tr>
<tr>
<td>Tricyclics and tetracyclics</td>
<td>Amitriptyline, Amoxapine, Butriptyline, Clomipramine, Desipramine, Doxepin, Imipramine, Maprotiline, Nortriptyline, Protriptyline, Trimipramine</td>
</tr>
<tr>
<td>Serotonin–norepinephrine reuptake inhibitors</td>
<td>Desvenlafaxine, Duloxetine, Venlafaxine</td>
</tr>
<tr>
<td>Serotonin antagonist and reuptake inhibitors</td>
<td>Trazodone</td>
</tr>
<tr>
<td>Atypical antipsychotics</td>
<td>Aripiprazole, Bupropion, Mirtazapine, Quetiapine</td>
</tr>
<tr>
<td>Monoamine oxidase inhibitors</td>
<td>Isocarboxazid, Moclobemide, Phenelzine, Selegiline, Tranylcypromine</td>
</tr>
<tr>
<td>Bipolar medications</td>
<td>Lithium, Carbamazepine, Divalproex, Lamotrigine, Valproate</td>
</tr>
</tbody>
</table>
many patients do not visit their primary care provider within a 1-year time frame.\textsuperscript{12}

**Variables of interest**

We examined whether the prevalence of a diagnosis of depression varied by patient characteristics, including age, sex, rural or urban residence, smoking status and body mass index (BMI). We also examined whether those with a diagnosis of depression had any of the other chronic conditions for which the Canadian Primary Care Sentinel Surveillance Network has a validated case definition (i.e., hypertension, diabetes, chronic obstructive pulmonary disease, osteoarthritis, dementia, epilepsy and parkinsonism) as well as the number of chronic conditions. Finally, we examined the type and number of medications prescribed for those with a diagnosis of depression (Table 1).

**Patient characteristics**

We determined patients’ residence in rural or urban areas using the first 3 digits of the practice’s postal code, also known as the forward sortation area. Following Canada Post’s procedure for classification, we coded residence as rural if there was a value of zero in the second digit of their forward sortation areas and urban for those with all other values.\textsuperscript{13} Smoking status was recorded in 3 categories: 1) patients who had never smoked were coded as “nonsmokers”; 2) patients who smoked, regardless of frequency and amount, were coded as “smokers”; and 3) patients who reported having quit smoking were coded as “past smokers.” Body mass index was calculated based on the most recent height and weight data available. The BMI values were classified as follows: underweight (< 18), normal (18–24), overweight (25–29) and obese (≥ 30). The last available record on these patient characteristics was included in the analyses.

**Medication**

We developed a list of commonly used medications when a diagnosis of depression is made (Table 1) to identify patients who have been prescribed medications used to treat depression. The medications were categorized as follows: selective serotonin reuptake inhibitors, tricyclics and tetracyclics, serotonin–norepinephrine reuptake inhibitors, serotonin antagonist and reuptake inhibitors, atypical antipsychotics, monoamine oxidase inhibitors and bipolar medications. The generic names of the prescribed medication were extracted from the electronic medical record.

**Analysis**

Data were analyzed by sex and as a total sample. We examined the lifetime prevalence of a diagnosis of depression among those who had visited their primary care provider in the last 2 years. Descriptive statistics were used to calculate the mean number of comorbidities, and type and number of medications prescribed. We used a series of age-adjusted log-binominal regression models to examine whether patient characteristics and type of comorbidity were significantly associated with a diagnosis of depression. The log-binominal approach is akin to a logistic regression approach but is more appropriate to use when trying to estimate the prevalence ratio, or relative risk.\textsuperscript{14} All analyses were done using SAS 9.3.

**Results**

As of Dec. 31, 2012, the database of the Canadian Primary Care Sentinel Surveillance Network contained data for a total of 304,412 patients who had at least 1 encounter with their

![Figure 1: Lifetime prevalence of a diagnosis of depression by age and sex. Total prevalence: observed = 13.6%, age–sex standardized = 13.1%. Data source: Canadian Primary Care Sentinel Surveillance Network 2012.](image)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Prevalence ratio (95% CI)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Residence</strong>*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urban</td>
<td>1.00 (reference)</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>Rural</td>
<td>0.90 (0.87–0.94)</td>
<td>0.92 (0.90–0.95)</td>
</tr>
<tr>
<td><strong>BMI†</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal (18–24)</td>
<td>1.00 (reference)</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>Underweight (&lt; 18)</td>
<td>0.91 (0.83–1.00)</td>
<td>0.96 (0.91–1.03)</td>
</tr>
<tr>
<td>Overweight (25–29)</td>
<td>0.95 (0.90–1.00)</td>
<td>1.06 (1.03–1.10)</td>
</tr>
<tr>
<td>Obese (≥ 30)</td>
<td>1.03 (0.98–1.08)</td>
<td>1.17 (1.13–1.20)</td>
</tr>
<tr>
<td><strong>Smoking‡</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>1.00 (reference)</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>Current</td>
<td>1.54 (1.46–1.64)</td>
<td>1.60 (1.54–1.66)</td>
</tr>
<tr>
<td>Past</td>
<td>1.17 (1.10–1.24)</td>
<td>1.32 (1.27–1.38)</td>
</tr>
</tbody>
</table>

Note: BMI = body mass index, CI = confidence interval.
*Data on residence missing for 10,650 patients (4,977 men, 5,673 women).
†Data on BMI missing for 117,374 patients (53,917 men, 63,457 women).
‡Data on smoking status missing for 201,139 patients (89,686 men, 111,453 women).
primary care provider between Jan. 1, 2011, and Dec. 31, 2012. Of these, 41 274 (14%) had a diagnosis of depression. Figure 1 shows that, in all age categories, a diagnosis of depression was more prevalent among women than men. Almost 17% (n = 28 526) of women who had seen their primary care provider during these 2 years had a diagnosis of depression, compared with 10% (n = 12 748) of men.

After adjustment for age, our regression models suggest that residence in a rural area was associated with a lower likelihood of diagnosis of depression for both sexes (Table 2). Both men and women who were current or past smokers had a significantly higher risk of having a diagnosis of depression. Women who were overweight or obese had a higher rate of diagnosis of depression than women with a normal BMI.

More than half of those with a diagnosis of depression had no other comorbidities recorded (Table 3). Yet, 1 out of 4 people with a diagnosis of depression also had 1 other chronic condition for which the Canadian Primary Care Sentinel Surveillance Network has a validated case definition. Table 4 shows that for those with a chronic condition, the prevalence of depression was significantly higher. The prevalence of depression was highest in those diagnosed with dementia, followed by parkinsonism and epilepsy.

The mean number of encounters with the primary care provider during a 12-month period was higher among those with a diagnosis of depression (Table 5). This pattern remained with both sexes and over a longer period (24 mo). Notably, even after controlling for age, sex, rural or urban residence, and all other chronic conditions (hypertension, diabetes, chronic obstructive pulmonary disease, osteoarthritis, dementia, epilepsy, parkinsonism), those with a diagnosis of depression had 1.5 (95% CI 1.5–1.6) times more visits to their primary care provider than those without the diagnosis (data not shown).

About 85% of patients with a diagnosis of depression were prescribed some form of medication for this condition. Almost half (48%) were prescribed 1 antidepressant medication, whereas about 23% were prescribed 2 medications (Table 6). More than one-third of patients (34% of men and 38% of women) were simultaneously prescribed more than 2 antidepressant medications. Table 7 shows that the most frequently prescribed medications were selective serotonin reuptake inhibitors (65% of men and 69% of women), followed by atypical antipsychotics (24% of men and 22.3% of women) and serotonin–norepinephrine reuptake inhibitors (19% of men and 22% of women).

**Interpretation**

In this large Canadian study, we were able to identify a number of patient characteristics associated with depression and describe the treatment of these patients. Across all age groups, women were found to have a higher prevalence of a diagnosis of depression than men. In both men and women, residence in a rural area was associated with a lower rate of depression, and patients who were considered current or past smokers had a significantly higher risk of having a diagnosis of depression. Moreover, women whose BMI indicated they were overweight or obese had a higher rate of depression than their counterparts with BMIs in the normal range. Of patients with a diagnosis of depression, 25% also had 1 or more other chronic conditions. Those with a diagnosis of depression have a higher number of visits to their primary care provider than those with no depression diagnosis.

Use of data from the Canadian Primary Care Sentinel Surveillance Network provided a novel approach to examining lifetime prevalence of a diagnosis of depression. Historically, the assessment of lifetime prevalence is based on retrospective assessment instruments and therefore subject to recall bias. Our prospective examination of the clinical data avoids the recall bias that has been thought to influence the pattern of age-specific lifetime prevalence. Although past studies have reported a decline in lifetime prevalence with age, our data suggest there is no decline in lifetime prevalence of a diagnosis of depression. Although we found a prevalence rate (13.6% total) for a diagnosis of depression that was higher than the 12-month prevalence found by Moussavi and colleagues, we would expect it to be higher given that we did not restrict the diagnosis to major depressive disorder. Notably, the prevalence of a diagnosis of depression for men and women in this study was similar to what has been found using the 2002 Canadian Community Health Survey Mental Health component. Our results are consistent with past work that showed a positive association between smoking status and having 1 or more chronic condition. For women, a BMI indicating overweight or obesity was another characteristic

**Table 3: Presence of a diagnosis of depression by number of other chronic conditions**

<table>
<thead>
<tr>
<th>No. of other conditions</th>
<th>No depression</th>
<th>Depression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>n = 118 424</td>
<td>n = 12 748</td>
</tr>
<tr>
<td>Women</td>
<td>n = 144 714</td>
<td>n = 28 526</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>n = 263 138</td>
<td>n = 41 274</td>
</tr>
<tr>
<td>0</td>
<td>84 009 (70.9)</td>
<td>6 932 (54.4)</td>
</tr>
<tr>
<td></td>
<td>105 812 (73.1)</td>
<td>16 695 (58.5)</td>
</tr>
<tr>
<td></td>
<td>189 821 (72.1)</td>
<td>23 627 (57.2)</td>
</tr>
<tr>
<td>1</td>
<td>22 983 (19.4)</td>
<td>3 351 (26.3)</td>
</tr>
<tr>
<td></td>
<td>25 344 (17.5)</td>
<td>6 937 (24.3)</td>
</tr>
<tr>
<td></td>
<td>48 327 (18.4)</td>
<td>10 288 (24.9)</td>
</tr>
<tr>
<td>2</td>
<td>9 018 (7.6)</td>
<td>1 740 (13.7)</td>
</tr>
<tr>
<td></td>
<td>10 577 (7.3)</td>
<td>3 395 (11.9)</td>
</tr>
<tr>
<td></td>
<td>19 595 (7.5)</td>
<td>5 135 (12.4)</td>
</tr>
<tr>
<td>≥ 3</td>
<td>2 415 (2.1)</td>
<td>725 (5.6)</td>
</tr>
<tr>
<td></td>
<td>2 981 (2.1)</td>
<td>1 499 (5.3)</td>
</tr>
<tr>
<td></td>
<td>5 395 (2.0)</td>
<td>2 224 (5.5)</td>
</tr>
</tbody>
</table>
associated with a diagnosis of depression. A high BMI for women could increase their negative perceptions about their bodies; sociological work suggests that women’s perceived body image is related to a diagnosis of depression. Yet, more work is needed to examine whether adverse effects of medications, particularly from atypical antipsychotics, cause excessive weight gain in women. Primary care providers may want to screen for depression in women with a BMI indicative of obesity, or communicate to patients that a known adverse effect of atypical antipsychotics is weight gain.

Given that women tend to use primary care more than men, primary care providers may be more likely to recognize depressive symptoms in women than in men. The manifestation of depressive symptoms may also be different in men and less easily recognized. Indeed, men will rarely mention any emotional or behavioural difficulties to their providers and may only discuss emotional problems in terms of “stress.”

