ABSTRACT

Schizophrenia and bipolar disorder are two debilitating mental health disorders, both of which manifest early in adulthood and are associated with severe impairment as well as increased suicide risk. In addition, factors affecting disease severity, such as substance abuse, are often prevalent in these patient populations. In the United States, the prevalence of bipolar disorder is believed to be ~3.5%, while the rate for schizophrenia is ~1%. Although each disorder presents with its own symptom profile, the approaches to treatment are similar and include early diagnosis and use of psychosocial therapy. Research initiatives, such as genetic studies, are used in both disorders as well. For schizophrenia, treatment typically includes the combination of an antipsychotic and psychosocial intervention. For bipolar disorder, clinicians commonly prescribe mood-stabilizing drugs (eg, lithium, valproic acid) as first-line treatment. Many of the second-generation antipsychotics have been approved by the US Food and Drug Administration for bipolar disorder treatment in the manic phase. Patients who are affected by either disorder also face the challenges of treatment nonadherence, which can be affected by substance abuse and can hinder symptom remission as well as spur unnecessary medication switches due to nonresponse. Family members play a key role in the treatment of either disorder.

This expert review supplement focuses on treatment options and research strategies being utilized for the management and advanced understanding of schizophrenia and bipolar disorder. Research examining the pharmacology of commonly used medications for the treatment of both disorders is also presented.
Accreditation Statement

This activity has been planned and implemented in accordance with the Essentials and Standards of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of the Mount Sinai School of Medicine and MBL Communications, Inc. The Mount Sinai School of Medicine is accredited by the ACCME to provide continuing medical education for physicians.

Target Audience

This activity is designed to meet the educational needs of psychiatrists.

Learning Objectives

• Recognize the etiology and genetic links between bipolar disorder and schizophrenia.
• Discuss existing and future treatments of schizophrenia and the importance of compliance and individualized treatment.
• Evaluate the existing and future treatments of bipolar disorder relating to mechanism of action and combination treatment.

Faculty Affiliation and Disclosures

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Dr. Buckley is a consultant to AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Janssen, Pfizer, Solvay, and Wyeth; receives grant/research support from AstraZeneca, the National Institute of Mental Health, Pfizer, Solvay, and Wyeth; and receives honorarium/expenses from Bristol-Myers Squibb, Janssen, and Pfizer.

Peer Reviewer

Eric Hollander, MD, reports no affiliation with or financial interest in any organization that may pose a conflict of interest. This activity was also peer reviewed by an anonymous reviewer who reports no affiliations with or financial interest in any organization that poses a conflict of interest.

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Impact of Schizophrenia and Bipolar Disorder on the Affected Populations

Schizophrenia and bipolar disorder are two of the most common psychiatric disorders, both listed by the World Health Organization as being among the most debilitating illnesses in the developed world. Both disorders tend to manifest early in adulthood, which contributes to their profound impact. Both illnesses also have a particularly high association with mortality. In addition, suicide attempts in patients with bipolar disorder are more likely to be lethal than for those in the general population. The overall rate of suicide in patients with bipolar disorder is ~1% annually, which is 60 times higher than in the general population. Among bipolar patients, 25% to 60% will attempt suicide at least once. Approximately ≤18.9% of deaths in this patient population are attributed to suicide, which is a rate three times higher than that in patients with other mood disorders.

Studies also indicate that substance use appears to play a role in suicide risk. Of bipolar patients with a substance use disorder, 39.5% attempt suicide compared to 23.8% of those without a substance use disorder. Other risk factors for suicide for patients with bipolar disorder include previous suicide attempt and feelings of hopelessness. Risk factors for suicidal behavior are family history of suicide, increasingly severe affective episodes, and early onset bipolar disorder (Slide 1).

Suicide risk aside, both bipolar disorder and schizophrenia are life-shortening conditions, and patients who suffer from either condition have a high rate of medical comorbidity and develop health problems at a significantly younger age than members of the general population (Slide 2).

