Achieving and Sustaining Remission in Depression and Anxiety Disorders: Introduction

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Major depressive disorder (MDD) is a prevalent medical condition that is frequently associated with comorbid psychiatric and medical conditions and has a high risk for morbidity and mortality (1). Approximately 8% of adults will experience MDD at some time in their lives, and the 1-year prevalence rate is 4.1% to 4.6% in Canada (2). Anxiety disorders affect an estimated 12% of Canadians at some point during their lifetime (2), and community lifetime prevalence rates range from 2.6% to 13.3% depending on the disorder (3). Anxiety disorders are highly comorbid, occurring in about 58% of patients with MDD (4). In addition, anxiety symptoms are highly prevalent in MDD, occurring in up to 80% of patients (5).

This series of articles was produced in conjunction with the Canadian Network for Mood and Anxiety Treatments (CANMAT, www.canmat.org) to address these findings and their impact on clinical practice.

Remission

In depression, full remission is defined as the virtual elimination of symptoms, which in most clinical trials and in this series of articles refers to depression scores within the normal range. This is most consistently defined as a score of ≤7 on the 17-item Hamilton Depression Rating Scale (HDRS17) (6). The term “response” generally indicates a 50% reduction in depression score. Recovery from depression is often equated with remission in the literature. It is also variably defined as remission for an extended period of time or the complete absence of symptoms. In this supplement, we propose that recovery represents the combination of symptom remission and return to full functioning (Table 1). In general, there appears to be a lag between return of full functioning and symptom remission, at least in chronic depression (7,8).

In truth, recovery also implies an absence of disease state. Recent exciting data from Mayberg and coworkers demonstrate a reversal of abnormal regional brain metabolism in responders to fluoxetine (9). However, we do not yet have specific neurobiological markers of recovery at a clinical level. Hence, an attainable goal of outcome at this time is a combination of symptom remission and recovery of function. Recent clinical trials in anxiety disorders, and to a lesser degree in depression, use the Sheehan Disability Scale (Table 2). This tool is also very friendly to clinical practice.

Evidence for the benefits of treating to remission in depression is clear: remitted patients are more likely to regain full functional recovery and suffer fewer relapses and recurrences (10). McIntyre and O’Donovan further clarify the benefits of full remission in their article on the cost of partial remission (11). Remission has become the accepted standard treatment goal in MDD, as seen in the most recent Canadian guidelines (1,12); in many recent clinical trials; and in the current National Institutes for Mental Health Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial, which views anything less than remission as treatment failure (13).

Like depression, remission in anxiety disorders should leave patients symptom-free (14). Although evidence for the importance of remission in anxiety disorders is less clear, intuitively it would seem likely that treating to remission would have an impact in these disorders similar to that seen in depression. Proposed remission goals for the anxiety disorders include cut-off values similar to the HDRS ≤7 for depression and a Hamilton Anxiety Rating Scale (HARS) score of ≤7 to 10; accepted scales specific to the various disorders may also be used. Kjernisted and Bleau provide clear and practical definition of remission for each of the anxiety disorders (15, Table 1). This contrasts starkly with clinical trials in the anxiety disorders, where few studies report remission rates and criteria for response are generally in the range of 25% to 35% improvement in structured rating scale scores.
It is clearly time to raise the bar in terms of acceptable goals of therapy for patients with anxiety disorders. The use of targeted cognitive-behavioural therapy (CBT), anxiolytic antidepressants with high remission rates, combination antidepressants, and augmentation with atypical antipsychotics and specific psychotherapy can help achieve this aim.

**Tools for Diagnosing and Assessing Treatment Response**

The use of structured rating scales to assess response to treatment can help ensure remission is achieved. A wide variety of standardized, validated tools are available that are specific to the mood (16–25) or anxiety (26–32) disorder being assessed (Table 2). Specific tools have also been developed for use in older patients that encompass cognitive assessment (33–35).

The HDRS is the most commonly used scale to assess symptoms of depression and is considered the gold standard in clinical trials (14). However, other instruments are also available (Table 2) (17–21). The abbreviated 7-item HDRS (HDRS7) devised and validated by McIntyre and colleagues (17) identifies a score ≤ 3 as remission and is quick and easy to administer. Although premenstrual dysphoric disorder (PMDD) and postpartum depression are also depressive disorders, specific tools have been developed for use in older patients that encompass cognitive assessment (33–35).