Data from our study indicate that many more patients with a diagnosis of depression are receiving a prescription for antidepressant medication (85%) than what has been reported in the past (60%). This could be reflective of widespread increasing use of antidepressant medications in Canada or the fact that these patients had stronger connections to primary care and therefore better access to treatment. The 15% of those in our study who are reported as having a diagnosis of depression but not taking any antidepressants may represent patients using non-medical treatments, such as cognitive behavioural therapy.

**Limitations**

Our study is not without limitations. These data are not representative of the entire Canadian population, but rather represent practices that are more engaged in chronic disease surveillance. Our case-finding definition for depression is imperfect in that it could misclassify other conditions as a diagnosis of depression, because the ICD-9 code 296 (affective psychoses) encompasses diagnostic subcategories for depression (ICD-9 296.2, 296.3, 296.9) and bipolar disorders. Due to the cross-sectional nature of the data, we were not able to determine whether chronic conditions occurred before a diagnosis of depression or vice versa or infer causality. It is possible that we have not captured the true proportion of patients taking medication, because antidepressants prescribed by a psychiatrist may not get recorded in the electronic medical record. Finally, it is not possible to differentiate severity of depressive symptoms using our data.

**Conclusion**

Our study provides information on a large cohort of patients with a diagnosis of depression in Canada using clinical data from electronic medical records. An area for future study could be patients who are reported as having a diagnosis of depression but not taking any antidepressants. It is not clear why patients with a diagnosis of depression do not take antidepressants. More work is needed to understand if these patients are not adhering to medication, or if something else has helped them with their depression. Our findings also suggest that more could be done to screen for depression among men visiting their primary care provider and among those who have a chronic condition, have been a past or current smoker, or women with a BMI indicative of overweight or obesity.

### Table 4: Age-adjusted prevalence ratios for a diagnosis of depression in men and women, by comorbidity

<table>
<thead>
<tr>
<th>Comorbidity</th>
<th>Prevalence ratio (95% CI)</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>1.15 (1.12–1.18)</td>
<td>1.14 (1.12–1.16)</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.23 (1.18–1.29)</td>
<td>1.36 (1.31–1.42)</td>
<td></td>
</tr>
<tr>
<td>COPD</td>
<td>1.78 (1.67–1.90)</td>
<td>1.82 (1.72–1.92)</td>
<td></td>
</tr>
<tr>
<td>Osteoarthritis</td>
<td>1.37 (1.31–1.43)</td>
<td>1.35 (1.32–1.39)</td>
<td></td>
</tr>
<tr>
<td>Dementia</td>
<td>3.23 (2.96–3.52)</td>
<td>2.47 (2.32–2.63)</td>
<td></td>
</tr>
<tr>
<td>Epilepsy</td>
<td>2.03 (1.77–2.33)</td>
<td>1.82 (1.63–2.04)</td>
<td></td>
</tr>
<tr>
<td>Parkinsonism</td>
<td>2.27 (1.86–2.77)</td>
<td>2.22 (1.83–2.70)</td>
<td></td>
</tr>
</tbody>
</table>

Note: CI = confidence interval, COPD = chronic obstructive pulmonary disease.

### Table 5: Number of encounters with a primary care provider in patients with and without a diagnosis of depression

<table>
<thead>
<tr>
<th>Period</th>
<th>No depression</th>
<th>Depressed</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Men n = 118,424</td>
<td>Women n = 144,714</td>
</tr>
<tr>
<td>12 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>3.7 ± 3.8</td>
<td>4.1 ± 4.0</td>
</tr>
<tr>
<td>Median</td>
<td>3.0</td>
<td>3.0</td>
</tr>
<tr>
<td>24 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>5.9 ± 6.4</td>
<td>7.0 ± 7.0</td>
</tr>
<tr>
<td>Median</td>
<td>4.0</td>
<td>5.0</td>
</tr>
</tbody>
</table>

SD = standard deviation.
Table 6: Number of medications used in treating depression taken by patients with a diagnosis of depression

<table>
<thead>
<tr>
<th>Classification</th>
<th>No. (%) of patients</th>
<th>No. (%) of patients</th>
<th>No. (%) of patients</th>
<th>No. (%) of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Classification</td>
<td>Men n = 12,748</td>
<td>Women n = 28,526</td>
<td>Total n = 41,274</td>
<td></td>
</tr>
<tr>
<td>Selective serotonin reuptake inhibitors</td>
<td>8,291 (65.0)</td>
<td>19,756 (69.3)</td>
<td>28,047 (68.0)</td>
<td></td>
</tr>
<tr>
<td>Atypical antipsychotics</td>
<td>3,067 (24.1)</td>
<td>6,350 (22.3)</td>
<td>9,417 (22.8)</td>
<td></td>
</tr>
<tr>
<td>Serotonin– norepinephrine reuptake inhibitors</td>
<td>2,478 (19.4)</td>
<td>6,401 (22.4)</td>
<td>8,879 (21.5)</td>
<td></td>
</tr>
<tr>
<td>Tricyclics and tetracyclics</td>
<td>1,384 (10.9)</td>
<td>4,026 (14.1)</td>
<td>5,410 (13.1)</td>
<td></td>
</tr>
<tr>
<td>Serotonin antagonist and reuptake inhibitors</td>
<td>1,142 (9.0)</td>
<td>2,988 (10.5)</td>
<td>4,130 (10.0)</td>
<td></td>
</tr>
<tr>
<td>Bipolar medications</td>
<td>508 (4.0)</td>
<td>976 (3.4)</td>
<td>1,484 (3.6)</td>
<td></td>
</tr>
<tr>
<td>Monoamine oxidase inhibitors</td>
<td>43 (0.3)</td>
<td>71 (0.3)</td>
<td>114 (0.3)</td>
<td></td>
</tr>
<tr>
<td>No depression medication</td>
<td>2,222 (17.4)</td>
<td>4,083 (14.3)</td>
<td>6,305 (15.3)</td>
<td></td>
</tr>
</tbody>
</table>

Table 7: Medications prescribed to patients with a diagnosis of depression

<table>
<thead>
<tr>
<th>Classification</th>
<th>No. (%) of patients</th>
<th>No. (%) of patients</th>
<th>No. (%) of patients</th>
<th>No. (%) of patients</th>
</tr>
</thead>
<tbody>
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<td>114 (0.3)</td>
<td></td>
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<td>2,222 (17.4)</td>
<td>4,083 (14.3)</td>
<td>6,305 (15.3)</td>
<td></td>
</tr>
</tbody>
</table>

References


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Contributors: All of the authors contributed to the collection and analysis of data, wrote and revised the manuscript, approved the version submitted for publication and agree to act as guarantors of the work.

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Supplemental information: For reviewer comments and the original submission of this manuscript, please see www.cmajopen.ca/content/2/4/E337/suppl/DC1
Depression is a complex mental illness that is associated with disability and reduced quality of life for the person with the disorder; it also poses a substantial societal burden. The prevalence of past-year episodes of depression in the Canadian population has been estimated to vary from 5% to 8.2% annually. In 2005, the Canadian Task Force on Preventive Health Care published a guideline on screening for depression among adults (18 years or older) at average or high risk for depression. In 2013, the task force released an updated guideline. The systematic review on which this paper is based provided evidence for that 2013 update.

The World Health Organization (WHO) Psychological Problems in General Health Care study, released in 1996, reported that primary care physicians diagnosed major depression in only 42% of adult patients who had the condition. The potential benefits of screening for depression in adults include improved detection of major depressive disorder, dysthymia and subsyndromal depression. Improvements in detection can lead to earlier treatment, and treatment of major depressive disorder in adults is thought to result in improved outcomes, such as better quality of life, better work life and minimization of the risk of suicide. One argument against screening is that screening instruments have low positive predictive value, meaning that many people with a positive screening result do not have depression. Although a previous review found no literature specifically evaluating the harms associated with screening for depression and related disorders, those with positive screening results who do not have the disorder may be exposed to stigmatization and further psychologic testing, as well as unnecessary psychologic and pharmacologic treatment regimes.

In preparing to update the guideline, the Canadian Task Force on Preventive Health Care undertook a de novo review, given the guideline’s focus on a comparison between screening for depression in people with no apparent symptoms versus no screening at all. This approach is not consistent with the 2013 update of the Canadian guideline and would not be justified in existing guideline recommendations that discuss the benefits and harms of screening for depression in average-risk or high-risk populations.
screening. Our review thus differed from the reviews by Pignone and colleagues and O’Connor and colleagues, which served as the evidentiary base for the 2009 US Preventive Services Task Force screening recommendations for adults. Those reviews included studies in which all members of the population were screened, the comparisons being treatment versus no treatment or feedback (providing depression score to the patient or physician) versus no feedback. The review by Gilbody and colleagues was also outside the scope of our review, because it was a review of depression screening tools.

In the current systematic review, we explored the benefits and harms of screening for depression in asymptomatic adults 18 years of age or older from the general population (at average risk for depression) and in adults at high risk for depression in both primary care and other outpatient settings.

**Methods**

The search strategy was developed by a librarian (M.R.) experienced in searches for systematic reviews. We searched several electronic databases, specifically MEDLINE, Embase, PsycINFO, the Cochrane Central Register of Controlled Trials and the Cochrane Database of Systematic Reviews, for the period 1994 to May 23, 2012. The MEDLINE search was updated in April 2013, 6 weeks before publication of the guideline, to identify any recent, potentially relevant randomized controlled trials. The search was broad, the only limitations being date of publication, research subjects (limited to humans) and language (English or French) (see Appendix 1 at www.cmajopen.ca/content/1/4/E159/suppl/DC1). In addition, we searched the grey literature (primarily Canadian sources) up to May 2012, using a number of keyword terms for depression and screening.

Eligible studies were those involving adults at least 18 years of age from unselected populations or high-risk groups (see Appendix 2 at www.cmajopen.ca/content/1/4/E159/suppl/DC1). The intervention of interest was routine screening, and we considered studies of any design that compared screening with no screening. The study settings were primary care or, for high-risk groups, specialty clinics. The outcomes of interest were quality of life, rates of suicidality (attempts or ideation), all-cause mortality, depression-related mortality, rates of hospital admission and changes in symptoms of depression (treatment response or remission). The harms of screening were screened all identified citations for relevance, inclusion criteria and study quality and performed the data extraction. Potentially relevant citations went through 2 levels of title and abstract screening. The first screening was broad, to eliminate citations that were obviously not on topic; the second screening had more specific exclusion criteria, such as age less than 18 years and study not representing primary research on screening. Any citation deemed potentially relevant was retrieved for full review. Pairs of reviewers (as described above) independently reviewed the potentially relevant studies, and for any studies excluded at this stage, agreement about the reason for exclusion was required. All disagreements were resolved through discussions. Reference lists of on-topic systematic reviews retained for analysis were searched to ensure that we considered all primary studies meeting our inclusion criteria.

**Quality assessment**

We used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system to determine the quality of the evidence. This widely used system has been endorsed by over 40 major organizations, including the WHO, the US Centers for Disease Control and Prevention, and the US Agency for Healthcare Research and Quality. GRADE considers 5 criteria (design, consistency, directness, precision and reporting bias) to rate the quality of evidence as high, moderate, low or very low; these ratings represent an assessment of the likelihood that further research will lead to changes in the estimate of effect. We assessed the risk of bias with the Newcastle–Ottawa tool. Two of the authors (H.K. and D.F.L.) independently assessed the evidence according to these criteria and reached agreement on the ratings and the overall quality of the summary statistics.

**Statistical analysis**

In the included studies, data were obtained before (baseline) and after implementation of the intervention or control measure. Two of the 5 identified papers included 2 control groups; the remaining 3 studies each had 1 control group. Four out of the 5 papers presented data using adjusted incidence rate ratios (IRR) and one reported adjusted odds ratios. This variation in data presentation necessitated calculation of the ratio of rate ratios (RRR) for each group (i.e., ratio of postimplementation rate to preimplementation rate in the geographic area where the intervention was applied divided by the corresponding ratio of postimplementation rate to preimplementation rate in the control area). We used Cochrane Review Manager software (RevMan, version 5.1, Nordic Cochrane Centre of the Cochrane Collaboration, Copenhagen, Denmark) to conduct the meta-analysis.

