**Canadian Network for Mood and Anxiety Treatments (CANMAT) consensus recommendations for functional outcomes in major depressive disorder**

**BACKGROUND:** Functional recovery is increasingly recognized as a priority in the treatment of major depressive disorder (MDD), by both clinicians and patients. However, symptom improvement remains the focus of traditional clinical trials for MDD and of the regulatory approval process for new medications and other interventions. Many studies have shown that functional outcomes do not always correspond to symptom-based outcomes.

**METHODS:** Representatives from clinical practice, professional societies, academia, industry, and government were invited by the Canadian Network for Mood and Anxiety Treatments to develop recommendations for the conceptualization and measurement of functional outcomes in clinical trials of MDD.

**RESULTS:** Definitions and conceptual frameworks to guide assessment of functioning are described, as well as research methodology applicable to the broad spectrum of treatments for MDD. Examples are given for validated instruments, including patient-reported outcome measures. Strategies for knowledge translation and dissemination are suggested and consensus recommendations summarized.

**CONCLUSIONS:** As the societal burden and financial costs of MDD continue to escalate, so does the need for evidence-based and cost-effective interventions that demonstrate improvement in functioning. Routine assessment of functional outcomes will benefit not only individuals with MDD but also diverse stakeholders concerned about the efficacy and cost-effectiveness of interventions.
INTRODUCTION

Major depressive disorder (MDD) is well characterized as complex, common, and costly to both those who experience it and to society more broadly. Worldwide, MDD is one of the most common medical conditions, with rates of both annual incidence and overall prevalence steadily increasing.¹ Decrement in health and costs to society and personal burden associated with MDD are greater than for other chronic health conditions,²−⁴ in part because of the relatively young age of onset in MDD means that affected individuals live with extended periods of dysfunction and disability.

The toll that depression can exact on day-to-day functioning has been documented relatively well.⁵−⁷ However, one of the challenges in reviewing this literature is a historical lack of precision about what the term “functioning” represents in the context of MDD. In this article, functioning refers to a person’s ability to perform the tasks of daily life and to engage in mutual relationships with other people in ways that are gratifying and that meet the needs of the individual and the community in which they live. Although the terms functioning and quality of life (QoL) sometimes are used interchangeably, most experts agree that they are not identical.⁸ Functioning typically refers to the objective or subjective assessment of performance in ≥1 behavioral domains (eg, occupational, social, or family functioning). In comparison, QoL tends to refer to well-being assessed across a wider variety of domains and is, in most cases, assessed subjectively. Daily functioning, rather than QoL, is the specific focus of this article.

From a clinical perspective, a compelling argument for assessing functioning in MDD is that patients often prioritize functional outcomes over symptomatic ones.⁹ Indeed, in keeping with clinical research and practice guidelines for other medical conditions, the assessment of functioning now is recommended as a routine and necessary component in the comprehensive management of MDD.¹⁰−¹²

From a research perspective, there also is increasing scientific investment in evaluating functional outcomes in MDD, for several reasons. First, it is clear that symptomatic and functional outcomes are not synonymous—functional recovery in MDD can lag well behind symptomatic or syndromal recovery.¹³,¹⁴ Second, even mild or subthreshold symptoms of MDD predict compromised functioning.¹⁵,¹⁶ Third, specific symptoms of MDD (eg, insomnia or cognitive impairment) can have a particularly adverse effect on functional outcomes.¹⁷−¹⁹ Fourth, although MDD can disrupt multiple domains of functioning simultaneously, it also can impact specific domains discretely, so restoration of functioning may occur in 1 domain but remain impaired in another.

In contrast to the large evidence base describing the importance of functioning in MDD, there is still sparse evidence that treatments improve or restore functional capacity in MDD, owing in part to the emphasis on short-term symptom relief in intervention studies of depression.²⁰ Clinical trials are systematic investigations of interventions and their outcomes. Randomized controlled trials (RCTs) remain the gold standard to demonstrate efficacy of interventions. Well-designed RCTs form the basis for evidence-based medicine and the foundation for development of clinical practice guidelines and best practices. Therefore, it is important that clinical trials incorporate outcomes that are meaningful for patients. However, most clinical trials in MDD do not incorporate functional outcomes, but instead are focused on symptom-based outcomes. Yet, as noted by McKnight and Kashdan,²¹ “symptoms provide an early sign of treatment response where, perhaps, functional outcomes provide an indicator of meaningful change.”

