The Care of Patients With Complex Mood Disorders

Zachary A. Cordner, M.D., Ph.D., Dean F. MacKinnon, M.D., J. Raymond DePaulo Jr., M.D.

This article focuses on some common dilemmas facing clinicians, patients, and families in managing the treatment of complicated mood disorders. Specifically, this article reviews the interaction of depressive states, including unipolar, bipolar, and mixed, with other adversities, including comorbid physical and psychological disorders, personality vulnerabilities, misuse of drugs and alcohol, and social and family problems. These issues are not always clearly differentiated from the depressive illness. Each of these adversities can worsen an existing mood disorder and influence the patient's resolve to persist with a treatment plan. Although this article is not focused strictly on treatment-resistant depression, these coexisting issues make depressive states harder to manage therapeutically. For brevity, the aim of this article has been limited to discussion of some complex situations that psychiatrists in general practice may encounter.

Focus 2020; 18:129–138; doi: 10.1176/appi.focus.20200007

Our aim in this article is to give some useful perspectives on managing treatment for adults with complex mood disorders. Such patients are frequently encountered by psychiatric providers in all settings. Although we come from the perspective of mood disorder specialists in an academic center, we have written this article primarily to aid clinicians in the ambulatory management of treatment for patients with complex and difficult-to-treat conditions. First, though, we review three important but somewhat ambiguous terms: *complexity*, *diagnosis*, and *polypharmacy*.

Complexity is inherent in mental life and thus in the treatment of all psychiatric patients. However, for the purposes of this article, by complexity, we mean those situations in which, and those patients for whom, clinical decisions require more time, more consideration, and more risk than usual. In this article, we summarize some of the complexities we most commonly face and provide evidence-based guidance and clinical experience-based suggestions. We include complexities that arise from comorbid medical and psychiatric disorders, personality dispositions, intellectual differences, habitually problematic behaviors, relationships and life events that have affected a patient's trust and openness to collaboration, and the limitations of some treatment settings. We also wish to clearly distinguish this discussion of complex cases from the concept of treatment-resistant depression. Although the difference between these concepts may seem subtle, it is our view that labeling a patient as treatment resistant suggests a high level of certainty that the case formulation is correct, that complexities have been identified and mitigated, and that treatment trials have been adequate. However, among the clinical difficulties we all face, it seems there is almost nothing more complex and troubling than treating a patient with a mood disorder who does not get better despite competent provision of usually effective treatment.

Diagnosis is not particularly complex in its primary goal of accurately assigning a categorical diagnosis (i.e., *DSM* or *ICD* code) to a patient's condition. This goal is essential, of course, but diagnosis historically, and we think properly, means much more. There are many useful exchanges and essays in the medical literature, including in psychiatry, about the limits and values of diagnosis as defined in a variety of settings (1–5). The word's Greek root means having a thorough understanding of a situation and an ability to discern or differentiate between alternative explanations. For our purposes, the aim of diagnosis, beyond assigning accurate *DSM* or *ICD* codes and the treatments thereby indicated, is to develop a collaborative, thorough, and sometimes evolving understanding of the patient and his or her difficulties within the context of an individual life story. The collaborative nature of this process—between patient, provider, and often family as well—cannot be overlooked. It is our view that enlisting patients, family, and other sources of support in the diagnostic process helps to maximize the value and minimize the risks of treatment. Fundamental keys to success in patient care are trusting partnerships with patients and families that allow for thorough clinical assessments which are discrete at first, then continuous, corrective as needed, and mostly incremental thereafter.

Finally, a few words about polypharmacy—literally, and simply, prescribing more than one medication. For patients with complex mood disorders, and in fact for many patients with straightforward cases of severe depression or mania, the necessity for polypharmacy, with its associated risks, can be great (6–8). In daily practice, being able to recognize when to avoid polypharmacy (almost always, at first) is important, as is knowing how to manage its risks when it can no longer be avoided. Beyond that, controlled studies of adequate duration assessing the utility as well as risks of specific multidrug regimens are sparse in comparison to the frequency of the practice.

CLINICAL CONTEXT

Among psychiatric problems, mood disorders carry the greatest burden of disease in the population and are consistently ranked among the most burdensome of all diseases (9, 10). Although there is variability in severity, mood disorders cause significant functional impairment: approximately half of all episodes result in substantial disability at home, work, or school and in intimate relationships and social life (11, 12). Fortunately, for patients and providers, mood disorders usually occur without other comorbid psychiatric problems (13) and are treatable, with gratifying results for patients and clinicians alike.

Many evidence-supported therapies are available, but success requires persistence. For example, antidepressant medication regimens work slowly, and the likelihood of full remission with a first antidepressant medication may be only 30% after 6–12 weeks of treatment. When the first-line treatment provides inadequate response, relief can often still be achieved with relatively straightforward approaches. Absent other complicating factors, an ambulatory patient who does not respond to the first antidepressant can hope to improve with a combination of medication and psychological intervention, albeit it may take as long as 3–18 months either to find the right strategy or for the depression to run its course (14).

Large retrospective studies have found inadequate responses after 1 to 2 years of treatment in approximately 20% of individual mood episodes (15). Thus, refractory or otherwise difficult-to-treat conditions occur often enough that health care providers will routinely encounter them. Although in the minority, this group of patients can disproportionately consume the clinician's resources, often faces additional risks associated with multidrug regimens (i.e., polypharmacy) (16), and bears the heaviest burden of illness (17). Therefore, all mental health care professionals must have a basic understanding of what makes some mood disorders complex, how to approach treatment for patients with these conditions, and when to escalate care. Although we attempt to provide a broad commentary on complex mood disorders, our discussion focuses on issues that arise among adult patients. In another article in this issue, our colleagues have addressed some of the complexities that arise in managing treatment of adolescents (18).

CHARACTERIZING COMPLEX MOOD DISORDERS

We use the term *complex* to differentiate patients with difficult-to-treat mood disorders commonly seen in practice from patients with *treatment-resistant* disorders that are chronic and truly refractory to treatment. Such cases are, of course, difficult for clinicians and patients and will be covered in part here. However, categorizing a mood disorder as treatment resistant is itself a fraught and sometimes controversial task that can lead to unintended consequences. First, the concept lacks a consensus definition, although several have been proposed (15, 19–21). More importantly, the term *treatment-resistant depression* suggests that depression is the primary contributor to treatment resistance and overlooks the many other ways in which the patient's condition may be complex.

Before concluding that a patient has a treatment-resistant mood disorder therefore, it is important for providers to at least consider a broader array of complicating factors. Perhaps the most common and most salient include other psychiatric comorbid conditions. Nearly half of people with a psychiatric disorder will also meet criteria for at least one other psychiatric diagnosis during the course of a year, with anxiety and substance use disorders being the most common (13). Although extensive discussion is beyond the scope of this article, the management of mood disorders in the setting of other comorbid psychiatric conditions has been extensively reviewed elsewhere (15, 22–27).

