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EXPERT REVIEW SUPPLEMENT

DOSING ATYPICAL ANTIPSYCHOTICS

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ABSTRACT

Atypical antipsychotic treatment strategies have tended to change significantly from the time new drugs are introduced to the market. Because these drugs are associated with so many side effects, dosing strategies are largely based on the avoidance of adverse effects. A great number of issues complicate the task of effectively dosing atypical antipsychotics, including great variability and unpredictability in individual response. This often leads to extensive periods of trial and error as well as patient suffering, while physicians search for an optimum treatment. The mechanisms of action of these drugs are not entirely understood; they can be effective for both psychosis and mood disorders, possibly via actions on different systems or circuits. Furthermore, a resolution to the dilemma of dosing once or twice daily depends on issues of patient compliance and drug efficacy. This supplement puts these issues into perspective by illustrating historical discrepancies in antipsychotic use between clinical trials and practice, discussing individual response variability to antipsychotic treatment, describing current theories of antipsychotic mechanisms of action, and speculating as to the future of antipsychotic treatment strategies.

The following unmet needs regarding dosing atypical antipsychotics were revealed following a vigorous assessment of activity feedback, expert faculty assessment, literature review, and through new medical knowledge: (1) although many clinicians generalize that higher doses are associated with greater efficacy and more side effects, the efficacy and tolerability profile for different doses of atypical antipsychotics are far less straightforward than that; (2) physicians continue to face huge issues of patient adherence when treating schizophrenia and bipolar disorder, which may be mitigated by addressing the most troublesome side effects caused by antipsychotics; (3) research on genetics, neurocircuitry, and new treatment methods in schizophrenia is ongoing; clinicians need to be educated on new treatment strategies as data accumulate so that they are prepared to implement these tools once they become available.



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Learning Objectives

After completing this activity, participants should be better able to:

- Develop treatment selection and dosing strategies that are designed to maximize patient adherence
- Consider the impact of common antipsychotic side effects on patient functionality when selecting treatment options
- Integrate novel treatment tools into clinical practice as they become available

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DOSING ATYPICAL ANTIPSYCHOTICS

By Andrew Cutler, MD, Sara Ball, MS, and Stephen M. Stahl, MD, PhD

Introduction

The task of prescribing, dosing, and switching antipsychotics is generally characterized by a process of trial and error, often resulting in suffering from side effects and/or lack of response while searching for the optimum treatment. Clinical trials often inaccurately predict optimum doses and titration schedules, leaving prescribers without precise guidance for how to use newer therapies in clinical practice. A tremendous amount of individual response variability further complicates the task of effectively dosing antipsychotics.

Hope for addressing this problem can be seen in the budding field of pharmacogenetics, which aims to inform optimum individual treatment plans by characterizing genetic profiles associated with pharmacologic response. Studies of this nature are still investigational, and although several have shown statistical significance, results are not yet sufficiently replicable to be clinically relevant. In the meantime, it is important for clinicians to utilize timely knowledge of body-drug and drug-body (ie, pharmacokinetic and pharmacodynamic) interactions and to maintain a perspective of common sense in order to make informed decisions regarding antipsychotic treatment. This article reviews the historical discrepancies between clinical trials and clinical practice in antipsychotic use, discusses individual response variability to antipsychotic treatment, describes current theories of antipsychotic mechanisms of action, and speculates as to the future of antipsychotic treatment strategies.

Do Trials Predict Practice?

In general, atypical antipsychotic treatment strategies have tended to change significantly over time. In particular, titration schedules, medication regimens, and dose amounts have changed as clinical evidence accumulates to reinforce the usefulness of new practices. Because these drugs are associated with many side effects, current dosing strategies are largely based on the avoidance of adverse effects. Some evidence indicates that the first 2 weeks of treatment is enough to predict symptom alleviation or development of adverse effects for that treatment.^{1,2} Likewise, minimal to no response in the first week³ or two⁴ of an adequate dose of a treatment may be indicative of nonresponse to that medication in general. This implies that switch-or-stay decisions might effectively be made earlier in treatment plans than previously thought, although most prescribers still recommend waiting 4–10 weeks if an initial partial response is observed.⁵ Early errors in dosing may lead to inappropriate discontinuation of a potentially useful atypical antipsychotic for that patient. Average prescribed doses and schedules have also changed

significantly from doses initially recommended by clinical trials, and some evidence is accruing for state-dependent dosing (eg, different doses for acute psychosis versus maintenance treatment of psychosis and different doses for acute bipolar mania versus bipolar depression or maintenance). Unlike conventional antipsychotics, most atypicals are often dosed higher for increased response before they are discontinued. Recent evidence from the Clinical Antipsychotic Trials in Intervention Effectiveness (CATIE), which was designed to include a flexible dosing schedule, provides a general example of differential dosing in current practice.⁶ Figure 1 compares major findings from trials to average clinical use for each of the major atypical antipsychotics currently available in the United States.^{7,8}

The Evolution of Dosing

Risperidone was tested in trials in a “1, 2, 3” titration schedule, with an initial dose of 1 mg BID to increase 1 mg BID each day, sometimes up to levels as high as 16 mg/day.⁹ Now, the average dose of risperidone is ~4–6 mg/day, and the original titration schedule is rarely adhered to in practice.¹⁰ Dose equivalents for long-acting risperidone injection are still under investigation. A study of 50 stable hospitalized patients suggested that those taking doses of oral risperidone <3 mg/day can be switched to the long-acting injectable form of risperidone at 25 mg every 2 weeks, patients taking oral risperidone 3–5 mg/day can be switched to injectable risperidone 37.5 mg every 2 weeks, and patients taking oral risperidone >5 mg/day should receive injectable risperidone 50 mg every 2 weeks.¹¹ These doses are not yet clinically well established.

