Unmasking Worry: Identifying and Managing Generalized Anxiety Disorder in Working-Age Patients

By Denis Audet, MD; and Martin Katzman, BSc, MD, FRCPC

Introduction

One in five Canadians will experience a mental illness in his or her lifetime.[1] This means that every primary-care physician likely has several patients suffering with mental illness in his or her practice, many of whom are undiagnosed.

Patients with anxiety disorders may be particularly likely to have their disease go undetected, as it can masquerade as a number of other possible diagnoses. For example, patients who frequently present with multiple or somatic symptoms that are not explained through further testing may have an anxiety disorder.[2,3]

By identifying these patients and effectively treating the underlying cause of their symptoms (*i.e.,* anxiety), physicians may be able to resolve these long-standing somatic complaints and, as a result, free up clinic time and reduce healthcare costs.[4-6]

This review focuses on generalized anxiety disorder (GAD), which is one of the most common anxiety disorders in the country, as well as specifically in primary care. It is also a disorder which affects working-age patients by impairing function to the point of work absenteeism.[7] The following pages discuss the epidemiology and impact of anxiety disorders in Canada, providing guidance on how to identify these patients in clinical practice and an overview of treatment modalities that have been shown to be most effective in treating GAD. Unfortunately, relative to many other areas of psychiatric medicine (*e.g.*, major depression), there is a comparative lack of data on GAD in the literature. The authors of a recent meta-analysis examining GAD treatments conceded that one of the limitations of their study was that "... the current evidence base used to inform this meta-analysis was limited."[8] With this limitation in mind, some of the points discussed in this review refer to the greater context of anxiety disorders in general.

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Epidemiology of Anxiety Disorders

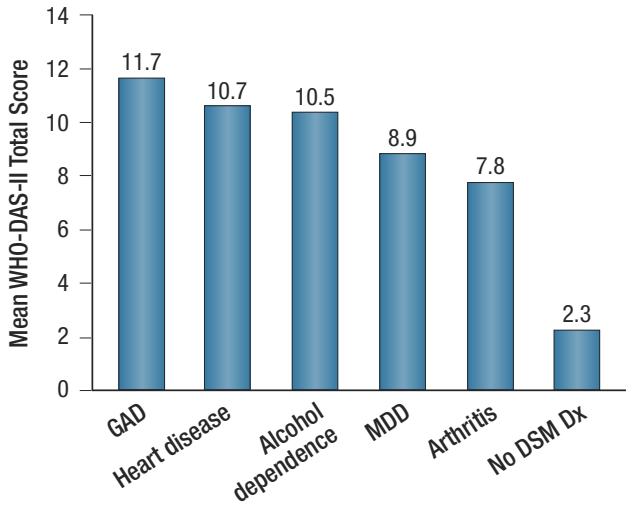
Anxiety disorders are the most common mental illness in Canada, more prevalent than mood disorders; 10% of Canadians will be affected in their lifetime and the prevalence in women is twice that observed in men.[9] Anxiety disorders are known to be particularly common in the working population.[10] An Ontario study estimated that 12% of adults aged 15 to 64 years had experienced an anxiety disorder in the previous year.[11] The estimated one-year prevalence of GAD in Canada among individuals aged 15 to 64 years is 1.1%.[9]

In primary care populations, the prevalence of GAD has been noted in almost 5.3% of the population (3.8% pure GAD and 1.6% comorbid GAD and depression).[7] Interestingly, in this study by Wittchen et al, pure GAD and major depressive episode (MDE) were associated with disability, high utilization of healthcare resources, and suicidality, which were even higher with comorbid GAD/MDE, but few patients received the correct diagnosis (64.3% for MDE and 34.4% for GAD). Although the majority of patients with recognized GAD or MDE were treated, only a small minority with GAD were prescribed medications or referred to specialists.[7]

There is a high comorbidity of GAD with other mood and anxiety disorders.[12-16] For example, in the German National

FIGURE 1.

