Implementing Treatment Strategies for Different Types of Depression

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Diagnosing and treating major depressive disorder (MDD) accurately and efficiently is challenging for many clinicians. Recent additions to the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM*) as well as potential moderators of antidepressant response such as pretreatment phenomenological characteristics (eg, body mass index, drug metabolism markers) may help physicians to better stratify patients and make informed decisions on the best course of treatment to obtain remission. The evidence base suggests that combining traditional antidepressant therapy with atypical antipsychotics may increase the chance for remission. Other strategies that may help include switching to another antidepressant as monotherapy or combining lithium, thyroid hormone, or psychotherapy. Moreover, in some cases, a manualized-based psychotherapeutic approach may be an appropriate first-line or alternative treatment avenue for adults with MDD.

(J Clin Psychiatry 2016;77[suppl 1]:9–15)

Major depressive disorder (MDD) is a common, often severe disorder associated with high rates of recurrence, nonrecovery, and interepisodic dysfunction.[1] It is heterogeneous in its phenomenology, pathoetiology, comorbidities, and treatment. The direct and indirect costs of MDD are staggering and are largely a consequence of impairment in role function.[2] Notwithstanding the foregoing composite of MDD, recent evidence suggests that health care providers may be informed by a variety of clinical characteristics that increase the probability of offering a patient an appropriate treatment and reduce the likelihood of providing an inappropriate treatment.

ACCURATE DIAGNOSIS

In 2013, the American Psychiatric Association published the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM-5*),[1] which introduced new definitions for mood disorders and separated MDD and other depressive disorders from bipolar disorders. Along with the differences between MDD and bipolar disorder, with respect to the number of episodes and phenomenological characteristics (eg, sadness, irritable mood, somatic and cognitive changes), the diagnoses have very different illness trajectories, patterns of comorbidity, response to treatment, and suicide risk.[1]

The *DSM-5* made no significant changes to the criteria needed to diagnose patients with MDD. A patient must present with at least 5 of the following symptoms, including at least 1 of the first 2 symptoms, for 2 weeks or more: depressed mood most of the time, loss of interest or pleasure in activities, significant weight change or change in appetite, sleep problems, slowing of thoughts or actions, fatigue or loss of energy, feelings of worthlessness or inappropriate guilt, inability to concentrate or make decisions, and suicidal thoughts or actions. Should patients present with symptoms not included in the above criteria, the *DSM-5* has added specifiers that may help clinicians to more accurately diagnose, prognosticate, and stratify their patients.[1]

One such specifier is "with anxious distress," which is the presence of at least 2 of the following symptoms: feeling tense, feeling unusually restless, worrying so much that concentration is impaired, feeling dread that something awful might happen, and fear of loss of control.[1] Another MDD specifier new to the *DSM-5* is "with mixed features," which requires patients to present with at least 3 of the following symptoms: elevated mood, high self-esteem, unusual talkativeness, racing thoughts, increased energy or goal-related activity, decreased restraint regarding risky behaviors, and decreased need for sleep. If a patient presents with what a clinician believes to be MDD and has 3 or more mixed features, the clinician should closely examine the patient for manic and hypomanic episodes to conclusively rule out a bipolar depression diagnosis.

Clinicians should also gather information related to the family history of mental disorders, diabetes mellitus, cardiovascular disease, and suicide throughout the family pedigree. Evidence suggests that patients with a family history of MDD in first-degree relatives have up to 3 times higher risk of developing the disease than those who do not.[3,4] It has been estimated that approximately 30%–40% of the liability for MDD may be related to genetic causation,[3] while around 60% of the variance in liability for MDD[3] is due

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This article is derived from the planning teleconference series "Improving the Care and Management of Patients With Inadequate Response to Depression Treatment," which was held in March 2015 and supported by an educational grant from Otsuka Pharmaceutical Development & Commercialization, Inc.

Dr McIntyre has received grant/research support from Stanley Medical Research Institute, Brain and Behaviour Research Foundation, National Institute of Mental Health, Eli Lilly, AstraZeneca, Lundbeck, Allergan, Takeda, Merck, Pfizer, Janssen-Ortho, Bristol-Myers Squibb, Otsuka, and Johnson & Johnson.

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dx.doi.org/10.4088/JCP.14077su1c.02

Clinical Points

- Clinicians and patients should collaboratively define and measure precise therapeutic objectives with antidepressant treatment.
- Some patients may not respond optimally to antidepressant treatment due to modifiable factors (eg, obesity); early improvement, or lack thereof, is a robust predictor of outcome with antidepressants.
- Augmenting traditional treatment for MDD with atypical antipsychotics may increase the chances for remission.

to individual-specific exposure to environmental pathogens such as early trauma, chronic stress, and loss.