Trials of quetiapine initially recommended that doses of 250–750 mg/day might be effective for schizophrenia. It is currently labeled at 150–750 mg/day (divided doses) for schizophrenia, 400–600 mg/day (divided doses) for acute bipolar mania, and 300–600 mg/day (single dose) for bipolar depression. Some studies have shown that low (150–450 mg/day) and high (600 or 750 mg/day) doses are equally efficacious compared to placebo in treating schizophrenia.¹² Other recent studies have shown that doses >800 mg/day of quetiapine are tolerable and sometimes necessary for certain patients, whereas maximal doses in published studies were previously restricted to 800 mg/day.¹³ Many prescribers have disregarded the upper-limit dose range of 750–800 mg/day, prescribing higher doses (up to 1,200 mg/day) to maximize therapeutic effect in acute cases of schizophrenia. In other patients, doses as low as 25–150 mg/day can be effective. Its active metabolite, norquetiapine, contributes to actions at high and low doses. Doses for bipolar disorder range between the high and low of

these numbers. The upper-dose range for quetiapine is still not well defined and the efficacy of high-dose usage is still under clinical and experimental scrutiny.¹⁴ Quetiapine seems to follow the trend for atypical antipsychotics, where higher doses are often necessary in schizophrenia and lower doses are effective for mood and anxiety disorders. Quetiapine is a sedative in high doses and can be a sedative in initial treatment at any dose. This antihistamine effect can sometimes be used advantageously when given at night to help patients sleep or in the morning to reduce anxiety. The Food and Drug Administration (FDA) recently approved quetiapine extended release in 200, 300, and 400 mg tablets for once-daily treatment of schizophrenia, and studies

have been filed for bipolar mania, bipolar depression, unipolar depression, and generalized anxiety disorder.

Early trials of ziprasidone suggested that doses as low as 40 mg/day (20 mg BID) would be effective. After 5 years on the market, the minimum effective dose is now considered to be about 120 mg/day (60 mg BID).¹⁵ The average dose range for ziprasidone in clinical practice is now 120–320 mg/day, with an average of 160 mg/day in schizophrenia. Doses of ziprasidone higher than the maximum label recommendation of 160 mg/day may improve efficacy but this is anecdotal and not yet confirmed in controlled trials. There is some evidence for the use of low-dose ziprasidone in mood disorders.¹⁶ Clinically important findings have emerged regarding

FIGURE 1

Comparison of Major Findings from Trials to Average Clinical Use for Each of the Seven Atypical Antipsychotics Currently Available in the United States.^{7,8}

Drug	Trial Dose (Label Recommendation)	Clinical Dose
Risperidone	1 mg BID day 1, 2 mg BID day 2, 3 mg BID day 3, etc., up to max of 16 mg/day Average recommendation for acute psychosis and bipolar disorder: 2–8 mg/day	Average 4–6 mg/day Some signs of low-dose efficacy 0.5–1 mg effective in depression with SSRI
Quetiapine	250–750 mg might be effective Schizophrenia: 150–750 mg/day (divided doses) Acute bipolar mania: 400–800 mg/day (divided doses) Bipolar depression: 300–600 mg/day (once daily)	Bimodal: low dose for anxiety/mood disorders; high dose for schizophrenia May be effective at 25–150 mg/day for anxiety/mood disorders Some patients with schizophrenia may require 800–1,200 mg/day Not well-defined upper dose range
Ziprasidone	Schizophrenia: 40–200 mg/day (divided doses) Bipolar disorder: 80–160 mg/day (divided doses) ZEUS (1 year relapse study) 20 mg BID effective	Average ~60 mg BID Must take with food (~400 calorie meals) Some can tolerate QD Raising dose above 160 mg/day (up to 320 mg/day) may improve efficacy and can be necessary in some patients
Aripiprazole	Label: 15–30 mg/day, start with 10–15 mg/day (some lower) Max recommendation: 30 mg/day Depression start at lower dose range Mania start at 30 mg (all in hospitalizable manic patients)	Schizophrenia: 15 or 20 mg, commonly used up to or beyond 30 mg in sicker patients Inverted u-shaped dose response in some patients <10 mg/day can be used for depression >30 mg/day can be used for acute mania or difficult-to-treat schizophrenia Akathisia can occur with SSRIs/SNRIs
Paliperidone	3–15 mg/day approved dose No titration required	Clinical experience limited 6 mg/day recommended starting dose
Olanzapine	10–20 mg/day Max approved dose: 20 mg/day For bipolar disorder can augment with 6–12 mg with fluoxetine (25–50 mg of olanzapine)	Often >20 mg/day (above product label recommendation) for difficult patients Anywhere from 5–30 mg as maintenance dose Higher doses (up to 40 mg/day) may be efficacious in some cases
Clozapine	Average 300–450 mg/day (divided doses over 300 mg) Max recommendation: 900 mg/day	300–500 mg/day most likely to be beneficial Sometimes up to 750 mg in one dose tolerable Can use blood levels to guide dosing
Asenapine	5 and 10 mg BID for mania and schizophrenia	Requires mucosal absorption; may limit use as QD drug
Loperidone	12–24 mg/day BID for schizophrenia	Might be possible to give once a day

SSRI=selective serotonin reuptake inhibitor; ZEUS=Ziprasidone Extended Use in Schizophrenia; SNRI=serotonin norepinephrine reuptake inhibitors; max=maximum.

the need to take ziprasidone with food.¹⁷ If not taken with food, ziprasidone cannot be absorbed properly and up to half of each dose is lost; this effect is not necessarily reversed by doubling the dose. Some prescribers have seen success with once-daily ziprasidone, but only when this food requirement is adhered to and only in some individuals, especially those taking >160 mg/day. There is as of yet little guidance as to which individuals may respond positively to once-daily ziprasidone.

Olanzapine was studied in trials at 10 mg/day, which is what the product label recommends.¹⁸ However, it is often dosed in practice at >20 mg/day,¹⁹ leading some to conclude that the full efficacy of olanzapine might be underestimated if it is “underdosed” below 15–20 mg/day or more. Though there is little controlled data to support the use of high-dose olanzapine, some have reported the drug’s safety at “high doses” (up to 30 mg/day)²⁰ similar to the upper dose range used for the CATIE trials.²¹ High-dose olanzapine trials have recently shown support for dosing olanzapine higher than the original product label.²² A recent small study²³ found high-dose olanzapine (25–45 mg/day) comparable to clozapine (300–900 mg/day) in treatment-refractory schizophrenia patients while another found clozapine (300–900 mg/day) preferable to olanzapine (20–30 mg/day).²⁴ Effective maintenance dose for olanzapine varies greatly among individuals; 5 mg/day is effective in some individuals while 30 mg/day or more may be required in others. Recent development of a long-acting injectable form of olanzapine resulted in a non-approvable letter from the FDA due to excessive sedation.