When considering the role of comorbid conditions, it is important to focus not only on disease-based complexity but also on other sources of psychiatric morbidity, including maladaptive behaviors (e.g., substance use disorders or chronic self-harm), temperamental vulnerabilities (e.g., the emotional instability characteristic of borderline personality), and situational distress (e.g., grief or stressful life circumstances). Problems in each of these domains may complicate treatment choices and recovery. Additionally, the approach to problems in each of these domains is distinctly different. For example, interrupting substance use behaviors by implementing recovery counseling, peer support (such as Alcoholics Anonymous or Narcotics Anonymous), and medication-assisted treatment may be a primary objective when managing treatment for a patient with comorbid or substance-induced mood symptoms (18). For patients with a mood disorder complicated by enduring temperamental vulnerabilities, the treatment approach will often require addition of intensive supportive therapy, psychoeducation, and an emphasis on social adaptation. In contrast, when patients experiencing an active mood episode have also encountered loss or stressors, treatment may first focus on managing the mood disorder

before delving far into the narrative and meaning of life events.

As a separate matter, somatic medical problems also can cause or perpetuate mood symptoms and thus complicate treatment. It is incumbent on the clinician to consider somatic medical conditions in the differential diagnosis, because depression associated with endocrine, infectious, oncological, cardiovascular, or other systemic disorder (22, 28) may not respond readily to simple antidepressant therapy. Similarly, neurological conditions, such as traumatic brain injuries, stroke, neurodevelopmental abnormalities, and neurodegenerative disorders are established causes of both depressive and manic states (29–35). Antidepressants may help some depressed patients with these adversities, but the provider must remain alert to the possibility that the patient's recovery may entail addressing lingering symptoms of systemic or neurological illness (15, 22).

Medical comorbid conditions may also limit treatment options. For example, patients may be unable to tolerate a therapeutic dose of medication if they experience intolerable side effects (e.g., gastrointestinal distress caused by selective serotonin reuptake inhibitors among patients with dysmotility) or are unable to safely use medication at adequate doses (e.g., lithium use by patients with chronic kidney disease). Beyond pharmacology, neurological disorders affecting cognition may forestall effective psychotherapy. For patients with such disorders, complexity arises out of restricted opportunities for treatment, rather than failed treatment response.

Diagnostic uncertainty often introduces another layer of complexity in mood disorder treatment. Although estimates vary widely, problems involving misdiagnosis have been demonstrated in large groups of the population, including children (36–38), the elderly (39, 40), and racial-ethnic minority groups (41, 42). Common errors specific to mood disorders include diagnosing bipolar disorder as unipolar depression and diagnosing an affective disorder with psychotic features as schizophrenia (37, 43, 44). One large study found that 69% of patients with bipolar disorder had been initially misdiagnosed and had consulted an average of four physicians before receiving a correct diagnosis (44). Strikingly, in a recent study, about 40% of patients referred for specialty care due to an established diagnosis of schizophrenia were instead found to have affective disorders (45). It is easy to imagine how such misdiagnoses can lead to ineffective treatment, which may result in patients labeled as having a treatment-resistant or otherwise atypical condition.

In summary, misdiagnosis in psychiatry is common but should be seen somewhat differently than misdiagnoses of somatic medical conditions, where diagnoses are confirmed or validated through specific tissue or laboratory analyses. When diagnoses are made only at the clinical symptom and syndrome level, even correct diagnoses have less than desired specificity. Providing guidance to the patient, anticipating how disease course may develop, and avoiding misdirection thus become of paramount importance. For patients with phenomenologically complex illness, diagnosis, and therefore treatment, is rendered more difficult (15, 46). Thus, informing the patient and family about the uncertainties of psychiatric diagnosis is good practice, as is outlining likely and less likely diagnoses and providing information about how treatment will be managed, including what may be needed (more data, perhaps, or more time) to develop a more complete and useful diagnostic formulation.

A final point about assessment is that failure to recognize and address any of these complexities could lead a provider to label a patient as having a treatment-resistant disorder when standard approaches fail. However, if a comorbid psychiatric problem or medical cause is not recognized, or the primary diagnosis is missed, or a patient is unable to tolerate adequate trials, then the patient's mood disorder is not treatment resistant—it simply has not been sufficiently treated. As such, we agree with our colleagues (46) who avoid the term *treatment resistant* in favor of acknowledging that many patients have conditions that are difficult to treat for reasons beyond the syndrome itself.

TREATMENT STRATEGIES AND EVIDENCE

Back to Basics

When managing treatment for patients diagnosed as having mood disorders that are complex from the start or that become complex as they unfold, we recommend a back-to-basics approach. That is, treatment management begins with a comprehensive history that incorporates family, personal, medical, psychiatric, premorbid, and present illness elements into a case formulation. Although this formulation serves as a starting point, the formulation must remain dynamic and open to change over time as additional information is gathered from the patient, collateral sources, and clinical observation. Whereas this exercise serves most obviously as a route to diagnosis, it is also therapeutic in the most fundamental way. It is central to the unifying process of psychotherapy that was perhaps best articulated by Jerome Frank—the thorough assessment becomes a form of role induction for the patient to consider all aspects of life as potentially salient, establishes a therapeutic alliance in the act of the patient entrusting the clinician with his or her life story, and the commitment of time and effort to the endeavor instills hope and confidence by the patient in the clinician's commitment and ability to help (47). The value of building alliance, both with patients and families, cannot be overemphasized; it has been shown to predict clinical outcomes across a range of treatment approaches (48–50). Especially for patients with complex conditions, who have already endured a diagnostic odyssey, treatment management and benefit often begin with the clinician listening to the patient's story and making a diagnosis, well before other therapies are applied.

Four essential points can be derived from these observations about assessment. First, and most simply, we have

highlighted the established goal for all patient-provider interactions to be in some sense psychotherapeutic. Second, we have emphasized that being heard and understood can be profoundly meaningful, and this may be particularly true for patients who have been misdiagnosed and so in that way, misunderstood. Third, this approach serves as a reminder that patients come to clinical attention asking questions about diagnosis, prognosis, and how to proceed and sometimes need to be encouraged to ask these questions directly. Simply answering these questions, including what we do not know, can be deeply meaningful and therapeutic (51–53). Clinicians also need to keep in mind that it is common for patients who have not achieved remission or adequate improvement in other settings to remain untrusting. Treatment management for such patients should be simple and carried out in an unfailingly straightforward way. Finally, treatment management for all patients, including those with the most complex conditions, necessarily involves some form of psychotherapy. This practice is, of course, not only deeply rooted in the humanistic goal of therapy—to be present with those who are suffering—but it has also been empirically shown to work in synergy with other treatment modalities (48, 54–56). A somewhat similar caveat about the use of medications also applies to psychotherapy approaches. That is, the severity of illness (and to some extent the complexity of the patient's clinical issues) should be inversely correlated to the complexity of therapy. That is, for patients with the most difficult and complicated conditions, it is often best to start by simply providing support, validating their distress, and prioritizing focus on functioning over an intensive search for deeper insights (1, 53, 57, 58). Moreover, insight-oriented or collaborative therapeutic styles (e.g., psychodynamic, interpersonal, and cognitive behavioral therapies) often founder or can be counterproductive for patients whose severe depression prevents them from seeing anything in a hopeful light. Experienced therapists using such techniques know when to temporarily adjust or narrow the focus (e.g., in the immediate aftermath of the loss of a loved one).

