The Neuropharmacology of Psychosis

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Antipsychotic drugs (APDs) are therapeutic in psychotic disorders. They are not specific treatments for schizophrenia (SZ) but useful in bipolar disorder (BD), psychotic depression, Alzheimers disease, and other psychotic diagnoses. In this perspective, we discuss the actions of APDs for the treatment of both SZ and bipolar-1 disorder (BD-1) with a specific focus on the implications of these data for the whole group of psychotic diagnoses. Both schizophrenic and BD-1 are characterized by several symptom dimensions, some overlapping and some distinctive. We discuss a dimensional approach to the diagnosis of BD and SZ and suggest that psychosis is an important dimension of each. In order to define the dimension of psychosis more carefully would require additional research to fill in the gaps in our knowledge. We propose that psychosis is a dimension that cuts through many psychiatric disorders, and the use of this dimension may be useful for clinical and research progress. We discuss the kinds of data necessary to further support the dimensional aspects of psychosis.

Key words: antipsychotic drugs/schizophrenia/bipolar disorder/dimensions of psychosis/psychiatric diagnoses/first-generation APDs/second-generation APDs

Introduction

This article reviews the drug treatments for psychotic illnesses for the purpose of considering whether “psychosis” is a more cohesive biological entity and illness category than the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) diagnostic entities which have psychosis as one of their symptoms. Because schizophrenia (SZ) and bipolar-1 disorder (BD-1) are the 2 diagnoses that have the most similar phenotypes, we have examined the pharmacology of these 2 diagnoses in detail, as illustrative of psychotic disorders. Scientists have often taken the mechanism of action of antipsychotic drugs (APDs) as a clue to the pathological mechanisms of psychosis itself. It is a logical postulate from this idea that psychotic symptoms, even across diagnoses, might be mechanistically related. Do commonalities in the treatment response of psychotic disorders suggest that psychotic illnesses should be considered dimensionally instead of diagnostically? The article is one of a series of reviews in this issue of Schizophrenia Bulletin based on different perspectives (eg, phenomenology, imaging, clinical genetics, molecular analysis) intended to address this same question: what are the data to support the consideration of the dimension of psychosis as a diagnostic entity?

We think that the following anecdote illustrates problems with diagnostic nomenclature. Dr William Sargent was a leading British psychiatrist, noted for his enthusiasm for drug treatment in mental disorders and his criticisms of psychoanalysis. He visited the National Institute of Mental Health in 1964. At the same time, a distinguished American psychoanalyst Dexter Bullard also visited. He was an enthusiast of psychoanalytic treatment and opposed to the use of medications for mental illness. Both distinguished psychiatrists jointly interviewed 6 patients on a clinical unit and then retired for an informal discussion. One remarked that it was obvious that 3 of the patients had one disorder and 3 patients had a different disorder. The other agreed exactly and remarked that it was surprising that they could agree on anything. It turned out that they were in agreement on which 3 individuals had one disorder and which 3 had the other disorder but were in disagreement about what the disorders were. Dr Sargent felt that 3 patients had depression (a biological disease) and 3 patients had hysteria with secondary depression (a psychoneurotic disorder). Dr Bullard thought that the first 3 patients had SZ and the second 3 patients had depression. The first 3 patients in modern DSM-IV categorization would be diagnosed as severe endogenous psychotic depression. We use this anecdote to raise the question of whether diagnostic categorization could be usefully augmented by dimensional considerations.

On a more general level, in the 1950s and early 1960s, there was substantial disagreement on diagnosis between...
British and American psychiatrists. In the United States, mania was uncommonly diagnosed and, if it was, it was generally applied to a euphoric mania without psychotic features. SZ was very broadly diagnosed in the United States. Mania with psychosis was more typically diagnosed in the United Kingdom. Since then, consensus diagnoses based on phenomenology and guided by accepted criteria have aided our ability to apply similar labels to a given clinical phenomenon. This system has not served to foster (and may have hindered) the identification of mechanisms of the mental illnesses and new treatment directions.