Further discrepancy is seen in the case of clozapine, which is labeled at 300–450 mg/day (divided doses over 300 mg). Although 300–500 mg/day is most likely to be effective, clozapine is now sometimes given in institutional settings in once-daily doses of up to 750 mg, an amount that trials would not have predicted would be tolerable.²⁵ Careful patient monitoring is required with the use of clozapine; weekly white blood cell monitoring is a minimum requirement at least during initial treatment. When prescribing clozapine at doses >550 mg/day, fastidious monitoring is of even greater importance.

Aripiprazole was tested in mania at a starting dose of 30 mg and in schizophrenia at 5–30 mg/day.²⁶ It is now clear that dosing aripiprazole, as is the case with other atypical antipsychotics, is dependent on the patient and the situation. Fifteen to 20 mg/day is commonly used for schizophrenia and up to 30 mg/day for sicker patients, although >30 mg/day is rarely needed. In fact, there is a suggestion of an inverted U-shaped dose response curve in some patients, with 30 mg/day being less effective as an antipsychotic than 10–20 mg/day.²⁷ For mood disorders, as with other atypical agents, aripiprazole is often started at the lower dosage range. In practice, clinicians are finding that >10 mg/day can be used for depression and >30 mg/day can be used for some cases of acute bipolar mania and difficult-to-treat schizophrenia. Some prescribers have found that using aripiprazole as an augmenting agent with risperidone or a conventional antipsychotic can reduce hyperprolactinemia²⁸ or as an augmenting agent with low-dose clozapine or in low doses with olanzapine may reduce metabolic problems.²⁹ When augmenting a selective serotonin reuptake inhibitor (SSRI) with aripiprazole for treatment-resistant

unipolar depression, doses as low as 2 mg may be used to prevent akathisia.³⁰

Paliperidone is the most recent atypical antipsychotic to be brought to market. It is the major active metabolite of risperidone. Paliperidone is an oral extended release atypical agent and does not require titration. It is approved at doses between 3–15 mg/day³¹ but the maximum recommended dose is 12 mg/day.³² Clinical experience is still too limited to know how doses will be used best in practice. The recommended starting dose is 6 mg/day, but some clinicians have found that higher doses may be required.

Ahead of the Learning Curve?

New atypical antipsychotics filed with the FDA are expected to emerge on the market soon. One of these, asenapine, has been tested for efficacy in dosages of 5 mg and 10 mg BID for schizophrenia³³ and for mania.³⁴ Asenapine is a sublingual drug that requires mucosal absorption, potentially limiting its use as a QD drug. Although sublingual drugs rarely come to market, asenapine may prove to fill a need in the antipsychotic panel with minimal titration, mild metabolic effects, and no major prolactin issues.

Another new agent, iloperidone, has been tested in doses up to 32 mg/day with similar side-effect profiles at low and high doses.³⁵ Initial concern about hypotension and the risk of QTc prolongation meant early trials of iloperidone used slow dose titration and lower doses; trials titrated iloperidone with BID administration from 2 mg/day, increasing 2 mg/day over 7 days to doses of 12, 16, 20, or 24 mg/day in phase III trials. Hypotension did not show up as a major adverse event in these trials and QTc prolongation was found to be mild and desensitized over time.³⁶

Iloperidone is expected to include a titration schedule with its label. Judging from historical data, labeled dose recommendations for a new drug will predict first usage in practice, but dosing is likely to change as clinical exposure accrues. Differential effects with high and low doses of iloperidone will require clinical exposure and further trials. For example, one might expect iloperidone to be dosed more quickly than the label suggests if tolerability is shown.

Some trial and error will be necessary with asenapine, too, as clinicians experiment with how much of a sublingual drug can be tolerated at one time and how the drug differentially affects different disease states. The dosing of asenapine sublingually may encounter mistakes akin to the dosing of ziprasidone without seriously enforcing the requirement to take ziprasidone with food; if the patient inadvertently swallows asenapine, it may lose drug absorption. On the bright side, there has been improvement in the learning curve to correctly dose new drugs; optimum dosing strategies for newly emerging drugs may be identified more quickly than previous agents. It is imperative that clinicians carefully monitor patients and trust their observations and judgment when prescribing off-label. There is clearly a certain amount of clinical judgment that evolves from the use of these drugs over the years; when conducted with prudence and care, off-label prescribing can be advantageous to patient outcomes.

State-Dependent Dosing

State-dependent dosing is one potential confound for data derived from clinical trials. Practice-based evidence and trials of some drugs like quetiapine suggest that the effective dose of one drug can vary for different disease states even in one individual. In the case of quetiapine, recent trials suggest that 300 mg/day is effective for bipolar depression³⁷ but double that may be necessary for mania.³⁸ Clinicians have observed that 25–150 mg/day of quetiapine can be effective in some patients, while others may require 800–1,200 mg/day, with higher doses for acute mania compared to depression. Olanzapine, ziprasidone, and especially aripiprazole are also sometimes dosed lower for the depressed phase of bipolar disorder and higher for the manic phase. When used for unipolar depression to augment SSRIs and serotonin norepinephrine reuptake inhibitors (SNRIs) in nonresponders, atypical antipsychotics often are dosed much lower than the doses used to treat schizophrenia or mania. Risperidone and paroxetine in combination appear to be no more effective at treating bipolar depression as either agent alone,³⁹ and this combination may even prove to be counterproductive because of the cytochrome P450 (CYP) 2D6 inhibitory properties of paroxetine (CYP metabolism is discussed in further detail below). More research is needed to verify the value of state-dependent dosing.

Sampling Issues

Another reason for the discrepancy between trials and practice may be that trials are often conducted in patients who do not accurately represent the populations in which they are eventually dosed. For example, trials of aripiprazole were conducted in hospitalized manic patients⁴⁰; results from such studies are likely to overestimate the necessary dose for non-hospitalized patients, leaving clinicians without guidelines for treating less severe cases. Conversely, agitated patients may be underrepresented in clinical trials as this is a difficult population in which to conduct studies, with requirements such as informed consent and compliance with medication schedules; therefore, doses might be underestimated for sicker patients. Low predictive value in trials may also be a result of a non-representative setting. For example, the Ziprasidone Extended Use in Schizophrenia (ZEUS) multidose trial was conducted in a controlled environment in European patients who may not have resembled acute schizophrenic patients in the United States.⁴¹ Especially in institutional settings, there is a paucity of accurately predictive guidelines for dosing atypical antipsychotics.