We calculated a weighted intervention effect across studies using data for overall population and data stratified by age and sex. An RRR of less than 1.0 indicates a reduction in the outcome IRR. We calculated standard errors for logarithms of rate ratios and 95% confidence intervals (CIs) for the RRR values, assuming that the number of events in each study area in each
Results

Study selection and characteristics

Our search identified 14,226 potentially relevant citations (Figure 1). Of these, 12,694 were excluded after screening of titles and abstracts. We retrieved a total of 1,532 papers and assessed them against the inclusion criteria; 1,527 of these papers were excluded. Five quasi-experimental studies (before–after design with a nonrandomized control group), all with the same first author, met the inclusion criteria and provided the evidence for the review questions (Table 1).17–21

Average-risk populations

The first question of interest for this review was, “What is the evidence for the benefit (i.e., improvement in clinical outcomes) of screening for depression in asymptomatic adults (18 years of age or older) from the general population, in either primary care or other outpatient settings?” No studies of...
screening for depression in the average-risk population as a whole met the inclusion criteria of this review. The 5 included studies focused on community-based screening for depression among older people (i.e., age ≥ 60 or age ≥ 65, depending on the study). These studies were conducted in rural regions of Japan, where suicide rates among older people ranged from 50 to 418 per 100 000 among women and from 113 to 326 per 100 000 among men. Oyama and associates developed a universal suicide prevention program, which included a screening component adapted from the WHO World Mental Health Survey. The program involved screening for depression, follow-up with mental health care or psychiatric treatment, and psychoeducation in the community setting. The control communities had similar demographic characteristics and were in the same geographic region as the intervention communities, but they received no components of the pro-

<table>
<thead>
<tr>
<th>Study</th>
<th>Description</th>
<th>Definition</th>
<th>Evaluation</th>
<th>Outcomes</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oyama et al. (5-yr quasi-experimental study in Matsudai, Japan [rural])</td>
<td>Total person-years: 11 567 for intervention, 15 055 for control</td>
<td>Older (≥ 65 yr) residents in 6 rural municipalities of southwest and central Japan</td>
<td>Screening instrument: SDS Other rating: RDC Confirmatory exam: ICD-9 No. of follow-up: 10 No. of stages: two 10-yr</td>
<td>Main outcome: Change in risk of completed suicide after intervention or control</td>
<td>Main outcome: Risk of completed suicide in intervention area reduced by 70% among women, no significant change among men Intervention: IRR 0.14–0.93) for women and 0.36 (95% CI 0.22–1.19) for men and 0.30 (95% CI 0.14–0.67) for women Control: No significant change</td>
</tr>
<tr>
<td>Oyama et al. (10-yr quasi-experimental study in Yasuzuka, Japan [rural])</td>
<td>Total person-years: 9791 for intervention, 16 032 for control</td>
<td>Older (≥ 65 yr) residents of agricultural rural area in Japan with high suicide rate</td>
<td>Screening instrument: SDS Other rating: RDC Confirmatory exam: ICD-9 No. of follow-ups: 7 No. of stages: two 10-yr</td>
<td>Main outcome: Change in risk of completed suicide after intervention or control</td>
<td>Main outcome: Risk of completed suicide in intervention area reduced by 64% among women, no significant change among men Intervention: IRR 0.51 (95% CI 0.22–1.19) for men and 0.36 (95% CI 0.14–0.83) for women Control: No significant change</td>
</tr>
<tr>
<td>Oyama et al. (10-yr quasi-experimental study in Joboji town, Japan [rural])</td>
<td>Total person-years: 9721 for intervention, 17 166 for control</td>
<td>Older (≥ 65 yr) residents of agricultural rural area in Japan with high suicide rate</td>
<td>Screening instrument: SDS Other rating: SADD Confirmatory exam: ICD-9 No. of follow-ups: 10 No. of stages: three 5-yr</td>
<td>Main outcome: Change in suicide rates</td>
<td>Main outcome: Risk of suicide in intervention area reduced by 73% among men and by 76% among women during implementation decade (relative to pre-implementation decade) Intervention: IRR 0.27 (95% CI 0.08–0.88) for men and 0.24 (95% CI 0.11–0.52) for women Control: No significant change</td>
</tr>
</tbody>
</table>

Continued
term and the long term. The outcome of interest was community-based depression screening program over both the short and long term. The overall aim of the studies was to evaluate the effectiveness of the community-based depression screening program over both the short and long term. The inclusion criteria were residents living in 6 rural municipalities of the Sanpachi Second Medical Zone of Japan (mostly agricultural region with high suicide rate). The nurses used Japanese translations of a standardized psychologic and somatic symptoms assessment for patients with depressive disorders and made a clinical decision about whether a medical examination by a psychiatrist was necessary. In all studies, more than 60% of men and more than 80% of women within the targeted groups of residents participated in the program during the implementation period.

All 5 studies involved implementation of the suicide prevention program, which had a 2-step process for screening and follow-up for depression. In the first step, older residents within the selected communities were called with an invitation to participate in an educational health workshop on the signs of and possible treatments for depression and suicide risk and also on how to use mental health services. Following the workshop, those who agreed to participate in the program completed the Japanese version of the Zung Self-rating Depression Scale, a 20-item scale that measures affective, psychologic and somatic symptoms associated with depression (used in all 5 of the included studies), or the 5-item Geriatric Depression Scale (used in 1 of the included studies). Those who did not attend the workshop were contacted the following day and asked to participate in the program. Examiners then visited all those who agreed to participate and conducted the suicide prevention program according to the same procedures. There were several examiners, including psychiatrists and public health nurses.

In the second step, public health nurses conducted a mental health assessment for each enrolled participant who had a positive screening result on the Self-rating Depression Scale. The nurses used Japanese translations of a standardized assessment for patients with depressive disorders and made a clinical decision about whether a medical examination by a psychiatrist was necessary.

<table>
<thead>
<tr>
<th>Study</th>
<th>Description</th>
<th>Definition</th>
<th>Evaluation</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oyama et al. (5-yr quasi-experimental study in Nagawa town, Japan [rural])</td>
<td>Total person-years: 1982 for intervention, 16754 for control</td>
<td>Older (≥ 65 yr) residents of agricultural rural area in Japan with high suicide rate</td>
<td>Screening instrument: SDS Other rating: RDC Confirmatory exam: ICD-9 No. of follow-ups: 6 No. of stages: two 6-yr</td>
<td>Main outcome: Change in risk of completed suicide Age-adjusted IRRs of completed suicide before and after intervention or control</td>
</tr>
<tr>
<td></td>
<td>Age, mean: NR Age, range: ≥ 65 yr Age, median: NR Sex, female: 59%–60.8% Ethnicity: Japanese Education: NR Dx: depression (unspecified)</td>
<td></td>
<td></td>
<td>Main outcome: Risk of suicide in intervention area reduced by 74% among women, no significant change among men</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Intervention: IRR 0.48 (90% CI 0.10–2.31) for men and 0.26 (90% CI 0.07–0.98) for women</td>
</tr>
<tr>
<td>Oyama et al. (5-yr quasi-experimental study in 6 rural municipalities of the Sanpachi Second Medical Zone, Japan [rural])</td>
<td>Total person-years: 28838 for intervention, 27633 for control</td>
<td>Older (≥ 60 yr) residents living in 6 rural municipalities of Sanpachi Second Medical Zone of Japan (mostly agricultural region with high suicide rate)</td>
<td>Screening instrument: CES-D, DSS, SDS, GDS-5 Other rating: CIDI Confirmatory exam: ICD-10 No. of follow-ups: 2 No. of stages: two 2-yr</td>
<td>Main outcome: Change in risk of completed suicide Age-adjusted IRRs of completed suicide before and after intervention or control</td>
</tr>
<tr>
<td></td>
<td>Age, mean: NR Age, range: ≥ 60 yr Age, median: NR Sex, female: 57.5% Ethnicity: Japanese Education: NR Dx: depression (unspecified)</td>
<td></td>
<td></td>
<td>Main outcome: Risk of suicide in intervention region reduced by 61% among men; no significant change among women</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Intervention: IRR 0.39 (90% CI 0.18–0.87) for men and 0.49 (90% CI 0.19–1.22) for women</td>
</tr>
</tbody>
</table>

Note: CES-D = Center for Epidemiologic Studies Depression Scale, CI = confidence interval, CIDI = Composite International Diagnostic Interview, DSS = Depression and Suicide Screen, Dx = diagnosis, GDS-5 = 5-item Geriatric Depression Scale, ICD = International Statistical Classification of Diseases, IRR = incidence rate ratio, NR = not reported, PHN = public health nurse, RDC = Research Diagnostic Criteria, SADD = schedules of Standardized Assessment of Patient with Depressive Disorders, SDS = Self-rating Depression Scale.
The meta-analysis of the target population involved 70,053 person-years and 65 completed suicides in the intervention groups and 113,324 person-years and 145 completed suicides in the control groups during the respective implementation periods. On the basis of the information provided in the included studies (specifically, average population sizes over 5 years and average percentage of people over the age of 65), we estimated that the overall sample sizes were 18,311 for the intervention groups and 19,736 for the control groups. The studies reported 6 sex- and age-specific target population groups (men and women aged 65–74, 75–84 and ≥ 85), with the exception of one study, which used age groups 60–69, 70–79 and ≥ 80. All 5 studies presented data stratified by age, sex and time periods for baseline and program implementation.

<table>
<thead>
<tr>
<th>Study</th>
<th>Log RRR</th>
<th>SE</th>
<th>Weight (%)</th>
<th>RRR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oyama et al.17</td>
<td>−1.23</td>
<td>0.43</td>
<td>21.5</td>
<td>0.29 (0.13–0.68)</td>
</tr>
<tr>
<td>Oyama et al.19</td>
<td>−0.31</td>
<td>0.41</td>
<td>23.2</td>
<td>0.73 (0.33–1.64)</td>
</tr>
<tr>
<td>Oyama et al.20</td>
<td>−0.19</td>
<td>0.38</td>
<td>26.0</td>
<td>0.83 (0.39–1.74)</td>
</tr>
<tr>
<td>Oyama et al.18</td>
<td>−0.99</td>
<td>0.68</td>
<td>9.9</td>
<td>0.37 (0.10–1.41)</td>
</tr>
<tr>
<td>Oyama et al.21</td>
<td>−1.07</td>
<td>0.46</td>
<td>19.4</td>
<td>0.34 (0.14–0.84)</td>
</tr>
<tr>
<td>Overall (I² = 21%)</td>
<td></td>
<td></td>
<td></td>
<td>0.50 (0.32–0.78)</td>
</tr>
</tbody>
</table>

Test for overall effect: Z = 3.06 (p = 0.002)

Figure 2: Meta-analysis of the effect of community-based suicide prevention programs, including screening for depression, on suicide rates reported in cohort studies. A rate ratio (RR) less than 1.0 indicates a benefit of suicide prevention programs. CI = confidence interval; RRR = ratio of rate ratios (rate ratio for intervention divided by rate ratio for control), where RRR less than 1.0 indicates a benefit of suicide prevention programs; SE = standard error.