With regard to medications, a good basic assessment entails digging as deep as necessary to develop a thorough review of prior medication trials. Ideally, this review will produce more than a list of past and current medications and will at least incorporate timing, dosage, duration of trials, side effects, and quality of therapeutic response. Once the history is clarified, and a decision is made to initiate or adjust medications, the psychotherapeutic alliance can aid in instilling hope in a patient who has been repeatedly disappointed or frustrated by treatment. We particularly believe information about duration of trials and response (even if partial) is important to know, because many patients and providers describe 4 weeks as adequate. In outpatient settings, we typically set 8 weeks at a usually therapeutic dose as the point at which no response or only the most limited hint of a response indicates that a trial has failed. Trials of a month or less have not had a reasonable chance to work. When embarking on trials that ask for such sustained patience, a trusting alliance—in which the patient is confident that he or she is getting competent care—often allows the patient to better bear the frustrations that are sometimes inevitable with complex conditions.

The importance of starting with a comprehensive formulation, attending to the patient as a whole, and striving for the simplest effective regimen is also paramount in the effort to focus on syndromes (e.g., depression, mania, or psychosis) and not merely to chase after symptoms (e.g., impaired concentration, which commonly occur in each of the previously noted syndromes) and thus to eschew "artisanal polypharmacy" that leaves patients using medications that have not been established as beneficial. Too often, polypharmacy arises out of an effort to manage side effects of other medications. Such polypharmacy is certainly appropriate when the side effect is extrinsic to the problem being treated, as would be the case with adding an anticholinergic for Parkinsonian side effects of a neuroleptic. But prescribing a stimulant, say, to arouse someone who is over sedated from the medication they are taking to promote sleep, is counterproductive—use less sedative in those instances.

Although this may seem like a simplistic part of standard practice, it is worth noting that psychiatric prescribers are more likely than other providers to use polypharmacy, patients with psychiatric disorders are more likely than patients with nonpsychiatric disorders to be prescribed multiple medications, and the use of polypharmacy for managing mood disorders has expanded over time (7, 16, 59, 60). Furthermore, at least for patients with bipolar disorder, prescribers move more quickly to add a new agent than to change the initial medication, and discontinuation is rare (61). There are times when targeting an individual symptom is the only way to quickly bring relief to a patient, at least until the overall therapeutic strategy takes hold. Thus, it is worth the risk of polypharmacy in some instances to provide, for example, a tranquilizing drug to alleviate severe anxiety or difficulty falling asleep, especially when these symptoms directly obstruct functional recovery. Additionally, for some patients, it is necessary to curate regimens that are highly individually tailored. However, there is little in the way of evidence-based medicine to guide complex combination approaches (7, 59). Therefore, polypharmacy should be managed thoughtfully on an individual basis with frequent review of the current benefit of each medication.

As a final point, some have suggested that an increasing focus on residual symptoms (e.g., lingering impairments in vital sense, motivation, or sleep), as opposed to focusing on function or syndrome-level severity, may at least partially explain expanding polypharmacy in psychiatry (16, 61). This focus would seem in line with the evolving goal of treating patients with even the most difficult cases to remission (62, 63). However, it is our view that all treatment efforts should focus on the basic goals of functioning, quality of life, and meaning making, even if definitive diagnosis and remission

of symptoms remain elusive. For many patients with complex and chronically disabling conditions, it may be reasonable to establish 80% improvement, 80% of the time, as a realistic intermediate goal (64). For patients who have been severely and persistently ill for years or sometimes decades, this level of treatment is consistent with much more ability to function. We have seen such patients experience additional improvement after finding renewed interest or fulfillment in work and relationships. Further disease-focused treatment should not be neglected, but may sometimes be delayed until a period of better functioning provides a boost in confidence or resilience, because each new medication trial risks new failures and side effects.

Augmented Treatment

As just alluded to, perhaps the most accessible strategy for treatment augmentation in the management of mood disorders is the mixing of different classes of medication, and there are now several well-studied applications of medication combinations. Although providing a comprehensive list here is beyond the scope of this article, such strategies have been previously reviewed (65–71). Instead, we note that, although many combinations are often tried and are sometimes effective, relatively few medication augmentation strategies have been validated. Of those that have been validated, the most thoroughly studied are second-generation neuroleptics and lithium.

After the addition of a second antidepressant, second-generation neuroleptics represent the most common augmentation strategy (6). Although the utility of neuroleptics in the management of mood disorders had long been clinically recognized (72), their wide use over the last 20 years has followed approval by the U.S. Food and Drug Administration of second-generation antipsychotics for the treatment of mood disorders (68, 73). Since then, a number of trials have supported their use in augmentation for treatment-resistant mood disorders (74–76). Their rapid onset of action, usefulness in both unipolar depression and bipolar disorder, and ability to treat psychotic mood states have been noted as advantages over other strategies, although low tolerability and side effects remain problematic with intermediate and long-term maintenance use (8, 65, 66, 76).

Lithium, in combination with tricyclic antidepressants, was one of the first augmentation strategies to be empirically supported (77, 78). Since then, a number of studies have supported the use of lithium in combination with antidepressants (71). Only a few studies have specifically assessed the utility of lithium for patients diagnosed as having complex mood disorders; the data are mixed but overall support its use (14, 79, 80). Interestingly, several studies have found that whereas lithium augmentation has a measurable sustained effect, its greatest benefits come early, in the first few weeks (71), perhaps providing an additional reason for its use for patients who have especially severe or refractory illness. Specifically, there is abundant evidence across mood disorders demonstrating lithium's antisuicidal effects (81). These observations have led to international guidelines advocating for the use of lithium for patients with mood disorders (82, 83), and some have recommended lithium augmentation as a first-line approach for patients with difficult-to-treat illness (82, 84). Despite the benefits of lithium, recent practice instead has been to augment with additional antidepressants and neuroleptics (6). We certainly find this prescribing practice to be true in our own clinical experience as consultants, consistently observing that lithium and tricyclic antidepressants (especially nortriptyline with therapeutic level monitoring) are frequently among the treatment options not yet tried.