GAD Correlates with a High Level of Disability[20]



WHO DAS-II = World Health Organization Disability Assessment Schedule II; GAD = Generalized Anxiety Disorder; MDD = Major Depressive Disorder; No DSM Dx = No diagnosis according to DSM-IV

Health Interview and Examination Survey, mental health supplement (GHS-MHS), 93.1% of individuals with a 12-month prevalence of GAD met criteria for at least one other 12-month disorder, while 32.7% met criteria for three or more comorbid mental disorders.[14] In the U.S. community-based National Comorbidity Survey (NCS) (n = 8,098, aged 15-54 years), 90.4% of the respondents meeting criteria for lifetime GAD reported having one or more other lifetime mental health disorders.[12] In the GHS-MHS (n = 4,181, aged 18-65 years) of all the 12-month GAD cases, 93% had another DSM-IV disorder, 59% fulfilled criteria for major depressive disorder (MDD) and 56% fulfilled criteria for any other anxiety disorder.[14] The most frequently occurring comorbid anxiety disorders with GAD were specific and social phobia (29% for both).[14] The proportion of patients with 12-month GAD also experiencing a comorbid DSM-IV eating disorder, comorbid alcohol abuse/dependence and drug abuse/dependence were 2.5%, 6.4% and 1.4%, respectively.[17]

In addition, bipolar disorders and GAD are also commonly comorbid; the proportion of patients with bipolar disorder having a lifetime GAD diagnosis was reported as 18.4%.[18]

Impact of GAD

People with anxiety disorders avoid situations that bring about their symptoms, and often find it "very or extremely difficult" to do their work, take care of things at home, or get along with other people.[19] In the German study by Wittchen et al involving almost 18,000 subjects, two thirds (66.7%) of those with GAD reported their symptoms kept them from being able to work for at least one day in the preceding month.[7]

Individuals with mental disorders experience even greater functional disability than those with other chronic debilitating diseases including arthritis and heart disease (Figure 1).[20]

Characteristics of GAD

Individuals with GAD are overly anxious and afraid of situations most people consider normal. They have intense, prolonged feelings of fear and distress disproportional to the actual threat, which interfere with normal daily functioning.[1]

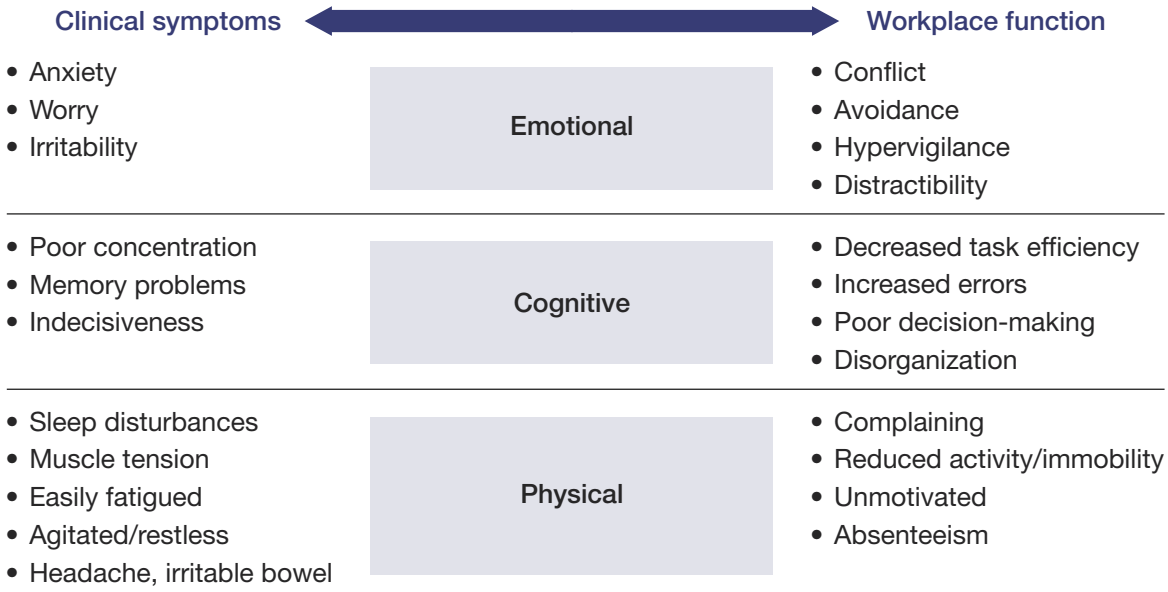
The origins of anxiety disorders are often seen in early childhood. For GAD, childhood risk factors include: internalizing problems, conduct problems, and a somewhat more behaviourally inhibited temperament.[21]