The underlying brain substrates in MDD that subserve the multidimensionality of this syndrome (the dimensions of mood, cognition, and physical symptoms) can be encompassed by the acronym CNN—circuits, nodes, and networks. In other words, MDD is multidimensional because of alterations in underlying circuitry as part of a delicate network of interacting systems that functionally and anatomically connect cortical and subcortical nodes (eg, prefrontal cortex, amygdala, anterior cingulate cortex).

Emerging evidence also suggests that many neurobiological substrates subserving disturbances in reward behavior, cognitive functions, affective processing, and emotional regulation are transdiagnostic and not specific to any particular brain illness. For example, a recent meta-analysis[5] of 193 studies involving over 15,000 individuals with 6 different psychiatric disorders indicated that loss of gray matter volume converged across diagnoses into 3 areas: the left insula, the right insula, and the dorsal anterior cingulate.[5] Few diagnosis-specific effects were found, except in schizophrenia and MDD. Taken together, the pathoetiology of all brain illnesses, including MDD, can be conceptualized as polygenetic and multifactorial. The relevance of putative etiologic factors may differ as a function of environmental exposure, as well as the timing of exposure to environmental pathogens throughout the developmental trajectory.

In addition to the direct morbidity and mortality associated with MDD, individuals are also differentially affected by both psychiatric and medical disorders. Individuals with depression frequently have comorbid substance use disorders, anxiety disorders, and eating disorders.[1] Common physical illnesses in patients with MDD are obesity, diabetes, and metabolic syndrome, increasing their risk for premature and excess cardiovascular morbidity and mortality.[6]

TREATMENT OUTCOMES

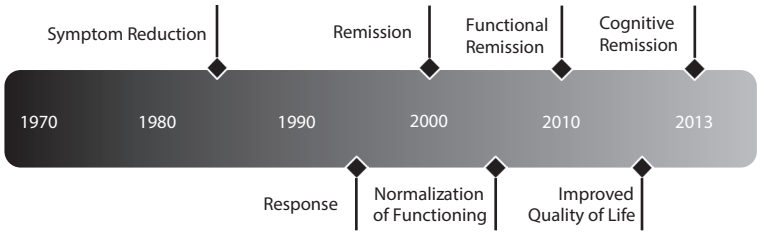
Notwithstanding progress in the development of treatment options for MDD during the past 4 decades, therapeutic outcomes in real-world settings remain highly suboptimal. Many modifiable factors across health systems and access to care have been identified. Even for individuals with access to integrated, guideline-concordant, measurement-based quality care, outcomes still remain inadequate. For example, with initial first-line pharmacotherapy, remission rates are approximately 30%, and sequential treatment (up to 4 therapies) leads to an overall remission rate of 67%.[7] However, over the past 40 years, treatment goals for MDD have evolved and are moving toward more effective treatment practices. From the introduction of antidepressant therapy in the 1950s through the 1980s, clinicians primarily sought to reduce depressive symptoms in their patients. By the 1990s, a categorical response of at least a 50% improvement from baseline symptom severity was sought (Figure 1).[8] During the late 1990s and early 2000s, evidence suggested that, due to the high rates of morbidity and mortality among patients with MDD, physicians should be actively striving toward remission instead of merely treatment response.[8] However, efforts to achieve remission have not always returned patients to normal levels of functioning or well-being, as residual symptoms may remain after remission and interfere with functioning. Current standards for treatment encourage clinicians to consistently monitor treatment outcomes to improve quantitative performance until their patients attain full symptom remission, normalization of functioning, and quality of life.[8]

A disconnect may exist between how clinicians define remission and what patients view as an appropriate therapeutic objective for antidepressant treatment. A study by Zimmerman et al[9] asked patients to describe what factors were very important to them to define remission. Their priorities focused on a feeling of positive mental health rather than symptom resolution. The most widely selected goals (in order) were the presence of optimism and self-confidence, feeling like your usual self, returning to usual functioning, feeling emotional control, participation in and enjoying relationships with friends and family members, and, finally, absence of depressive symptoms.[9] While clinicians and patients share the common goals of achieving symptom remission and normal functioning, it is important for psychiatrists to understand that their patients also seek positivity and a return to feeling normal.