There is also a high rate of substance abuse among patients with schizophrenia as well as among those with bipolar disorder (56%). Researchers theorize that the frequency of substance abuse in these populations may be an attempt at self-medication for the patient. Additionally, recent research suggests that there may even be a genetic vulnerability that could explain in part why some patients with schizophrenia abuse drugs.

The need for physical healthcare and prolonged psychiatric care, the impact of crisis management and possibly legal management, comorbidity, substance abuse, and the burden of care on families and society—including the loss of human potential and productivity—all contribute to the difficulty and importance of addressing these two disorders.

Prevalence

The prevalence of bipolar disorder was traditionally believed to be ~1%, but more recent evidence suggests that subtypes of the disorder have been underrepresented and the actual prevalence rate may be closer to 3.5%. Schizophrenia is believed to be less common than bipolar disorder and has a prevalence of ~1%. There is currently no conclusive evidence that either condition is increasing or decreasing in prevalence. There are noted regional variations in prevalence, and both conditions appear to be overrepresented in immigrants (although there is some conflicting evidence for that finding).
Exploring Multifactorial Etiology

Both schizophrenia and bipolar disorder are highly familial, with heritability estimates ranging from 59% to 87%. These estimates suggest that genes are overwhelmingly important in both disorders, which indicates that these disorders may be more similar in etiology than previously suspected. The genetics of both schizophrenia and bipolar disorder are common and complex. There is some overlap in chromosome 13 and 15 linkage, which suggests that dichotomy between these two disorders may be less significant than suspected (Slide 3).

Environmental contributions to the disorders may be quite broad. Obstetric complications had occurred in 20% of mothers of schizophrenia patients, with no particular complication specifically indicated. In addition, there is the curious finding that patients with schizophrenia are more likely to have been born from February through May, during the so-called “season of birth effect.” There is also growing interest in the age of parents when they conceive, with several studies suggesting that children born to older fathers have a higher risk of schizophrenia.

There is no clear single factor that accounts for either schizophrenia or bipolar disorders. There are multiple contributing factors, and some researchers have suggested that neither disease constitute one single condition. Perhaps one set of symptoms is more determined by genetic factors and another by environmental factors. These are complex disorders, and much more research is needed before they are fully understood.

Diagnosis in the Prodromal Stage

The pathways by which patients affected by bipolar disorder and/or schizophrenia are diagnosed and present for care are highly variable. Both of these disorders are stigmatizing conditions that often occur in youth or early adulthood (Slide 4) and often have a prodrome phase during which the symptoms are not as florid or obvious as in the full-blown course of the disorder (Slides 5 and 6). The symptoms of these disorders can be mistaken for physical illness, moodiness, and substance abuse. It may not be obvious to the patient or their family that bipolar disorder or schizophrenia is the cause of the symptoms and/or behaviors.

There appears to be a period during which patients develop more florid illness before they are able to connect with treatment services; this period is referred to as the “duration of untreated illness.” If clinicians can shorten that duration, they may be able to deliver more effective treatment approaches, particularly in regard to prevention of secondary disability related to serious mental illness. Addressing this treatment gap will require public health assistance.

Diagnosis is also impeded by the high rate of alcohol and drug use in these patient populations. When substance abuse is a part of the clinical picture, it can be very difficult to piece together the pathway to deterioration. Availability of good collaborative information from family or friends is an important element to diagnosis.

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**SLIDE 3**
Genes of Interest in Both Schizophrenia and Bipolar Disorder

<table>
<thead>
<tr>
<th>Schizophrenia</th>
<th>Both Disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>DTNBP1</td>
<td>DAOA(G72)</td>
</tr>
<tr>
<td>DAO</td>
<td>DISC1</td>
</tr>
<tr>
<td>RGS4</td>
<td>NRG1</td>
</tr>
</tbody>
</table>

DTNBP1=dystrobrevin binding protein 1; DAO=D-amino-acid oxidase; RGS4=regulator of G-protein signalling 4; DAOA(G72)=D-amino acid oxidase activator; DISC1=disrupted in schizophrenia 1; NRG1=neuregulin 1; BDNF=brain-derived neurotrophic factor.