Although the onset of anxiety typically occurs in childhood or early adulthood, recognition and diagnosis is often delayed due to the condition being masked as a number of other possible diagnoses.[5,22] The disorder is characterized by pervasive, excessive, and uncontrollable worry and anxiety for more than six months about ordinary experiences. It involves physical symptoms, such as restlessness, fatigue, sleep problems, difficulty concentrating, irritability, and muscle tension, which cause significant distress or functional impairment.[23]

Often, it is the physical manifestation that leads patients to seek treatment.[7] The primary goal of acute treatment for GAD is to ameliorate symptoms such as sleep difficulties, concentration, irritability, recurrent headaches, and muscle pain.[24]

Not surprisingly, GAD can have significant negative effects on workplace functioning, where anxiety and worry often manifest as distractibility, hypervigilance, avoidance, and interpersonal conflicts (Figure 2).[25] Poor concentration and indecisiveness can manifest as increasing errors, disorganization, and poor decision-making, while sleep disturbances,

FIGURE 2.
Anxiety Disorders Impair Workplace Functioning[25]



muscle tension and restlessness can present as complaining, lack of motivation, inactivity, and absenteeism.[25] It is important to note that the symptoms and sequelae of GAD (and other anxiety disorders) are distinct from those that arise from job-related stress; anxiety and stress are not synonymous. However, there are some commonalities between the two states. Work-related stress (*e.g.*, high demands, low decision latitude) coupled with individual factors (*e.g.*, inability to dispel negative thoughts, worry) can lead to deep and entrenched stress with severe physical and mental effects.[26,27] Similar to GAD, many patients with job stress present with somatic or cognitive rather than mood-related symptoms (*e.g.*, upset stomach, sleep disturbances, headache, difficulty concentrating)[28] and they might try self-medicating with alcohol, tobacco, or drugs.[29]

While the presence of job stress by itself is not diagnostic of an anxiety disorder, there is research that demonstrates a significantly increased risk of GAD among those who have substantial job-related stress.[30] In the Dunedin study (a 1972-1973 longitudinal birth cohort) investigators assessed the influence of work stress on the incidence of GAD using data from 2004 to 2005 (n = 972, cohort aged 32 years). The research showed that, compared to participants who reported the lowest level of psychological job demands, those with high levels of psychological job demands were 2.06 (men) to 2.76 (women) times more likely to meet criteria for GAD.[30] Other researchers have also reported a link between job stress and elevated risk of GAD.[31,32]

Identifying GAD in Clinical Practice

Only a minority of patients (approximately one third) with GAD seek treatment specifically for the anxiety symptoms in the first year of the disorder.[33] The average delay in initial treatment contact is more than a decade among people who delay beyond the first year.[33] However despite the relative lack of presentation specifically for GAD, patients with the disorder do commonly present for reasons other than anxiety symptoms, typically for minor physical problems (*e.g.*, fatigue, diarrhea, palpitations, dyspnea, abdominal pain, headache or chest pain).[3,33]

In the German study by Wittchen et al[7] mentioned earlier, investigators observed that 47.8% of patients with anxiety presented with somatic illness and complaints, while only 13.3% presented with "anxiety." Pain (34.7%) and sleep

TABLE 1.
Hallmarks of the Patient with GAD[7,37-41]

- Presents with somatic complaints, insomnia, and depression
- Makes frequent office visits (4-6 or more in 12 months)
- Has a heavy and thick patient file
- Has multiple negative tests for medical illness
- Has depression and other anxiety and substance-use disorders

disturbance (32.5%) were also common presenting complaints.[7]

Clinical presentation strongly influences primary-care physicians' recognition of depression and anxiety.[34] Patients who present with somatic symptoms are far less likely to be diagnosed with GAD than those who present with psychological symptoms.[19,34-35] However, the above observations indicate that one might suspect the possibility of GAD if the symptoms are vaguely described, do not conform to known pathophysiologic mechanisms, persist after ruling out other causes and/or are not resolved by reassurance.[3,4]

The Canadian Guidelines for the Management of Anxiety Disorders provide a list of tests that can be performed to rule out medical conditions prior to assessing for an anxiety disorder.[5] One way to recognize a patient with an anxiety disorder is to pose the question, "During the past four weeks, have you been bothered by feeling worried, tense or anxious most of the time?" The vast majority (90%) of people with GAD will answer "yes."[36] Other signs of anxiety include the types of somatic complaints at presentation, how often the patient visits the doctor's office, and a thick patient file from many previous visits and tests (Table 1).[7,37-41]