A much smaller number of trials, each involving relatively few patients, have investigated other augmentation strategies specifically for patients with difficult-to-treat conditions. Among them include studies supporting augmentation with bupropion or buspirone (85), pindolol (70), thyroid hormone (86, 87), mirtazapine (88), lamotrigine (89), and several psychostimulants (66). Although these strategies remain promising, and many are widely used, much work remains to determine the patients and circumstances for which these approaches are most effective.

Even when these various efforts result in inadequate response, many alternative pathways for treatment, and reasons to continue to instill hope in patients, remain. Perhaps the most underused, but also most promising approach, is neurostimulation. Whereas neurostimulation has been historically viewed as an effort of last resort, guidelines are increasingly advocating for its use earlier during treatment. Given the abundant evidence demonstrating benefit, safety, and limited contraindications, electroconvulsive therapy (ECT) is now considered a preferred therapy for patients with difficult-to-treat conditions (90). In fact, several major groups have advocated for use of ECT as an overall first-line treatment for some patients diagnosed as having mood disorders with psychotic features or acute suicidality (82, 90, 91). For patients with lower acuity who have not responded to at least one antidepressant trial, repetitive transcranial magnetic (rTMS) stimulation offers another validated option (92–95), although the superiority of ECT compared to rTMS has been repeatedly demonstrated (90). Other promising neurostimulation treatments, such as transcranial direct current stimulation and vagus nerve stimulation, are increasingly available and supported by evidence (90) but are underused. ECT perhaps provides the most striking example of underuse. Despite decades of evidence supporting ECT as one of the most effective treatments for mood disorders, including remission rates of about 50% among patients with treatment-refractory conditions (96), only about 0.25% of patients with mood disorders receive ECT (97), even though approximately 20% of mood episodes remain refractory after 1–2 years of medication management alone (15). Although patient preferences and availability of neurostimulation play some role in this discrepancy, ironically clinicians' enduring negative views also contribute (98).

More recently, there have been exciting developments regarding several novel medication-based strategies for the treatment of patients with severe and difficult-to-treat mood disorders. Among them, ketamine and its derivatives, the progesterone metabolite brexanolone, and psychedelic drugs such as psilocybin, have gathered the most attention and are beginning to have wider clinical use. Although promising, these approaches remain either entirely experimental or require unique clinical considerations and should be used in coordination with specialized consultants.

Expanding the Treatment Team

Although medication management in combination with psychotherapy represents the mainstay of outpatient treatment for complex mood disorders, as already noted, many patients continue to experience residual symptoms and require a higher level or additional components of care. Fortunately, several other specialized approaches can be integrated into routine practice, highlighting the value of the multidisciplinary and multimodal care models that have emerged across psychiatry (99–102). Disciplines that now have well-defined roles within psychiatric care include social work, occupational therapy, case management, vocational counseling, and psychiatric nursing (99). Although studies of each individual discipline as applied specifically to patients with complex mood disorders are limited or lacking, the integration of these roles into higher levels of care for patients with severe mental illness (e.g., assertive community treatment) has been supported (103–106). A related resource that should be considered is family engagement. Although routinely a part of child, adolescent, and young adult care, the value of family involvement is likely underappreciated in adult psychiatry. Family engagement has demonstrated benefits for treatment retention, medication adherence, patient satisfaction with care, and reduction of depressive symptoms (107–110), so when feasible, it becomes a critical component of care for patients with complex conditions.

Another opportunity to improve patient engagement comes with implementation of measurement-based care—a systematic process of data collection and integration to monitor progress and inform decision-making. Although recognized as beneficial and central to evidence-based psychiatry for more than a decade, routine use of measurement-based care has been largely confined to research and large practice settings, with only about 5% of providers regularly using any standardized progress measure (111). Now, with wide adoption of electronic records, the process of collection, analysis, and interpretation of measurements is becoming less burdensome for providers and patients. The approach, which has been associated with improved alliance, also provides objective data that can facilitate diagnosis and treatment progress (112–117), which would benefit patients with complex conditions for whom a definitive formulation remains elusive or when benefit from treatment is uncertain. Additionally, for patients with mood disorders, measurement-based care has been associated with improved insight, more rapid and greater treatment response, and better assessment of functional improvement (115, 116). For patients who have medically complex conditions, the approach seems to facilitate communication among multiple members of a care team, which has also been associated with improved control of both general medical and psychiatric problems (118).

Several other measures that may aid in diagnosis and/or treatment are also now routinely available. Perhaps one of the more common and most broadly useful is neuropsychological assessment to identify potential complicating or comorbid conditions, such as personality vulnerabilities, learning and memory impairment, executive functioning problems, and functional deficits. Such testing may be useful in managing treatment for patients with complex adversities. In fact, neuropsychological testing has been successfully used for patients with difficult-to-treat depression to distinguish between subjective report of symptoms and objective cognitive and functional performance (119, 120), which can be challenging to distinguish in typical clinical encounters. An additional benefit is that neuropsychological assessment can be personalized, with a battery of instruments tailored to the individual presentation and the provider's questions. Brain imaging techniques represent another set of widely available tools that can be complementary to routine psychiatric evaluation. Whereas a variety of structural abnormalities have been reported among patients diagnosed as having mood disorders, with evidence of differences between unipolar depression and bipolar disorder (121–124), the changes are often subtle and far from universal. Therefore, structural imaging is not currently diagnostic for mood disorders per se but can be useful when considering other brain disorders, such as those resulting from traumatic injury, dementing illnesses, or inflammatory processes as complicating factors. More recently, functional brain imaging has identified changes among individuals with mood disorders, and there is some suggestion that functional techniques may be useful in predicting responsiveness to different medication classes (125), although this possibility remains in an investigational stage of development. Among many other techniques developed to empirically aid medication choice and dosage, genetic and pharmacogenetic testing appear to be the most rapidly developing. Pharmacogenetic testing, currently based on predicting pharmacokinetics and identifying individuals with uncommon polymorphisms for whom certain medications or drug combinations could carry increased risk, may be useful for patients who have unexpectedly little benefit or adverse reactions to a medication trial (126, 127). Although testing is not currently able to predict individual treatment response to a specific psychiatric medication, one study (128) suggests that such testing may be useful for patients with severe affective disorders who are new to treatment. Use and integration of these tools into routine practice may be hampered by relatively limited exposure

of clinicians to genetic testing, interpretation, and counseling during psychiatric training (129).