<table>
<thead>
<tr>
<th>Study</th>
<th>Log RRR</th>
<th>SE</th>
<th>Weight (%)</th>
<th>RRR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oyama et al.17</td>
<td>−1.36</td>
<td>0.69</td>
<td>8.6</td>
<td>0.26 (0.07–0.99)</td>
</tr>
<tr>
<td>Oyama et al.20</td>
<td>0.42</td>
<td>0.54</td>
<td>14.1</td>
<td>1.52 (0.53–4.39)</td>
</tr>
<tr>
<td>Oyama et al.19</td>
<td>−0.18</td>
<td>0.57</td>
<td>12.7</td>
<td>0.84 (0.27–2.55)</td>
</tr>
<tr>
<td>Oyama et al.18</td>
<td>−0.30</td>
<td>1.01</td>
<td>4.0</td>
<td>0.74 (0.10–5.36)</td>
</tr>
<tr>
<td>Oyama et al.21</td>
<td>−0.91</td>
<td>0.62</td>
<td>10.7</td>
<td>0.40 (0.12–1.36)</td>
</tr>
<tr>
<td>Overall (men) (I² = 21%)</td>
<td></td>
<td></td>
<td></td>
<td>0.67 (0.35–1.27)</td>
</tr>
</tbody>
</table>

Test for overall effect: Z = 3.06 (p = 0.002)

<table>
<thead>
<tr>
<th>Study</th>
<th>Log RRR</th>
<th>SE</th>
<th>Weight (%)</th>
<th>RRR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oyama et al.17</td>
<td>−1.15</td>
<td>0.56</td>
<td>13.1</td>
<td>0.32 (0.11–0.95)</td>
</tr>
<tr>
<td>Oyama et al.19</td>
<td>−0.46</td>
<td>0.61</td>
<td>11.1</td>
<td>0.63 (0.19–2.09)</td>
</tr>
<tr>
<td>Oyama et al.18</td>
<td>−1.58</td>
<td>0.94</td>
<td>4.7</td>
<td>0.21 (0.03–1.30)</td>
</tr>
<tr>
<td>Oyama et al.20</td>
<td>−0.87</td>
<td>0.57</td>
<td>12.7</td>
<td>0.42 (0.14–1.28)</td>
</tr>
<tr>
<td>Oyama et al.21</td>
<td>−1.25</td>
<td>0.70</td>
<td>8.4</td>
<td>0.29 (0.07–1.13)</td>
</tr>
<tr>
<td>Overall (women) (I² = 0%)</td>
<td></td>
<td></td>
<td></td>
<td>0.37 (0.21–0.66)</td>
</tr>
</tbody>
</table>

Test for overall effect: Z = 3.06 (p = 0.002)

Figure 3: Meta-analysis of the effect of community-based suicide prevention programs, including screening for depression, on suicide rates by sex, as reported in cohort studies. A rate ratio (RR) less than 1.0 indicates a benefit of suicide prevention programs. CI = confidence interval; RRR = ratio of rate ratios (rate ratio for intervention divided by rate ratio for control), where RRR less than 1.0 indicates a benefit of suicide prevention programs; SE = standard error.
The outcome measure in each study was an IRR based on binary data (i.e., suicide/no suicide, calculated for both implementation and control groups before and after the intervention). There was no significant heterogeneity among the studies ($F = 21\%, \chi^2 = 5.04, p = 0.28$). When the data for men and women were analyzed separately, there was no significant heterogeneity among the studies (for men, $F = 21\%, \chi^2 = 5.07, p = 0.28$; for women, $F = 0\%, \chi^2 = 1.41, p = 0.84$). Publication bias could not be assessed because the number of included studies was small.

The difference between pooled IRRs and corresponding 95% CIs for completed suicide was calculated using the generic inverse variance weighting method for the overall study population and for women and men separately. The pooled data from the 5 studies showed a statistically significant reduction in the number of completed suicides after implementation of the community-based depression screening program (RRR 0.50, 95% CI 0.3–0.78) (Figure 2). RRRs also indicated a significant reduction in the suicide rate among women (RRR 0.37, 95% CI 0.21–0.66) but no significant effect among men (RRR 0.67, 95% CI 0.35–1.27) (Figure 3).

### High-risk populations

We found no studies that examined the benefits of screening high-risk populations (defined using the factors in Appendix 2) versus not screening.

### Harms of screening

The second question of interest for this review was “What is the evidence for harm (i.e., decline in clinical outcomes) of screening for depression in asymptomatic adults from the general population, in either primary care or other outpatient settings?” We found no studies meeting our inclusion criteria that could help to answer this question.

### GRADE rating

According to the GRADE system for assessing quality, observational evidence (including evidence from studies with a cohort design) begins with a “low” rating. We downgraded the rating because of indirectness, given that the included studies all involved older populations in a rural Japanese setting, who are unlikely to be representative of Canadians. We also downgraded the evidence because the studies used community-based depression screening programs that incorporated education and treatment; as such, their results cannot be attributed solely to the screening component of the programs. Thus, the overall GRADE rating applied to this evidence was very low quality (see Table 2).

### Interpretation

We found no direct evidence for benefit of screening in the average-risk population; rather, we identified 5 studies of older populations conducted by the same primary researcher in rural Japan. Although these 5 studies met the inclusion criteria for our review, their results provide limited evidence on the effectiveness of screening for depression in the average-risk population or high-risk groups. The potential generaliz-
ability of the findings of these studies should be considered with caution, as Japan has a national suicide rate much higher than that in Canada or the United States. Among Japanese women 75–84 years of age, for whom benefit of screening was observed in the included studies, the suicide rate is more than 7 times higher than among Canadian women of the same age group (23.4 v. 3.3 per 100 000, respectively).26 In addition, the geographic regions included in the study had average rates of suicide much higher than even the Japanese average.27–29 We can draw no conclusions about the potential harms of screening for depression, as we found no studies of such harms that met our inclusion criteria.

These results are consistent with previous guidelines and evidence reviews. The 2009 systematic evidence review of the US Preventive Services Task Force30 found no evidence of any benefit of screening for depression in the absence of treatment programs. The lack of direct evidence to support general screening programs has also been recognized by the National Institute for Health and Care Excellence31 and the Scottish Intercollaborating Guidelines Network.32 neither of these organizations recommend screening of asymptomatic people in the general population. The National Institute for Health and Care Excellence guideline for people with chronic illness recommended that physicians remain alert to the possibility of depression,33 and another guideline for perinatal women34 recommended screening women postpartum, yet those recommendations were based on indirect evidence of a benefit of treatment, rather than direct evidence of effectiveness of screening or case-finding for depression.

Limitations
The findings of this review are affected by the limitations of the literature search and of the studies that were included. Because of resource limitations, we limited our search to papers written in English or French, as those could be assessed by the team. It is possible that we missed papers written in other languages.12 We chose 1994 as the start date for the search, as that was the publication date for the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders, which changed the definition of major depression.35 The studies that were reviewed here evaluated the effectiveness of community-based depression screening programs that incorporated screening for depression, follow-up with mental health care or psychiatric treatment, and health education in community settings in rural Japan that had higher-than-average suicide rates. As such, the observed reduction in suicide rates or recovery from depression cannot be attributed solely to the screening component of these programs. As well, given that the program involved community psychoeducation, it is likely that people in the area were more aware of depression and suicide, which may have altered the reporting of deaths as suicide.

Conclusion
The ultimate goal of screening for depression is to reduce associated morbidity and mortality. This review found limited evidence to estimate the effectiveness of screening for depression in primary care among individuals at average risk for depression, no evidence of screening in high-risk populations and no evidence of the harms of screening. Randomized controlled trials comparing screening and no screening should help to clarify these issues. Future research must have a broader demographic, geographic and cultural scope. Trials on the effectiveness of screening among people who are at increased risk of major depressive disorder are also needed to help in the early diagnosis and treatment of those most likely to be affected by depression. More evidence is needed on the harms of screening for depression (e.g., false positive rates) and the related potential for unnecessary, and possibly harmful, diagnostic and therapeutic procedures. Finally, more research on the most effective method of screening for depression in relation to clinically important outcomes is needed in populations with increased risk of depression.

References

**Affiliations:** McMaster Evidence Review and Synthesis Centre and Department of Clinical Epidemiology and Biostatistics (Keshavarz, Rice, Ali, Shannon, Raina); McMaster Evidence Review and Synthesis Centre and School of Nursing (Fitzpatrick-Lewis); Department of Psychiatry and Behavioural Neurosciences (Streiner), McMaster University, Hamilton, Ont.; Department of Psychiatry (Streiner), University of Toronto, Toronto, Ont.

**Contributors:** Homa Keshavarz, Donna Fitzpatrick-Lewis, David Streiner, Maureen Rice, Usman Ali, and Parminder Raina were involved in conceptualizing the study, analyzing the data and writing the manuscript. Harry Shannon contributed to analyzing the data and provided manuscript revisions. Homa Keshavarz and Donna Fitzpatrick-Lewis were also involved in designing the methods, collecting the data and coordinating the project. Maureen Rice performed the literature search. All of the authors approved the final manuscript.

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**Supplemental information:** For reviewer comments and the original submission of this manuscript, please see www.cmajopen.ca/content/1/4/E159/suppl/DC1

**Editor's note:** This paper is based on a full systematic review entitled “Screening for depression,” which can be found at: http://canadiantaskforce.ca/guidelines/depression/
Depression is a mood disorder that affects the way a person feels, thinks or behaves, which may impair social or occupational functioning. The onset of depression can be triggered by biological, psychosocial or environmental factors, such as traumatic life events. Those who experience an episode of depression are at increased risk of experiencing future episodes. Major depression is characterized by 1 or more major depressive episodes. A major depressive episode is defined by the presence of 5 or more of 9 key symptoms of depression during a 2-week period and a change from previous functioning (Box 1).

The 2002 Canadian Community Health Survey reported that 1 in every 8 adults met the criteria for major depression at some point during their lifetime and that 1 in every 20 individuals aged 15 or older met the criteria in the past 12 months. In 2005, the 1-year incidence of major depressive disorder was estimated at 3% (1 in every 30 Canadians was newly diagnosed with depression in a 1-year period). (See Box 2 for definitions of screening, incidence and prevalence.)

Certain subgroups of the population have a higher prevalence of depression than others. There is a strong association between some chronic medical conditions (with or without pain) and an increased prevalence of major depression. Major depression is also more common among people of Aboriginal origin, women during the postpartum period and people with a history of substance abuse.

Long-term consequences of depression include reduced quality of life, risk of suicide, increased rates of hospital admission, and an increased risk of chronic physical conditions. Major depression is among the leading causes of disability-adjusted life-years worldwide. In addition, the economic burden of depression is considerable: in Canada alone, the estimated annual productivity losses owing to depression were $4.5 billion in 1998.

Because depression is potentially treatable, there has been interest in screening patients who present to primary care settings. However, guidelines on screening for depression differ between countries. The US Preventive Services Task Force recommends universal screening where supports are in place to ensure appropriate follow-up. The UK National Institutes for Health and Clinical Excellence recommends targeted case identification (people with a history of depression or with current chronic physical health problems and associated functional impairment, or both) rather than general population screening.

This document updates the 2005 Canadian Task Force on Preventive Health Care guideline, which recommended screening for depression in adults in primary care settings with both feedback to the clinician regarding depression status and a system for managing treatment (antidepressant medications and psychotherapeutic interventions). The absence of current Canadian recommendations, the high prevalence of major depression in the Canadian population and the difference in recommendations between countries during the past 12 years were the basis for revisiting this topic. This update was produced using the revised methodology of the task force and is based on current evidence of the harms and benefits of screening for depression.

**Key points**

- The systematic review for this guideline did not identify high-quality evidence of the effectiveness of screening for depression.
- Although the systematic review did not identify direct evidence of the harms of screening, we remain concerned about false-positive diagnoses with unnecessary treatment.
- For adults with no apparent symptoms of depression, who are at average risk of depression or who may be at increased risk of depression, we recommend not routinely screening for depression in primary care settings.
- Clinicians should be alert to the possibility of depression, especially in patients with characteristics that may increase their risk of depression, and should look for it when there are clinical clues, such as insomnia, low mood, anhedonia and suicidal thoughts.
- Randomized controlled trials with an unscreened control group that evaluate the effect of screening for depression on clinically relevant outcomes should be a high research priority, especially in populations at increased risk of depression.
Guidelines

Methods

The Canadian Task Force on Preventive Health Care is an independent panel of clinicians and methodologists that makes recommendations about clinical manoeuvres aimed at primary and secondary prevention (www.canadiantaskforce.ca). Work on each set of recommendations is led by a workgroup of 2 to 6 members of the task force. Each workgroup establishes the research questions and analytical framework for the guideline.