Everybody is Different

It is valuable to remember that part of the difficulty in predicting optimum doses from trials stems from the fact that trials are conducted in relatively small samples intended to predict usage of a new drug for entire populations. Most trials are designed as part of the regulatory approval process and have strict inclusion criteria. Further, general biological research does not account for population differences in variables such as age, gender, race, and lifestyle, which with practice can be used as predictive indicators for dosing strategies. It

seems reasonable that there is an “adjustment period” as new drugs arrive on the market. Average responses of the general sample of patients may not be accurate in predicting individual patient response.

Gloomy Remission Rates

Little is predictable about the therapeutic effect of atypical antipsychotics for any given individual. In general, current treatments result in discouragingly low remission rates for the most common psychiatric disorders, as evidenced by large trials such as CATIE, the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, and the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) study. In the CATIE schizophrenia trials, 26% of participants completed the 18-month trial on the drug to which they were initially assigned.⁴² The STAR*D study for alternative treatments in nonpsychotic major depression observed an overall remission rate of 27%.⁴³ The STEP-BD study on the treatment of bipolar disorder returned a higher overall remission rate of 58% but 48.5% of these experienced a recurrence of symptoms within the 2-year follow-up period.⁴⁴ A 12-month outcome study of patients with bipolar disorder observed a 48% syndromal recovery but only 26% of patients achieved symptomatic remission and only 24% remitted to functional recovery.⁴⁵ Relapse rates for schizophrenia are between 70% and 80% in 5 years.⁴⁶ These numbers are unfavorable to say the least.

Undoubtedly, disappointing results are due to inadequate systems of care for patients with mental illness, but there is also some consensus that the pharmacotherapies currently available comprise an inadequate toolbox with which to treat these psychiatric disorders. Regardless, these tools must be optimized through familiarity with their use combining evidence from clinical trials (evidence-based prescribing) with evidence from clinical practice (prescribing-based evidence). Carefully monitoring complex mood disorders, comorbid conditions, polypharmacy, and other changing conditions in patient presentation ensures treatment decisions are based on individually relevant data, which can greatly enhance patient outcome.⁴⁷ Adjunct psychotherapy and psychosocial intervention is beneficial for improving these low remission rates, also offering improved life satisfaction and relationship functioning.⁴⁸ Psychoeducational and/or cognitive-behavioral therapy adjunct to continuing pharmacotherapy enhances long-term mood stability.⁴⁹ At least three types of psychosocial intervention have received empirical support for improving quality of life in patients with bipolar disorder.⁵⁰

Compliance

A great deal of individual response variability to atypical antipsychotics has to do with compliance; drugs cannot work if they are not taken appropriately. Anywhere from one half to two thirds of patients are noncompliant with medication regimens in the first year of treatment.⁵¹ Compliance can be increased by finding a better-tolerated medication and with proper education regarding the illness and its treatment. The goals of psy-

chosocial therapies are to educate patients (and often families or caretakers) on their disease and the need for treatment and to develop self-management strategies for interepisode periods. Psychoeducational and cognitive-behavioral strategies can be particularly important in long-term treatment and prevention of relapse.⁵²

For partially compliant patients, clinicians suggest psychosocial treatment as a primary means of improvement; long-acting injectables are experts' first choice for obviously noncompliant patients.⁵³ Dosing once daily is also known to improve compliance. Some antipsychotics with BID recommended labels are being dosed QD in attempts to improve compliance. When monitored for tolerability, some antipsychotics can be effectively dosed this way. A more detailed discussion as to the pharmacodynamic evidence for dosing antipsychotics QD can be found below.

Lifestyle, Environment

Variability in antipsychotic response is also dependent on individual factors such as lifestyle, environment, and genetics. For example, smoking may account for some of the variability observed with clozapine⁵⁴ and olanzapine⁵⁵ plasma concentrations, suggesting that some smokers may require higher doses to achieve an equivalent response compared to nonsmokers or that new nonsmokers might need a dose reduction.⁵⁶ Gender has also been found to factor into plasma drug levels, although the effect is not as large as with smoking.⁵⁷ Individual drug metabolism also varies among individuals, decreasing or increasing drug plasma levels in fast or slow metabolizers, respectively. Environmental changes, if monitored appropriately, can play a predictable role in drug response. Dosing has to be appropriate to an individual's circumstances, which can change in a different environment. Many of these issues will be further explored in a later discussion of pharmacokinetics. There is also a great heterogeneity among brains with psychiatric disorders. The brain of a first-episode patient may respond differently to antipsychotic treatment compared to the brain of a patient who has been heavily medicated for years. For example, lower doses of medication may be effective for the former patient but not for the latter patient, where permanent brain differences may have resulted from extensive treatment. In general, first-episode patients are more responsive to lower doses of antipsychotics.⁵⁸ Individual variability in drug response is a newly appreciated matter in psychopharmacology. Evidence correlating particular variables to individual antipsychotic response has historically been poorly characterized and has only recently begun to improve.

Genetics

Genetics also might play a large role in response to antipsychotic treatments. Mood, anxiety disorders, and schizophrenia have the highest known genetic contributions among psychiatric disorders, ranging from 30% for unipolar depression to 67% for bipolar disorder.⁵⁹ First-degree relatives who have undergone psychiatric treatment may be able to inform drug choice, dose, and response with a high degree of accuracy, though no strong evidence has been collected to support

this hypothesis. Treating close relatives with similar approaches may actually be an under-exploited practice in psychiatry. Genetics of psychiatric disorders is also currently being explored in the new field of pharmacogenetics, which may eventually offer clinical insight for individualizing optimum treatment plans (see below).⁶⁰ As psychiatry awaits new advances in informing and predicting treatment response, treatment decisions must be based on clinical observations and trends and a thorough understanding of the basic mechanisms of drugs and disease states.

Neurobiology and Pharmacodynamics

Dosing strategies may be informed by knowledge of receptor occupancy and mechanisms of action. Presently, the literature offers many candidate neuromechanisms hypothetically involved in the pathology and treatment of psychosis and mood disorders.⁶¹ The idea that schizophrenia is merely a result of hyperactive dopamine is known to be too simplistic to explain the complexity of this disease. Likewise, unstable neurotransmission associated with mania involves a variety of incompletely understood mechanisms, some of which are turning out to be targeted by atypical antipsychotics. It is not known whether these drugs are effective in bipolar disorders by acting on the same mechanisms as in psychosis or if therapeutic effects derive from totally different systems. Some of the mechanisms of atypical antipsychotics are known to reduce positive, negative, and other symptoms of psychosis as well as to reduce extrapyramidal symptoms (EPS), which are associated with dopamine hypoactivation in the nigrostriatal pathway. Understanding these key mechanisms can help prescribers make informed drug selection and dosing decisions.