**SLIDE 4**
Age of Schizophrenia Onset with Family History

**Mean Age of Onset**
- Males: 27.8 years
- Females: 31.5 years

Age of onset was later for females with positive family history; positive family history did not affect the median age of onset for males.

**SLIDE 5**
Prodromal Symptoms in Bipolar Disorder

- **Manic:**
  - Increased energy or goal-directed activity

- **Manic or psychotic:**
  - Grandiose ideas

- **Psychotic:**
  - Strange or unusual (non-grandiose) idea
  - Suspiciousness
  - Hallucinatory experiences

**SLIDE 6**
Scale of Prodromal Symptoms for Schizophrenia Version

1. **Positive**
   - 1.1 Unusual thought content
   - 1.2 Suspiciousness
   - 1.3 Grandiosity
   - 1.4 Perceptual abnormalities
   - 1.5 Conceptual disorganization

2. **Negative**
   - 2.1 Social isolation or withdrawal
   - 2.2 Avolition
   - 2.3 Decreased expression of emotion
   - 2.4 Decreased experience of emotion
   - 2.5 Decreased ideational richness
   - 2.6 Deterioration in role functioning

3. **Disorganization**
   - 3.1 Odd behavior or appearance
   - 3.2 Bizarre thinking
   - 3.3 Trouble with focus and attention
   - 3.4 Impairment in personal hygiene

4. **General Symptoms**
   - 4.1 Sleep disturbance
   - 4.2 Dysphoric mood
   - 4.3 Motor disturbances
   - 4.4 Impaired tolerance to stress
Treatment of Schizophrenia

In schizophrenia, as in bipolar disorder, medications are the bedrock of treatment. However, medications are only partially effective, and their mechanism of action is still poorly understood.

Antipsychotics function in a variety of methods. Thus far, researchers have yet to identify an antipsychotic that does not have appreciable binding to dopamine (D). Binding to D₂ receptors is important, but is not the only effective mechanism of action. One of the most powerful agents, clozapine, binds very weakly to dopamine receptors. Aripiprazole causes a fine-tuning effect on the dopamine system. Some agents bind strongly to D receptors while some bind weakly. Some agents find a balance between D and serotonin (5-HT) receptors while other drugs bind to many neurotransmitters with little discernment. Despite showing some efficacy in many cases, there is no single defined mechanism by which these antipsychotics function.

Medications are only one facet of successful schizophrenia treatment. It is extremely important that patients with serious mental illness receive the highest level of support, not only from family members but also from friends, colleagues, and the community in general. It is also important that the patient’s family receive guidance and support from clinicians. This support will not only enable them to better assist the patient in daily interactions, but also helps them manage the stress that accompanies having severe mental illness in the family. Families play a major role in care.

Establishing this support base is of particular importance in enabling patients to successfully return to work. While current treatment approaches for schizophrenia are generally effective in terms of treating positive symptoms, many are less successful in establishing community support and enabling patients to return to leading generally productive lives.

A strong relationship between caregiver and patient has been shown to have a positive influence on the career and work performance for schizophrenia patients, and vocational rehabilitation programs and psychosocial therapy specifically targeted toward improving social and job functioning have shown some promise. These programs and therapy options have helped in removing barriers to job seeking, although patient readiness and effort to return to the work force continues to be a major factor.

For patients with more severe illness who would generally be admitted to a public inpatient facility, Assertive Community Treatment (ACT) can be an option. In ACT, patient care is managed by a multidisciplinary team (at least comprising of a psychiatrist, nurse, psychologist, and social worker) and is tailored specifically to meet the patient’s individual needs. Care is available 24 hours a day, and support is provided to family members as well (Slide 7). The cost of this focused, interdisciplinary treatment is high, but it has been shown relatively effective at rehabilitating schizophrenia patients and reducing relapse rates.