The current work was led by a workgroup of 6 members of the task force, supported by scientific staff at the Public Health Agency of Canada and the University of Alberta (members of the guideline writing group are listed at the end of the article). The research questions and analytical framework for this guideline (available in Appendix 1) were incorporated into the search protocol. The task force chose to focus on clinically relevant outcomes: quality of life, rates of suicidality (attempts or ideation), all-cause mortality, depression-related mortality, rates of hospital admission and changes in symptoms of depression (treatment response or remission).

The recommendations were revised and approved by the entire task force and underwent external review by experts in the field and by stakeholders. Details about the task force’s methods can be found elsewhere. The systematic review on which the recommendations are based was performed independently by the Evidence Review and Synthesis Centre at McMaster University. The review was performed according to the final, peer-reviewed protocol (available at http://canadiantaskforce.ca/wp-content/uploads/2012/12/Proposal-Screening-for-Depression-120312_FINAL_2.pdf?9d7bd4). The task force used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system to determine the quality of evidence and strength of recommendations (Box 3).

Recommendations

A summary of the recommendations for clinicians and policy-makers is shown in Box 4 and Appendix 2. More detailed explanations of the evidence base of the recommendations are available in Appendix 3.

Adults at average risk

For adults at average risk of depression, we recommend not routinely screening for depression. (Weak recommendation; very-low-quality evidence.)

The systematic review for this guideline did not find any studies evaluating the benefits of screening the average-risk population for depression in primary care settings. The review found 5 quasi-experimental studies (before–after design with a nonrandomized control group) that examined the effect of community-based screening for depression on suicide rates among people aged 65 and older (Table 1). These 5 studies were conducted in Japanese rural regions with suicide rates that ranged from 49.6 to 418.4 per 100 000 among women and 113 to 326 per 100 000 among men. All of the studies showed a statistically significant reduction in the number of completed suicides after implementation of the program (relative risk reduction 0.51, 95% confidence interval 0.34–0.75). However, these studies have several important methodological limitations that compromise their internal validity. For example, it is uncertain what portion of

Box 1: Definition of a major depressive episode according to DSM-IV-TR criteria

A major depressive episode is defined by the presence of 5 or more of the following 9 key symptoms of depression during a 2-week period and a change from previous functioning. At least 1 of the symptoms is either depressed mood or loss of interest:

- Depressed mood most of the day, nearly every day, as indicated either by subjective report (e.g., feels sad or empty) or observations made by others (e.g., appears tearful).
- Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated either by subjective account or observation made by others).
- Significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day.
- Insomnia or hypersomnia nearly every day.
- Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down).
- Fatigue or loss of energy nearly every day.
- Feeling of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick).
- Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others).
- Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or specific plan for committing suicide.


Box 2: Defining incidence and prevalence

- By definition, screening is used to identify only new cases of depression. Screening does not apply to patients who are known to have depression, have a history of depression or are receiving treatment for depression.
- "Incidence" refers to new cases of depression. "Prevalence" refers to the presence of depression during a specified period regardless of when the episode began; it includes new, recurrent and chronic cases.
the reported outcomes involved people who actually received the intervention. The number of reported suicides (before and after the intervention) was based on independent statistics reported by the local health agency, not a follow-up of people who were screened. Also, because of the community-based nature of the intervention, there is a particularly high risk of bias, because the people classifying the deaths as suicides were not blinded to the group assignments. Given that the studies compared a small number of suicides in both the intervention and control groups, any influence on even a few classifications could have affected the results.

Further, the generalizability of these results to the Canadian population is uncertain given that the prevalence of depression among older people living in the rural Japanese communities is 5 times higher than the prevalence among older Canadians as a whole (10.4% v. 2%). and the suicide rate among elderly Japanese women is more than 7 times higher than the rate among comparably aged Canadian women (23.4 v. 3.3 per 100 000 among women aged 75–84 yr). Other factors that limit the applicability of these results are the cultural and social differences between Canada and Japan.

Previous reviews included multiple studies in which both the treatment and control groups were screened, with only the former receiving treatment if depression was found (Appendices 4 and 5). Rather than studying the effect of screening per se, such studies actually compared the addition of treatment to screening alone. In addition, screening all participants may increase awareness of depressive symptoms, which can either overestimate or underestimate any benefits. If participants in the control group are more aware of their symptoms, they may present themselves as more depressed, inflating apparent differences between groups. If, on the other hand, screening leads participants in the control group to engage in some form of treatment (this could be as simple as exercise or self-care), the apparent differences between the 2 groups may be reduced.

The systematic review for the current guideline did not identify any eligible studies measuring the harms of screening for depression. Potential harms of screening include false-positive diagnoses, with subsequent unnecessary treatment; adverse effects of medical therapy among people correctly identified as having depression; and the consequences of labelling and stigma.

By definition, any health benefits of screening would accrue among newly identified cases of depression (not among patients who are known to have depression or are receiving treatment). Detecting new cases of depression and treating patients identified as having depression is a desired outcome of screening but does not constitute a health benefit by itself. The net benefit of screening would depend on earlier identification and successful treatment and would require that the benefits of such treatment outweigh any harms, such as adverse effects of medications.

**Box 3: Grading of recommendations**

- Recommendations are graded according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system. GRADE offers 2 strengths of recommendation: strong and weak. The strength of recommendations is based on the quality of supporting evidence, the degree of uncertainty about the balance between desirable and undesirable effects, the degree of uncertainty or variability in values and preferences, and the degree of uncertainty about whether the intervention represents a wise use of resources.
- Strong recommendations are those for which the task force is confident that the desirable effects of an intervention outweigh its undesirable effects (strong recommendation for an intervention) or that the undesirable effects of an intervention outweigh its desirable effects (strong recommendation against an intervention). A strong recommendation implies that most people will be best served by the recommended course of action.
- Weak recommendations are those for which the desirable effects probably outweigh the undesirable effects (weak recommendation for an intervention) or undesirable effects probably outweigh the desirable effects (weak recommendation against an intervention) but appreciable uncertainty exists. A weak recommendation implies that most people would want the recommended course of action, but many would not. For clinicians, this means they must recognize that different choices will be appropriate for each individual, and they must help each person arrive at a management decision consistent with his or her own values and preferences. Policy-making will require substantial debate and involvement of various stakeholders. Weak recommendations result when the balance between desirable and undesirable effects is small, the quality of evidence is lower, or there is more variability in the values and preferences of patients.
- Evidence is graded as high, moderate, low or very low, based on how likely further research is to change our confidence in the estimate of effect.

The GRADE companion document to task force guidelines is available at www.canadiantaskforce.ca/guidelines/other-publications/

**Box 4: Summary of recommendations for clinicians and policy-makers**

Recommendations on screening for depression in primary care settings are provided for people 18 years of age or older who present at a primary care setting with no apparent symptoms of depression. These recommendations do not apply to people with known depression, with a history of depression or who are receiving treatment for depression.

- For adults at average risk of depression,* we recommend not routinely screening for depression. (Weak recommendation; very-low-quality evidence)
- For adults in subgroups of the population who may be at increased risk of depression,† we recommend not routinely screening for depression. (Weak recommendation; very-low-quality evidence)

*The average-risk population includes all individuals 18 years of age or older with no apparent symptoms of depression who are not considered to be at increased risk.
†Subgroups of the population who may be at increased risk of depression include people with a family history of depression, traumatic experiences as a child, recent traumatic life events, chronic health problems, substance misuse, perinatal and postpartum status, or Aboriginal origin.
Table 1: Summary of the evidence of benefits associated with screening for depression through community-based suicide prevention*

<table>
<thead>
<tr>
<th>No. of studies</th>
<th>Quality assessment</th>
<th>Summary of findings</th>
<th>GRADE quality of evidence</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Design</td>
<td>Risk of bias</td>
<td>Inconsistency</td>
<td>Indirectness</td>
</tr>
<tr>
<td>5 studies 19-23*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age 65-74 yr</td>
<td>Observational</td>
<td>Not serious†</td>
<td>No serious inconsistency†</td>
<td>Very serious§</td>
</tr>
<tr>
<td></td>
<td>studies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age 75-84 yr</td>
<td>Observational</td>
<td>Not serious†</td>
<td>No serious inconsistency†</td>
<td>Very serious§</td>
</tr>
<tr>
<td></td>
<td>studies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age ≥ 85 yr</td>
<td>Observational</td>
<td>Not serious†</td>
<td>No serious inconsistency†</td>
<td>Very serious§</td>
</tr>
<tr>
<td></td>
<td>studies</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: CI = confidence interval, GRADE = Grading of Recommendations Assessment, Development and Evaluation, RR = risk ratio.

*Our systematic review of benefits associated with screening for depression in adults17 identified 5 quasi-experimental studies with control groups (before–after design with a nonrandomized control group).

†The quality-assessment tools identified a few issues with the studies (e.g., selection of non-exposed cohort, blinding and reporting of withdrawals and dropouts); however, the evidence was not downgraded for these reasons.

‡No significant heterogeneity (I² = 0%).

§Directness was downgraded because of concerns regarding characteristics of the study populations. All of the included studies focused on elderly Japanese populations in rural areas, which are unlikely to be representative of Canadians at average or increased risk of depression. Directness was downgraded for the second time because of concerns regarding the nature of the screening programs: the studies reviewed here evaluated the effectiveness of community-based programs of screening for depression, which incorporated screening for depression, follow-up with mental health care or psychiatric treatment, and health education in the community setting. As such, the observed reduction in suicide rates cannot be attributed solely to the screening component of these programs.

¶The number of events is small (< 300, a threshold rule-of-thumb value for dichotomous outcomes); however, given the specific outcome, the evidence was not downgraded.

**Insufficient number of included studies (n = 5) to assess publication bias with confidence (≥ 10 papers is the threshold rule-of-thumb value).
Weighing the likelihood of such a net benefit requires consideration of several factors. First, the effectiveness of screening tools in identifying new cases of depression (the objective of screening) is uncertain. Second, evidence shows that people with mild depression may not benefit from treatment, which suggests that some treatments triggered by screening are actually unnecessary. Third, some patients with diagnosed depression will decide not to accept treatment or will stop treatment prematurely, before remission, in which case screening will likely not lead to benefit. Given the lack of evidence for net benefit, the task force recommends against routine screening for depression in people at average risk in primary care settings.

This recommendation places a relatively high value on the importance of showing a clear net benefit before recommending routine screening for an entire population, and on the potential harms that may result from screening. The recommendation places a relatively low value on the unproven likelihood that early identification and subsequent treatment of depression may lead to better health outcomes. Physicians who believe that their patients (or a subset of their patients) place a high value on the potential benefits of screening for depression and are less concerned with the potential harms could reasonably choose to implement screening for depression in these patients.

Adults at increased risk
For adults in subgroups of the population who may be at increased risk of depression, we recommend not routinely screening for depression. (Weak recommendation; very-low-quality evidence.)

The incidence of depression (and prevalence of undetected depression) may be higher in populations at increased risk, which in theory would be expected to favourably influence the potential benefit of screening. However, the efficacy and adverse effects of treatment, the performance of screening tools and the possibility of harms likely also differ among subgroups of the population who may be at increased risk of depression. Therefore, one cannot assume that screening will benefit people at increased risk simply because they may have a higher incidence and prevalence of depression.

The systematic review for the current guideline did not identify any eligible studies showing benefits or harms of screening for depression in subgroups of the population at increased risk of depression. Subgroups that we considered as being at increased risk (based on the systematic review for the current guideline) included people with a family history of depression, traumatic experiences as a child, recent traumatic life events, chronic health problems, substance abuse, and perinatal or postpartum status. Given the lack of evidence for net benefit, the task force recommends against routine screening for depression in these groups at increased risk.

Factors influencing this recommendation were similar to those discussed in the preceding section for people at average risk. Physicians who believe that their patients (or a subset of their patients) place a high value on the potential benefits of screening for depression and are less concerned with the potential harms could reasonably choose to implement screening for depression in these patients.

Considerations for implementation

Patients with clinical clues to depression
Screening for depression refers to the detection of depression among patients with no apparent symptoms. Yet, clinicians can use symptoms of depression (e.g., insomnia, low mood, anhedonia and suicidal thoughts) to identify patients with potential depression. Evidence suggests that detecting depression based on clinical symptoms tends to identify patients with more severe depression, who may be more likely to benefit from treatment. Clinicians should be alert to the possibility of depression in patients with clinical clues, especially those at increased risk of depression, and implement treatment as appropriate when depression is diagnosed.