In many cases, and especially when the patient's presentation defies a clear formulation, it is advisable to seek opinions from a colleague or specialty consultation team. Although the potential goals of doing so are many, we believe the most important point is that expert consultation should offer more than a diagnosis and list of treatment recommendations. Instead, the process should provide a reconsideration of the entire history and formulation through a different lens, critical assessment of past treatment trials, options and rationale for future treatment management, and the opportunity for ongoing guidance. However, despite the best efforts of treatment teams, patients with the most complex conditions may be too acutely ill to be safely treated in a typical outpatient setting. For these patients, there are several options for higher levels of care. Depending on the individual situation, psychiatric rehabilitation programs, intensive outpatient programs, partial hospitalization programs, residential programs, or assertive community treatment may be appropriate and, ultimately, acute inpatient hospitalization may be required. In fact, there is some evidence that the need for psychiatric admission is rising, with psychiatric stays being the only major type of hospitalization to increase from 2004 to 2014, and mood disorders now ranked seventh among all causes of hospitalization (130). Although the patient trajectories and ultimate rationales for inpatient admission vary widely, we view the objectives of admission as relatively narrow. Certainly, safety is always the primary objective. Other objectives may include acute stabilization in a therapeutic milieu, diagnostic clarification and accelerated medical workup, intensive longitudinal assessment, accelerated medication change with close monitoring for high risk patients, or initiation of neurostimulation. Meanwhile, when patients are struggling not only with their mood symptoms and other complicating factors, but also the distress and frustration that can come with multiple ineffective trials and escalating care needs, it becomes increasingly important for providers to rely on the therapeutic alliance and the patient's support network to remain present during times of patient distress and steadfastly committed to an appropriately optimistic future.

CONCLUSIONS

In managing care for patients with complex mood disorders, our first aim is to anticipate complicating problems, when possible, before treatment begins or rebegins. A second precept is that, regardless of the degree of complexity or refractoriness of a patient's distress, clinicians should seek to make all encounters, at all stages, psychotherapeutic. Third, the clinician often needs a thorough understanding of alternative treatment approaches as well as a trusted set of multidisciplinary consultants, therapists, and specialists (medical and psychological) and access to quality residential and hospital units. Fourth, a support structure is critical for each patient, which is usually but not always, a family engaged in and supportive of the patient's care. A fifth and somewhat more nuanced principle is that treatment complexity, when possible, should have an inverse relationship to the complexity of the patient's adversities.

Finally, it is important to acknowledge that, in many instances, the clinician is left with substantial uncertainties surrounding treatment decisions, such as when to augment, use neurostimulation, try new or experimental options, involve consultants, or recommend a higher level of care. These are questions that clinicians often confront, the answers to which are unique to each individual patient. After all, unique patients and highly heterogeneous clinical conditions often defy attempts to apply treatment algorithms or universal guidelines. Instead, we hope that this review will serve as a synthesis of the various ways in which clinicians may proceed in evaluating, managing, and instilling hope even for patients with the most difficult conditions.

AUTHOR AND ARTICLE INFORMATION

Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore (Cordner, MacKinnon, DePaulo). Send correspondence to Dr. DePaulo (jrd@jhmi.edu).

Dr. DePaulo serves as an unpaid consultant for Assurex Health, Inc. on behalf of the National Network of Depression Centers (NNDC), which is compensated for his consultation; he holds stock in CVS Health; he has a fiduciary but unpaid relationship with the NNDC as Chairperson of the Board of Directors, and he receives travel reimbursement from the NNDC (about $2,500 per year). The other authors report no financial relationships with commercial interests.

REFERENCES

1. Tumulty PA: What is a clinician and what does he do? N Engl J Med 1970; 283:20–24
2. Christakis NA: The ellipsis of prognosis in modern medical thought. Soc Sci Med 1997; 44:301–315
3. Vickers AJ, Basch E, Kattan MW: Against diagnosis. Ann Intern Med 2008; 149:200–203
4. Croft P, Altman DG, Deeks JJ, et al: The science of clinical practice: disease diagnosis or patient prognosis? Evidence about "what is likely to happen" should shape clinical practice. BMC Med 2015; 13:20
5. Improving Diagnosis in Health Care. Washington, DC, National Academies Press, 2015
6. Valenstein M, McCarthy JF, Austin KL, et al: What happened to lithium? Antidepressant augmentation in clinical settings. Am J Psychiatry 2006; 163:1219–1225
7. Mojtabai R, Olfson M: National trends in psychotropic medication polypharmacy in office-based psychiatry. Arch Gen Psychiatry 2010; 67:26–36
8. Cohen BM: Evidence-based drug treatment of acute depression in bipolar disorder. JAMA Psychiatry 2019; 76:1314–1315
9. Lopez AD, Murray CC: The global burden of disease, 1990–2020. Nat Med 1998; 4:1241–1243
10. Whiteford HA, Degenhardt L, Rehm J, et al: Global burden of disease attributable to mental and substance use disorders: findings from the Global Burden of Disease Study 2010. Lancet 2013; 382:1575–1586
11. Kessler RC, McGonagle KA, Zhao S, et al: Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States. Results from the National Comorbidity Survey. Arch Gen Psychiatry 1994; 51:8–19