It is generally recognized that while other symptoms may play a small role, cognitive deficits such as impaired memory and the inability to concentrate most severely impact the ability of a patient with schizophrenia to find and maintain employment. Accordingly, there has been a good deal of interest in treatments geared toward cognitive enhancement. Several psychosocial and cognitive-behavioral therapies (CBT) have attempted to target cognitive functioning, generally with limited success.

Recent evidence has suggested that the very high prevalence of tobacco use among schizophrenia patients (≥80%) may be partially explained by the positive effect of nicotine on cognitive functioning. The 5-HT₄ antagonist properties of nicotine temporarily offset the suppression of cognitive functioning caused by some medications, which may be useful knowledge for the development of medications to improve functioning in this patient population.

There has also been particular interest in whether existing medications may enhance cognitive functioning. When atypical antipsychotics were introduced, reports surfaced that detailed encouraging, but modest, cognitive benefits. However, the most recent research provides little support for a pervasive and robust effect.

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**SLIDE 7**

**Principles of the ACT Model**

<table>
<thead>
<tr>
<th>Primary provider of services</th>
<th>ACT teams aim to provide complete, uninterrupted mental health services without the need for outside referral</th>
</tr>
</thead>
<tbody>
<tr>
<td>Out-of-office services</td>
<td>Patients are treated at home and in various community settings</td>
</tr>
<tr>
<td>Individualized services</td>
<td>Treatment is fine tuned to meet the specific needs of each patient, and is frequently updated to maintain maximum effectiveness</td>
</tr>
<tr>
<td>Assertive approach</td>
<td>Care providers are proactive in helping patients remain in treatment and resume a more independent life</td>
</tr>
<tr>
<td>Long-term services</td>
<td>Treatment is geared toward providing the continuing support over the period of recovery, which often lasts a number of years</td>
</tr>
<tr>
<td>Vocational services</td>
<td>Patients are assisted in finding employment</td>
</tr>
<tr>
<td>Substance abuse services</td>
<td>Any required substance abuse treatment is provided by the ACT team</td>
</tr>
<tr>
<td>Psychoeducation and family support</td>
<td>Patients and patients’ families are educated and empowered to aid in the treatment process, bolstering the patients support system and increasing autonomy</td>
</tr>
<tr>
<td>Community integration</td>
<td>Patients are encouraged to take part in community activities and join organizations</td>
</tr>
<tr>
<td>Health care</td>
<td>ACT teams educate patients on health care and coordinate general health services</td>
</tr>
</tbody>
</table>

ACT = Assertive Community Treatment.
Researchers are evaluating the use of a variety of different medications, such as those prescribed for Alzheimer’s disease, to treat the cognitive deficits associated with schizophrenia. However, it is important to note that none of these medications have been approved by the United States Food and Drug Administration for this indication. There is also increased interest in drugs with more selective targets, such as the glutamate system and D2 receptors. The US government has funded investigations in an important initiative treating cognition in schizophrenia as a core outcome measure. These investigators are developing and field testing new metrics and novel compounds.

Some of the compounds being tested now are particularly novel and require equally novel methods for testing.

**Treatment Response**

Results of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study have been debated not only by academic professionals but also by members of the public policy field. Perhaps the most unifying conclusion is a reaffirmation that treatment of schizophrenia is highly individualized. Two treatments may match up well, but that does not indicate that a particular patient on a certain drug would not have a better outcome on another medication. Inevitably, the clinician must match the symptom profile of each patient with susceptibility to adverse events and the tolerability profile of the medication, while simultaneously evaluating the current understanding of the robustness of the treatment effect for each class of medications. Furthermore, each medication or combination must be given a reasonable trial period with attention to dosing (Slide 8).