Patient preferences
Although there was high variability in patient preferences and values, patients generally consider screening for depression to be important and the screening tools to be acceptable. However, most studies of the acceptability of screening for depression that were identified in the systematic review focused on perinatal women. There was some evidence that any treatment in identified cases should be culturally sensitive and that matching treatment to patient preferences improves outcomes.

Resource implications
Evidence from a modelling study in the United States suggested that one-time screening for depression may be cost-effective. However, this conclusion was based on a low-cost screening approach (maximum $6 per person) and on high remission rates associated with treatment (settings that can achieve full remission in 45% of patients and partial remission in an additional 25%). Given the lack of support for these assumptions, the validity of this conclusion is uncertain.

The time clinicians take to screen for depression reduces their availability to deliver other
services of known clinical benefit (opportunity cost). Evidence from a Canadian modelling study suggests that routine screening to identify new cases of depression, resulting in increased rates of treatment, may not reduce the burden of depression. Instead, focusing efforts on reducing episodes of relapse (e.g., through long-term treatment in patients with known depression) may be a more efficient use of resources.

**Integrated staff-assisted systems**

Integrated staff-assisted systems engage case managers, care support and coordination staff, or social workers, who play a central role in working with primary care physicians, mental health specialists and nurse practitioners to provide depression management and follow-up. Evidence suggests that such integrated systems may be more effective than usual care in increasing the likelihood of successful treatment of depression. However, it is unclear whether screening is a necessary component of these programs. Nevertheless, clinicians practising in a setting where there are integrated staff-assisted systems may be more inclined to choose screening given that treatment is more likely to be effective in this setting.

**Other guidelines**

The current recommendation (to not routinely screen for depression in adults at average or increased risk of depression in primary care set-

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### Table 2: Summary of available recommendations on screening for depression in adults

<table>
<thead>
<tr>
<th>Organization</th>
<th>Risk assessment</th>
<th>Recommendation</th>
<th>Screening test</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Canadian Task Force on Preventive Health Care (current)</strong></td>
<td>No recommendation*</td>
<td>• Recommend not routinely screening adults at average risk in primary care settings</td>
<td>No recommendation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Recommend not routinely screening subgroups of the population in primary care settings who have characteristics that may increase their risk of depression (e.g., people with a family history of depression or with chronic health problems)</td>
<td></td>
</tr>
<tr>
<td><strong>Canadian Task Force on Preventive Health Care (2005)</strong></td>
<td>No recommendation</td>
<td>• Recommend screening adults for depression in primary care settings with both feedback to the clinician regarding depression status and a system for managing treatment (antidepressant medications and psychotherapeutic interventions)</td>
<td>No recommendation</td>
</tr>
<tr>
<td><strong>UK National Institute for Health and Clinical Excellence — adults</strong></td>
<td></td>
<td>• History of depression</td>
<td>Whooley questions†</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Chronic physical health problem with associated functional impairment</td>
<td></td>
</tr>
<tr>
<td><strong>UK National Institute for Health and Clinical Excellence — perinatal women</strong></td>
<td></td>
<td>• Past or present severe mental illness (e.g., schizophrenia, bipolar disorder, psychosis in the postnatal period and severe depression)</td>
<td>Whooley questions† plus help question‡</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Previous treatment (including in-patient care) by a psychiatrist or specialist mental health team</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Family history of mental illness during perinatal state</td>
<td></td>
</tr>
<tr>
<td><strong>UK National Institute for Health and Clinical Excellence — people with chronic illnesses</strong></td>
<td></td>
<td>• History of depression</td>
<td>Whooley questions†</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Chronic physical health problem with associated functional impairment</td>
<td></td>
</tr>
<tr>
<td><strong>US Preventive Services Task Force</strong></td>
<td>No recommendation</td>
<td>• Recommend screening for depression in adults in clinical practices that have systems in place to assure accurate diagnosis, effective treatment and follow-up</td>
<td>No recommendation</td>
</tr>
</tbody>
</table>

*The task force did not formulate a recommendation on risk assessment because the topic was out of scope of the current guideline.
†Whooley questions: During the last month, have you often been bothered by feeling down, depressed or hopeless? During the last month, have you often been bothered by having little interest or pleasure in doing things?
‡If the patient answers Yes to either of the Whooley questions, a third question should be considered: Is this something you feel you need or want help with?
tions) is a change from the 2005 task force guideline, which recommended screening adults for depression in primary care settings where integrated staff-assisted systems are available to manage treatment. The 2005 recommendation was based on an analysis of a literature review done in 2002 for the US Preventive Services Task Force, which showed that screening improved the accuracy of diagnosis of depression and that benefit was more likely in settings where screening was linked to effective follow-up and treatment. Many of the trials included in the 2002 literature review did not exclude people with prior or known depression, which may have overestimated the benefits of screening.

In contrast, the current task force recommendations place a higher value on the lack of evidence showing a direct benefit of screening for depression and place less value on indirect evidence and on trials that evaluated the merits of detecting and treating depression in integrated staff-assisted systems (Appendices 4, 5 and 6), especially because availability of integrated staff-assisted systems in Canada is varied. Of note, the updated (2009) systematic review for the US Preventive Services Task Force concluded that, although treatment of depression is more likely to be effective in integrated staff-supported systems, it is unclear whether screening for depression is a necessary component of these programs.

Table 2 provides a comparison between the current and previous task force guidelines, as well as recommendations from other groups. Explanation for the differences in guidelines between countries may relate to different judgments about the quality of available evidence.

Gaps in knowledge

Better information is needed about the diagnostic accuracy of screening instruments for depression (especially in people with characteristics that may increase their risk for depression) and about the best way to screen for depression in primary care settings. High-quality randomized controlled trials with an unscreened control group that evaluate the effect of screening for depression on clinically relevant outcomes (e.g., sustained remission or depression-related mortality) should be a high priority, especially in populations with a higher baseline prevalence of depression. Future clinical trials should also report on the potential harms of screening, including labelling and stigma, false-positive diagnoses and inappropriate treatment. In particular, such trials should carefully examine the implications of earlier detection in people who would be identified only through screening.

Conclusion

Our recommendations highlight the lack of evidence about the benefits and harms of routinely screening for depression in adults. In the absence of a demonstrated benefit of screening, and in consideration of the potential harms, we recommend not routinely screening for depression in primary care settings, either in adults at average risk or in those with characteristics that may increase their risk of depression. However, clinicians should be alert to the possibility of depression, especially in patients with characteristics that may increase their risk of depression, and should look for it when there are clinical clues, such as insomnia, low mood, anhedonia and suicidal thoughts.

References


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The appendices for this article are available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.130403/DC1
Major depressive disorder is among the most prevalent psychiatric disorders and is a leading cause of morbidity and lost productivity. The 1-year prevalence of major depressive disorder in the Canadian population is 3.2%–4.6%. A large, multisite prospective trial showed that only 28% of patients experience remission following monotherapy with a serotonin reuptake inhibitor. Further, remission rates following antidepressant use decrease with each successive treatment failure, such that after 12 months of follow-up and up to 4 attempts at symptom control with different medications, only 60% of patients experience remission. The remaining patients can be classified as having treatment-refractory depression.

The failure of monoamine-modulating medications to successfully treat a significant percentage of cases of major depressive disorder challenges the traditional conception of this condition as a monoamine deficiency state. Accordingly, and in light of neurocircuitry models of the brain (Appendix 1, available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.121317/-/DC1) and advances in technology allowing various means of modulating activity in key structures of the brain, interest in the therapeutic potential of neuromodulation for difficult-to-treat mood disorders has increased in recent years. In this review, we outline the mechanisms, safety and clinical evidence for neuromodulation in treatment-refractory major depression. The quality of evidence for the different neuromodulation strategies varies substantially, ranging from small, open-label case series to blinded, randomized controlled trials and meta-analyses (Box 1).

What are the neuromodulation options for major depression?

Neuromodulation is either noninvasive or invasive, based on the extent to which the technology interacts directly with the brain (Figure 1). Noninvasive options include electroconvulsive therapy, transcranial magnetic stimulation and transcranial direct current stimulation. Invasive options include vagal nerve stimulation and deep brain stimulation. Here we focus on the 3 modalities for which the most evidence is currently available: electroconvulsive therapy, transcranial magnetic stimulation and deep brain stimulation.

Electroconvulsive therapy

Electroconvulsive therapy is the oldest neuromodulatory modality still used to treat major depressive disorder. It arguably remains the gold-standard to which other antidepressant treatments are compared, yet it is underused. Electroconvulsive therapy involves the administration of an electrical current to the brain via the scalp to induce a seizure while the patient is in a state of general anesthesia. Although its mechanisms are unknown, the superiority of real electroconvulsive therapy over sham electroconvulsive therapy (anesthesia, with or without a subconvulsive dose of electrical current) suggests that the induction of the seizure plays a role in the antidepressant effects of this treatment.

Meta-analyses comparing electroconvulsive therapy to antidepressant medication (Table 1) have found that electroconvulsive therapy is superior to medication in reducing depressive symptoms (effect size 0.80, 95% confidence interval [CI] 0.29–1.29) and in achieving an antidepressant response, defined as a 50% or greater reduction in patients’ scores on the Hamilton Rating scale for Depression compared with baseline (odds ratio [OR] 3.72, 95% CI 2.60–5.32). Traditionally, it has been thought that the melan-
cholic subtype of major depressive disorder was the most responsive to electroconvulsive therapy, although recent studies have suggested that electroconvulsive therapy can produce an antidepressant response across multiple subtypes of major depressive episodes. Data from the multicentre study by the Consortium for Research in Electroconvulsive Therapy suggest that the median number of electroconvulsive therapy treatments required to produce an antidepressant response is 3, the number for resolution of suicidal thoughts is 4, and the number for remission is 7. Given that electroconvulsive therapy is typically administered 2 or 3 times per week during an acute course, achieving a clinically significant response in 1–3 weeks with electroconvulsive therapy compares favourably with the 4–6 weeks typically required with antidepressant medications.

Routine use of general anesthesia, muscle relaxants, continuous oxygenation, vital sign monitoring and brief electrical stimuli have minimized the risks associated with electroconvulsive therapy. The mortality rate has been estimated to be less than 1 death per 73,440 treatments. The most common adverse effects (myalgia [1 in 5 patients], headache [1 in 3 patients]) are transient, lasting minutes to hours, and can be treated with analgesics. Electroconvulsive therapy is associated with immediate posttreatment disorientation.

Box 1: Evidence used in this review
We searched PubMed for articles about neuromodulation in major depression. We used the following search terms alone or in combination: “electroconvulsive therapy,” “transcranial magnetic stimulation,” “deep brain stimulation,” “vagal nerve stimulation,” “direct current stimulation,” “major depression” and “treatment resistant depression;” we also searched using the acronyms “DBS,” “ECT” and “TMS.” We did not limit our searches by date. There were no meta-analyses of deep brain stimulation in depression, but we found 21 meta-analyses on electroconvulsive therapy and 17 on transcranial magnetic stimulation. We found no published randomized controlled trials of deep brain stimulation for the treatment of depression. We identified 134 articles on transcranial magnetic stimulation for depression, as well as 230 articles on electroconvulsive therapy. All results were manually searched. We included only those that were relevant and enhanced our discussion and those with clearly defined patient populations and outcome measures.