**Dimensional Aspects of Diagnoses**

In this chapter, we will review and discuss the neuropharmacology of psychotic illnesses, particularly SZ and BD-1. We have selected these 2 diagnoses as illustrative among the psychoses because of their phenomenological similarities. We will review their common and distinctive pharmacologic characteristics. In time, this perspective could be used to refine clinical targets for treatment development for psychosis. We will speculate on the possibility of a common mechanism or a common "final pathway" for the psychoses. Whether this should be the basis of a new dimensional categorization among psychotic illnesses is a related question, but one for which we have little pertinent data.

APDs are widely used and effective in the treatment of psychosis across many psychotic diagnostic classifications, including such diagnoses as SZ, bipolar disorder (BD), psychotic depression (Major Depressive Disorder), dementia, dopamine agonist induced psychoses, various organic psychoses, and certain aggressive or self-injury behavior in the mentally retarded. Psychosis is a pathological mental state characterized by the abnormal interpretation, organization, and/or use of cognitive stimuli, those generated internally and encountered externally. It includes an inability to distinguish between real and not real stimuli. Gardner, Baldessarini, and Waraich\(^1\) describe the use of APDs for psychosis:

"Antipsychotic drugs are useful for treating a range of severe psychiatric disorders. Applications include the short-term treatment of acute psychotic, manic and psychotic-depressive disorders as well as agitated states in delirium and dementia and the long-term treatment of chronic psychotic disorders, including SZ, schizoaffective disorder and delusional disorders."

It is common within diagnostic categories to describe symptoms phenomenologically, using domains. Domains are groups of symptoms that resemble each other and correlate with each other over disease course and across individuals. This categorization was originally done to aid diagnostic classification. But, more recently, scientists have explored its usefulness in identifying clinical targets for drug development.\(^5\) A recent example of the use of a domain orientation in augmenting drug development has been the focus on cognition in SZ. The emphasis on cognition developed because of the realization that psychosis in SZ is reasonably well treated with first- and second-generation APDs; but, the residual impairments in cognition impede full psychosocial recovery. This realization suggested an emphasis on treatment development for cognition in SZ, a project lead by the MATRICS group and now represented by TURNS.\(^3\) The SZ domains commonly include psychosis, cognitive dysfunction, and negative symptoms. Within SZ, these domains developed from factor analytic studies of large patient data sets (reviewed in Carpenter and Buchanan\(^4\)). These data sets established that the domains are independent and, therefore, could have their own mechanisms. It is only logical to speculate about whether similar domains across diagnostic categories share biological mechanisms and clinical prognosis, especially if their pharmacology is similar. In parallel, BD could be said to include some similar and some unique symptom domains: psychosis, cognitive dysfunction and mood dysregulation with mania and depression. Less is known about negative symptoms in bipolar illness. However, the extent to which the domains in SZ and BD-1 with similar names are fact the same construct is not known. For example, is the psychosis domain across SZ and BD-1 the same clinically, genetically, and mechanistically, and do both domains show the same treatment response?

Psychiatric practice and controlled studies in specific diagnostic groups suggest that the psychotic symptom domain is treated with similar medications across diagnoses; and we know that psychosis responds therapeutically to those treatments. Nonetheless, these are clinical observations drawn from clinical practice, not results from controlled clinical trials inclusive of multiple diagnoses. Multiple questions exist, including whether or not the psychotic symptoms overlap descriptively (rated with the same scale), whether they respond on the same time course, and the extent to which associated domains are also treated. It is important to note that not all symptom domains currently have effective treatments. Within the diagnosis of SZ, eg, effective treatments exist primarily for psychosis, while neither cognitive deficits nor core negative symptoms have demonstrated drug treatments.\(^5\)

In this article, we will review therapeutic data from the fields of SZ and BD-1 research and examine the extent to which psychosis is treated similarly across these 2 diagnoses. We will do this as an example of studying domain treatment across diagnoses. We will review data on efficacy and effectiveness of APDs in each diagnosis, of side effect patterns, of their influence on co-occurring symptoms and on the postulated mechanisms of APD action. It is important to notice before starting that the data required to directly answer the questions raised in this section have not been collected, ie, data where the same set of drugs are compared across diagnoses in the same study.
with parallel methodologies. So, this review will not be able to arrive at a final answer, only the commonalities in clinical responses.