Despite efforts to optimize treatment, many patients do not respond well after intervention. Treatment refractory schizophrenia continues to be a substantial clinical challenge. Before determining that a medication is ineffective for a patient, the clinician must confirm that the patient is demonstrating compliance with treatment (Slide 9). Noncompliance with treatment is strongly associated with substance use, which complicates prognosis and may lead a clinician to erroneously deem the patient’s condition as treatment refractory. It is also essential to make certain the patient is adhering to the recommended medication dosing. For many newer medications, information is not yet available on proper dosing for patients who exhibit signs of treatment refractory illness.

Although it is often a necessary element of treatment, switching medications further complicates the course of treatment. Many patients may not stay on one medicine for a long enough duration to obtain full benefit, and it is difficult to determine whether a patient is truly refractory or not. For truly refractory patients, the medication that has shown the most efficacy is clozapine. However, clozapine also has a substantial side-effect profile. Thus, there may be a tendency for clinicians to avoid this drug, although both the CATIE study and the Cost Utility of the Latest Antipsychotics in Severe Schizophrenia study suggest that it may have a more robust effect on refractory patients (Slide 10).

**Future Research**

Clearly, the clinical decision-making about treatment of schizophrenia remains complex and perhaps involves more art than science. Much of the research that may one day drive new treatment approaches is focused on theories of the etiology and pathophysiology of schizophrenia. Researchers are now moving into genome research, searching for associations between particular candidate genes that may be relevant for neurotransmitter metabolism and examining how these genes are expressed in relation to particular aspects of the illness.

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**SLIDE 8**

**Texas Medication Algorithm for Schizophrenia**

**Choice of antipsychotic should be guided by considering the clinical characteristics of the patient and the efficacy and side-effect profiles of the medication.**

**Any stage(s) can be skipped depending on clinical picture or history of antipsychotic failure and returning to an earlier stage may be justified by history of past response.**

- **Stage 1** - Trial of a single SGA (Aripiprazole, Olanzapine, Quetiapine, Risperidone, or Ziprasidone)§
  - Partial or Nonresponse
  - Consider earlier trial of clozapine in patients with a history of recurrent suicidality, violence, or comorbid substance abuse. Persistence of positive symptoms >2 years warrants >5 years requires a clozapine trial, independent of number of preceding antipsychotic trials.

- **Stage 2** - Trial of a single SGA or FGA (not SGA tried in Stage 1)§
  - Partial or Nonresponse

- **Stage 3** - Clozapine
  - Partial or Nonresponse†
  - Inconsistent results in RCTs
  - Value in clozapine failures not established

- **Stage 4** - Trial of a single agent FGA or SGA (not tried in Stages 1 or 2)§
  - Combination Therapy (eg, SGA + FGA, combination of SGAs, FGA or SGA + ECT, FGA or SGA + other agent (eg, mood stabilizer))§

- **Stage 6** - Case reports, no controlled studies of combinations in long term treatment of schizophrenia

* First-episode patients usually require lower antipsychotic dosing and should be closely monitored due to greater sensitivity to medication side effects. Lack of consensus on inclusion of FGAs as option for first episode.
† If patient is inadequately adherent at any stage, the clinician should assess and consider a long-acting antipsychotic preparation, such as risperidone microspheres, haloperidol decanoate, or fluphenazine decanoate.
§ A treatment refractory evaluation should be performed to reexamine diagnosis, substance abuse, medication adherence, and psychosocial stressors. CBT or psychosocial augmentation should be considered.
§ Whenever a second medication is added to an antipsychotic (other than clozapine) for the purpose of improving psychotic symptoms, the patient is considered to be in stage 6.

SGA=second-generation antipsychotic; FGA=first-generation antipsychotic; ECT=electroconvulsive therapy; RCT=randomized controlled trial; CBT=cognitive-behavioral therapy.
A variety of counseling options can assist patients in mediating stress between brain cells and to explore complex interactions between dopamine and other neurotransmitters. Time will tell just how much these novel approaches will translate into the clinical realm.