12. Demyttenaere K, Bruffaerts R, Posada-Villa J, et al: Prevalence, severity, and unmet need for treatment of mental disorders in the World Health Organization World Mental Health Surveys. JAMA 2004; 291:2581–2590
13. Kessler RC, Chiu WT, Demler O, et al: Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry 2005; 62: 617–627
14. Rush AJ, Trivedi MH, Wisniewski SR, et al: Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. Am J Psychiatry 2006; 163: 1905–1917
15. Souery D, Lipp O, Massat I, et al. The Characterization and Definition of Treatment-Resistant Mood Disorders; in Treatment-Resistant Mood Disorders. Edited by Amsterdam JD, Hornig M, Nierenberg AA. Cambrige, UK, Cambridge University Press, 2001.
16. Frye MA, Ketter TA, Leverich GS, et al: The increasing use of polypharmacotherapy for refractory mood disorders: 22 years of study. J Clin Psychiatry 2000; 61:9–15
17. Greden JF: The burden of disease for treatment-resistant depression. J Clin Psychiatry 2001; 62(Suppl 16):26–31
18. Welsh JW, Matacyznski M, Sarvey DB, et al: Management of complex co-occurring psychiatric disorders and high-risk behaviors of adolescents Focus 2020; 18:139–149
19. Thase ME, Rush AJ: When at first you don't succeed: sequential strategies for antidepressant nonresponders. J Clin Psychiatry 1997; 58(Suppl 13):23–29
20. Fava M: Diagnosis and definition of treatment-resistant depression. Biol Psychiatry 2003; 53:649–659
21. Conway CR, George MS, Sackeim HA: Toward an evidence-based, operational definition of treatment-resistant depression: when enough is enough. JAMA Psychiatry 2017; 74:9–10
22. Hirschfeld RM: Personality disorders and depression: comorbidity. Depress Anxiety 1999; 10:142–146
23. O'Reardon JP, Amsterdam JD: Overview of treatment-resistant depression and its management; in Treatment-Resistant Mood Disorders. Edited by Amsterdam JD, Hornig M, Nierenberg AA. Cambridge, UK, Cambridge University Press, 2001
24. Quello SB, Brady KT, Sonne SC: Mood disorders and substance use disorder: a complex comorbidity. Sci Pract Perspect 2005; 3: 13–21
25. Sung SC, Dryman MT, Marks E, et al: Complicated grief among individuals with major depression: prevalence, comorbidity, and associated features. J Affect Disord 2011; 134:453–458
26. Rosenbluth M, Macqueen G, McIntyre RS, et al: The Canadian Network for Mood and Anxiety Treatments (CANMAT) task force recommendations for the management of patients with mood disorders and comorbid personality disorders. Ann Clin Psychiatry 2012; 24:56–68
27. Shear MK: Clinical practice. Complicated grief. N Engl J Med 2015; 372:153–160
28. Cassem EH: Depression and anxiety secondary to medical illness. Psychiatr Clin North Am 1990; 13:597–612
29. Robinson RG, Starr LB, Kubos KL, et al: A two-year longitudinal study of post-stroke mood disorders: findings during the initial evaluation. Stroke 1983; 14:736–741
30. Robinson RG, Kubos KL, Starr LB, et al: Mood disorders in stroke patients. Importance of location of lesion. Brain 1984; 107:81–93
31. Jorge RE, Robinson RG, Starkstein SE, et al: Secondary mania following traumatic brain injury. Am J Psychiatry 1993; 150: 916–921
32. Jorge RE, Robinson RG, Moser D, et al: Major depression following traumatic brain injury. Arch Gen Psychiatry 2004; 61: 42–50
33. Kanner AM: Is major depression a neurologic disorder with psychiatric symptoms? Epilepsy Behav 2004; 5:636–644
34. Rickards H: Depression in neurological disorders: Parkinson's disease, multiple sclerosis, and stroke. J Neurol Neurosurg Psychiatry 2005; 76(Suppl 1):i48–i52
35. Xue Ming, Brimacombe M, Chaaban J, et al: Autism spectrum disorders: concurrent clinical disorders. J Child Neurol 2008; 23: 6–13
36. Weller EB, Weller RA, Fristad MA: Bipolar disorder in children: misdiagnosis, underdiagnosis, and future directions. J Am Acad Child Adolesc Psychiatry 1995; 34:709–714
37. Singh T, Rajput M: Misdiagnosis of bipolar disorder. Psychiatry (Edgmont Pa) 2006; 3:57–63
38. Bhargava Raman RP, Sheshadri SP, Janardhan Reddy YC, et al: Is bipolar II disorder misdiagnosed as major depressive disorder in children? J Affect Disord 2007; 98:263–266
39. Baker FM: Misdiagnosis among older psychiatric patients. J Natl Med Assoc 1995; 87:872–876
40. Woolley JD, Khan BK, Murthy NK, et al: The diagnostic challenge of psychiatric symptoms in neurodegenerative disease: rates of and risk factors for prior psychiatric diagnosis in patients with early neurodegenerative disease. J Clin Psychiatry 2011; 72: 126–133
41. Whaley AL: Ethnicity/race, paranoia, and psychiatric diagnoses: clinician bias versus sociocultural differences. J Psychopathol Behav Assess 1997; 19:1–20
42. McKenzie KW: Moving the misdiagnosis debate forward. Int Rev Psychiatry 1999; 11:153–161
43. Gonzalez-Pinto A, Gutierrez M, Mosquera F, et al: First episode in bipolar disorder: misdiagnosis and psychotic symptoms. J Affect Disord 1998; 50:41–44
44. Hirschfeld RM, Lewis L, Vornik LA: Perceptions and impact of bipolar disorder: how far have we really come? Results of the National Depressive and Manic-Depressive Association 2000 survey of individuals with bipolar disorder. J Clin Psychiatry 2003; 64:161–174
45. Coulter C, Baker KK, Margolis RL: Specialized consultation for suspected recent-onset schizophrenia: diagnostic clarity and the distorting impact of anxiety and reported auditory hallucinations. J Psychiatr Pract 2019; 25:76–81
46. Rush AJ, Aaronson ST, Demyttenaere K: Difficult-to-treat depression: a clinical and research roadmap for when remission is elusive. Aust N Z J Psychiatry 2019; 53:109–118
47. Frank JD, Frank JB: Persuasion and Healing: A Comparative Study of Psychotherapy. Baltimore, MD, Johns Hopkins University Press, 1993
48. Arnow BA, Constantino MJ: Effectiveness of psychotherapy and combination treatment for chronic depression. J Clin Psychol 2003; 59:893–905
49. Arnow BA, Steidtmann D, Blasey C, et al: The relationship between the therapeutic alliance and treatment outcome in two distinct psychotherapies for chronic depression. J Consult Clin Psychol 2013; 81:627–638
50. Castonguay LG, Constantino MJ, Holtforth MG: The working alliance: where are we and where should we go? Psychotherapy (Chic) 2006; 43:271–279
51. Helm BM: Exploring the genetic counselor's role in facilitating meaning-making: rare disease diagnoses. J Genet Couns 2015; 24: 205–212
52. Oliveri S, Ferrari F, Manfrinati A, et al: A systematic review of the psychological implications of genetic testing: a comparative analysis among cardiovascular, neurodegenerative and cancer diseases. Front Genet 2018; 9:624
53. Gunderson JG, Choi-Kain LW: Working with patients who self-injure. JAMA Psychiatry 2019; 76:976–977
54. Krystal JH: Neuroplasticity as a target for the pharmacotherapy of psychiatric disorders: new opportunities for synergy with psychotherapy. Biol Psychiatry 2007; 62:833–834