Treating the GAD Patient: The Overall Plan

Identification and assessment. A treatment plan should start with an assessment of the severity of the disorder using an appropriate screening tool. Early recognition and management of anxiety disorders enhance the quality of life of patients and reduce the risk of secondary disorders such as depression and substance abuse. A number of mental-health assessment scales can be completed by the patient in the waiting room in less than five minutes and can provide a baseline. Since depression scales may fail to identify depressed patients with co-existing disabling anxiety, clinicians should screen patients for depression and anxiety.[19,42]

The GAD-7,[41] a seven-item anxiety scale, is a validated and efficient screening tool for the identification of GAD and estimation of its severity. Increasing GAD-7 scores are strongly associated with multiple domains of functional impairment and disability days, and a score of 10 or higher represents a reasonable cut-off point for identifying cases of GAD. By identifying patients with this tool, physicians also obtain a baseline for the level of impairment that can be quickly monitored serially using the same tool during follow-up.

The Sheehan Disability Scale (SDS)[43] is another useful tool in a physician's arsenal. Although it does not provide specific diagnoses, it can help assess functionality and is an important measure of disease severity in three domains: work, social life and family life. As such, it can be helpful for patients with GAD to fill out the GAD-7 and SDS at baseline and subsequent visits. Furthermore, these tests are patient-scored and will not place any extra demands on a physician's time. While self-report scales have their challenges (for instance, patients might fill them out inaccurately wanting to please the reviewer) they are highly practical in the work place.

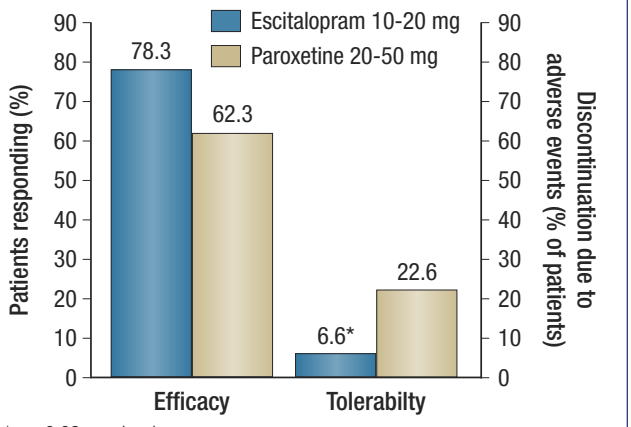
Patient education. Once diagnosed, patients must be made aware that they have an anxiety disorder and that treatment can help. They should receive information about the disorder, a general prognosis, and treatment options, specifically including psychotherapy and pharmacotherapy. Explaining to patients that somatic symptoms are common with GAD and that successful treatment can also help prevent these symptoms in the future can be helpful for motivating patients to agree to a course of pharmacotherapy. Even in patients with suspected GAD who are reluctant to accept a diagnosis or initiate treatment, reinforcing the potential link between somatic symptoms and GAD each time they present with a somatic complaint might make them more amenable to discussing treatment options. When patients with GAD are treated with pharmacotherapy, they need to understand that while the type of medication being

TABLE 2.
GAD Pharmacotherapy Options[5]

Position	Agents
First-line	Escitalopram, paroxetine, sertraline,* venlafaxine XR
Second-line	Alprazolam, bromazepam, bupropion XL*, buspirone, diazepam, imipramine*, lorazepam, pregabalin*
Third-line	Citalopram*, hydroxyzine*, mirtazapine, adjunctive olanzapine*, risperidone*, trazodone*
Not recommended	Beta-blockers* (propranolol)

*Refer to individual product monographs for complete indications.

FIGURE 3.
Efficacy and Tolerability of Escitalopram and Paroxetine in GAD[69]



*p = 0.02 vs. placebo.

prescribed is called an "antidepressant," it is a proven therapy for anxiety disorders and that this — not depression — is the reason for the prescription.

Serial use of objective metrics (*e.g.,* the GAD-7 and SDS scales)[41,43] can help to reassure patients they are doing better and to determine treatment efficacy and whether adjustments to treatment are required. By encouraging patients to play an active role in managing their disorder it is hoped they will feel more motivated to adhere to the therapy as prescribed.