Serotonin-Dopamine Antagonism

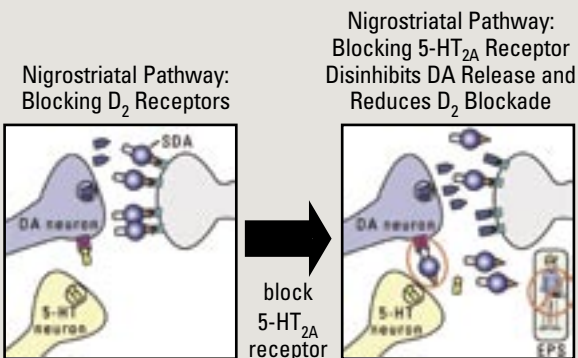
Clozapine, risperidone, paliperidone, olanzapine, quetiapine, ziprasidone, aripiprazole, asenapine, and iloperidone all have some serotonin antagonist action. Atypical antipsychotics that have features of both serotonin and dopamine antagonism are called serotonin-dopamine antagonists (SDAs); these two systems are hypothesized to act in complementary ways in brain circuits associated with symptoms these drugs target. One of the features of SDAs is that they block both serotonin and dopamine receptors in the nigrostriatal pathway, disinhibiting dopamine and allowing it to compete with the SDA for its receptor. This reverses the dopamine blockade associated with EPS thereby reducing the likelihood of such side effects with these antipsychotics (Figure 2).⁶¹

Serotonergic actions are also hypothesized to be relevant in improving symptoms of psychosis. Both pre- and postsynaptic serotonin receptors are involved in atypical antipsychotic actions and each have subtypes that are differentially thought to contribute to SDA efficacy. Presynaptic receptors are autoreceptors that shut down or slow neuronal impulse flow in the presence of serotonin. They exist as both somatodendritic and terminal autoreceptors. In the presence of serotonin, both somatodendritic autoreceptors and terminal autoreceptors will slow the flow of serotonin from the presynaptic neuron.

Postsynaptic receptors, on the other hand, translate messages from serotonin to the postsynaptic neuron. Postsynaptic receptors have regulatory effects on other systems; they can excite or inhibit cortical pyramidal neurons, regulate hormones and other neurotransmitters, and play a role in a variety of functions including sleep, hallucinations, mood, cognition, and metabolism.

FIGURE 2

*Serotonin-Dopamine Antagonist Action in the Nigrostriatal Pathway*⁶¹



A. When only the D₂ blocking action of an atypical antipsychotic is active, the drug only binds to and blocks postsynaptic D₂ receptors. **(B)** The dual action of SDAs involves both D₂ and 5-HT_{2A} receptor blockage. In doing so, 5-HT_{2A} antagonism reverses D₂ antagonism action, disinhibiting D₂ and causing dopamine to pour out of the neuron. Therefore, dopamine can compete with the SDA for the D₂ receptor, reversing inhibition and thereby causing few or no extrapyramidal symptoms or tardive dyskinesia.

SDA=serotonin-dopamine antagonist; 5-HT_{2A}=serotonin 2A; D₂=dopamine-2 receptor; DA=dopamine

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Hit-and-Run

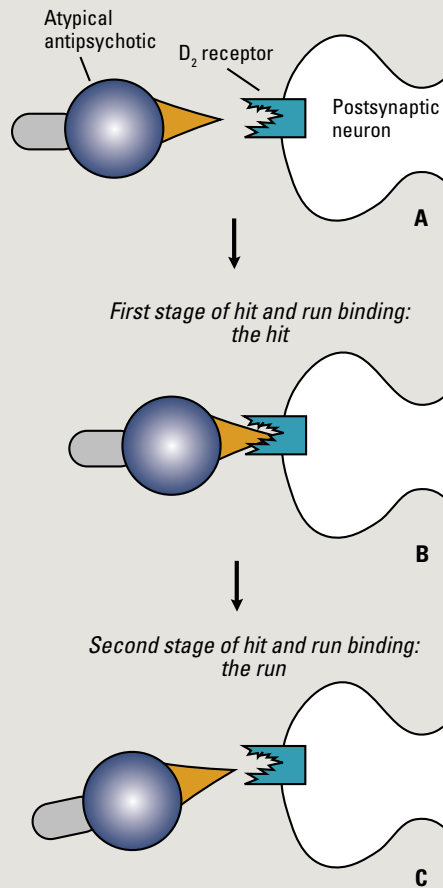
In addition to *where* atypical antipsychotics bind, *how* they bind is relevant to dosing of these drugs. Unlike conventional antipsychotics, most atypical antipsychotics do not persistently bind to receptors. Instead, their actions at the receptor level can be thought of as a "hit and run" mechanism, meaning that they can rapidly dissociate from receptors. This concept is illustrated in Figure 3.⁶¹ By not interminably binding to receptors, atypical antipsychotics are posited to remain on a receptor long enough to exert therapeutic effect, dissociating before causing EPS or worsening of negative symptoms.

This mechanism demonstrates that it may not be necessary for drugs to act constantly in order to be effective. Rather, it seems that a certain amount of receptor occupancy is required for a drug to be effective and that amount is not necessarily 100%. But how much is it?

Do Half-lives Inform Dosing Schedules?

For drugs such as ziprasidone, quetiapine, and clozapine, which have shorter half lives than other atypical agents (6–7 hours, 6–7 hours, and ~10 hours, respectively^{62,63}), this is a clinically relevant question. If constant pharmacologic action were required for effective

FIGURE 3
*"Hit and Run" Binding of Atypical Antipsychotics*⁶¹



(A) Atypical antipsychotics bind loosely to postsynaptic dopamine receptors, illustrated by a smooth binding site that does not fit into the teeth of the receptor. **(B)** The hit: atypical antipsychotic binds to the receptor. Note that it fits loosely into its receptor without getting locked into the grooves of the receptor as do conventional antipsychotics. **(C)** The run: this loose fit allows atypical antipsychotics to rapidly dissociate, or slip off easily after binding only briefly.

