Summary for Treatment of Major Depressive Disorder

Roger S. McIntyre, M.D., FRCPC
Professor of Psychiatry and Pharmacology, University of Toronto
Director, Depression and Bipolar Support Alliance (DBSA)

Introduction

Convergent evidence from international studies indicates that Major Depressive Disorder (MDD) is one of the most common mental disorders affecting adult populations. Within the broader category of "non-communicable" chronic diseases (i.e., NCDs), MDD is associated with relatively higher rates of disability (e.g., impairment in role function) when compared to most other NCDs (e.g., diabetes mellitus) and is also associated with premature mortality of up to 10 years of potential years of life lost. In addition to being a highly disabling disorder, MDD is also a risk factor for several other NCDs (e.g., cardiovascular disease) and has been demonstrated to complicate health outcomes from conditions ranging from cardiovascular disease and diabetes to obesity.

Emerging evidence indicates that, in some cases, MDD exhibits a neuroprogressive process as evidenced by changes in brain structure, volume, and connectivity as a function of illness duration and episode frequency. This observation provides the basis for pressing the point strongly that screening for MDD should be paramount in clinical care settings that are likely to be utilized by individuals with MDD (e.g., primary care). The DSM-5 Field Trials sought to determine the inter-observer agreement of the MDD phenotype. These trials reported a somewhat underwhelming kappa correlation coefficient of 0.28. Translationally, the foregoing finding comports with other lines of evidence that a large percentage of adults with MDD are either not diagnosed accurately and/or are receiving the diagnosis many years after observable characteristics of the illness appear.

Along with individual risk and aspects of heritability that are well-described in MDD, there is growing interest in the role of social determinants in both predisposing and in some cases, offering resiliency to MDD. For example, poverty and exposure to physical and sexual trauma are not only common in the life narrative of individuals with MDD, but are identified as accounting for substantial variability in the risk for MDD. Moreover, protective factors including but not limited to, social connectedness, spirituality, and meaningful interpersonal relationships have all been identified as buffering individuals against the effects of chronic uncontrollable stress. The national and global interest in loneliness involves many aspects that interdigitate with risk and resiliency for depression but the current state of the art is such that we are uncertain whether the so-called "loneliness epidemic" represents a discrete phenomenon entirely or to some extent intersects with the phenotype of MDD.

The criteria items for a depressive episode, the essential feature of MDD, are well-known to clinicians. Emerging evidence now indicates that select symptoms and domains disproportionately account for adverse patient reported outcomes (PROs) (e.g., decreased quality of life, poor functioning, life satisfaction and vitality). A consistent finding amongst patient surveys is that patients assign greater priority, relative to clinicians, to achieving optimal PROs as a therapeutic objective of antidepressant treatment. This observation further underscores of defining the therapeutic objectives in treating MDD collaboratively with affected individuals.

Principles of Treatment

Similar to the ***2017-2018 Florida Best Practice Psychotherapeutic Medication Guidelines for Adults***, the emphasis for the 2019-2020 guidelines is the emphasis on full functional recovery and integration as a priority therapeutic objective in MDD. Towards this overarching and patient-desired aim, it is essential that clinicians consider self-rating instruments when screening for MDD. It is also essential that once the clinical diagnosis of MDD has been established that therapeutic objectives include full symptom mitigation and consensually agreed upon therapeutic objectives in collaboration with patients. Available evidence also indicates that individuals with MDD who function at a higher level, despite being depressed, are more likely to respond and remit with antidepressant therapy. Along with underscoring the complex interrelationship between symptoms and function in MDD, the improved symptomatic outcomes in higher functioning adults with MDD provides the impetus for simultaneously targeting symptoms and functioning in patients with MDD.

Along with careful attention to the presence of depressive symptoms, the relatively high rates of medical and mental disorder comorbidity in the MDD population provides the basis for careful attention to preventing and, when present, treating comorbidity in MDD populations. Commonly encountered comorbidities (e.g., anxiety disorder, substance use disorders, attention deficit hyperactivity disorder, eating disorders), as well as medical disorders (e.g., cardiovascular disease, obesity, diabetes mellitus) should be part of routine assessment of any adult with MDD. Moreover, as with all patients, assessing for imminent risk of suicide is critical. Unfortunately, psychiatry is unable to predict suicide in ways that are robust, evidence-based and clinically applicable. The hope is that the future, perhaps through artificial intelligence machine-learning, we position clinicians to better predict lethal self-harm.

For many individuals presenting with depression of mild severity, manual-based psychotherapy may be a preferred option. Moreover, exercise therapy has also demonstrated symptom mitigating effects in individuals with depressive episodes of milder severity. For others presenting with depression of moderate to severe depressive episodes as part of MDD, pharmacotherapy should certainly be considered. In many cases, manual-based psychotherapy can also be an alternative and/or adjunctive treatment. The current evidence base indicates that for adults with treatment-resistant MDD, manual-based psychotherapy is most effective when combined with pharmacotherapy. Moreover, combination pharmacotherapy-manual based psychotherapy approaches are recommended for persons with persistent depressive disorder, MDD with select comorbidities (e.g., obsessive compulsive disorder) and situations where patients report histories of childhood trauma and/or manifest maladaptive personality traits.