**Efficacy of APDs in Schizophrenia**

In clinical practice, the treatment of psychosis in SZ is approached using either the second- or the first-generation APDs. These drugs are used for acute treatment and for maintenance. Deciding on the specific APD among the candidates is characteristically made on an individual basis, taking drug action and side effects into consideration. There is excellent evidence that both first-generation antipsychotics (FGAs) and second-generation antipsychotics (SGAs) substantially benefit SZ better than placebo alone based on over 30 recent double-blind studies and consistent with a much larger number of controlled studies done over 20 years ago (reviewed in Davis). There are also a number of comparisons of second-generation drugs vs first-generation drugs and a smaller number of comparisons among second-generations where one of the comparators was olanzapine. In table 1, we show a summary of the effect sizes of studies contrasting FGA with SGA APDs. It is only clozapine that shows moderate to large effect size differences from FGAs on clinical outcome. Olanzapine and risperidone show low to moderate effect size differences from FGAs, but not in every study. Below, we discuss the results of several recent studies. These data are interpreted differently by various observers.

<table>
<thead>
<tr>
<th>Comparator</th>
<th>Davis FGA</th>
<th>Cochrane FGA</th>
<th>Geddes FGA</th>
<th>Leucht FGA</th>
<th>Leucht Low-Potency FGA</th>
<th>CATIE-1(a) FGA</th>
<th>CATIE-T(b) FGA</th>
<th>CATIE-Eff(b) FGA</th>
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<td>−0.04</td>
<td>0.22</td>
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<td>0.03</td>
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*Note:* FGA, first-generation antipsychotics; SGA, second-generation antipsychotics.

\(a\)Duration of successful treatment of CATIE-1 is similar to efficacy. We calculated the effect size by using the \(P\) values under the column label Perphenazine and the sample size of this drug and of the SGAs without tardive dyskinesia. Because CATIE-T and Catie-Eff did not have a typical arm, we expressed the effect size of each of the other drugs based on its difference from olanzapine, and assigned olanzapine the same effect size as CATIE-1. This is only an approximation but does put all effect sizes as a comparison of typical.

\(b\)Drug efficacy in effect size units of SGAs compared against FGAs like Haloperidol. A “0.00” would indicate no difference; a positive number indicates that the second-generation drug is more efficacious.

In SZ, one of the most recent, naturalistic studies of second-generation APDs in SZ is the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study. The large patient sample (\(N = 1493\)) makes these data important and its comparison of olanzapine, risperidone, quetiapine, ziprasidone, and perphenazine make the data broadly relevant. The naturalistic design makes the data more representative, while the methodology is less controlled. In the CATIE study, there were subsequent treatment opportunities after discontinuing, so that “discontinuation” could more aptly be called “switching.” In this context, the study discontinuation rate was surprisingly high: overall, 74% of the volunteers discontinued phase 1 before 18 months, with 64% discontinuing olanzapine; 75%, perphenazine; 82%, quetiapine; 74%, risperidone; and 79%, ziprasidone. Olanzapine was the most effective drug in phase 1 as measured by “rate of discontinuation” (which was the study’s primary outcome measure) and on several of the secondary efficacy outcomes; but, also, it was associated with the highest weight gain and greatest increases in metabolic measures.