**SLIDE 9**  
**Reasons for Nonadherence**

**Patient-Related Factors**
- Symptoms
- Cognitive function
- Healthcare beliefs
- History of substance abuse
- Previous nonadherence

**Medication-Related Factors**
- Lack of efficacy
- Distressing side effects
- High doses
- Medication type
- Regimen complexity

**Environmental Factors**
- Caregiver support
- Family and social support
- Financial cost
- Practical barriers

**Clinician-Related Factors**
- Poor therapeutic alliance
- Attitude of staff

**SLIDE 10**  
**Drug Efficacy Pathway: Clinical Antipsychotic Trials for Intervention Effectiveness (CATIE) Phase 2**

- 44% of patients choosing clozapine in the efficacy pathway of the CATIE phase 2 trial were able to remain on clozapine for the remainder of the study, as opposed to 18% of patients receiving other atypical antipsychotics.
- Patients remained on clozapine for an average of 10 months, as opposed to an average of 3 months for other antipsychotics.
- Symptom reduction was greater for patients taking clozapine than for patients taking other antipsychotics.

Patients with bipolar disorder often abuse alcohol and drugs—most commonly, alcohol and marijuana are abused, followed by cocaine and other opiates. A relationship may exist in which reward circuits in the brain may cause a higher propensity for patients with mental illness to engage in drug abuse. The effects of drug abuse for bipolar disorder patients include more frequent and prolonged affective episodes, decreased compliance with treatment, a lower quality of life, and increased suicidal behavior.

The most commonly used medication for the treatment of bipolar disorder is lithium, which is one of the oldest and frequently-used mood-stabilizing drugs available. Lithium has shown efficacy in the treatment of bipolar disorder symptoms throughout the course of the illness and may be particularly effective in preventing suicide. A variety of anticonvulsants and anti-epilepsy medications, such as valproic acid and carbamazepine, have also shown variable degrees of efficacy in mood stabilization.

Increasingly, clinicians have begun to use second-generation antipsychotics, such as aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone, for variable degrees of efficacy in mood stabilization. Many of these drugs have been tested and are FDA-approved for acute stabilization in the manic phases. Over time, some of these medications have obtained indications for and are being increasingly used in the maintenance phase of the illness. However, it is also important to recognize that many of these drugs do not have approval for use in mood disorders, either in the acute or maintenance phase of the illness. It is important that clinicians remain aware of the approval status of these drugs, particularly as off-label use of antipsychotics is strongly discouraged.

Some studies are examining medication/therapy combination treatment of bipolar disorder, including a variety of different treatment techniques. Among the psychosocial and counseling options are general counseling and support, focused CBT, and interpersonal therapy (Slide 12).

Although each of these therapy modalities have been shown to be helpful in reducing relapse over time in patients with bipolar disorder, researchers have not determined if one option is better than another. What researchers have concluded is that despite the type of medication or counseling intervention, when medication is used as the bedrock of treatment in order to achieve mood stability in a patient and is combined with any psychological therapy, the effect of the medication is boosted.

**SLIDE 11**  
**Elements of Comprehensive Care for Bipolar Disorder**

- Education for monitoring early warning signs of relapse
- Counseling, support, and psychosocial interventions
- Attention to psychiatric and physical comorbidities
- Involvement and support of family members and others in the patient’s life
- Appropriate pharmacotherapy
- Attention to medication side effects
- Support to gain/maintain employment

**TREATMENT OF BIPOLAR DISORDER**

For bipolar disorder, a mainstay of treatment includes use of medications in conjunction with psychosocial interventions, which is similar to treatment approaches for schizophrenia. With a stable mood, psychosocial and other counseling options can assist patients in mediating stressors that may contribute to relapse, reduce hospitalizations, and improve general functioning. Without intervention, the likelihood that medication alone will buffer against relapse is low, as is the likelihood that patients will continue to take medication as prescribed for as long as is necessary. A comprehensive approach works best (Slide 11).
High levels of support are also extremely important for patients with any mental illness including bipolar disorder. Patient family, friends, and community are all key in helping patients maintain a medication regimen, which, in turn, better assures that the patient will improve. In addition, the Depression Bipolar Support Alliance, which manages support groups for patients with these disorders and creates information literature on mental health, is an excellent resource for patients.68 While researchers have studied the effects of positive family and community intervention for patients with mental illness, additional studies are warranted to assess the types of interventions that are most beneficial.69 Clinicians should also work with patients with bipolar disorder on reentering other areas of their lives also affected by disorder symptoms, such as the work environment.