PREDICTORS OF ANTIDEPRESSANT RESPONSE

Antidepressant pharmacotherapy is often clinicians' first line of treatment after diagnosing patients with MDD. However, as noted above, a majority of patients do not achieve remission with initial treatment, wasting valuable time and resources. Ideally, clinicians would have clinical or biological information—or both—to identify which treatment is the correct one for a patient and which treatment is incorrect. That is the hope for the future. For now, such a deterministic approach is unavailable, but a probabilistic approach can be used. In other words, data suggest that some factors increase or decrease the probability of response to a given therapy.[10] These possible predictors of response include clinical factors, genetic factors, biomarkers, body mass index (BMI), and anxiety symptoms.

Figure 1. The Evolution of Treatment Goals for Patients With Major Depressive Disorder[a]



[a]Adapted with permission from McIntyre.[8]

Table 1. Assessment Tools for Screening, Diagnosis, and Outcome Measurement in Depression[a]

Screening Tools	Diagnostic Tools	Symptom Severity Tools
2-Item Patient Health Questionnaire (PHQ-2)	PHQ-9	PHQ-9
9-Item Patient Health Questionnaire (PHQ-9)	Mini International Neuropsychiatric Interview (MINI)	HADS
Center for Epidemiological Studies Depression Scale (CES-D)	Primary Care Evaluation of Mental Disorders (PRIME-MD)	Beck Depression Inventory (BDI)
Hospital Anxiety and Depression Scale (HADS)	Psychiatric Diagnostic Screening Questionnaire (PDSQ)	Clinically Useful Depression Outcome Scale (CUDOS)
Zung Self-Rating Depression Scale (Zung SDS)	Structured Clinical Interview for *DSM-IV* Axis I Disorders, Clinician Version (SCID-CV)	Hamilton Depression Rating Scale (HDRS)
		Inventory of Depressive Symptomatology (IDS)
		Montgomery-Åsberg Depression Rating Scale (MADRS)
		Quick Inventory of Depressive Symptomatology (QIDS)

[a]Adapted with permission from Gelenberg.[11]

Clinical Metrics

Assessment tools should be used to provide clinical metrics as physicians screen for depression, diagnose depression, and evaluate the presence and severity of depressive symptoms as treatment progresses (Table 1).[11] For example, the 9-Item Patient Health Questionnaire (PHQ-9) is a simple, self-administered questionnaire that covers all of the *DSM* criteria for depression.[12] Patients can fill out the questionnaire on their own before meeting with a clinician to save time, and using the data allows the clinician to offer precision, consistency, and appropriateness of care. Each question within the PHQ-9 asks patients to rate their experience with the problem areas on a scale of 0 (not at all) to 3 (nearly every day). The use of such metrics allows the clinician to determine whether the treatments being offered to patients are achieving the therapeutic objectives.

There is no single pretreatment phenomenological characteristic that is sufficiently predictive of response to treatment (ie, has specific and actionable information related to treatment assignment) with the exception of the presence of psychotic features, subsyndromal hypomanic features (ie, mixed features specifier), and a prior history of hypomania or mania. One of the most robust posttreatment initiation predictors of whether a chosen antidepressant is the correct method of treatment is how well a patient is responding after 2 weeks. Szegedi et al[13] found that nonimprovement in the early weeks of exposure to an antidepressant can be viewed as a predictor of negative treatment outcome. Among patients not exhibiting a 20% or greater improvement after 2 weeks of therapy, only 11% had a stable response and 4% had a stable remission after more time receiving that intervention. Conversely, among patients who did show early improvement (that is, 20% or greater in the first 2 weeks), 53% achieved stable response and 25% achieved stable remission.[13]

Genetic Predictors

Research has not yet provided robust genetic predictors of response to antidepressants using pharmacodynamic targets. A meta-analysis was conducted based on data from 3 genome-wide pharmacogenetic studies (the Genome-Based Therapeutic Drugs for Depression [GENDEP] project, the Munich Antidepressant Response Signature [MARS] project, and the Sequenced Treatment Alternatives to Relieve Depression [STAR*D] study).[14] This analysis included over 2,000 patients of northern European descent who received up to 12 weeks of treatment for MDD. The results indicated that only 1%–2% of variance in antidepressant response was explained by genetic profiling using pharmacodynamic targets, which is not a useful predictor of response for clinicians.[14] However, the low rate of clinical utility offered by pharmacodynamic genetic testing today is in stark contrast to the possibility that pharmacokinetic genetic testing may be of some benefit. The phenotypic heterogeneity of response to antidepressants is so vast that it is not compelling that any biomarker, or combination of biomarkers, will be ideal. The available evidence suggests that prediction of response using biomarkers would be better informed by the use of a more dimensional or domain behavioral outcome in MDD.