In the phase 2 CATIE study, where volunteers terminated phase 1 for “ineffectiveness,” 99 volunteers were tested with clozapine compared with olanzapine, risperidone, or quetiapine. The results of this comparison showed a large effectiveness advantage for clozapine, with its time-to-discontinuation nearly 3 times longer than time-to-discontinuation with the other SGAs. In the phase 2 CATIE study, where volunteers terminated...
Aripiprazole, given its later entrance into the APD market, has fewer studies available, especially nonsponsor studies. In this context, its registration studies show a significant antipsychotic action of aripiprazole against placebo and of equivalent magnitude with comparator drugs.17–20 El-Sayeh and Morganti21 in a Cochrane Database Systematic Review conclude that aripiprazole has equal efficacy to FGA and SGA APDs with some benefits in side effect profile (lower akathisia, less prolactin elevations, and QTc prolongation). Later studies demonstrate that aripiprazole shows equal efficacy to olanzapine in chronic stable patient volunteers as well as in those with acute relapse,22 but with aripiprazole showing a better safety profile with respect to motor and to metabolic side effects.

Clinical practice for maintenance of antipsychotic effect in SZ includes the chronic administration of APDs for the lifelong duration of illness.6 Those studies that have tested the need for maintenance of APDs in early psychosis have characteristically been unsuccessful because of the high rate of relapse once psychosis is manifest. Predictors for relapse exist.23–25 In early SZ, haloperidol and olanzapine were found to have comparable efficacy on symptom reduction; however, olanzapine showed an advantage on 2 secondary measures: time to study discontinuation and remission rates.26,27

A 1-year comparison of haloperidol, olanzapine, and risperidone showed a greater cognitive benefit of the 2 SGAs on several aspects of cognitive performance compared with haloperidol; the 2 SGAs were not different from each other.27 Harvey28 compared quetiapine and risperidone on cognitive outcomes in a large acute treatment study which included measures of social cognition. He found that both SGA treatments, even though studied only for 8 weeks, improved some domains of cognitive dysfunction; he assessed social cognition in parallel and correlated changes in social cognition with neuropsychological gains. Lack of efficacy with traditional or new APDs prompts the use of clozapine in SZ.29

Monotherapy with mood stabilizers (lithium, the carbamazepines, valproate, lamotrigine) or antidepressants (tricyclic, monoamine oxidase inhibitor, serotonin uptake inhibitors, or other antidepressants) or the benzodiazepines do not improve psychosis in SZ. However, these drugs are often used along with APDs to treat affective symptoms of the illness. But even as recent data show no benefits to outcome for concomitant psychotropic medications in chronic SZ and challenge this aspect of clinical practice.30 We know of no evidence that lithium, carbamazepine, oxcarbazepine, or valproate produce an additional long-term benefit in most schizophrenic patients. There is some evidence that schizophrenic patients who seem to have recurrent episodes of depression superimposed on top of their SZ may benefit from antidepressants. For space reasons, we cannot review the many control studies of polypharmacy and the very large anecdotal literature.

**Efficacy of APDs in BD-1 Psychosis**

Lithium, divalproate, or the carbamazepines were traditionally used to treat BD-1. Once SGA became available (in contrast to the FGA APDs whose motor side effects in BD were limiting), the SGAs were broadly applied to BD psychosis. APD treatment has been shown to be just as effective in the treatment of active BD-1 psychosis as mood stabilizers.26,31–33 It is possible that APDs could have inherent mood stabilizing properties, given the effectiveness of some of the SGAs in maintenance.