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therapeutic therapy, a short half life would suggest that these drugs should not be effective if taken only once daily. However, they are sometimes effectively prescribed as a single daily dose in efforts to increase long-term adherence.⁶⁴ Similarly, practice-based evidence suggests it is uncommon to experience a withdrawal phase late in the day with quetiapine or even clozapine dosed once daily. The fact that such agents could be effective in QD dosing schedules that would not otherwise be predicted by their rapid dissociation further suggests that constant occupation at the receptor level may not be necessary for effective treatment. Of course, another factor to consider when devising a treatment plan is that metabolism for these drugs varies among individuals, a concept discussed in further detail in regards to pharmacokinetics. Although more research is required to identify optimum receptor occupancy levels for atypical agents, it does seem that continuous, high levels of occupancy are not critical for maximum drug efficacy. Downstream effects of antipsychotics are still

active after the drug has left the receptor; these downstream effects may be related to efficacy, such that constant action at the receptor level is not actually entirely necessary. This concept is relevant to dosing strategies because knowledge of effective receptor occupancy levels can directly inform individual prescribing decisions. It may turn out to be that there is no pharmacodynamic reason to dose antipsychotics more than once a day.

Binding Profiles

Each atypical antipsychotic has a relatively unique set of affinities for the numerous receptors it targets. Examining the binding profiles of the seven atypical antipsychotics provides an understanding of the relative degree to which each of these agents acts on different classes of therapeutically relevant receptors. Individuals respond differently to these agents, likely due to the unique nature of individual symptom profiles. Understanding receptor occupancy profiles and their therapeutic and side-effect relevancy can aid in dosing and treatment selection. For example, the serotonin 5-HT_{2C} receptor, especially when blocked simultaneously with histamine H₁ receptors, is implicated in obesity, mood, and cognition. Using a symptom-based treatment algorithm, one might select an antipsychotic with high 5-HT_{2C} affinity for a patient with prominent cognitive or affective symptoms, but not if the patient already has metabolic problems such as diabetes or obesity.

Antipsychotic action at dopamine receptors is thought to reduce positive, negative, cognitive, and affective symptoms but to increase EPS and prolactin elevation. Antipsychotic action at 5-HT_{2A} receptors is thought to also aid in reduction of positive, negative, cognitive, and affective symptoms but also to reduce EPS and prolactin elevation. The precise mechanisms of each receptor action are not known. Nevertheless, a study recently found ACP-103 (pimavanserin), a 5-HT_{2A} antagonist, added to risperidone 1 mg had the same efficacy as risperidone 6 mg alone, also ameliorating weight gain associated with risperidone monotherapy.⁶⁵ This might suggest that more 5-HT_{2A} receptor occupancy is correlated to higher efficacy in treating symptoms of schizophrenia. However, very low doses of clozapine (25–50 mg) blocks all 5-HT_{2A} receptors with no therapeutic effect in either schizophrenia or mood disorders at these doses, suggesting the need to combine 5-HT_{2A} antagonism with D₂ antagonism for the treatment of schizophrenia. Although not all receptor functions are precisely known, knowledge of receptors implicated in therapeutic efficacy and the presence of side effects can assist drug comparison to select appropriate medication regimens.

Figure 4 displays simplified binding profiles of the seven major atypical antipsychotics currently available in the United States.^{66,67} Ideally, a drug has higher therapeutic receptor affinities and lower side-effect receptor affinities but this is not always the case. With knowledge of receptor functions, comparing receptor binding affinity among these agents can aid in directing symptom-based treatment for individual patients. Figure 5 displays the binding profiles for asenapine and iloperidone, two antipsychotics expected to emerge on the market soon.⁶⁸⁻⁷⁰ Asenapine binding profile displays broad ranging effects showing potential to be effective

in a wide range of symptoms. Iloperidone binding profile displays targeted dopamine, norepinephrine, and serotonin receptors, also showing potential to be effective in a wide range of symptoms. These receptor occupancy data are not sufficient to explain the complex actions of atypical antipsychotics. If the mechanisms of action of these drugs were truly understood in terms of dopamine and serotonin receptor occupancy, the repeated observation that individuals differentially and unpredictably respond to different drugs in this class makes little sense. Atypical agents tend to work differently for different individuals; higher or lower receptor binding affinities may have more therapeutic effects in some patients than others. The question remains as to whether the effectiveness of atypical antipsychotics in treating bipolar disorder, and even as augmenting agents for treatment-refractory unipolar depression, is due to similar or completely different pharmacologic properties as those thought to be effective for the symptoms of psychosis.

That atypical antipsychotics have various mechanisms of action and that individuals differ greatly in their response to these drugs highlights the complexity of psychosis and reinforces the knowledge that mental disorders do not derive from a single aberrant neurotransmitter or neurocircuit. While these drugs are the best options currently available for alleviating the symptoms of psychotic disorders, none of them is completely curative. They have broad actions outside the scope of those they are intended to treat. It is imperative for the prescribing clinician to stay informed of the interactions between brain, body, and pharmacotherapies. Making informed, individualized treatment decisions will greatly enhance patient outcome.

Pharmacokinetics

Pharmacodynamics explains how drugs act on the body. Pharmacokinetics, on the other hand, explains how the body acts on drugs. Significant effects of this latter kind include the necessity for lower doses in elderly patients, the effects of smoking on clozapine and olanzapine, ziprasidone absorption with or without food, and may potentially include issues with sublingual asenapine absorption. Some smokers may require higher doses of some antipsychotics that interact with smoking whereas patients who quit smoking may require decreased dose of such antipsychotics with increased monitoring.⁵⁶ Smoking can affect plasma levels of clozapine and this may have to do with the fact that smoking interacts with the metabolic processes of CYP 1A2, which metabolizes clozapine, lowering plasma levels by increasing the rate of metabolism.⁷¹ Clozapine is the only drug for which plasma tests are actually used to inform healthcare providers whether a patient is taking a drug appropriately.

Much attention in psychiatry has also been given to the CYP 2D6 and 2C19 isoforms. For a fee, individuals can even have their genome scanned for these alleles. Although some variants of these alleles do have effects on some drugs, the clinical significance of these effects have yet to be decisively established and it is not clear that the cost of this test is yet justified by the usefulness of the information it provides.