Treatment selection. The goals for the management of GAD include: reduction of the core symptoms of the illness (*e.g.*, worry, tension, irritability), improvement of somatic symptoms (*e.g.*, gastrointestinal distress, headache, fatigue), better quality of life (QoL) and symptom remission.[44] Moreover GAD is associated with an impairment in daily functioning relative to the general population;[45] improvement in both the psychiatric and somatic areas might also help restore normal function. The choice of psychotherapy or pharmacotherapy depends on a number of factors, including patient preference and motivation, clinician skill and experience, availability of psychological resources, and the presence of a comorbid psychiatric or physical disorder. Either cognitive behavioural therapy (CBT) or pharmacotherapy alone is recommended for first-line treatment of anxiety disorders. At present, there is little evidence demonstrating that combining the two approaches is more effective than either approach in isolation.[46] Still, with the goal of managing a patient to remission/wellness, it is important to provide a number of treatment modalities, (polypharmacy or providing medication and psychotherapy) to ensure patients experience progress. As such, once on the path towards wellness, patients should be appropriately monitored and followed for at least 12 months.[5] If remission is not achieved, further treatment must be provided to help them move further along their road to recovery.

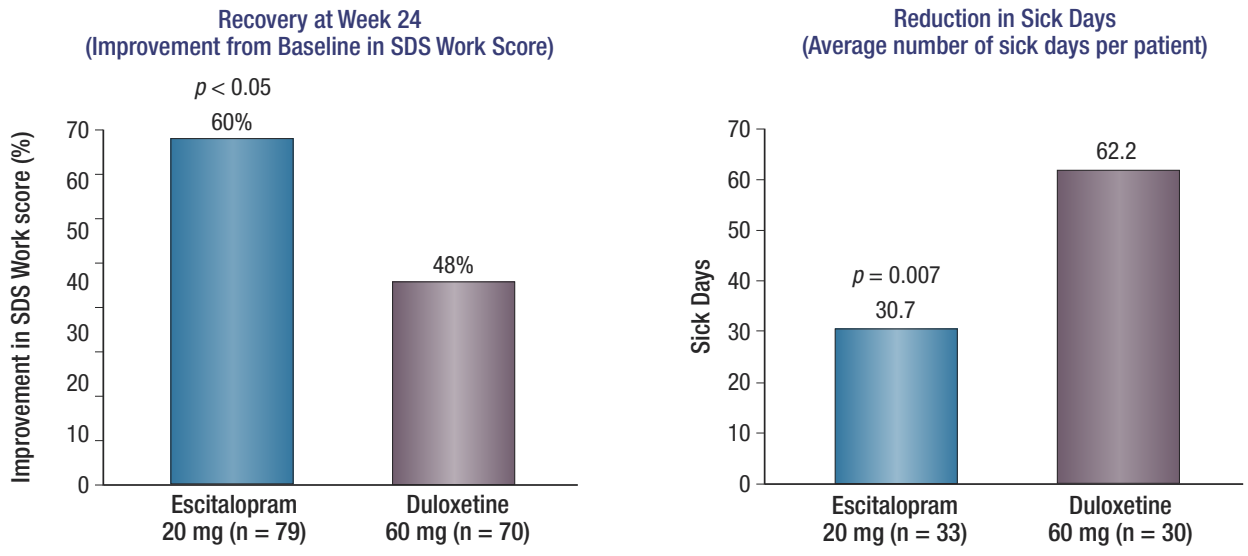
Psychological management. CBT focuses on intervening in the thoughts and behaviours that influence emotions. It typically involves one or more of the following: cognitive re-evaluation, problem-solving training, applied relaxation, anxiety-management training, exposure-based interventions, and relapse-prevention approaches.[5,23] CBT reduces anxiety symptoms and is more effective than no treatment and non-specific psychological treatment methods for GAD. The magnitude of benefits is comparable to those of antidepressant drugs, and the benefits of therapy tend to be maintained over six months to two years of follow-up.[5]

Recently, mindfulness-based stress reduction (MBSR) has been investigated as a treatment for GAD.[47-49] A number of studies have supported a role for mindfulness-based treatments in patients suffering from anxiety disorders.

Pharmacotherapy. Pharmacotherapies available to treat GAD are listed in Table 2.[5] It should be noted that the recommendations in the table are from the most recent

FIGURE 4.

Recovery vs. Sick Day Reduction in Major Depressive Disorder[71,73]



SDS = Sheehan Disability Scale.