The efficacy of lithium in BD mania was discovered in 1949; the drug was approved by the Food and Drug Administration (FDA) for this indication in 1970. The discovery of lithium predates the discovery of the antipsychotic action of chlorpromazine in 1953. Chlorpromazine was found effective for acute mania also in the early 1950’s. It was FDA approved for the same indication in 1973. In Europe, FGAs were used to treat acute episodes of mania, with mood stabilizers reserved for long-term maintenance. It should not be surprising that if FGA benefit acute mania, SGAs’s would also do so. This has been demonstrated in several studies.34 All the SGA have been approved for the treatment of acute mania in BD, but with cautions regarding side effects.35,36 Olanzapine was the first of the SGA to be approved in 2000 and the other SGAs followed quickly, with risperidone approval in 2003 and quetiapine, ziprasidone, and aripiprazole in 2004.33 While in only 2000, clinicians were cautious about accepting SGAs as antimanic,37 the literature burgeoned in the following decade convincing clinicians of their efficacy.38

Efficacy is no longer doubted for the treatment of an acute manic episode in BD. However, the tolerability of the APDs in BD is always questioned.39 especially, the FGA which have a high incidence of parkinsonism and tardive dyskinesia (higher in affective than in nonaffective patients40). In a medication utilization study done in 2004, the proportion of a large (n = 155) first-admission cohort with BD-1 receiving APD at hospitalization discharge was 80%, compared with 52.3% who received antimanic drugs. But after 1 year, 44.6% of the BD-1 cohort were medication free, with only 19.4% taking APDs and 38.8% taking antimanic.41 APA treatment guidelines acknowledge the efficacy of SGA in BD, acute mania with psychosis, and even in maintenance treatment for either persistent psychosis or psychosis prophylaxis.32 In acute mania, however, mood stabilizers are also effective antimanic agents.42
even though 25%–67% of all acute manic episodes include delusions and 13%–40% include hallucinations. With mood stabilizer monotherapy, many patients achieve syndromal remission without functional remission.43 With SGA treatment, affective psychosis achieves higher rates of both syndromal and functional recovery than does nonaffective psychoses.44

There is evidence that a combination of SGAs with mood stabilizers results in a better response than either treatment alone in BD-1. Schatzberg45 emphasizes that drugs for mood disorders have distinct actions on different BD symptoms, dependent on their mechanism of pharmacological action; APDs decrease psychosis, lithium and valproate stabilize mood dysregulation, and lamotrigine affects depression. With combination treatment using a SGA and mood stabilizer, relapse rates are reduced, efficacy increased, and time to clinical effectiveness reduced.46 Several reviews31,46 emphasize safety and tolerability in selecting a treatment for BD-1 because compliance is critical in maintaining positive drug effect.

APD treatments benefit psychosis in both SZ and BD, including in psychotic and nonpsychotic mania. This leads us to conclude that psychosis in these 2 categories responds therapeutically to APDs. But these clinical observations provide little certainty of how the outcomes in both diagnoses would compare if responses were tested in a single experiment using similar rating scales; whether treatment responses would be the same across the diagnoses still has to be demonstrated. A firm hypothesis that similar psychosis mechanisms operate across disease diagnoses would require careful, controlled experiments with relevant disease categories represented in the study populations.

Treatment of Other Affective Dimensions

The two previous sections reviewed the APD treatments for SZ and BD-1 in detail. There are similar clinical literatures available for other psychotic disorders as well, some of which are included in other articles in this issue. APDs in general are used to treat psychotic symptoms no matter what the diagnosis. In contrast to antipsychotics, drugs for affective disorders are somewhat less specific. Before the antipsychotic, antidepressant, and mood stabilizer drugs were discovered, electroconvulsive therapy (ECT) was widely used in psychiatry. It produced no lasting important benefit in most schizophrenic patients, although it was dramatically effective in both mania and depression.47 A small group of schizophrenic patients were benefited by ECT at least in the short term. Lamotrigine has not been shown to be an effective treatment in acute episodes of mania or in the prevention of recurrences of the manic phase.48,49 Aripiprazole maintenance prevents recurrence of the mania but not the depressive relapse. Lithium is effective in treating acute manic attack; it prevents the recurrence of both a manic and depressive episodes during long-term maintenance treatment.50,51 Lithium is effective in preventing suicide in bipolar disease.50–52 It does a marginally better job of preventing the recurrence of mania rather than depression, but these are small differences. The effect of lithium compared with placebo in preventing mania or depression is substantial and significant. Lithium is a weak antidepressant for the acute episode of depression but does prevent the recurrence of recurrent unipolar depression.50,51