55. Stahl SM: Psychotherapy as an epigenetic 'drug': psychiatric therapeutics target symptoms linked to malfunctioning brain circuits with psychotherapy as well as with drugs. J Clin Pharm Ther 2012; 37:249–253
56. Craighead WE, Dunlop BW: Combination psychotherapy and antidepressant medication treatment for depression: for whom, when, and how. Annu Rev Psychol 2014; 65:267–300
57. McWilliams N: Psychoanalytic Diagnosis: Understanding Personality Structure in the Clinical Process. New York, Guilford Press, 2011
58. Gunderson J, Masland S, Choi-Kain L: Good psychiatric management: a review. Curr Opin Psychol 2018; 21:127–131
59. Comer JS, Olfson M, Mojtabai R: National trends in child and adolescent psychotropic polypharmacy in office-based practice, 1996–2007. J Am Acad Child Adolesc Psychiatry 2010; 49: 1001–1010
60. Greil W, Häberle A, Haueis P, et al: Pharmacotherapeutic trends in 2231 psychiatric inpatients with bipolar depression from the International AMSP Project between 1994 and 2009. J Affect Disord 2012; 136:534–542
61. Baldessarini RJ, Leahy L, Arcona S, et al: Patterns of psychotropic drug prescription for US patients with diagnoses of bipolar disorders. Psychiatr Serv 2007; 58:85–91
62. Bakish D: New standard of depression treatment: remission and full recovery. J Clin Psychiatry 2001; 62(Suppl 26):5–9
63. Trivedi MH, Daly EJ: Treatment strategies to improve and sustain remission in major depressive disorder. Dialogues Clin Neurosci 2008; 10:377–384
64. DePaulo JR Jr, Horvitz LA: Understanding Depression: What We Know and What You Can Do About It. Hoboken, NJ, John Wiley & Sons, 2002
65. Bowden CL: Atypical antipsychotic augmentation of mood stabilizer therapy in bipolar disorder. J Clin Psychiatry 2005; 66(Suppl 3):12–19
66. Fava M, Rush AJ: Current status of augmentation and combination treatments for major depressive disorder: a literature review and a proposal for a novel approach to improve practice. Psychother Psychosom 2006; 75:139–153
67. Carvalho AF, Cavalcante JL, Castelo MS, et al: Augmentation strategies for treatment-resistant depression: a literature review. J Clin Pharm Ther 2007; 32:415–428
68. Philip NS, Carpenter LL, Tyrka AR, et al: Augmentation of antidepressants with atypical antipsychotics: a review of the current literature. J Psychiatr Pract 2008; 14:34–44
69. Fleurence R, Williamson R, Jing Y, et al: A systematic review of augmentation strategies for patients with major depressive disorder. Psychopharmacol Bull 2009; 42:57–90
70. Whale R, Terao T, Cowen P, et al: Pindolol augmentation of serotonin reuptake inhibitors for the treatment of depressive disorder: a systematic review. J Psychopharmacol 2010; 24:513–520
71. Nelson JC, Baumann P, Delucchi K, et al: A systematic review and meta-analysis of lithium augmentation of tricyclic and second generation antidepressants in major depression. J Affect Disord 2014; 168:269–275
72. Robertson MM, Trimble MR: Major tranquillisers used as antidepressants. A review. J Affect Disord 1982; 4:173–193
73. Crystal S, Olfson M, Huang C, et al: Broadened use of atypical antipsychotics: safety, effectiveness, and policy challenges: expanded use of these medications, frequently off-label, has often outstripped the evidence base for the diverse range of patients who are treated with them. Health Aff 2009; 28(Suppl1): s770–s781
74. Nierenberg AA, Ostacher MJ, Calabrese JR, et al: Treatment-resistant bipolar depression: a STEP-BD equipoise randomized effectiveness trial of antidepressant augmentation with lamotrigine, inositol, or risperidone. Am J Psychiatry 2006; 163:210–216
75. De Fruyt J, Deschepper E, Audenaert K, et al: Second generation antipsychotics in the treatment of bipolar depression: a systematic review and meta-analysis. J Psychopharmacol 2012; 26:603–617
76. Zhou X, Keitner GI, Qin B, et al: Atypical antipsychotic augmentation for treatment-resistant depression: a systematic review and network meta-analysis. Int J Neuropsychopharmacol 2015; 18:pyv060
77. Dé Montigny C, Grunberg F, Mayer A, et al: Lithium induces rapid relief of depression in tricyclic antidepressant drug non-responders. Br J Psychiatry 1981; 138:252–256
78. Price LH, Charney DS, Heninger GR: Variability of response to lithium augmentation in refractory depression. Am J Psychiatry 1986; 143:1387–1392
79. Nierenberg AA, Papakostas GI, Petersen T, et al: Lithium augmentation of nortriptyline for subjects resistant to multiple antidepressants. J Clin Psychopharmacol 2003; 23:92–95
80. Bauer M, Dell'osso L, Kasper S, et al: Extended-release quetiapine fumarate (quetiapine XR) monotherapy and quetiapine XR or lithium as add-on to antidepressants in patients with treatment-resistant major depressive disorder. J Affect Disord 2013; 151: 209–219
81. Lewitzka U, Severus E, Bauer R, et al: The suicide prevention effect of lithium: more than 20 years of evidence—a narrative review. Int J Bipolar Disord 2015; 3:32
82. Bauer M, Pfennig A, Severus E, et al: World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for biological treatment of unipolar depressive disorders, part 1: update 2013 on the acute and continuation treatment of unipolar depressive disorders. World J Biol Psychiatry 2013; 14:334–385
83. Grunze H, Vieta E, Goodwin GM, et al: The World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the biological treatment of bipolar disorders: update 2012 on the long-term treatment of bipolar disorder. World J Biol Psychiatry 2013; 14:154–219
84. Bauer M, Adli M, Ricken R, et al: Role of lithium augmentation in the management of major depressive disorder. CNS Drugs 2014; 28:331–342
85. Trivedi MH, Fava M, Wisniewski SR, et al: Medication augmentation after the failure of SSRIs for depression. N Engl J Med 2006; 354:1243–1252
86. Joffe RT, Singer W: A comparison of triiodothyronine and thyroxine in the potentiation of tricyclic antidepressants. Psychiatry Res 1990; 32:241–251
87. Aronson R, Offman HJ, Joffe RT, et al: Triiodothyronine augmentation in the treatment of refractory depression. A meta-analysis. Arch Gen Psychiatry 1996; 53:842–848
88. Carpenter LL, Yasmin S, Price LH: A double-blind, placebo-controlled study of antidepressant augmentation with mirtazapine. Biol Psychiatry 2002; 51:183–188
89. Barbosa L, Berk M, Vorster M: A double-blind, randomized, placebo-controlled trial of augmentation with lamotrigine or placebo in patients concomitantly treated with fluoxetine for resistant major depressive episodes. J Clin Psychiatry 2003; 64: 403–407
90. Milev RV, Giacobbe P, Kennedy SH, et al: Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 clinical guidelines for the management of adults with major depressive disorder: section 4. Neurostimulation treatments. Can J Psychiatry 2016; 61:561–575
91. Yatham LN, Kennedy SH, Parikh SV, et al: Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) 2018 guidelines for the management of patients with bipolar disorder. Bipolar Disord 2018; 20:97–170
92. Lisanby SH, Kinnunen LH, Crupain MJ: Applications of TMS to therapy in psychiatry. J Clin Neurophysiol 2002; 19:344–360