Some individuals are considered slow metabolizers of antidepressants, meaning that they have a low rate of drug biotransformation, which is determined genetically. As a

consequence, these individuals may accumulate medication, resulting in intolerability or the inability to convert the medication to its active moiety thereby reducing the effectiveness of treatment. Many antidepressants are major substrates of the cytochrome P450 2D6 enzyme.[15] Under conditions of 2D6 slow metabolism, an individual receiving these antidepressants can be expected to have more side effects and decreased efficacy of treatment. In some circumstances in clinical practice, phenotyping of cytochrome P450 enzymes may be relevant. However, sufficient high-quality, replicated, and controlled studies demonstrating that pharmacogenetics and pharmacogenomics reliably improve health outcomes in MDD are not yet available.

Biomarkers

Is there a role for baseline biomarkers or biosignatures to play in predicting antidepressant therapy response today? Currently, the answer is no, but preliminary lines of evidence give some suggestions as to what the future may hold.[16] A recently published post hoc analysis by Uher et al[17] indicated that baseline levels of C-reactive protein (CRP), a marker of systemic inflammation, may influence the possibility of positive response to a selective serotonin reuptake inhibitor (SSRI) or to a tricyclic antidepressant. The CRP level at baseline differentially predicted treatment outcome as measured by the Montgomery-Asberg Depression Rating Scale (MADRS) score. Individuals with low CRP levels had a preferential response to escitalopram. Those with high CRP levels had a greater response to nortriptyline than escitalopram. By evaluating this inflammatory biomarker, researchers were able to explain more than 10% of individual-level variance in treatment outcome.[17]

Obesity and BMI

Patients with MDD commonly experience problems with obesity and metabolic abnormalities, which may contribute to poor cognitive performance.[18] Recent evidence indicates that baseline BMI may be a useful tool for predicting the efficacy of antidepressants. For example, one study[19] found that increased BMI is associated with a decreased likelihood of remission with fluoxetine. Another study[20] found that baseline obesity decreased response to nortriptyline but not to escitalopram. Clinicians are encouraged to carefully monitor and evaluate weight, BMI, and waist circumference in individuals receiving antidepressant therapy because lowering a patient's weight presumably increases the likelihood of success with antidepressant treatment.[19]

Anxiety

One of the most replicated findings in the study of MDD has been that baseline anxiety symptoms and anxiety disorders can negatively influence outcomes with antidepressant therapy. Fava et al[21] compared the results of 2 STAR*D treatment phases in over 2,800 patients, of whom 53% had anxious depression. Regardless of the antidepressant agents used in the 2 phases, patients with anxiety had lower remission rates and longer times to remission than those without anxiety. The presence of anxiety is often associated with greater severity of depressive symptoms and functional impairment, chronicity of MDD, unemployment, and an increased risk of suicide.[21] Individuals with depression and prominent anxiety symptoms should be expected to have an inferior response to SSRIs and serotonin-norepinephrine reuptake inhibitors (SNRIs), and this should be preempted with targeted treatment.[15]