An important issue in affective illness is to distinguish between drug efficacy for acute phases of a manic or depressive episode and the prevention of recurrences of manic and depressive episodes. Some SGAs are active on all phases,53,54 but many have not been studied in all illness phases. Olanzapine/fluoxetine combination and quetiapine are useful in acute bipolar depression.55–60 We would caution against the assumption that because one member of a class of drugs has a beneficial effect in a given phase that other members of the class will show a beneficial effect. Efficacy in distinct illness phases needs to be demonstrated. For example, it was once assumed that anticonvulsants would treat manic-depressive disease; gabapentin was widely used for this reason. Unfortunately, controlled studies found that gabapentin failed to have efficacy in manic-depressive disease.61 In psychotic depression, both antipsychotics and antidepressants are needed for the successful treatment. Antipsychotics benefits the psychoses and antidepressants the depression.

One clinically important question in all psychotic illnesses is the extent to which an effective drug in one domain will influence symptoms in another domain. This question becomes especially relevant, when considering whether mood stabilizer treatment in psychotic mania affects just mood regulation or treats the psychotic symptoms as well. Because controlled studies show efficacy for both mood stabilizers and APDs in BD-1, clinical practice is confirmed. If the psychosis is not primary, but secondary to mood instability, then psychosis treatment could be effective with either drug. This would support an idea of different mechanisms for psychosis in BD-1 and SZ. The question posed here is not currently answered. This will also become interesting in the area of SZ therapeutics when effective cognitive enhancers are available. Then we will be able to distinguish whether APDs influence cognitive dysfunction to some degree in SZ or only psychosis and vice versa?

Problems With Dimensional Treatments and the Weakness of Domain Diagnosis

The proposal to treat diseases by dimensions rather than by traditional diagnosis implies that there is more than one independent component to an illness. Therefore, the “rational” treatment would be done with more than one targeted treatment, individualized to a domain.
One problem with this approach to therapeutics is that it encourages polypharmacy. Studies of medication administered in actual psychiatric practice indicate that there are already substantial degrees of polypharmacy. The use of polypharmacy can only rarely be supported by controlled clinical trials. Many clinical scientists are critical of polypharmacy. Patients may be kept on drugs because the physician is not certain that there is no clinical benefit. It is often unclear which medications help and which do not, without highly systematized follow-up. Controlled studies are important to guide clinician practice. In lieu of these kinds of data, recording the presence or absence of benefits of a new drug for a particular patient is particularly important in clinical practice. Each physician needs to be committed to discontinuing medications that are not beneficial. Testing the discontinuation of existing medications will help clarify for an individual person whether combined treatment is more useful than a core single treatment.

In general medicine, several disease entities can produce impairment in a psychophysiological process common to these entities. For example, infectious diseases and autoimmune diseases both produce fever; many etiologies produce arrhythmias. In a more general sense, the strategy of breaking down phenomena into different dimensions has been used by a wide variety of sciences and is commonly used in psychology. But, at the present time, there is not full agreement as to how to subclassify schizophrenic or bipolar patients into categories or into meaningful dimensions. Drug response within either subcategories or dimensions has not been uniformly studied. The action of APDs in the psychosis domain of SZ or BD-1 is an example where this has been established, yet not with the diagnostic groups together. Also, it is difficult to be precise about similarities or differences because assessments are made with different instruments. A dimensional approach to psychopathology can be useful in diagnostic nomenclatures and in research, where they are specifically defined and studied in parallel. For example, if mania had been classified as psychotic vs nonpsychotic when lithium was initially tested, this information could have been obtained from early clinical trials. Then, we would already know whether lithium is effective in the psychotic component of mania.

