ANNALS OF CLINICAL PSYCHIATRY 2015;27(2):XXX-XXX

REVIEW ARTICLE

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

Raymond W. Lam, MD
Department of Psychiatry
University of British Columbia
Vancouver, British Columbia, Canada

Sagar V. Parikh, MD
Department of Psychiatry
University of Toronto
Toronto, Ontario, Canada

Erin E. Michalak, PhD
Department of Psychiatry
University of British Columbia
Vancouver, British Columbia, Canada

Carolyn S. Dewa, MPH, PhD
Department of Psychiatry
University of Toronto
Toronto, Ontario, Canada

Sidney H. Kennedy, MD
Department of Psychiatry
University of Toronto
Toronto, Ontario, Canada

CORRESPONDENCE
Raymond W. Lam, MD
Department of Psychiatry
University of British Columbia
2255 Wesbrook Mall
Vancouver, BC, V6T 2A1 Canada

E-MAIL
r.lam@ubc.ca

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] Decrements 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 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 amongindividuals and are vulnerable to non-constant influences, such as physical health status, cognition, and health expectations.[23-25] 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.[26] 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.[27] 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)[28] or the Montgomery-Åsberg Depression Rating Scale.[29] 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.[14] 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.[30-32] However, the lack of clarity and the lower priority given to functional out-

TABLE 1
Examples of validated functional outcome assessment scales used in MDD studies

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

MDD: major depressive disorder.

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,[7,33] 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**).[34-47] However, many of these scales were developed with reference to general populations and not specifically for MDD.

Some of these measures are performance-based[48] 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-

TABLE 2
Optimal characteristics of PRO measures for clinical trials

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

MCID: minimum clinically important differences; MDD: major depressive disorder; PRO: patient-reported outcome.

ple, in many jobs it is impossible to objectively measure productivity; therefore, assessment of occupational functioning often relies on PRO measures. Regulatory agencies, including the FDA, have endorsed standard criteria for PRO instruments used in clinical trials.[49,50] Use of PRO measures has increased in recent years but still is limited to a minority of registered clinical trials.[51] Because self- and clinician-rated scales only are correlated moderately, assessment of real-world functional outcomes ideally would incorporate subjective, objective, and collateral-report measures, particularly if multiple domains will be studied concurrently.[52]

Particularly important for an outcome measure in clinical trials is the demonstration of responsivity (sensitivity to change) and the minimum clinically important difference (MCID). The MCID is defined as the smallest change in score that is important or meaningful to patients, and must be determined via scientifically justifiable approaches.[53-55] Many functional outcome measures have not demonstrated both responsivity to change and MCID (see Reference 56).

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,[10,57] and despite compelling arguments for including functional outcomes as endpoints in both acute and maintenance phases of pharmacotherapy.[13] 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.[58,59] 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

and prominence on multiple fronts and across disciplines.[61-63] 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[64] 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[40] 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.[65,66] 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.[67] Although MDD remains a complex disorder, and treatment always must by 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.

ACKNOWLEDGMENTS: Funding for the Consensus Conference was provided by CANMAT and an educational grant from RxD Research Foundation.

DISCLOSURES: Dr. Lam is on speaker/advisory boards for, or has received research grants from AstraZeneca, Bristol Myers Squibb, Canadian Institutes of Health Research, Canadian Psychiatric Association, Canadian Psychiatric Association Foundation, CANMAT, Eli Lilly, Lundbeck, Lundbeck Institute, Medscape, Merck, Mochida, Pfizer, Servier, St. Jude Medical, UBC Institute of Mental Health/ Coast Capital Savings, Takeda, University Health Network Foundation, and Wyeth. Dr. Parikh has received honoraria or research or educational conference grants from AstraZeneca, Bristol-Myers Squibb, Canadian Institutes of Health Research, CANMAT, Canadian Psychiatric Association, Eli Lilly, Lundbeck, Mensante, and Pfizer. Dr. Michalak has received research funds or speaking honoraria from Canadian Institutes of Health Research, CANMAT, Canadian Psychiatric Association, Coast Capital Depression Research Fund, Lundbeck, Michael Smith Foundation for Health Research, Vancouver Coastal Health Research Institute, and Vancouver Foundation. Dr. Dewa reports no financial relationships with any company whose products are mentioned in this article or with manufacturers of competing products. Dr. Kennedy has received research funds or grants from Bristol-Myers Squibb, Canadian Institutes of Health Research, Clera, Lundbeck, Ontario Brain Institute, St Jude Medical, and has received speaking fees and is a member of advisory boards for Eli Lilly, Lundbeck, Lundbeck Institute, Pfizer, Servier, and Forest. ■