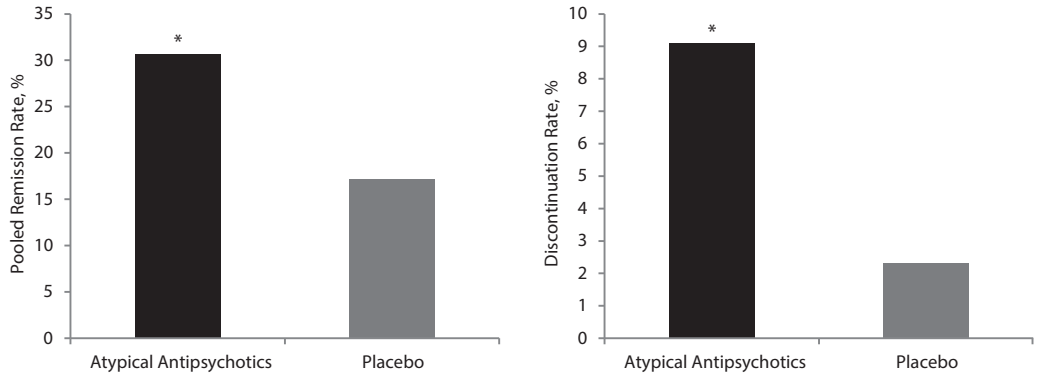
TREATMENT SELECTION

Many different antidepressants in several categories are currently first-line options for treating MDD.[22] However, no convincing data—based on pooled analysis, meta-analysis, or network analysis—suggest that any particular antidepressant is superior to another antidepressant in reducing overall depressive symptoms in patients with heterogeneous presentations of depression.[22] Individuals with a subphenotype may be more likely to respond to one antidepressant than another. That is, when large, heterogeneous groups of patients with depression are grouped into subpopulations, differential responses may be seen. An example of this is in patients who have psychotic depression, for whom the combination of antidepressant and antipsychotic agents is preferred over the antidepressant alone, or electroconvulsive therapy may be used.[15] Depression with atypical features (ie, marked mood reactivity with at least 2 of the following symptoms: rejection sensitivity, increased appetite/weight, hypersomnia, leaden paralysis) may preferentially respond to monoamine oxidase inhibitors over tricyclic or other antidepressants.[15] However, in a trial[23] that examined remission in subgroups of patients with atypical, anxious, and/or melancholic depression, no differences in responses to SSRI or SNRI treatment were found as a function of these pretreatment phenomenological characteristics.

What happens when a patient is not sufficiently benefiting from initial therapy? If the clinician has already achieved an optimal therapeutic dosage of the prescribed antidepressant (and the patient has had good adherence), then 2 strategies are available: to switch the treatment or to combine it with another therapy.[22] Both strategies have advantages and disadvantages. Switching therapies is the better choice when patients have had minimal or no improvement with the initial treatment.[15] By switching treatments, the patient keeps a simple monotherapy regimen, reduces the risk of drug interactions and side effects, and may avoid additional acquisition costs. However, disadvantages include the risk of discontinuation symptoms and a longer time needed for switching than augmenting treatment.

Intuitively, it seems reasonable to switch to an agent with a different mechanism of action, but several studies have shown no major differences in outcomes when switching within a class (eg, from one SSRI to another) compared to switching out of class (eg, from an SSRI to a non-SSRI agent).[24] However, a meta-analysis by Papakostas et al[25] discovered a slight advantage to prescribing SNRI therapy

Figure 2. Meta-Analysis of Remission Rates and Rates of Discontinuation Due to Adverse Events Among Patients With Major Depressive Disorder Treated With Atypical Antipsychotics[a]



[a]Data from Nelson and Papakostas.[28]
*$P < .00001$ versus placebo.

versus SSRIs to patients (response rates were 63.6% and 59.3%, respectively; $P = .003$).[25] This analysis comprised a large number of people (N = 17,036) in 93 different trials, and it is reasonable to hypothesize that in subpopulations differential responses may occur.

When a patient has had a partial response to the initial antidepressant, continuing and adding another pharmacotherapy may be more beneficial than switching and may be preferred by patients. Clinicians may want to consider either combining the current antidepressant with another that has a different mechanism of action or augmenting treatment with a medication that is off-label. Augmentation approaches not only have the advantage of building upon preexisting therapeutic momentum, but also clinicians can often target residual symptoms like anxiety, agitation, sleep disturbances, and any mixed features that have been observed.[15] In some cases, these strategies may be an antidote to adverse events of the index therapy. However, disadvantages of augmentation strategies include potential adverse effects and drug interactions. Health care providers using combination treatments should be aware that polypharmacy could be associated with decreased compliance when compared to monotherapy.[26] Patients, however, sometimes prefer add-on strategies if they experience significant therapeutic benefit.[27]

A recent meta-analysis compared the augmentation of antidepressants with either antipsychotics or placebo.[28] The remission rate for those taking antipsychotics was significantly superior to that of those taking placebo (30.7% vs 17.2%, respectively; $P < .00001$), but the discontinuation rate related to adverse events was significantly higher ($P < .00001$; Figure 2).[28] Specifically, aripiprazole, quetiapine, and olanzapine were examined as add-on treatment for people who had responded insufficiently to SSRI or SNRI therapies, and risperidone was added to various antidepressants.[28] Although lower mean doses of antipsychotic agents are used for antidepressant augmentation rather than for treating psychosis, clinicians should advise patients about potential adverse effects including weight gain, extrapyramidal symptoms, and sedation.[15]

Other augmentation strategies include lithium, thyroid hormone, and psychostimulants.[15] The human thyroid hormone is better established in combination with tricyclics than with SSRIs and SNRIs.[29] Lithium is also capable of reducing suicidality (with most evidence obtained from ecological studies), but does require blood monitoring for safety, as organ toxicities (eg, thyroid, renal) can occur.[15] Psychostimulants have equivocal evidence in reducing overall depressive symptoms in MDD, but they may be beneficial in mitigating symptoms such as fatigue, apathy, amotivation, and sleepiness.[15] Recent data[30] also suggest that psychostimulant augmentation may improve self-reported measures of executive function.