There is insufficient research to definitively answer questions of the usefulness of dimensional classification even between SZ and BD-1. A common rating scale for use across diagnoses in rating the dimension of psychosis has not been critically developed, nor has it been applied to tracking clinical improvement during drug treatment in the psychosis dimension of different diagnoses. The development and use of assessment methodologies as well as the support of actual trials using dimensional classifications would facilitate the gathering of data to answer dimensional questions. In this issue of Schizophrenia Bulletin, the implications of various domains of psychiatric research for the diagnosis of mania and bipolar and their subtypes are presented. It would be of interest and potentially clinically important if one of these subtypes or dimensions identified patients who may have a differentially better clinical response to antipsychotic medicines or a subclass of antipsychotic medicines. In order for this research to elucidate these relationships, it is necessary (1) to identify a dimension or subtype, (2) to assess it in patients of diverse diagnoses in a clinical trial, and (3) measure the difference in response either in global improvement or on specific dimensions. This could lead to a conclusion that targeting patients with the psychosis dimension with a given treatment will lead to a distinctive outcome.

**Putative Mechanisms of APD Action**

It is important to evaluate the possibility posed earlier in this article that similar drug responsiveness within a multidimensionality dimension (if this could be rigorously demonstrated) might signal a common pathophysiology for psychosis. Evidence rather convincingly suggests that antipsychotic actions are effected through D2 dopamine receptor blockade. However, the functional mechanisms whereby that D2 dopamine receptor blockade translates into an antipsychotic action in SZ or BD has not been fully defined. Moreover, establishing the mechanism for antipsychotic effects across different psychotic diagnoses would be informative no matter what the outcome. If similar regions and pathways of action were demonstrated, it would strengthen the explanation of mechanism. If differences in these parameters were found, it would provide more opportunity for the study of cerebral mechanisms.

Biomarkers of APD actions not only mark drug effects but also can contribute to an understanding of disease mechanisms. In the case of the discussion of the commonality of psychosis dimensions, biomarkers can also help define which illness characteristics belong to a biological entity. The use of biomarkers have already been applied in psychiatric genetic studies and can be a model in this regard. The association of specific genes with psychiatric diagnoses has been not as robust as hoped. Therefore, scientists have proceeded to use what Gottesman calls “endophenotypic” characteristics of the illness to associate with genetic markers. These are reflections of brain function close to its biology. Hence, they include characteristics of eye movements, evoked potential responses to sensory stimuli, estimates of sensory gating, and brain volume and functional characteristics of brain response. These measures of genetics, human brain imaging, molecular analysis of postmortem tissue, electrophysiology, and startling have already been applied to diagnoses, but not yet applied to understanding the dimensional borders within diagnoses. Across SZ and BD-1, data show that...
several genes associate with both diagnoses (e.g., NRG1, BDNF, DISC, G72/DAAO), while some associate specifically with SZ (e.g., dysbindin, COMT, and RGS4) and others specifically with BD (e.g., Clock, BMAL1, and Period). Brain volume characteristics of BD-1 with psychosis are more like SZ than like nonpsychotic BD, but still distinctive in some respects from SZ. The use of these kinds of biomarkers to examine the domain of psychosis across diagnoses would be valuable in pursuing these questions about domain biology.