Figure 1: (A) Transcranial magnetic stimulation is thought to produce durable changes in synaptic strength via the NMDA-receptor-dependent mechanisms of long-term potentiation and long-term depression. Simultaneous stimulation of presynaptic and postsynaptic neurons strengthens or weakens the synaptic connection, depending on the frequency and pattern of stimulation. When applied to areas of prefrontal cortex that are hypoactive in depression, repetitive transcranial magnetic stimulation gradually increases their activity, thereby relieving the illness. (B) With deep brain stimulation, electrodes are inserted under stereotactic guidance into regions of the brain believed to drive maladaptive thoughts and behaviours. Constant electricity, provided by an implanted pulse generator, disrupts neural activity both at local sites (i.e., at the target) and at remote, yet connected, structures, comprising a “mood circuit.” (C) Electroconvulsive therapy induces ictal activity, as shown by the electroencephalographic recording.
and retrograde amnesia. Although these effects are generally short lived, a 6-month longitudinal follow-up study found that retrograde amnesia persisted in about 1 in 8 patients (12.4%). The amnestic effects of electroconvulsive therapy are greater for recent events (i.e., within 3 mo of first treatment) than for remote events (i.e., greater than 3 yr). Factors associated with greater cognitive impairment following electroconvulsive therapy include pre-existing cognitive impairment, older age and the use of bilateral electroconvulsive therapy. There are no absolute contraindications to electroconvulsive therapy, and it can be used safely during pregnancy.

**Repetitive transcranial magnetic stimulation**

Repetitive transcranial magnetic stimulation uses powerful (>2 Tesla), focused magnetic field pulses to noninvasively stimulate cortical neurons by use of an external electromagnetic coil placed against the patient’s scalp. Unlike electroconvulsive therapy, repetitive transcranial magnetic stimulation does not require the administration of anesthesia, and it does not aim to produce a seizure for its therapeutic effects. Trains of repeated stimulation can produce long-lasting changes in neural excitability. The frequency of stimulation determines the effects of transcranial magnetic stimulation. Low-frequency (< 5 Hz) stimulation inhibits neuronal firing, and high-frequency (> 5 Hz) stimulation increases neuronal firing rates.

Transcranial magnetic stimulation typically involves 10–30 treatment sessions of 15–45 minutes duration, administered once daily, 5 days a week on an outpatient basis. High-frequency stimulation to the dorsolateral prefrontal cortex is the typical protocol for patients with major depressive disorder, based on neuroimaging evidence that this location in the brain is underactive in people with major depression.

Transcranial magnetic stimulation has been shown to be consistently more effective than sham treatment for major depressive disorder across several meta-analyses and large randomized controlled trials (Table 2). In a large meta-analysis involving 24 studies and 1092 patients, active transcranial magnetic stimulation, compared with sham stimulation, was associated with higher pooled rates for response (25% v. 9%) and remission (17% v. 6%); this translates to a number needed to treat of 7 for remission.

### Table 1: Studies examining the use of electroconvulsive therapy for the treatment of major depressive disorder

<table>
<thead>
<tr>
<th>Study</th>
<th>Study type</th>
<th>No. of patients; condition</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sackeim et al.</td>
<td>Multicentre RCT, sham control</td>
<td>290 patients; MDD</td>
<td>• Decreased 6-mo relapse rates following ECT with combination of nortriptyline and lithium (39%) v. nortriptyline alone (60%) or placebo (84%)</td>
</tr>
<tr>
<td>UK ECT Review Group</td>
<td>Meta-analysis</td>
<td>22 trials involving 1408 patients; MDD</td>
<td>• Real ECT was more effective than sham ECT (difference in HRSD = 9.7, 95% CI 5.7–13.5)</td>
</tr>
<tr>
<td>Pagnin et al.</td>
<td>Meta-analysis</td>
<td>13 RCTs involving 892 patients; MDD</td>
<td>• Antidepressant response was more likely with real ECT than with sham ECT (OR 4.77, 95% CI 2.39–9.49)</td>
</tr>
<tr>
<td>Husain et al.</td>
<td>Multicentre, prospective, open-label</td>
<td>253 patients; MDD</td>
<td>• Median time to response: 3 ECT treatments</td>
</tr>
<tr>
<td>Kellner et al.</td>
<td>Multicentre, prospective, open-label</td>
<td>131 patients; MDD and expressed suicidal ideation or acts</td>
<td>• Median time to relief of suicidal ideation: 4 ECT treatments</td>
</tr>
<tr>
<td>Kellner et al.</td>
<td>Multicentre, parallel-design RCT</td>
<td>201 patients; MDD successfully treated with ECT</td>
<td>• Continuation ECT was equally effective in preventing relapse (6-mo relapse rate 37.1%) as was combination of nortriptyline and lithium (6-mo relapse rate 31.6%)</td>
</tr>
<tr>
<td>Kellner et al.</td>
<td>Multicentre, double-blind RCT</td>
<td>230 patients; MDD or bipolar disorder</td>
<td>• Equivalent remission rates were seen with bitemporal (64%, 95% CI 53%–75%), bifrontal (61%, 95% CI 50%–71%) and high-dose right unilateral ECT (55%, 95% CI 43%–66%)</td>
</tr>
</tbody>
</table>

Note: CI = confidence interval, ECT = electroconvulsive therapy, HRSD = Hamilton Rating Scale for Depression, MDD = major depressive disorder, NA = not applicable, OR = odds ratio, RCT = randomized controlled trial.
and 6 for antidepressant response. Recent open-label and randomized controlled studies using newer techniques, such as stronger dosing and longer treatment courses, have consistently achieved remission rates of 30%–35% and response rates of 40%–55%.

Randomized controlled trials have found that electroconvulsive therapy is superior to transcranial magnetic stimulation in achieving remission (59.1% v. 16.7%) and reducing suicidal thoughts (mean decrease 2.0 v. 0.5 points on the suicide item of the Hamilton Rating scale for Depression) in short-term studies. Safety, tolerability and noninvasiveness are the major advantages of transcranial magnetic stimulation over electroconvulsive therapy. Transcranial magnetic stimulation does not require general anesthesia or neuromuscular blockade, and patients remain awake throughout treatment. Most studies have found no immediate or prolonged negative effects of transcranial magnetic stimulation on cognition. A study involving 30 patients with major depressive disorder found that, one week after finishing the course of treatment, cognitive performance remained constant or improved (v. pretreatment) among patients who received transcranial magnetic stimulation to the left dorsolateral prefrontal cortex, while deficits in anterograde memory were observed among patients who underwent right unilateral electroconvulsive therapy.

Transcranial magnetic stimulation may produce transient headache or local pain in 30%–40% of patients. These effects diminish within a few days after treatment and typically respond to over-the-counter analgesics. More serious adverse effects include the emergence of hypomania or suicidal behaviour in less than 1% of patients. Very rarely (< 0.1% of patients), high-frequency stimulation may induce seizure. There are no known maternal or fetal risks associated with transcranial magnetic stimulation in pregnancy.

### Deep brain stimulation

Deep brain stimulation is the treatment of pathological brain states by the chronic, reversible use of direct electrical current, applied focally to neural elements; this treatment aims to alter their function in isolation or within larger networks. Deep brain stimulation is a well-established therapy for Parkinson disease, essential tremor and dystonia. The efficacy and safety of deep brain stimulation in treating movement disorders — combined with its advantages over traditional ablative neuurosurgical procedures (e.g., reversibility, ability to modify stimulation parameters) — have spurred its recent application to psychiatric disorders, including major depressive disorder.

Deep brain stimulation is performed through neuurosurgically implanted intracranial electrodes connected to a programmable pulse generator in the patient’s chest wall; this therapy is the most invasive of all currently available neuromodulation approaches. Once implanted, stimulation is always on and typically continues indefinitely, with periodic adjustment of stimulation parameters to maintain therapeutic benefit.

The precise mechanisms by which deep brain stimulation exerts its effects are still debated. The early theory that deep brain stimulation simply creates a reversible inhibitory lesion has been

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**Table 2: Transcranial magnetic stimulation studies**

<table>
<thead>
<tr>
<th>Study</th>
<th>Study type</th>
<th>No. of patients; condition</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lam et al.</td>
<td>Meta-analysis</td>
<td>24 RCTs involving 1092 patients; MDD or bipolar disorder</td>
<td>• Pooled 25% response (v. 9% with sham) and 17% remission (v. 6% with sham) with 1–6 weeks (5–30 sessions) of active tRMS of the right, left or bilateral DLPFC</td>
</tr>
<tr>
<td>O’Reardon et al.</td>
<td>Multicentre RCT, sham control</td>
<td>301 patients; MDD</td>
<td>• 25% response (v. 13.7% with sham) and 16% remission (v. 8.9% with sham) on HRSD-17 with 6 weeks (30 sessions) of active tRMS of the left DLPFC</td>
</tr>
<tr>
<td>George et al.</td>
<td>Multicentre RCT, sham control</td>
<td>190 patients; MDD</td>
<td>• 15% response (v. 5.0% with sham) and 14% remission (v. 5.1% with sham) on HRSD-17 with variable 3-6 weeks (15–30 sessions) active tRMS of the left DLPFC</td>
</tr>
<tr>
<td>Fitzgerald et al.</td>
<td>Multicentre open-label RCT</td>
<td>219 patients; MDD, bipolar I/II</td>
<td>• 53% response and 32% remission on HRSD-17 with 4 weeks (20 sessions) active tRMS of the left, right or bilateral DLPFC, on HRSD-17; no significant differences across target sites</td>
</tr>
<tr>
<td>McDonald et al.</td>
<td>Multicentre RCT, sham control</td>
<td>141 patients; MDD</td>
<td>• 41% response and 31% remission on HRSD-24 with variable 6–12 weeks (30–60 sessions) active tRMS of left DLPFC</td>
</tr>
<tr>
<td>Galletly et al.</td>
<td>Multicentre open-label RCT</td>
<td>77 patients; MDD, bipolar disorder I/II</td>
<td>• 43% response and 33% remission on HRSD-21 with 4–6 weeks (18–20 sessions) active tRMS of left and right DLPFC</td>
</tr>
</tbody>
</table>

Note: DLPFC = dorsolateral prefrontal cortex, HRSD = Hamilton Rating Scale for Depression, MDD = major depressive disorder, NA = not applicable, RCT = randomized control trial, tRMS = repetitive transcranial magnetic stimulation.
supplanted by data suggesting that it produces both immediate and long-term, target-specific effects on neuronal firing rates and patterns. In major depressive disorder, deep brain stimulation has been used to target nodes within dysregulated mood circuits that perpetuate the depressed state. The most commonly targeted area has been the subgenual cingulate cortex, although the ventral caudate/striatum, nucleus accumbens and inferior thalamic peduncle have also been investigated (Appendix 2, available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.121317/-/DC1).

Two prospective, open-label trials of deep brain stimulation of the subgenual cingulate cortex have shown its efficacy and safety. A Canadian trial performed at 3 centres reported a 6-month response rate of 48%, but a somewhat more disappointing 12-month response rate of 29%. Another open-label trial that included patients with major depressive disorder or bipolar disorder found a 58% remission rate and a 92% response rate at 2 years. This trial included a 4-week single-blind sham lead-in phase to control for placebo response; the authors report that there was a modest stimulation effect of the sham therapy. In both studies, deep brain stimulation was well-tolerated, with no manic or hypomanic episodes, and no suicides were reported. As an invasive neurosurgical procedure, deep brain stimulation carries a small risk of serious complications (e.g., intracranial hemorrhage) and other perioperative risks (e.g., wound infection, anesthetic complications). Larger multicentre trials with longer sham-stimulation periods and true double-blinding are pending.

**Which patients should be referred for neuromodulation?**

Box 2 presents a fictional case in which the results of this review are applied in clinical practice. Recent Canadian guidelines about the use of neuromodulation for major depressive disorder have been published (Table 3). There are currently no Canadian studies examining the cost-effectiveness of neuromodulation strategies for major depressive disorder. Such studies are complex to perform, and they must balance equipment and personnel costs with lost wages and the public health impact of a serious and highly prevalent mental illness.

Currently, electroconvulsive therapy is the most widely used neuromodulation strategy, and it is available in most hospital psychiatric settings.