Clinicians should be aware that while combination antidepressant therapy for MDD is very common, the evidence base supporting its efficacy is small.[31] Few large, randomized, placebo-controlled trials have directly compared an antidepressant combination strategy with a well-established strategy, such as the augmentation of an SSRI or SNRI with an atypical antipsychotic agent. In the initial step of acute treatment, Rush and colleagues[32] found no differences in remission rates for patients with MDD treated with escitalopram monotherapy, escitalopram plus bupropion, or venlafaxine plus mirtazapine.

FUTURE DIRECTIONS

Because current pharmacologic treatments for MDD are often insufficient, innovative approaches are being explored. These new approaches include treatments that target glutamate systems, such as ketamine, rapastinel, and minocycline. Ketamine has demonstrated antidepressant efficacy in MDD,[33] and data also suggest that ketamine may reduce suicidality.[34]

Other treatments like minocycline may also target the inflammatory system. Much interest has surrounded applying agents such as nonsteroidal anti-inflammatory

drugs (NSAIDs) and cyclooxygenase-2 (COX-2) inhibitors to MDD.[35] Other novel treatments may have effects on oxidative stress pathways.[36]

Clinicians, however, should not forget that although pharmacologic treatment represents a viable and important treatment option, it is not the only available treatment option. Adjunctive psychotherapy, such as cognitive-behavioral therapy (CBT), interpersonal therapy (IPT), and behavioral activation therapy, can be very helpful for many patients with depression, alone or in combination with antidepressants.[37] The addition of psychotherapy may result in increased efficacy and can be tried before switching or augmenting with other medications.[15] CBT and IPT have shown efficacy in combination with antidepressants for patients with MDD.[38] Moreover, aerobic exercise and resistance training also have compelling evidence of antidepressant properties.[15]

Finally, neuromodulatory approaches such as electroconvulsive therapy, repetitive transcranial magnetic stimulation (rTMS), and, where applicable, deep brain stimulation may help some patients.[15]

CONCLUSION

Therapeutic outcomes in MDD have been disappointing, but many of the deficiencies are modifiable. Timely and accurate diagnosis, measurement-based care, and guideline-concordant treatment selection are principles that facilitate improved health outcomes. Treating to remission is encouraged, inviting the need for specific quantitative metrics. There is no pretreatment biomarker that is reliable, robust, scalable, and proven to be appropriate for clinical application. The field has tried to identify baseline biobehavioral markers that are predictive of response in MDD, with very disappointing results. At this point, the prediction of treatment response to broadly defined depressive episodes seems unlikely to be clinically applicable in the short term. A more likely scenario would be the prediction of response to antidepressant medications with a narrowly defined phenotype of interest (eg, cognitive function, anhedonia).

In the interim, pretreatment phenomenological characteristics (eg, subsyndromal hypomania, psychotic symptoms) as well as a prior history of hypomania or mania have direct implications for treatment selection during a major depressive episode. Advantages and disadvantages exist for combination and augmentation treatment approaches. The preponderance of approved agents for augmentation, as well as those proven to be most effective via large randomized controlled trials, are atypical antipsychotic agents. Limitations of atypical agents include but are not limited to adverse events, which can be mitigated by using the lowest effective doses. An integrated approach incorporating lifestyle modification, psychoeducation, and manualized-based therapies provides better outcomes for individuals with multiepisode, later-stage illnesses.

Drug names: aripiprazole (Abilify and others), bupropion (Wellbutrin, Aplenzin, and others), escitalopram (Lexapro and others), fluoxetine (Prozac and others), ketamine (Ketalar and others), lithium (Lithobid and others), minocycline (Dynacin, Minocin, and others), mirtazapine (Remeron and others), nortriptyline (Pamelor and others), olanzapine (Zyprexa and others), quetiapine (Seroquel and others), risperidone (Risperdal and others), venlafaxine (Effexor and others).

Disclosure of off-label usage: Dr McIntyre has determined that, to the best of his knowledge, rapastinel is not approved by the US Food and Drug Administration for the treatment of depression.

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