REFERENCES

1. World Health Organization. The global burden of disease: 2004 update. Geneva, Switzerland: WHO Press, 2008.
2. Druss BG, Rosenheck RA, Sledge WH. Health and disability costs of depressive illness in a major U.S. corporation. Am J Psychiatry. 2000;157:1274-1278.
3. Wells KB, Stewart A, Hays RD, et al. The functioning and well-being of depressed patients. Results from the Medical Outcomes Study. JAMA. 1989;262:914-919.
4. Moussavi S, Chatterji S, Verdes E, et al. Depression, chronic diseases, and decrements in health: results from the World Health Surveys. Lancet. 2007;370:851-858.
5. Adler DA, McLaughlin TJ, Rogers WH, et al. Job performance deficits due to depression. Am J Psychiatry. 2006;163:1569-1576.
6. Weissman MM. Social functioning and the treatment of depression. J Clin Psychiatry. 2000;61(suppl 1):33-38.
7. Moore DJ, Moseley S, Atkinson JH. The influence of depression on cognition and daily functioning. In: Marcotte TD, Grant I, eds. neuropsychology of everyday functioning. New York, NY: Guilford Press; 2010:419-440.
8. Coons SJ, Rao S, Keininger DL, et al. A comparative review of generic quality-of-life instruments. Pharmacoeconomics. 2000;17:13-35.
9. Zimmerman M, McGlinchey JB, Posternak MA, et al. How should remission from depression be defined? The depressed patient's perspective. Am J Psychiatry. 2006;163:148-150.
10. Greer TL, Kurian BT, Trivedi MH. Defining and measuring functional recovery from depression. CNS Drugs. 2010;24:267-284.
11. Lam RW, Filteau MJ, Milev R. Clinical effectiveness: the importance of psychosocial functioning outcomes. J Affect Disord. 2011;132(suppl 1):S9-S13.
12. Langlieb AM, Guico-Pabia CJ. Beyond symptomatic improvement: assessing real-world outcomes in patients with major depressive disorder. Prim Care Companion J Clin Psychiatry. 2010;12. doi: 10.4088/PCC.09r00826blu.
13. Bech P. Social functioning: should it become an endpoint in trials of antidepressants? CNS Drugs. 2005;19:313-324.
14. Kennedy N, Foy K, Sherazi R, et al. Long-term social functioning after depression treated by psychiatrists: a review. Bipolar Disord. 2007;9:25-37.
15. Beck A, Crain AL, Solberg LI, et al. Severity of depression and magnitude of productivity loss. Ann Fam Med. 2011;9:305-311.
16. Judd LL, Schettler PJ, Akiskal HS. The prevalence, clinical relevance, and public health significance of subthreshold depressions. Psychiatr Clin North Am. 2002;25:685-698.
17. Asche CV, Joish VN, Camacho F, et al. The direct costs of untreated comorbid insomnia in a managed care population with major depressive disorder. Curr Med Res Opin. 2010;26:1843-1853.
18. Fava M. Daytime sleepiness and insomnia as correlates of depression. J Clin Psychiatry. 2004; 65(suppl 16):27-32.
19. Wisniewski SR, Rush AJ, Bryan C, et al. Comparison of quality of life measures in a depressed population. J Nerv Ment Dis. 2007;195:219-225.
20. Frank E, Prien RF, Jarrett RB, et al. Conceptualization and rationale for consensus definitions of terms in major depressive disorder. Remission, recovery, relapse, and recurrence. Arch Gen Psychiatry. 1991;48: 851-855.
21. McKnight PE, Kashdan TB. The importance of functional impairment to mental health outcomes: a case for reassessing our goals in depression treatment research. Clin Psychol Rev. 2009;29:243-259.
22. Kennedy SH, Lam RW, Parikh SV, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) clinical guidelines for the management of major depressive disorder in adults. J Affect Disord. 2009; 117:S1-S64.
23. Berardi D, Berti Ceroni G, Leggieri G, et al. Mental, physical and functional status in primary care attenders. Int J Psychiatry Med. 1999;29:133-148.
24. Mondloch MV, Cole DC, Frank JW. Does how you do depend on how you think you'll do? A systematic review of the evidence for a relation between patients' recovery expectations and health outcomes. CMAJ. 2001;165:174-179.