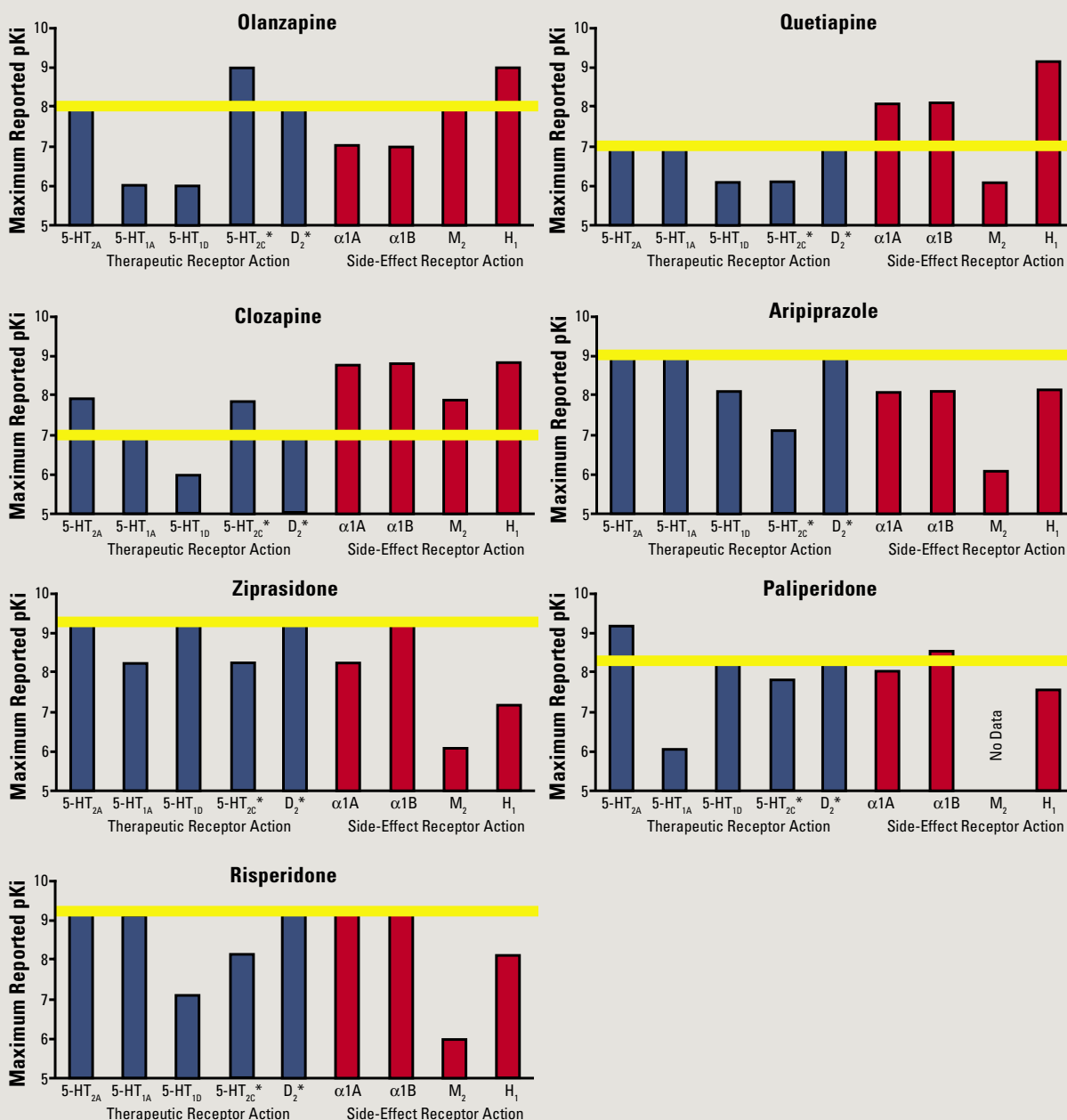
The effect of smoking on antipsychotic activity is fairly well established in the literature but it is now becoming apparent that this effect may be less dramatic than that of not taking ziprasidone with food. Up to one third of the dose of ziprasidone can be lost if this drug is not taken with food.⁷² Pharmacokinetic interactions might be highly relevant to asenapine as a new sublingual drug, while prescribers experiment with appropriately dosing such an agent. That is, the bioavailability of asenapine falls dramatically if a patient swallows it or rinses their mouth too soon after taking it sublingually.

Another pharmacokinetic issue with atypical antipsychotics arises from drug-drug interactions. For example, when quetiapine, risperidone, or aripiprazole (which are metabolized by CYP 2D6 and 3A4) are combined with drugs that induce or inhibit these enzymes (such as fluvoxamine, paroxetine, and modafinil), dose adjustment may be necessary. Paliperidone is the only atypical antipsychotic that is not metabolized by any CYP isoform.

Pharmacokinetics informs dosing schedules in regard to how the body acts on a drug. Pharmacodynamics informs dosing schedules in regard to how a drug acts

FIGURE 4

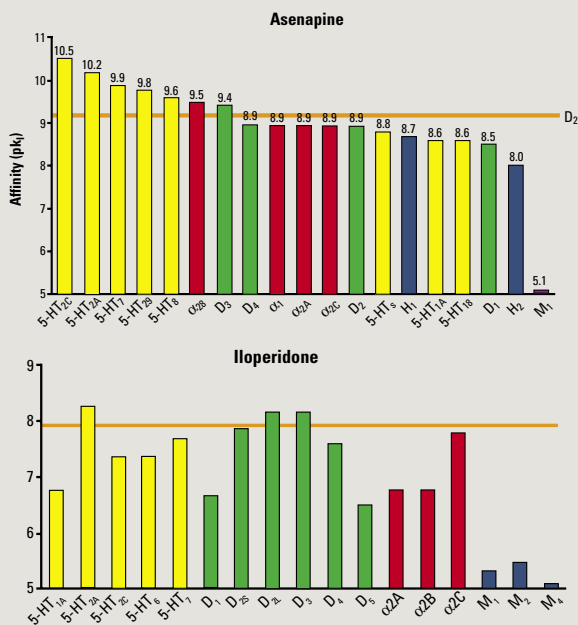
Simplified Binding Affinity Profiles for the Seven Major Atypical Antipsychotics Available in the United States^{66,67}



Potentially important therapeutic receptor binding affinities are shown in blue. Potentially important side-effect receptor binding affinities are shown in red. The two receptors with asterisks, 5-HT_{2C} and D₂, are thought to be both therapeutic and side-effect inducing. The yellow line indicates the D₂ affinity level for each drug. Ideally, a drug should have therapeutic receptor affinities within this same range and side-effect receptor affinities at lower ranges.