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**Box 2: Applying the results of this review in clinical practice (fictional case)**

YL is a 60-year-old retired pharmacist and a divorced mother of 3. She originally received a diagnosis of major depressive disorder when she was 42 years of age. She has received outpatient care for the past 6 years, following a brief stay in hospital for suicidal ideation around the time of separation from her husband. Her condition was initially controlled by a combination of sertraline and bupropion; however, she no longer appears to be responding to previously effective therapies. She underwent cognitive behavioural therapy, but this provided only a modest improvement in her symptoms. Repeated trials of more aggressive pharmacologic regimens (including nortriptyline plus lithium) and subsequently a monoamine-oxidase inhibitor (tranylcypromine) were also unsuccessful. She has now lost weight, is growing increasingly despondent and depressed, and her condition is seemingly resistant to pharmacologic treatment.

YL was referred for repetitive transcranial magnetic stimulation and completed a course of 20 sessions of dorsolateral prefrontal cortex stimulation over 4 weeks. Although the procedure was well tolerated and her condition showed some improvement, she did not meet the response (> 50% reduction in Hamilton Rating Score for Depression) or remission criteria (Hamilton Rating Score for Depression < 8), 2 months later, she was admitted to hospital after an attempted suicide by medication overdose. She underwent 12 electroconvulsive therapy sessions on an inpatient basis over 6 weeks without appreciable benefit. Reassessment of her diagnosis did not identify major personality pathology, comorbid substance misuse or modifiable life stressors. She was referred to a multidisciplinary team, including a psychiatrist and functional neurosurgeon, for consideration of deep brain stimulation. After discussion of risks and benefits, she elected to proceed with the surgery. Three months later, she underwent successful bilateral implantation of deep brain stimulation electrodes in the subcallosal cingulate, with no adverse effects. By 2 months after implantation, her symptoms were reduced by more than half, and by 6 months she had achieved criteria for remission. Pharmacotherapy was maintained with nortriptyline and lorazepam. Although her condition was in remission, she was able to successfully complete a course of cognitive behavioral therapy; she reported this to be helpful regarding negative thoughts. Two years after implantation, she continues to meet remission criteria and is doing well.

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**Table 3: Canadian Network for Mood and Anxiety Treatments guidelines for neurostimulation**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Overall recommendation</th>
<th>Acute efficacy data</th>
<th>Relapse prevention data</th>
<th>Safety and tolerability data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Electroconvulsive therapy</td>
<td>First-line therapy for major depressive episode with psychosis or suicidal ideation; second-line therapy for treatment-resistant populations</td>
<td>Level 1*</td>
<td>Level 1*</td>
<td>Level 2†</td>
</tr>
<tr>
<td>Repetitive transcranial magnetic stimulation</td>
<td>Second-line therapy</td>
<td>Level 1*</td>
<td>Level 3†</td>
<td>Level 1*</td>
</tr>
<tr>
<td>Deep brain stimulation</td>
<td>Investigational</td>
<td>Level 3†</td>
<td>Level 3†</td>
<td>Level 3†</td>
</tr>
</tbody>
</table>

*Level 1 data: > 2 randomized controlled trials and/or meta-analysis with narrow confidence interval.
†Level 2 data: > 1 randomized controlled trial and/or meta-analysis with wide confidence intervals.
‡Level 3 data: Nonrandomized, controlled prospective studies, case series or retrospective studies.
Guidelines recommend electroconvulsive therapy as a first-line treatment for major depressive disorder in patients with acute suicidal ideation or with psychotic features and as a second-line treatment for major depressive disorder resistant to pharmacotherapy (Table 3). Electroconvulsive therapy should also be considered for patients who do not have access to transcranial magnetic stimulation or whose condition does not respond to it.

Transcranial magnetic stimulation is available in most academic centres and in a small, but growing, number of community clinics. It may be used either as an add-on treatment to medication or as a stand-alone alternative for patients who decline or do not tolerate medication; it may be a good option for patients whose condition has proven refractory to initial trials of medication.

Deep brain stimulation is reserved for patients who meet the criteria for severe and intractable major depression and whose condition has failed to respond to at least 4 different treatments, including appropriate trials of antidepressant medication, evidence-based psychotherapy and electroconvulsive therapy. Currently, patients who meet these or other similarly rigorous criteria can be referred for assessment to selected centres with a multidisciplinary psychiatric surgery team. In Canada, deep brain stimulation for major depressive disorder has largely been undertaken within clinical trials, but it may be offered as an off-label procedure in select cases.

References
32. McDonald WM, Durkalski V, Ball ER, et al. Improving the antidepressant efficacy of transcranial magnetic stimulation: maximizing the number of stimulations and treatment location in treatment-resistant depression. J ECT 2010;26:146-20.


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Contributors: Nir Lipsman and Peter Giacobbe conceived the article. All of the authors contributed to writing and revising the manuscript and approved the final version submitted for publication.
Major depressive disorder is a common, disabling and costly illness. At least one-third of patients with major depressive disorder do not respond to antidepressants or psychotherapy. Treatment-resistant depression (defined as failure of ≥2 adequate medication trials) affects about 2% of Canadians, or 700 000 individuals. New treatments are therefore urgently needed.

Novel brain-stimulation treatments are being used for an increasingly wide variety of neurologic and psychiatric disorders. Although several techniques are in development, one type in particular is currently transitioning from investigational to publicly funded clinical use in Canada: repetitive transcranial magnetic stimulation (rTMS).

What is rTMS?

Repetitive transcranial magnetic stimulation uses powerful, focused magnetic field pulses to induce electrical currents in target brain regions. The pulses are delivered via a hand-held or helmet-shaped induction coil placed against the scalp over the target area (Figure 1). Single rTMS pulses are powerful enough to induce action potentials in the target region. Repeated trains of pulses cause changes in synaptic connections, via the mechanisms of neuroplasticity. High-frequency stimulation (5–20 Hz) is considered excitatory and low-frequency stimulation (1–5 Hz) inhibitory. Multiple sessions of rTMS, delivered over several days, can produce durable increases or decreases in the activity of target brain regions, lasting weeks to months. Repetitive transcranial magnetic stimulation can thus normalize the activity of frontal lobe regions that are hyperactive or hypoactive in major depressive disorder.

How is it delivered?

A therapeutic course of rTMS involves 20–30 sessions, usually delivered once daily on weekdays over four to six weeks, in an outpatient setting. Therapeutic rTMS is delivered by a trained technician or nurse, under physician supervision. Unlike with electroconvulsive therapy, no seizure is induced, and no anesthesia or activity restrictions are required. The conventional rTMS target in major depressive disorder is the dorsolateral prefrontal cortex, using high-frequency left-sided or low-frequency right-sided stimulation, or both. Other targets and protocols are also under investigation.

Who is eligible?

Patients with treatment-resistant depression (i.e., those who have not responded to antidepressant medications and/or psychotherapy) are potentially eligible for rTMS. Patients who have not tolerated antidepressant medications may also be eligible. Adult (18–65 yr) and geriatric (>65 yr) populations are eligible; patients younger than 18 years are less well studied but are not considered ineligible. Patients should be screened for comorbid medical illnesses that can cause depressive symptoms (e.g., hypothyroidism and anemia). Ideally, patients should reside within commuting distance of the rTMS clinic because of the need for four to six weeks of treatment. For patients who are actively suicidal or too severely ill for outpatient treatment, electroconvulsive therapy offers higher remission rates.
Repetitive transcranial magnetic stimulation is now available in 7 of 10 Canadian provinces, having gained Health Canada approval in 2002. Clinics accept referral in at least 13 major urban areas, comprising a total population of more than 17.5 million Canadians (see Appendix 1, available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.151316/-/DC1 or consult www.rtmscanada.ca). Treatment with rTMS is publicly covered in Quebec and Saskatchewan, and has been recommended for public coverage in Ontario and Alberta.

What are the possible harms?

The most common adverse effects of rTMS are scalp pain during stimulation (35%–40%), and transient headache after stimulation (25%–30%); these symptoms diminish progressively over the treatment course and typically respond to over-the-counter analgesics. About 2%–4% of patients discontinue treatment because of pain. The all-causes discontinuation rate for rTMS is about 5%.

Cases of rTMS-induced mania or hypomania have been reported, with an overall incidence of about 0.9%. Rare cases of rTMS-induced seizure have also been reported, with an overall incidence of less than 0.01%; in one series of more than 10,000 sessions, no seizures occurred. No cases of rTMS-kindled epilepsy have been reported.

Excitatory rTMS is generally considered contraindicated in patients with epilepsy and relatively contraindicated in patients with a history of seizure. Repetitive transcranial magnetic stimulation is also contraindicated in patients with intracranial foreign metal bodies or implanted devices (e.g., deep brain stimulator, cochlear implant, implanted medication pump, implanted cardiac defibrillator and pacemaker).

Unlike with electroconvulsive therapy, rTMS effects on cognition appear benign. Meta-analyses report no significant evidence of impairment across a variety of neuropsychologic domains; some studies show significant cognitive improvement.

What is the evidence so far?

The most widely cited recent meta-analysis of rTMS in major depression (n = 1371 patients, 29 trials) reported 29.3% v. 10.4% response (odds ratio [OR] 3.3, 95% confidence interval [CI] 2.35–4.64) and 18.6% v. 5.0% remission (OR 3.3, 95% CI 2.04–5.32) for active v. sham rTMS. Another recent meta-analysis reported 29% v. 8% response (OR 3.38, 95% CI 2.24–5.10; n = 643 patients, 7 trials) and, in a separate sample, 30% v. 6% remission (OR 5.07, 95% CI 2.50–10.30; n = 332 patients, 7 trials) for active v. sham rTMS. Another meta-analysis reported 29% v. 8% response (OR 3.38, 95% CI 2.24–5.10; n = 643 patients, 15 trials) and, in a separate sample, 30% v. 6% remission (OR 5.07, 95% CI 2.50–10.30; n = 332 patients, 7 trials) for active v. sham rTMS (mean difference in score on the Hamilton Depression Rating Scale 4.53, 95% CI 2.96–6.11). The authors of the meta-analysis concluded that “for MDD [major depressive disorder] patients with 2 or more antidepressant treatment failures, rTMS is a reasonable, effective consideration.”

In the United States, rTMS carries Food and Drug Administration (FDA) approval for major depressive disorder in patients who have not responded to one or more antidepressant trials. The 2007 study that supported FDA approval (n = 301) reported 24.5% v. 13.7% response (OR 2.23, 95% CI 1.20–4.13) and 15.5% v. 8.9%
remission (OR 2.85, 95% CI 1.23–6.63) for active v. sham rTMS (mean difference in score on the Hamilton Depression Rating Scale 2.8, 95% CI 1.2–4.4). A 2015 study that supported FDA approval for a helmet-shaped device for “deep” TMS (n = 212) reported 38.4% v. 21.4% response and 32.6% v. 14.6% remission for active v. sham rTMS (mean difference in score on the Hamilton Depression Rating Scale 3.11, 95% CI 0.83–5.40).11

Regarding comparative clinical efficacy, a meta-analysis of head-to-head trials of electroconvulsive therapy v. rTMS (n = 425 patients, 9 trials) reported superior efficacy for electroconvulsive therapy at 64.4% v. 48.7% response (OR 1.41, 95% CI 1.04–1.90) and 52.9% v. 33.6% remission (OR 1.38, 95% CI 1.10–1.74); both were superior to the remission rates of about 10%–20% reported for trials of additional medication or psychotherapy in treatment-resistant depression. Current evidence, therefore, positions rTMS efficacy slightly higher than that of psychotherapy and medications, but rather lower than electroconvulsive therapy, in a sequential treatment approach to major depressive disorder (Figure 2).

What can we expect in the future?

Brief protocols

Conventional rTMS sessions are lengthy (30–60 min), limiting clinic capacity and increasing wait times. Newer protocols such as theta-burst stimulation require just one to three minutes. Studies currently underway will establish whether theta-burst stimulation protocols match or exceed conventional treatment efficacy, thus improving capacity.

Accelerated courses

Four to six weeks of once-daily stimulation is standard; however, some emerging research suggests that rTMS may be delivered multiple times per day, thereby substantially reducing the length of the course of treatment, while preserving response and remission rates. Future studies will establish whether rTMS courses can be completed in one to two weeks while preserving efficacy.

References


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