We have previously studied the pathways of functional antipsychotic action in human SZ volunteers using in vivo functional brain imaging to define brain regions affected by APD.65 In this study, 12 volunteers with SZ were given haloperidol or placebo, each compound for 1 month in random order; a positron emission tomography (PET) scan using fluorodeoxyglucose was carried out at the end of each month. The resulting data set included 12 sets of within-subject, functional imaging PET scans after haloperidol or placebo. The analysis showed an increase in neuronal activity (as indicated by an increase in glucose utilization) in the basal ganglia when the volunteers were taking haloperidol, both in caudate and putamen, as expected. And it also showed that the APD increases glucose utilization in the anterior thalamus and decreases activity in the dorsolateral prefrontal cortex (DLPFC) and in the anterior cingulate cortex (ACC) (figure 1). Because these regions represent areas important to the cortico-striato-thalamic pathways already well defined for motor function,66 it was most parsimonious to make the interpretation that APDs use the brain’s own long-tract neuronal pathways to project the effects of D2 dopamine receptor blockade from the basal ganglia through the thalamus to the anterior aspects of the neocortex, particularly to the DLPFC and to the ACC (figure 2). Our studies comparing first- and second-generation APDs in animals67 lead us to postulate that both of these groups of APDs will act through this pathway, but the SGA will be more selective regionally within the striatum in targeting the ventral striatum; this will lead to a more selective activation/inhibition within the long-track pathways and eventually to a more selective action in the cortical target regions. Also, the SGAs will exert additional actions directly in cortex because of the plethora there of 5HT2 serotonin
The example detailed above illustrates the use of a translational methodology applied to the understanding of antipsychotic actions of APDs in SZ. Had we used this approach across diagnostic classes (eg, in SZ and BD-1), we could comment on the similarities and dissimilarities of APD actions in these different diagnoses. However, the above patient group included only volunteers with schizophrenic psychosis. In a test of dimensional vs diagnostic approaches, one could examine different diagnostic groups with functional brain imaging in their response to the same APD treatments. This experiment would recruit people with psychosis and different diagnoses according to an a priori definition and study them in a parallel manner. This would include using a cross-diagnosis, validated psychosis rating scale, following treatment response across diagnoses and correlating treatment response with functional imaging data in all volunteers. Such a study would characterize the antipsychotic response across diagnostic groups. The approach would provide answers to questions of commonality of antipsychotic mechanisms across diagnostic groups. Moreover, it would rely on validated psychosis rating scales for marking psychosis response. Ideally, such comparative studies would also include other biomarkers, like electrophysiological characteristics, brain regional volumes, eye movement paradigms, and neuropsychological measures all of which are used to characterize “endophenotypes” across diagnoses.

The task of defining and validating a common psychosis dimension across diagnostic boundaries will need to include clinical, epidemiologic, phenotypic, imaging, and molecular evidence as well as the pharmacological data we have presented here. The strength of the current DSM diagnostic system for mental disorders is its reliability, not its validity, the latter being still unknown for most psychiatric diagnoses. One consideration is whether we will need to use additional “bining” systems in order to identify valid molecular characteristics of mental conditions or if dimensional definitions will improve the detection of etiologic and pathophysiologic mechanisms. Brain and symptom response to pharmacologic agents, especially APDs, will be an important aspect of this examination.

It is the development of data sets like the one proposed above that would begin to give us some information about the biology of antipsychotic response across diagnostic groups and help us verify (or not) dimensional concepts of psychosis, as suggested, but not demonstrated, in the literature. Overall, even when tested with pharmacology, the data are inadequate to rigorously demonstrate that psychosis across SZ and BD is the same construct. As psychiatry gradually gains information about the altered brain mechanisms in its illnesses, diagnoses will be resorted, based on firm knowledge of pathophysiology.

Nonetheless, asking questions of diagnoses provides obvious pathways to studies that will contribute to defining pathophysiology.

**Summary: Using Pharmacology to Define Psychosis as a Dimension That Crosses Diagnostic Boundaries**

This article reviews the clinical treatment response data in SZ and BD-1. Based on these data, we can say that the psychosis domain of both diagnoses respond therapeutically to APDs. But, this commonality of response has not been examined side-by-side in the same study. Therefore, the phenomenology of the psychosis, the course of response, and the pharmacology across APDs of the treatment response still has to be characterized. The use of pharmacological approaches to examine the dimension of psychosis across diagnoses is highly indicated and could be done. The characterization of treatment response to APDs would be most valuable in the context of a broader phenotyping effort in an attempt to use clinical genetic methodologies to define dimensional borders within and across diagnoses.

### References


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