The knowledge gap between the importance of functional outcomes in clinical care and the lack of functional outcome assessment in clinical trials was the impetus for the Canadian Network for Mood and Anxiety Treatments (CANMAT, www.canmat.org) consensus meeting on the topic of functioning in MDD. The objectives of the meeting were to: (1) explore the benefits, barriers, and limitations of functional outcome assessment; and (2) develop a set of consensus recommendations to promote the measurement of functional outcomes in clinical trials.

METHODS

CANMAT is a federally incorporated not-for-profit academic organization linking health care professionals across Canada that has been active in advocacy and research, including the development of clinical guidelines for MDD.²² In 2012, CANMAT convened a meeting of clinician-researchers (representing diverse health disciplines including family medicine, nursing, occupational therapy, pharmacy, psychiatry, psychology, and social work), health advocates, community agency,
industry, government, and insurance company representatives to discuss functional outcomes in clinical trials for MDD. Representatives from Health Canada (Bureau of Cardiology, Allergy, and Neurological Sciences) also attended the session as observers. A full list of meeting participants and their respective agencies/organizations is available from the authors. Executive members of CANMAT summarized the conference proceedings and created a draft report, which was circulated to participants for revisions and comments.

RESULTS

The presentations and discussions focused on the systematic assessment of functional outcomes to generate interpretable and meaningful data in clinical trials. Recommendations are intended to encompass trials for the broad spectrum of medical and psychosocial interventions for MDD, both current and investigational.

Definition considerations
In depression, the concept of “functional recovery” is difficult to operationalize, given not only the heterogeneity of MDD but also the individual, sociodemographic, and clinical contexts of people with MDD. Indeed, even within the consensus group, the basic meanings of functioning and recovery proved to be multifaceted and used in different ways. Functional abilities vary considerably among individuals and are vulnerable to non-constant influences, such as physical health status, cognition, and health expectations. Assessment of functioning appears to warrant multidimensional metrics. That is, a valid measurement of functioning is believed to provide a “snapshot” of one’s abilities in a particular domain(s) at a specific point in time, such as baseline or post-intervention; therefore, everyone always is considered functional to some degree, even if minimally. As noted, the term “recovery” carries its own rich and often disputed history, and definitions of the term depend greatly on the context of its use. Thus, recovery can be viewed as both an outcome and a process—both the destination and the journey in the treatment of MDD.

Trial design considerations
In studying functional outcomes in MDD, clinical trials must be designed with specific and careful consideration of whichever functional domain(s) an intervention is predicted to influence. As with any randomized, double-blind, placebo-controlled clinical trial—still upheld as the most scientifically rigorous method of inquiry—the goals and intent of each study must be clearly identified at the outset. Typically, trials adhering to the Consolidated Standards of Reporting Trials Statement, intended as publication guidelines but also useful for study design/development, exert due consideration of such crucial factors, such as entry criteria, time points, expected degree of change, statistical analysis, etc. The type/phase of a proposed trial also will constrain the outcomes to be studied, as earlier phase II and III trials allow for larger-scale statistical modeling but require “cleaner” participant populations enrolled under strict criteria, whereas phase IV trials might have fewer entry criteria, allowing for study of “real-world” patients and more naturalistic treatment in clinical settings without specialized resources.

In traditional clinical trials of MDD, primary assessment measures are powered on discrete, symptom-based outcomes, such as change scores on a depression rating scale like the Hamilton Depression Rating Scale (HAM-D) or the Montgomery-Åsberg Depression Rating Scale. Clinical outcomes also may include response or remission rates, but these are defined according to scores from the same symptom-based measures. Functional assessments, if they occur at all, are usually consigned to secondary or exploratory analyses. In many trials, the study design reinforces an acute-care approach to treating MDD that is typically too brief to capture the more complicated trajectory of functional improvement. The duration of the clinical trial usually is set as the minimum time, typically 6 to 8 weeks, needed to show meaningful change in the primary symptom-based outcome, even though functional capacities might require several months to demonstrate change. Longitudinal assessment over 3 to 6 months, at minimum, may be needed to detect meaningful functional improvement in MDD.