An important new entry and FDA-approved treatment for MDD in 2019 is the approval of intranasal esketamine. Intranasal esketamine is approved for adults with treatment-resistant MDD (TRD), i.e., insufficient outcome with at least 2 conventional antidepressant approaches. Consensus amongst the panel was that before a patient is identified as having TRD, it is essential to assure that they have had optimal antidepressant trials including duration and dose optimization. The committee also agreed that dose optimization for any antidepressant should occur within 2–4 weeks of initiation in keeping with "response trajectory" studies which provide replicated evidence that early

improvement in mood symptoms (i.e., within 2–4 weeks) has modest positive predictive value that the index agent and dose are sufficient. What is more compelling is that the lack of clinically significant improvement within 2–4 weeks (i.e., greater than or equal to 20% improvement in mood symptoms) has powerful negative predictive value (i.e., approaching 85%–90%) that the index agent and dose are insufficient, providing impetus for dose optimization at 2–4 weeks. Intranasal esketamine is approved as an adjunct to a recently initiated antidepressant; although evidence suggests that disparate ketamine formulations may mitigate suicidal ideation, it remains unclear whether ketamine formulations are capable of reducing suicide. What also remains unclear is which formulation of ketamine and/or route of delivery is superior with respect to PROs and patient acceptability. It is also strongly recommended that ketamine only be delivered in treatment centers capable of offering multidisciplinary care to patients with treatment-resistant MDD.

In addition to ketamine, intravenous brexanalone was approved for post-partum depression in 2019 by the U.S. FDA. Clinicians are encouraged to consider all treatment options for post-partum depression noting that brexanalone was the first treatment specifically developed for post-partum depression. Clinicians are also encouraged to carefully screen for the possibility of bipolar disorder in any clinical presentation of depressive symptoms, notably in individuals presenting with new onset depressive symptoms during reproductive life events (e.g., post-partum period).

Insufficient response to antidepressant medication, alone or in combination with manual-based psychotherapy, would provide the basis for recommending neurostimulation. The panel was of the view that the current state of science would support superior overall efficacy for electroconvulsive therapy (ECT) when compared to repetitive transcranial magnetic stimulation (rTMS). Notwithstanding, there are likely advantages in patient acceptability and perhaps tolerability in some cases with rTMS when compared to ECT.

Major Depressive Disorder Without Mixed Features

The DSM-5 introduced mixed features specifier in the manual published in 2013. Mixed features refers to subthreshold hypomanic symptoms occurring during a depressive episode in an individual with MDD. The panel was of the view that the hazards posed by mixed features (e.g., a more complex illness presentation, higher rates of comorbidity, suicidality) as well as diminished response to conventional antidepressants warrants assessment as to the presence or absence of mixed features. In an adult who is presenting MDD without mixed features, clinicians are encouraged to select and sequence treatments according to the ***2019–2020 Florida Best Practice Psychotherapeutic Medication Guidelines for Adults***.

Major Depressive Disorder with Mixed Features

For patients presenting with MDD and mixed features, the panel was of the view that it is important to consider the possibility that the identified patient may possibly have bipolar disorder. Longitudinal studies indicate that the majority of individuals with MDD and mixed features exhibit phenotypic stability across time (i.e., they retain the diagnosis of MDD). Notwithstanding, the relative risk for bipolar disorder in adults with MDD and mixed features is increased relative to the general population. Conventional antidepressants can and should be considered with careful attention for any amplification and/or new onset hypomanic symptoms. Symptom intensification

manifests in many ways including, but not limited to, anxiety, agitation, irritability, dysphoria and sleep disruption. Preliminary evidence suggests that for some adults with MDD with mixed features, second-generation antipsychotics may not only be efficacious but may also be better tolerated in this particular population. As per the Florida Best Practice Psychotherapeutic Medication Guidelines for Adults, the panel agreed that despite the lack of rigorous evidence, other agents with mood stabilizing properties (e.g., lithium, lamotrigine) may also be considered in MDD with mixed features as an adjunct to antidepressants or perhaps in some cases, as a treatment alternative.

Major Depressive Disorder with Psychosis

There was no substantive change in the panel's recommendation in treatment for MDD with psychosis. MDD with psychosis affects at least 20% of individuals with MDD. Results from a recently completed randomized control trial provide results that comport with clinical impression that the combination of a conventional antidepressant and antipsychotic is the preferred, acute, and recurrence-prevention treatment option when compared to conventional antidepressant monotherapy. Indeed, electroconvulsive therapy is an alternative treatment option for MDD with psychosis; antidepressant monotherapy as well as manual-based psychotherapy as stand-alone treatment are not recommended.

Maintenance Treatment in Major Depressive Disorder

Evidence indicates that the majority of individuals with MDD are at risk of recurrence. Furthermore, episode frequency is a powerful predictor of future episodes. Delineating which patients should be considered for longer-term therapy is informed by identifying recurrence vulnerability factors (e.g., number of prior episodes, residual symptoms, cognitive symptoms, comorbidity, stressors). Clinicians are encouraged to consider long-tern tolerability and safety concerns (e.g., weight gain, glucose homeostatic disturbances) when selecting antidepressants acutely. Evidence also indicates that manual-based psychotherapy as well as mindfulness-based psychotherapeutic approaches can be helpful adjunctive and/or alternative treatment strategies during the maintenance treatment of MDD in individuals who have acutely responded to antidepressant monotherapy. The overarching therapeutic objective of maintenance treatment in MDD is to assist patients in full functional recovery in achieving consensually agreed upon PROs.

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