25. Baum CM, Katz N. Occupational therapy approach to assessing the relationship between cognition and function. In: Marcotte TD, Grant I, eds. Neuropsychology of everyday functioning. New York, NY: Guilford Press; 2010:62-90.
26. Faerden A, Nesvåg R, Marder SR. Definitions of the term 'recovered' in schizophrenia and other disorders. Psychopathology. 2008;41:271-278.
27. Moher D, Schulz KF, Altman DG. The CONSORT statement: revised recommendations for improving the quality of reports of parallel group randomized trials. BMC Med Res Methodol. 2001;1:2.
28. Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry. 1960;23:56-62.
29. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. Br J Psychiatry. 1979;134:382-389.
30. Barton KN. Health Canada Regulatory Considerations for Functional Outcomes in Depression. Plenary session at the CANMAT Consensus Statement Conference on Functional Outcomes in Depression Clinical Trials. Ottawa, ON: Canadian Network for Mood and Anxiety Treatments, February 10, 2012.
31. European Agency for the Evaluation of Medicinal Products. Note for Guidance on Clinical Investigation of Medicinal Products in the Treatment of Depression. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003526.pdf. Published 2002. Accessed April 12, 2011.
32. U.S. Department of Health and Human Services–Food and Drug Administration. Description of the Hamilton Depression Rating Scale (HAMD) and the Montgomery-Asberg Depression Rating Scale (MADRS). http://www.fda.gov/ohrms/dockets/ac/07/briefing/2007-4273b1_04-descriptionofmadrshamddepressionr%281%29.pdf. Published 2007. Accessed April 12, 2011.
33. Gotlib IH, Joormann J. Cognition and depression: current status and future directions. Annu Rev Clin Psychol. 2010;6:285-312.
34. Carswell A, McColl MA, Baptiste S, et al. The Canadian Occupational Performance Measure: a research and clinical literature review. Can J Occup Ther. 2004;71:210-222.
35. Leon AC, Olfson M, Portera L, et al. Assessing psychiatric impairment in primary care with the Sheehan Disability Scale. Int J Psychiatry Med. 1997;27:93-105.
36. Endicott J, Spitzer RL, Fleiss JL, et al. The global assessment scale. A procedure for measuring overall severity of psychiatric disturbance. Arch Gen Psychiatry. 1976;33:766-771.
37. Bosc M, Dubini A, Polin V. Development and validation of a social functioning scale, the Social Adaptation Self-evaluation Scale. Eur Neuropsychopharmacol. 1997;7(suppl 1):S57-S70; discussion S71-S71.
38. Weissman MM, MHS Staff. Social Adjustment Scale–Self Report (SAS-SR): User's Manual. North Tonwanda, NY/Toronto, ON: Multi-Health Systems Inc.; 1999.
39. Diagnostic and statistical manual of mental disorders, 4th edition, text revision. Washington, DC: American Psychiatric Association; 2000.
40. World Health Organization. WHO psychiatric disability assessment schedule (WHO/DAS): with a guide to its use. Geneva, Switzerland: WHO Press; 1988.
41. Kessler RC, Barber C, Beck A, et al. The World Health Organization Health and Work Performance Questionnaire (HPQ). J Occup Environ Med. 2003; 45:156-174.
42. Endicott J, Nee J. Endicott Work Productivity Scale (EWPS): a new measure to assess treatment effects. Psychopharmacol Bull. 1997;33:13-16.
43. Lam RW, Michalak EE, Yatham LN. A new clinical rating scale for work absence and productivity: validation in patients with major depressive disorder. BMC Psychiatry. 2009;9:78.
44. Koopman C, Pelletier KR, Murray JF,et al. Stanford presenteeism scale: health status and employee productivity. J Occup Environ Med. 2002;44:14-20.
45. Lerner D, Amick BC 3rd, Rogers WH, et al. The work limitations questionnaire. Med Care. 2001;39:72-85.
46. Reilly MC, Zbrozek AS, Dukes EM. The validity and reproducibility of a work productivity and activity impairment instrument. PharmacoEconomics. 1993; 4:353-365.