In clinical trials designed to support regulatory approval for new treatments for MDD, North American and European regulatory agencies continue to prioritize symptom-related data (such as HAM-D change scores, or response/remission rates calculated from those same scores) for efficacy claims. Functional outcomes still are considered secondary data, although some regulatory agencies allow for results of functional assessments to be incorporated into supplementary labeling claims for pharmaceutical compounds. However, the lack of clarity and the lower priority given to functional out-
comes make it difficult for pharmaceutical companies to significantly change trial protocols to focus primarily on functional outcomes.

**Measurement considerations**

To date, there is no gold standard tool for measuring functional capacities in MDD specifically, let alone one that accounts for the condition’s complex phenomenology and differential impact on multiple domains. Functional outcomes might vary significantly among depressed individuals depending on the severity of symptoms, clinical subtype (eg, psychotic or melancholic, postpartum onset), pattern of episodes (eg, chronic or recurrent episodes, seasonal pattern), treatment-resistance, medical/psychiatric comorbidities, and any combination thereof. Assessment of functional outcomes warrants tools that are specific to MDD and that also can address certain symptoms, such as cognitive dysfunction, with disproportionately adverse impact on overall functioning.

For functional outcomes to become a primary focus for clinical trials, appropriate assessment measures must be available. Depending on the needs of a trial, researchers can choose from several standardized, validated assessment tools that are already well-known and widely used in research settings (Table 1). However, many of these scales were developed with reference to general populations and not specifically for MDD.

Some of these measures are performance-based and/or clinician-administered, but others are based on self-report by patients, also known as patient-reported outcome (PRO) measures (Table 2). For many aspects of functioning, only PRO measures are available. For exam-

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**Table 1**

<table>
<thead>
<tr>
<th>Scale</th>
<th>Population focus</th>
<th>Domain(s) assessed</th>
<th>Response format</th>
<th>Completion time (minutes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canadian Occupational Performance Measure^34</td>
<td>Generic</td>
<td>Global/occupational functioning</td>
<td>Clinician-administered</td>
<td>&lt;30</td>
</tr>
<tr>
<td>Sheehan Disability Scale^35</td>
<td>Generic</td>
<td>Global/multi-domain</td>
<td>Self-report</td>
<td>&lt;5</td>
</tr>
<tr>
<td>Global Assessment of Functioning^36</td>
<td>Generic in psychiatric disorders</td>
<td>Global</td>
<td>Clinician-administered</td>
<td>&lt;5</td>
</tr>
<tr>
<td>Social Adaptation Self-evaluation Scale^37</td>
<td>Depression-specific</td>
<td>Social functioning</td>
<td>Self-report</td>
<td>15</td>
</tr>
<tr>
<td>Social Adjustment Scale—Self-Rated^38</td>
<td>Generic</td>
<td>Social functioning</td>
<td>Self-report or Clinician-administered</td>
<td>15</td>
</tr>
<tr>
<td>Social and Occupational Functioning Assessment Scale^39</td>
<td>Generic in psychiatric disorders</td>
<td>Global</td>
<td>Clinician-administered</td>
<td>&lt;5</td>
</tr>
<tr>
<td>World Health Organization Psychiatric Disability Assessment Scale^40</td>
<td>Generic in psychiatric disorders</td>
<td>Social functioning</td>
<td>Clinician-administered</td>
<td>20</td>
</tr>
<tr>
<td>World Health Organization Health and Work Performance Questionnaire^41</td>
<td>Generic</td>
<td>Occupational functioning</td>
<td>Self-report</td>
<td>25</td>
</tr>
<tr>
<td>Endicott Work Productivity Scale^42</td>
<td>Generic</td>
<td>Occupational functioning</td>
<td>Self-report</td>
<td>15</td>
</tr>
<tr>
<td>Lam Employment Absence and Productivity Scale^43</td>
<td>Depression-specific</td>
<td>Occupational functioning</td>
<td>Self-report</td>
<td>5</td>
</tr>
<tr>
<td>Stanford Presenteeism Scale^44</td>
<td>Generic</td>
<td>Occupational functioning</td>
<td>Self-report</td>
<td>5</td>
</tr>
<tr>
<td>Work Limitations Questionnaire^45</td>
<td>Generic</td>
<td>Occupational functioning</td>
<td>Self-report</td>
<td>15</td>
</tr>
<tr>
<td>Work Productivity and Activity Impairment^46</td>
<td>Generic</td>
<td>Occupational functioning</td>
<td>Self-report</td>
<td>5</td>
</tr>
<tr>
<td>Work and Social Adjustment Scale^47</td>
<td>Generic</td>
<td>Occupational and social functioning</td>
<td>Self-report</td>
<td>5</td>
</tr>
</tbody>
</table>