Medication Limitations

Investigators at the National Institute of Mental Health recently published results of two important and large pragmatic trials: the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) and CATIE.71,72 Researchers in the CATIE study examined the use of antipsychotics in the treatment of schizophrenia, while the STEP-BD study assessed patients with bipolar disorder. Both studies showed that there are limitations in current treatment in terms of effectiveness, the ability of medication to treat target symptoms, and presence of drugs side effects (Slide 13).71 Because medications are often not as effective as clinicians would like, many patients are switched numerous times in order to find the most effective treatment with the lowest side-effect profile.

Future Bipolar Disorder Treatments and Research: Mood Stabilizers

Medications approved for the treatment of epilepsy may be investigated by researchers for mood stabilization.73 Newer antipsychotics are also investigated for mood stabilization properties alone and in combination with other mood stabilizers for a more additive effect. Add-on treatments have also been investigated. One idea that attracted much attention involved adding omega-3 fatty acids to boost response to primary medication. This investigation was controversial and did not pan out as originally promised.74 Although various add-on strategies have been investigated (usually in small pilot studies), there is a lack of real evidence regarding these strategies. Accordingly, clinicians need to be extremely careful in off-label use of medications, which is to be strongly discouraged and avoided. Moreover, the promotion of medications for uses not formally approved by the Food and Drug Administration (FDA) is not acceptable. Thus, clinicians should remain cognizant of what is, and even more importantly, what is not approved for use in bipolar disorder.

Etiology and Pathophysiology Research

Genetics is now moving forward into the area of the genome, in which researchers seek to find associations between particular candidate genes. These genes may be relevant for the metabolism of a neurotransmitter. In addition, expression in patients with serious mental illness or expression in relation to a particular aspect of illness are also related to these genes. Beyond classical genetics, association genetics works to tease out particular abnormalities, and then examine protein expression.

Pharmacology of Bipolar Disorder

The structure and function of various medications continue to be an area of great interest and challenge for researchers. There is no unified method of action for drugs that treat mental health disorders, including bipolar disorder. There is also not a single condition or mechanism that the medications are counteracting or even a final common pathway on which the medications are working.

For example, lithium is a very complex drug in that it does not act directly on receptors and appears to have more downstream effects on cells and metabolism. Anticonvulsants may have selective effects on particular neurotransmitters, particularly γ-aminobutyric acid (GABA) or glutamate, but these drugs may also have effects in terms of reducing excitability in epilepsy and altering second messenger systems. If anticonvulsants, such as carbamazepine, valproate, or lamotrigine, have treatment effects for patients with mental health conditions similar to effects found in patients with epilepsy, these drugs may provide stabilization for patients with mood disorders.70

SLIDE 12

Psychosocial Treatments Used in Bipolar Disorder62

Collaborative Care
Patients are provided with educational materials geared toward training them to take an active role in managing their own symptoms, periodically meeting with a clinician

Cognitive-Behavioral Therapy
Patients are educated about the course of bipolar disorder and then trained in problem solving, mood episode intervention, and cognitive restructuring

Interpersonal and Social Rhythm Therapy
Treatment focus is on disruption of social routines and sleep/wake cycles. Therapists aid patients in conflict resolution and provide strategies for maintaining a constant cycle of rising and going to bed

Family-Focused Therapy
Therapists meet with both patients and patients’ relatives, guiding them in understanding the course of bipolar disorder and collaboratively adopting strategies to prevent manage mood episodes