The HARS can be used across all anxiety disorders, although it does not adequately capture symptomatology specific to the disorder. It has become standard to administer the HDRS concurrently because of the high comorbidity and the strong representation of anxiety symptoms on this scale, as well as on the abbreviated HDRS7.

**Special Issues**

In addition to comorbid psychiatric disorders, other issues, including sex, age, and physical illness, can complicate management of depression.

Sex appears to play a role in the prevalence, symptom profile, and treatment of depression. Women suffer depression more frequently than men and have a more severe clinical course (36,37). In this supplement, MacQueen and Chokka provide an extremely thorough overview of depressive disorders in the premenstrual, pregnant, postpartum, and perimenopausal phases of a woman’s life (38). Early hormone-related mood disorders predict later mood difficulties in a woman’s hormonal life. For example, PMDD is a risk factor for postpartum depression. The authors suggest that known differences in drug bioavailability may explain higher side effect rates and treatment dropout in women. They review the substantial evidence provided by the Toronto Motherisk program and others that continues to point to the safety of antidepressants during pregnancy and lactation and the consequences of untreated depression for both mother and child (39,40). Evidence supports the use of CBT in PMDD and of both CBT and interpersonal therapy (IPT) in postpartum depression. It is disappointing that, in the Cochrane review of treatment of postpartum depression, there was only 1 randomized placebo-controlled trial of antidepressants. This study showed superiority of fluoxetine over placebo (41). The review also concludes that postpartum estrogen may be of modest value in severe cases and that synthetic progesterone should not be used. Estrogen replacement therapy has shown benefit, predominantly in an augmenting role in perimenopausal women in some but not all studies.

In PMDD, the efficacy of cyclic intermittent antidepressant treatment and the rapidity of onset of response to antidepressants continue to challenge our understanding of this disorder and the treatment of depressive disorder in general.
### Table 2 Structured rating scales to assess mood and anxiety disorders