MDD: major depressive disorder.
In psychiatric disorders, recovery-oriented care already is incorporating evidence-based guidelines, and vice versa, but such exchanges are complicated and sometimes problematic.60 Within health care delivery systems, communication among patients, health care professionals, and researchers is typically fragmentary and ad hoc, although integrated knowledge translation (KT) strategies are garnering considerable recognition.

Applications/future directions
In treatment trials for MDD, functional outcomes are rarely primary outcomes even though adverse functioning can result from mild or subthreshold depression, and despite compelling arguments for including functional outcomes as endpoints in both acute and maintenance phases of pharmacotherapy. Nonetheless, because functional outcomes in MDD only are correlated moderately with symptomatic outcomes, but not so well as to be redundant, inclusion of functional assessments will help to evaluate treatment outcomes that are most relevant and meaningful to persons experiencing depression.21

A depression-specific scale for functional outcomes ideally would complement the general measures of functioning previously listed. Although the creation of the “perfect” scale is implausible, a more realistic goal is the development of a depression-specific scale for measuring functional outcomes in clinical trials that could be used or adapted for clinical care settings. Such a new or adapted scale might include items addressing each of various functional domains that aggregate to an overall score for global functioning. Whether a newly developed scale or an existing scale, to be considered as a primary outcome in clinical trials, a functional assessment scale must be validated in MDD, demonstrate responsivity and, ideally, have an identified MCID.

Clinical trials with functional outcomes can provide useful models for assessing treatment outcomes for MDD in non-specialized settings such as outpatient clinics, private psychiatrist offices, and physician-led primary care. Such models also are logical offshoots of measurement-based care for MDD using sequenced treatment algorithms with reference to critical decision points within a set visit schedule.60,59 With this consensus statement and future activities, our group will promote appropriate assessment tools for functional outcomes as an initial step to improving clinical trial methodology in MDD and also to focus research efforts and clinical approaches toward functional recovery in MDD. Ideally, systematic assessment of functional improvement in MDD would become routine in research and clinical settings and ultimately would inform treatment decisions by patients, physicians, and other health care providers.

In psychiatric disorders, recovery-oriented care already is incorporating evidence-based guidelines, and vice versa, but such exchanges are complicated and sometimes problematic.60 Within health care delivery systems, communication among patients, health care professionals, and researchers is typically fragmentary and ad hoc, although integrated knowledge translation (KT) strategies are garnering considerable recognition.

<table>
<thead>
<tr>
<th>TABLE 2</th>
<th>Optimal characteristics of PRO measures for clinical trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valid, by showing both content and construct ability</td>
<td>Reliable, by demonstrating internal consistency, test-retest reliability, and (for interviewer-administered items) both intra- and inter-interviewer reliability</td>
</tr>
<tr>
<td>Interpretable according to MCIDs</td>
<td>Able to detect change over time from baseline</td>
</tr>
<tr>
<td>Able to assess specific functional domains, such as occupational, social, and cognitive functioning</td>
<td>Re-administered over appropriate time periods and at reasonable intervals</td>
</tr>
<tr>
<td>Able to consider the complex and heterogeneous nature of MDD</td>
<td>Supplemented with measures of insight, given that subjective assessments of functioning may be influenced by mood state</td>
</tr>
<tr>
<td>Acceptable to respondents and administrators, with respect to item length, format, legibility, literacy level, and clarity of instructions</td>
<td>Developed through an iterative, consultative process with stakeholders</td>
</tr>
</tbody>
</table>

MCID: minimum clinically important differences; MDD: major depressive disorder; PRO: patient-reported outcome.
and prominence on multiple fronts and across disciplines. This consensus statement will act as a starting point for promoting functional measurement tools and for developing broad strategies for dissemination, education, training, and engagement in research and clinical communities alike.