SLIDE 13

Results of the Systematic Treatment Enhancement Program for Bipolar Disorder Study71
58.5% of participants symptomatic at entry had recovered by 2-year follow-up
48.5% of participants had experienced symptom recurrence by 2-year follow-up
70% of recurrences were to the depressive pole

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Brain structure is another important area of research in the understanding of bipolar disorder. Structural imaging of patients with schizophrenia and bipolar disorder has provided ample evidence that brain structure is altered in patients with serious mental illness.\(^7\) That is not a finding found through the study of one patient. However, this brain alteration is prevalent when disorders are studied at a group level. Such changes in brain structure may actually get worse over time, particularly in patients who do not respond to medication.

There is also great interest in the role of neurotrophins and neuromodularity in bipolar disorder and in schizophrenia, for example, brain derived neurotrophic factor (BDNF) promotes cell development and synaptogenesis. Impaired BDNF expression has been reported in mood disorders and reduced BDNF has been associated with relapse of depression.\(^10\) There is also evidence for abnormalities of neurotrophins in schizophrenia.\(^77\)

**Conclusion**

Although bipolar disorder and schizophrenia each present with a varied and differing symptom profile, there are some similarities in approaches to treatment for both disorders. Treatment of schizophrenia and bipolar disorder often include use of medications in conjunction with psychosocial interventions. Mood-stabilizing medications are typically used for bipolar disorder treatment, while newer-generation antipsychotics are often first-line for schizophrenia. Psychosocial therapies have been shown to be effective when paired with appropriate medications for both disorders. Ongoing research continues to develop new therapies, and approaches to treatment and medication management. Understanding the mechanism of etiology is possible.

**References**


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An expert review of clinical challenges in psychiatry

Update on the Etiology and Treatment of Schizophrenia and Bipolar Disorder

By Peter F. Buckley, MD

An audio CME PsychCast™ version will also be available online in March 2008 at cmepsychcast.mblcommunications.com and via iTunes.
UPDATE ON THE ETIOLOGY AND TREATMENT OF SCHIZOPHRENIA AND BIPOLAR DISORDER

1. Which of the following statistic(s) is/are true about bipolar disorder-related suicide rates?
   A. Suicide rates are ~1% annually, 60 times greater than the general population
   B. Up to 18.9% of deaths in this population are related to suicide
   C. None of the above
   D. Both A and B

2. Both bipolar disorder and schizophrenia:
   A. Have high rates of medical comorbidity
   B. Are typically not diagnosed until after 30 years of age
   C. Usually improve over time
   D. Both B and C

3. Among the following symptoms, which can be mistaken for bipolar disorder and schizophrenia?
   A. Moodiness, physical illness
   B. Physical illness, selfishness
   C. Substance abuse
   D. Both A and C

4. Which of the following options does “duration of untreated illness” refer to?
   A. The total span of time during which symptoms arose
   B. Patient’s self-recall of symptom onset
   C. Conjecture of symptom onset using clinical scales
   D. Period where illness develops before treatment onset

5. The mechanism of action for antipsychotic medications:
   A. Never entails blocking the dopamine (D) system
   B. Sometimes entails blocking the D system
   C. Is quite diverse
   D. B and C

6. Assertive Community Treatment does not:
   A. Describe a collaborative care structure
   B. Require patients to meet rehabilitation thresholds
   C. Provide 24-hour care
   D. Reduce relapse rates

7. Improvement of cognitive function in schizophrenia patients is:
   A. Sometimes associated with nicotine consumption
   B. An area that has very little research
   C. The main outcome measure of schizophrenia
   D. Never seen with atypical antipsychotics

8. Before deeming a patient’s condition as treatment refractory, what should clinicians do?
   A. Determine patient’s treatment compliance
   B. Determine whether the patient engages in substance use
   C. Determine that correct dosing is being prescribed
   D. All of the above

CME QUESTIONS

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