Canadian guidelines for GAD, which were published in 2006. Since the development of these recommendations, other medications (*e.g.*, duloxetine),[50-53] have been approved for use in GAD. Furthermore, significant evidence exists suggesting first-line efficacy for pregabalin[54-57] and quetiapine XR.[58-62]

First-line therapy for virtually all anxiety disorders is SSRI or SNRI treatment, with or without CBT. With respect to the selection of an individual agent, the Canadian guidelines specifically recommend escitalopram, paroxetine, sertraline or venlafaxine XR as first-line treatment choices.[24] Although some of the therapeutic agents listed in Table 2 are not specifically indicated for GAD, they have shown promise in the clinical setting. Benzodiazepines may be useful as adjunctive therapy, particularly at the start of treatment while patients wait for the onset of antidepressant efficacy, but are generally recommended only for short-term use.[5]

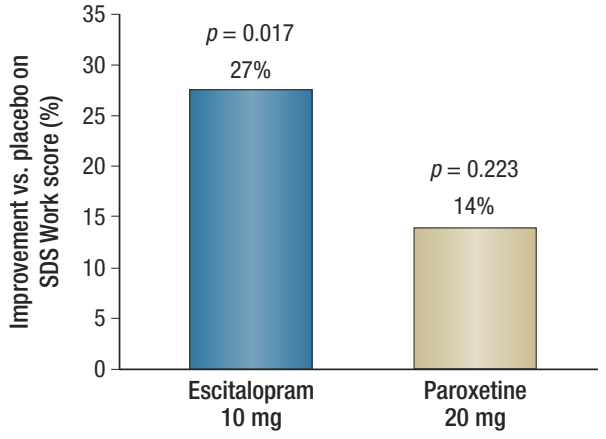
The ideal antidepressant for managing anxiety disorders should combine efficacy and tolerability. It should have an early onset of efficacy, providing symptom alleviation without symptom exacerbation. It should not have any significant immediate tolerability or long-term tolerability issues, and it should restore normal patient functioning in all areas of life, including work.

Patients must receive therapeutic dosages for an adequate duration before a therapy is deemed ineffective. Some patients experience some symptom improvement within the first couple of weeks of therapy, while it may take six to 12 weeks for others to see a significant reduction of symptoms, with improvements accruing for six to 12 months. Because patients with anxiety disorders are more sensitive to bodily changes than non-anxious individuals and because antidepressants are often associated with an initial exacerbation of anxiety among anxious patients, treatment could be initiated at lower doses and titrated up over the first few weeks of treatment.[42,63]

The Canadian guidelines for the management of anxiety disorders state that approximately 20% to 40% of patients with GAD will relapse within six to 12 months after ending treatment.[5] This suggests that long-term treatment is often needed. This recommendation is supported by the findings of two long-term, placebo-controlled studies in which patients who were switched to placebo had significantly higher relapse rates than those who stayed on active therapy (paroxetine[64] or escitalopram[65]) more than six to 18 months.

Among these recommended treatment options, a number of head-to-head studies have been completed, but these have not shown marked differences in efficacy measures. For

FIGURE 5.
Impact of Escitalopram, Paroxetine or Placebo on Work Function in GAD[74]



example, venlafaxine XR and paroxetine were compared in a randomized, open-label study involving 46 patients with GAD.[66] There were no significant differences reported in efficacy or tolerability in this trial. Nor were there any significant efficacy or tolerability differences reported between sertraline and paroxetine in a randomized, double-blind study involving 55 patients with GAD.[67]

Studies comparing escitalopram and paroxetine in GAD have found that escitalopram is at least as effective as paroxetine. In a 2006 study involving 681 patients with GAD, escitalopram 10 mg daily was found to be superior to paroxetine 20 mg daily for the primary efficacy endpoint of change in HAMA total score from baseline to week 12.[68] One hypothesis is that these results may reflect a decrease in tolerability with paroxetine 20 mg daily compared to lower doses, along with a similar efficacy to escitalopram. Although this study was not powered (nor of long enough duration) to demonstrate differences between the agents, the above reasoning or explanation could be supported by another comparative study involving 121 patients with GAD, in which the efficacy of escitalopram and paroxetine was found to be broadly similar and in which approximately four times more patients withdrew from paroxetine therapy than from escitalopram therapy due to adverse events (Figure 3).[69]

In addition to the individual head-to-head trials, a systematic review and meta-analysis has been conducted in an attempt to clarify which agents might be preferred relative to other approved agents. The authors of this systematic review concluded that, based on a review of all the available evidence, duloxetine, escitalopram, and pregabalin might offer some advantages over venlafaxine and paroxetine.[8]