Since the 2012 conference and development of this consensus statement, DSM-5 has been published by the American Psychiatric Association and adopted by many clinicians. DSM-5 no longer uses the multiaxial diagnostic system, and the explicit designation of Axis V for functional assessment has been lost. Instead, separate notations for functional disability are embedded within the primary diagnoses. The DSM-5 also includes the World Health Organization Disability Assessment Scale as a functional assessment scale in Section III, Assessment Measures. It will be important to study whether these changes in DSM-5 will promote functional outcome assessment in clinical trials and clinical care.

In addition to well-established channels for translating knowledge, recent advances in technology, telecommunications, and social media offer intriguing possibilities for changing public discourse on depression. Various stakeholders will be encouraged to participate in these processes and will stand to benefit from systematic inquiries into functional outcomes. People experiencing MDD, family members, community agencies, advocates, medical professionals, health care practitioners, employers, insurance companies, regulatory agencies, research funding agencies, policymakers, and pharmaceutical companies all can share and learn from methods to assess functioning in MDD, especially because such knowledge is germane to the effectiveness and public health costs of specific interventions for depression.

CONCLUSIONS

In MDD, improvement and restoration of functioning is already recognized as a viable treatment goal beyond the longstanding clinical focus on reducing symptoms and, more recently, on achieving remission. Optimizing functional outcomes will become the primary goal in treating MDD, through the same processes and efforts deployed by clinicians and researchers to establish remission as the accepted goal of treatment in MDD. Although MDD remains a complex disorder, and treatment always must be dictated by individual clinical needs, a focus on functional outcomes should guide clinical decision-making toward the factors that matter most to the people who hope to recover fully from depression.

Summary of recommendations

All stakeholders should recognize the clinical significance of functional outcomes in the management of MDD. Functional outcomes, including social (family and friends), occupational and role functioning, often are recognized by patients as more important and meaningful than symptom relief. Patient advocacy, health care, academic, regulatory, pharma, and government/policy communities should collaborate to promote the inclusion of functional assessments in evaluating interventions for MDD.

Valid and reliable tools for measuring functional outcomes should be developed, evaluated, and disseminated. There is no gold standard assessment of functionality, and there is not likely to be one for MDD, given its heterogeneity. Instead, an appropriate tool must be selected depending on the specific question and focus for research. A number of validated measurement tools are available to assess overall functioning and specific domains of functioning. Any functional outcome tools used in treatment studies should be validated in MDD and demonstrated to be responsive and sensitive to change, including identification of the MCID.

Clinical trials should be designed with functional outcomes as primary or co-primary outcomes. Clinical trials for all interventions in MDD, whether involving pharmacologic, psychosocial, somatic, or other types of treatments, should include functional outcomes as primary or key secondary outcomes. The duration of clinical trials for MDD may need re-evaluation, as functional improvement may take more time than symptom improvement.

Stakeholders involved in funding, regulation, and knowledge transition of clinical trials should promote and ensure the inclusion of functional outcomes. For example, funding agencies and journal editors should ensure that scientific review of clinical trials include evaluation of functional outcomes. Pharma and industry sponsors should include functional outcomes in all industry-initiated and supported investigator-initiated clinical trials. Regulatory agencies should incorporate functional outcomes in the reviews for approval of new products and in the listing for current products.
**Measurement-based care should incorporate functional outcome measures.** Functional assessment should be conducted routinely alongside symptom assessment in clinical care for MDD. Simple, easy-to-use, self-rated, and observer-rated tools must be developed and disseminated to assess functional outcomes in clinical practice settings. Evidence-based treatment guidelines and algorithms should focus on interventions to optimize functioning.

**Research about functional outcomes should be shared widely through integrated KT strategies.** Academic clinicians should assume a leadership role in developing strategies for dissemination, education, training, and discussion about functional outcomes in MDD. As such, the contributions of various stakeholders (consumers, health professionals, educators, government agencies, journal editors, and industry-based sponsors) would greatly enhance and enrich KT activities and their participation is both desirable and encouraged. In time, methods used during research trials might be applied in clinical practice and decision-making in the treatment of MDD, and influence public-health policy and general discourse on functional recovery in depression.

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**REFERENCES:**


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