47. Mundt JC, Marks IM, Shear MK, et al. The Work and Social Adjustment Scale: a simple measure of impairment in functioning. Br J Psychiatry. 2002;180:461-464.
48. Moore DJ, Palmer BW, Patterson TL, et al. A review of performance-based measures of functional living skills. J Psychiatr Res. 2007;41:97-118.
49. Frost MH, Reeve BB, Liepa AM, et al. What is sufficient evidence for the reliability and validity of patient-reported outcome measures? Value in Health. 2007;10(suppl 2):S94-S105.
50. U.S. Department of Health and Human Services – Food and Drug Administration. Guidance for industry: patient-reported outcome measures: use in medical product development to support labeling claims. http://www.fda.gov/downloads/Drugs/Guidances/UCM193282.pdf. Published December 2009. Accessed February 20, 2015.
51. Scoggins JF, Patrick DL. The use of patient-reported outcomes instruments in registered clinical trials: evidence from ClinicalTrials.gov. Contemp Clin Trials. 2009;30:289-292.
52. Carter JD, Frampton CM, Mulder RT, et al. The relationship of demographic, clinical, cognitive and personality variables to the discrepancy between self and clinician rated depression. J Affect Disord. 2010;124:202-206.
53. Copay AG, Subach BR, Glassman SD, et al. Understanding the minimum clinically important difference: a review of concepts and methods. Spine J. 2007;7:541-546.
54. Crosby RD, Kolotkin RL, Williams GR. Defining clinically meaningful change in health-related quality of life. J Clin Epidemiol. 2003;56:395-407.
55. Revicki DA, Cella D, Hays RD, et al. Responsiveness and minimal important differences for patient reported outcomes. Health Qual Life Outcomes. 2006;4:70.
56. Abma FI, van der Klink JJ, Terwee CB, et al. Evaluation of the measurement properties of self-reported health-related work-functioning instruments among workers with common mental disorders. Scand J Work Environ Health. 2012;38:5-18.
57. Backenstrass M, Frank A, Joest K, et al. A comparative study of nonspecific depressive symptoms and minor depression regarding functional impairment and associated characteristics in primary care. Compr Psychiatry. 2006;47:35-41.
58. Trivedi MH. Tools and strategies for ongoing assessment of depression: a measurement-based approach to remission. J Clin Psychiatry. 2009;70(suppl 6):26-31.
59. Trivedi MH, Daly EJ. Measurement-based care for refractory depression: a clinical decision support model for clinical research and practice. Drug Alcohol Depend. 2007;88(suppl 2):S61-S71.
60. Davidson L, Drake RE, Schmutte T, et al. Oil and water or oil and vinegar? Evidence-based medicine meets recovery. Community Ment Health J. 2009; 45:323-332.
61. Scott SD, Albrecht L, O'Leary K, et al. A protocol for a systematic review of knowledge translation strategies in the allied health professions. Implement Sci. 2011;6:58.
62. Canadian Institutes of Health Research. Innovation in Action: The CIHR Knowledge Translation Strategy 2004-2009. Ottawa, ON: Government of Canada; 2004.
63. World Health Organization. Bridging the "know-do" gap: meeting on knowledge translation in global health. Geneva, Switzerland: WHO Press; 2006.
64. Diagnostic and statistical manual of mental disorders, 5th edition. Washington, DC: American Psychiatric Association; 2013.
65. Bakish D. New standard of depression treatment: remission and full recovery. J Clin Psychiatry. 2001; 62(suppl 26):5-9.
66. Keller MB. Past, present, and future directions for defining optimal treatment outcome in depression: remission and beyond. JAMA. 2003;289:3152-3160.
67. Kelsey JE. Clinician perspective on achieving and maintaining remission in depression. J Clin Psychiatry. 2001;62(suppl 26):16-21.