<table>
<thead>
<tr>
<th>Disorder and structured rating scale</th>
<th>Rating scale description</th>
<th>Reference</th>
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<tr>
<td><strong>Major depressive disorder</strong></td>
<td></td>
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<tr>
<td>Hamilton Depression Rating Scale (HDRS)</td>
<td>17-item, clinician-rated instrument, easy to use, highly accepted gold standard</td>
<td>Hamilton (16)</td>
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<tr>
<td>HDRS&lt;sub&gt;17&lt;/sub&gt;</td>
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<tr>
<td>HDRS&lt;sub&gt;7&lt;/sub&gt;</td>
<td>7 items from the 17-item HDRS identified to occur most frequently and be the most responsive to change</td>
<td>McIntyre and others (17)</td>
</tr>
<tr>
<td>Montgomery–Asberg Depression Rating Scale</td>
<td>10-item clinician-rated severity scale</td>
<td>Montgomery and others (18)</td>
</tr>
<tr>
<td>Beck Depression Inventory</td>
<td>Self-rated instrument</td>
<td>Beck and others (19)</td>
</tr>
<tr>
<td>Clinical Global Impression Scale-I</td>
<td>Unidimensional measure of clinical improvement</td>
<td>Guy (20)</td>
</tr>
<tr>
<td>Global Assessment of Functioning Scale</td>
<td>Comprehensive rating of functional status, usually based on face-to-face interviews</td>
<td>Endicott and others (21)</td>
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<tr>
<td><strong>Premenstrual dysphoric disorder (PMDD)</strong></td>
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<tr>
<td>Daily Record of Severity of Problems</td>
<td>21 items, assesses 11 DSM-IV symptoms of PMDD on 6-point scales</td>
<td>Endicott and Harrison (23)</td>
</tr>
<tr>
<td>Calendar of Premenstrual Experiences</td>
<td>22 items (12 psychological, 10 physical) assessed on 3-point scales</td>
<td>Mortola and others (24)</td>
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<tr>
<td>Daily Symptom Report</td>
<td>17-item daily symptom report</td>
<td>Freeman and others (25)</td>
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<tr>
<td><strong>Postpartum depression</strong></td>
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<tr>
<td>Edinburgh Postnatal Depression Scale</td>
<td>10-item self-report instrument</td>
<td>Cox and others (22)</td>
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<td><strong>Older patients</strong></td>
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<tr>
<td>Mini-Mental State Examination</td>
<td>Test for reduced global cognitive function</td>
<td>Folstein and others (33)</td>
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<td>Cornell Scale for Depression in Dementia</td>
<td>Clinician-rated instrument</td>
<td>Alexopoulos and others (34)</td>
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<td>Geriatric Depression Scale</td>
<td>Self-rated instrument</td>
<td>Yesavage and others (35)</td>
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<td><strong>Anxiety disorders</strong></td>
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<tr>
<td>Hamilton Anxiety Rating Scale</td>
<td>Clinician-rated, 14 items assessed on 4-point scales</td>
<td>Hamilton (26)</td>
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<tr>
<td>Clinician Administered Posttraumatic Stress Disorder (PTSD) Scale-2 (CAPS)</td>
<td>Assesses frequency and intensity of symptoms using standard questions and behaviourally anchored rating scales; lengthy to administer</td>
<td>Blake and others (27)</td>
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<tr>
<td>Treatment Outcome PTSD Scale</td>
<td>8-item clinician-rated scale, highly correlated with CAPS but shorter and easier to use</td>
<td>Davidson and Colket (28)</td>
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<td>Yale-Brown Obsessive Compulsive Scale</td>
<td>10-item clinician-rated instrument</td>
<td>Goodman and others (29)</td>
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<td>Liebowitz Social Anxiety Scale</td>
<td>24-item clinician-rated instrument; measures both severity of fear and anxiety</td>
<td>Liebowitz (30)</td>
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<tr>
<td>Sheehan Disability Scale</td>
<td>Self-rated score of disability in 3 areas: work, social life, and family life</td>
<td>Leon and others (31)</td>
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<tr>
<td>Panic Disorder Severity Scale</td>
<td>Clinician-rated, 7 dimensions of panic disorder assessed on 4-point scales</td>
<td>Shear and others (32)</td>
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Although there are unique concerns with treatment of depression in the elderly, depression should not be seen as a normal part of aging. In Canada, older patients with depression are frequently underdiagnosed and undertreated (42). In this supplement, Rabheru reviews the data on the use of antidepressants, particularly in achieving full remission (43). The numbers needed to treat reviewed in this paper is a convenient method of appreciating efficacy. Both venlafaxine and the selective serotonin reuptake inhibitors (SSRIs) show clear benefit over placebo, with the possible exception of fluoxetine. CBT and IPT have demonstrated benefit, as has the combination of antidepressants and psychotherapy. The impact of altered physiology and multiple medication use in the older patient on treatment is discussed, as is comorbid illness in general.

Finally, Lam and Kennedy provide a clear and succinct review of metaanalyses and recent randomized controlled trial data on evidence-based treatment strategies to achieve and maintain remission, explaining and using odds ratio and effect size (44). This methodology has significantly improved our ability to critically appraise clinical trials evidence in a clinically meaningful fashion. The long-standing European suspicions that tricyclic antidepressants produce higher remission rates than SSRIs has been augmented by clear evidence that venlafaxine, as a dual-action agent, has remission rates superior to those of the SSRIs. Remission rates in psychotherapy studies are clearly superior to placebo. The authors discuss a recent controversial antidepressant and psychotherapy combination study showing double the remission rates achieved with the use of antidepressants alone.

Are there specific limitations to the evidence of the superiority of venlafaxine over SSRIs in achieving remission rates? The SSRIs in these metaanalyses were classified as a group, and hence we cannot exclude the possibility that one SSRI in particular might produce superior remission rates. Similarly, none of the studies excluded patients who had previously failed to respond to SSRIs, and therefore the differences in remission rates may reflect the inferior results of the subgroup of prior nonresponders.

Are these results generalizable to ordinary clinical practice? All these studies were short-term and carry the usual limitations of clinical trials, that is, a highly selected patient group without comorbidity. Large-scale randomized trials with few or no exclusionary criteria are being undertaken in mental health in the UK (45) and in medicine in Canada (46) to answer simple questions on real-life outcomes of treatment. Such a trial assessing treatment outcome in depression would supplement in a complementary way the evidence provided in these metaanalyses and is perhaps the next step in confirming the superiority of venlafaxine over SSRIs.

In clinical practice, it behooves us to adequately assess and treat depressive and anxiety disorders to remission. Both clinicians and researchers should continue to raise the bar for both short- and long-term outcome in these disorders.

References


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