93. Janicak PG, Nahas Z, Lisanby SH, et al: Durability of clinical benefit with transcranial magnetic stimulation (TMS) in the treatment of pharmacoresistant major depression: assessment of relapse during a 6-month, multisite, open-label study. Brain Stimul 2010; 3:187–199
94. Mantovani A, Pavlicova M, Avery D, et al: Long-term efficacy of repeated daily prefrontal transcranial magnetic stimulation (TMS) in treatment-resistant depression. Depress Anxiety 2012; 29:883–890
95. Bakker N, Shahab S, Giacobbe P, et al: rTMS of the dorsomedial prefrontal cortex for major depression: safety, tolerability, effectiveness, and outcome predictors for 10 Hz versus intermittent theta-burst stimulation. Brain Stimul 2015; 8:208–215
96. Heijnen WT, Birkenhäger TK, Wierdsma AI, et al: Antidepressant pharmacotherapy failure and response to subsequent electroconvulsive therapy: a meta-analysis. J Clin Psychopharmacol 2010; 30:616–619
97. Wilkinson ST, Agbese E, Leslie DL, et al: Identifying recipients of electroconvulsive therapy: data from privately insured Americans. Psychiatr Serv 2018; 69:542–548
98. Payne NA, Prudic J: Electroconvulsive therapy: Part I. A perspective on the evolution and current practice of ECT. J Psychiatr Pract 2009; 15:346–368
99. Liberman RP, Hilty DM, Drake RE, et al: Requirements for multidisciplinary teamwork in psychiatric rehabilitation. Psychiatr Serv 2001; 52:1331–1342
100. Heinemann GD: Teams in health care settings; in Team Performance in Health Care. Edited by Heinemann GD, Zeiss AM. Boston, Springer, 2002
101. Vreeland B: Bridging the gap between mental and physical health: a multidisciplinary approach. J Clin Psychiatry 2007; 68(Suppl 4): 26–33
102. Reeves G, Anthony B: Multimodal treatments versus pharmacotherapy alone in children with psychiatric disorders: implications of access, effectiveness, and contextual treatment. Paediatr Drugs 2009; 11:165–169
103. Burns BJ, Santos AB: Assertive community treatment: an update of randomized trials. Psychiatr Serv 1995; 46:669–675
104. Stein LI, Santos AB: Assertive Community Treatment of Persons With Severe Mental Illness. New York, WW Norton & Co, 1998
105. Bond GR, Drake RE, Mueser KT, et al: Assertive community treatment for people with severe mental illness. Dis Manag Health Outcomes 2001; 9:141–159
106. Phillips SD, Burns BJ, Edgar ER, et al: Moving assertive community treatment into standard practice. Psychiatr Serv 2001; 52: 771–779
107. Ingoldsby EM: Review of interventions to improve family engagement and retention in parent and child mental health programs. J Child Fam Stud 2010; 19:629–645
108. Bolkan CR, Bonner LM, Campbell DG, et al: Family involvement, medication adherence, and depression outcomes among patients in Veterans Affairs primary care. Psychiatr Serv 2013; 64:472–478
109. Haine-Schlagel R, Walsh NE: A review of parent participation engagement in child and family mental health treatment. Clin Child Fam Psychol Rev 2015; 18:133–150
110. Ofonedu ME, Belcher HME, Budhathoki C, et al: Understanding barriers to initial treatment engagement among underserved families seeking mental health services. J Child Fam Stud 2017; 26:863–876
111. Jensen-Doss A, Haimes EMB, Smith AM, et al: Monitoring treatment progress and providing feedback is viewed favorably but rarely used in practice. Adm Policy Ment Health Ment Health Serv Res 2018; 45:48–61
112. Trivedi MH, Rush AJ, Wisniewski SR, et al: Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: implications for clinical practice. Am J Psychiatry 2006; 163:28–40
113. Trivedi MH, Rush AJ, Gaynes BN, et al: Maximizing the adequacy of medication treatment in controlled trials and clinical practice: STAR(*)D measurement-based care. Neuropsychopharmacology 2007; 32:2479–2489
114. Harding KJ, Rush AJ, Arbuckle M, et al: Measurement-based care in psychiatric practice: a policy framework for implementation. J Clin Psychiatry 2011; 72:1136–1143
115. Scott K, Lewis CC: Using measurement-based care to enhance any treatment. Cognit Behav Pract 2015; 22:49–59
116. Lewis CC, Boyd M, Puspitasari A, et al: Implementing measurement-based care in behavioral health: a review. JAMA Psychiatry 2019; 76:324–335
117. Zandi PP, Wang Y-H, Patel PD, et al: Development of the National Network of Depression Centers mood outcomes program: a multisite platform for measurement-based care. Psychiatr Serv 2020; s201900481
118. Katon WJ, Lin EH, Von Korff M, et al: Collaborative care for patients with depression and chronic illnesses. N Engl J Med 2010; 363:2611–2620
119. Gupta M, Holshausen K, Best MW, et al: Relationships among neurocognition, symptoms, and functioning in treatment-resistant depression. Arch Clin Neuropsychol 2013; 28:272–281
120. Mohn C, Rund BR: Neurocognitive profile in major depressive disorders: relationship to symptom level and subjective memory complaints. BMC Psychiatry 2016; 16:108
121. Soares JC, Mann JJ: The anatomy of mood disorders—review of structural neuroimaging studies. Biol Psychiatry 1997; 41:86–106
122. Beyer JL, Krishnan KR: Volumetric brain imaging findings in mood disorders. Bipolar Disord 2002; 4:89–104
123. Strakowski SM, Adler CM, DelBello MP: Volumetric MRI studies of mood disorders: do they distinguish unipolar and bipolar disorder? Bipolar Disord 2002; 4:80–88
124. Lorenzetti V, Allen NB, Fornito A, et al: Structural brain abnormalities in major depressive disorder: a selective review of recent MRI studies. J Affect Disord 2009; 117:1–17
125. Osuch E, Gao S, Wammes M, et al: Complexity in mood disorder diagnosis: fMRI connectivity networks predicted medication-class of response in complex patients. Acta Psychiatr Scand 2018; 138:472–482
126. Greden JF, Parikh SV, Rothschild AJ, et al: Impact of pharmacogenomics on clinical outcomes in major depressive disorder in the GUIDED trial: a large, patient- and rater-blinded, randomized, controlled study. J Psychiatr Res 2019; 111:59–67
127. Genetic Testing and Psychiatric Disorders. Brentwood, TN, International Society of Psychiatric Genetics, 2019.https://ispg.net/genetic-testing-statement. Accessed Jan 17, 2020
128. Bradley P, Shiekh M, Mehra V, et al: Improved efficacy with targeted pharmacogenetic-guided treatment of patients with depression and anxiety: a randomized clinical trial demonstrating clinical utility. J Psychiatr Res 2018; 96:100–107
129. Nurnberger JI Jr, Austin J, Berrettini WH, et al: What should a psychiatrist know about genetics? Review and recommendations from the Residency Education Committee of the International Society of Psychiatric Genetics. J Clin Psychiatry 2018; 80: 17nr12046
130. McDermott KW, Elixhauser A, Sun R. Trends in Hospital Inpatient Stays in the United States, 2005–2014. HCUP statistical brief 225. Rockville, MD, Agency for Healthcare Research and Quality, 2017. https://www.hcup-us.ahrq.gov/reports/statbriefs/sb225-Inpatient-US-Stays-Trends.pdf. Accessed Jan 17, 2020