If a patient responds inadequately to therapy with a first-line agent, dosing should be optimized and adherence assessed prior to switching or augmentation. If a patient continues to respond inadequately to optimal dosages of a first-line agent or tolerance becomes an issue after eight to 12 weeks of therapy, another first-line agent should be substituted before a second-line medication is considered. If initial treatment was an SSRI and is ineffective after optimization, switching the patient to a second SSRI or an agent with a different mechanism of action (*e.g.,* SNRI) may be beneficial.[5,24]

Studies on pharmacotherapies for anxiety disorders typically use symptom reduction and remission rates as primary outcome measures.[66-69] In other psychiatric domains, such as major depressive disorder (MDD), cognitive and functional restoration are increasingly being included as measures of treatment efficacy in recognition of the fact that symptomatic improvement does not necessarily correlate equally with functional recovery.[70,71] SSRIs such as paroxetine and SNRIs such as duloxetine have demonstrated significantly greater improvement in functionality, including work function, relative to placebo in MDD.[72] Additional trials have aimed to evaluate functional differences between treatments. For example, Wade et al[71] conducted a double-blind,

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comparative study to evaluate the effect of escitalopram and duloxetine on functional outcomes of patients with MDD. Although remission rates were comparable in the two treatment groups, escitalopram-treated patients exhibited significantly greater ($p < 0.05$) improvements in function than patients treated with duloxetine (Figure 4).[71] In a separate report on the same study, Wade et al showed that the average number of workdays missed by patients was significantly lower for those taking escitalopram versus duloxetine (Figure 4).[73] While this was a depression study, it does suggest that the value of escitalopram lies in its tolerability, which likely contributed to fewer days of work missed by those receiving this treatment. Whether this would be seen in GAD remains to be determined. The evidence regarding work function is currently limited in anxiety disorders, but given the fact that GAD, like MDD, is associated with impairment of functional abilities, it would be desirable to quantify the impact of treatment modalities for GAD on functional outcomes in clinical trials.

Nevertheless, there are some data on functional outcomes available with escitalopram and paroxetine, which were each compared to placebo in a randomized, controlled study involving 682 patients with GAD.[74] One of the study's pre-specified secondary endpoints was change in SDS from baseline to 12 weeks. Escitalopram 10 mg was found to have a significant benefit relative to placebo for each of the SDS domains (work, social life and family life). Paroxetine 20 mg separated from placebo only for the family life domain. The results in the work domain are shown in Figure 5. Patients in the escitalopram 10 mg group improved by an average of 3.22 points (27% improvement vs. placebo, $p = 0.017$ [mean improvement in placebo group: 2.53 points]). The 2.88-point improvement with paroxetine 20 mg daily was not found to be significantly different from placebo (14% difference, $p = 0.223$) (Figure 5).[74] Since the study was not designed to detect differences between escitalopram and paroxetine, one can only speculate as to the effect on sick days either medication would have compared with placebo.

Summary & Conclusions

Chronic disorders, such as arthritis, heart disease, depression and alcohol dependence, are associated with a high level of disability. What is perhaps surprising is that individuals with GAD experience the highest level of disability among those living with these chronic conditions. Roughly 10% of Canadians will be affected by an anxiety disorder, with GAD being the most common. Many patients visiting primary care clinics with somatic complaints, multiple times during the year, are affected by GAD and often fail to present with specific anxiety symptoms unless prompted. Early recognition and management of GAD can enhance patients' function—at work, home and socially—and reduce the risk of secondary disorders, such as depression and substance abuse. The GAD-7 and SDS are potentially very helpful questionnaires for effectively and efficiently identifying GAD and functional impairment, and providing a baseline against which treatment success can be measured.

Patient preference and motivation, clinician skill and experience, availability of psychological resources, and the presence of comorbid psychiatric or physical disorders influence treatment choice. First-line pharmacological recommendations for anxiety disorders, based on the most recent guidelines, include escitalopram, paroxetine, sertraline and venlafaxine XR. Data with other newer pharmacological agents provide direction for other options to further manage patients suffering from GAD. Non-pharmacologic treatments, specifically CBT, also have data suggesting benefit as first-line treatment.

Early and appropriate treatment can promote functional recovery, enhance quality of life and reduce risk of and treat comorbid conditions.

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