5-HT_{2A}=serotonin-2A receptor; 5-HT_{1A}=serotonin-1A receptor; 5-HT_{1D}=serotonin-1D receptor; 5-HT_{2C}=serotonin-2C receptor; D₂=dopamine-2 receptor; α1A=adrenergic α-1A receptor; α1B=adrenergic α-1B receptor, M₂=muscarinic-2 receptor, H₁=histaminergic-1 receptor.

FIGURE 5
Binding Affinity Profiles for Two Emerging Atypical
Antipsychotics⁶⁸⁻⁷⁰



Asenapine binding profile displays broad ranging effects showing potential to be effective in a wide range of symptoms. Iloperidone binding profile displays targeted dopamine, norepinephrine, and serotonin receptors, showing potential to be effective in a wide range of symptoms. Iloperidone and asenapine both have a greater affinity for 5-HT_{2A} receptors than for D₂.

5-HT_{2A}=serotonin-2A receptor; 5-HT_{1A}=serotonin-1A receptor; 5-HT_{1B}=serotonin-1B receptor; 5-HT_{1C}=serotonin-1C receptor; 5-HT_{2C}=serotonin-2C receptor; D₂=dopamine-2 receptor; α_{1A}=adrenergic α-1A receptor; α_{2A}=adrenergic α-2A receptor; M₂=muscarinic-2 receptor; H₁=histaminergic-1 receptor.

on the body. Together, knowledge of drug actions and drug metabolism can provide tools to aid in the selection of treatment strategies. In the future, methods for better predicting individual responses to antipsychotics need to be developed to further aid in this process.

Pharmacogenetics for Psychiatry

The study of how genetic variation affects antipsychotic response is currently blossoming; although few findings are currently clinically relevant, the direction of this research offers the potential for predictive value for how individuals will respond to psychopharmacologic agents. The field of pharmacogenetics has already seen clinical utility in other areas of medicine (most notable might be trastuzumab⁷³ and pertuzumab⁷⁴ for breast cancer and the anticoagulant warfarin⁷⁵).

Candidate Genes

In the field of psychiatry, CYP (especially the 2D6 isoform) is the single candidate gene that has received the most attention in pharmacogenetics research. This is likely due to the fact that it has pharmacologically wide-ranging metabolic influence. CYP 2D6 has more than 100 genetic variants causing several broad categories of enzyme activity. CYP 2D6 plays a role in metabolizing aripiprazole, atomoxetine, codeine, nortriptyline, paroxetine, and risperidone, among other drugs. It is

currently understood that plasma levels of these drugs are affected to some degree by CYP 2D6 function.⁷⁶ However, although it is highly variable among different races, only 10% to 15% of Caucasians are either rapid or slow CYP 2D6 metabolizers, meaning that findings related to dosing 2D6-metabolized drugs on the basis of individual CYP 2D6 genotype will not affect 85% to 90% of Caucasians.⁷⁷ Regardless, CYP has been considered the best prospect for clinical utility among the single-candidate markers currently under investigation.

COMT is another gene that has received a great deal of attention, although its potential for clinical utility is still in question. Val¹⁵⁸Met polymorphism on the COMT gene has been shown to affect the frontal cortex in potentially significant pharmacological ways. Thus, it is suspected that COMT genotype does not directly affect drug response but does indirectly alter frontal lobe effects of some drugs.⁷⁸ Studies have shown a relationship between COMT genotype in schizophrenia and working memory and executive function.⁷⁹ During treatment with olanzapine in one study for example, the Met allele was associated with greater improvement in cognitive symptoms of schizophrenia such that those with a homozygous Met genotype improved greatly, heterozygous Met/Val improved moderately, while those with homozygous Val genotypes did not change.⁸⁰ Although these studies show a clear relationship between genes and cognitive response to antipsychotics, it is as of yet unclear how reproducible this finding is or how important this variant actually is to quality of life, and to what degree it might be predictive in clinical practice.

Findings from CYP and COMT studies represent one approach to pharmacogenetics known as the candidate gene approach. Candidate gene studies involve a priori analysis of particular single nucleotide polymorphisms (SNPs) thought to be relevant to a particular phenotype. Upon identifying potentially relevant genes, researchers attempt to associate its various alleles with particular treatment outcomes. Candidate gene studies are being aided by the development of large databanks of publicly accessible SNPs and haplotypes^{81,82} through projects like HapMap. The National Institutes of Health public database now contains more than 6 million validated SNPs.⁸³ With this accumulation of data, the tedious and costly process of searching for significant natural mutations is becoming more streamlined.

Genome-Wide Associations

Another approach to pharmacogenetics known as genome-wide association (GWA) is also becoming more feasible. The premise of GWA studies is to analyze hundreds of thousands of SNP variants to see if any of them may be associated with a phenotype; this post hoc approach requires more knowledge of the human genome and its extant functional variants. GWA studies are likely to show more promise than the single candidate gene approach, as we now understand that illnesses are not a manifestation of one genetic aberration but rather the result of complex interactions among several genes and environmental stressors.

Multi-gene approach to pharmacogenetics may prove to have the highest clinical utility in the near future; it is unlikely that any clinical test for drug response will only include a single gene. However, single can-

didate gene studies are valuable as they bring us closer to understanding the architecture of interacting genes that may eventually predict treatment outcomes. Though all of these pharmacogenetic studies are still in their infancy, technological advances are now greatly facilitating GWA progress. Microarrays and DNA chips that measure large volumes of common genetic variations are becoming increasingly more obtainable.

One example of the GWA approach to pharmacogenetics in psychiatry was recently conducted for the experimental drug iloperidone (Figure 6),⁸⁴ which has recently completed Phase III clinical trials. Genetic associations to iloperidone response in this study revealed significance at the statistical level, and need to be validated prospectively in order to determine whether they will prove to be predictive at the clinical level. This hypothesis-generating study can be seen as an early example of potential direction in which pharmacogenetics may take psychiatric research.

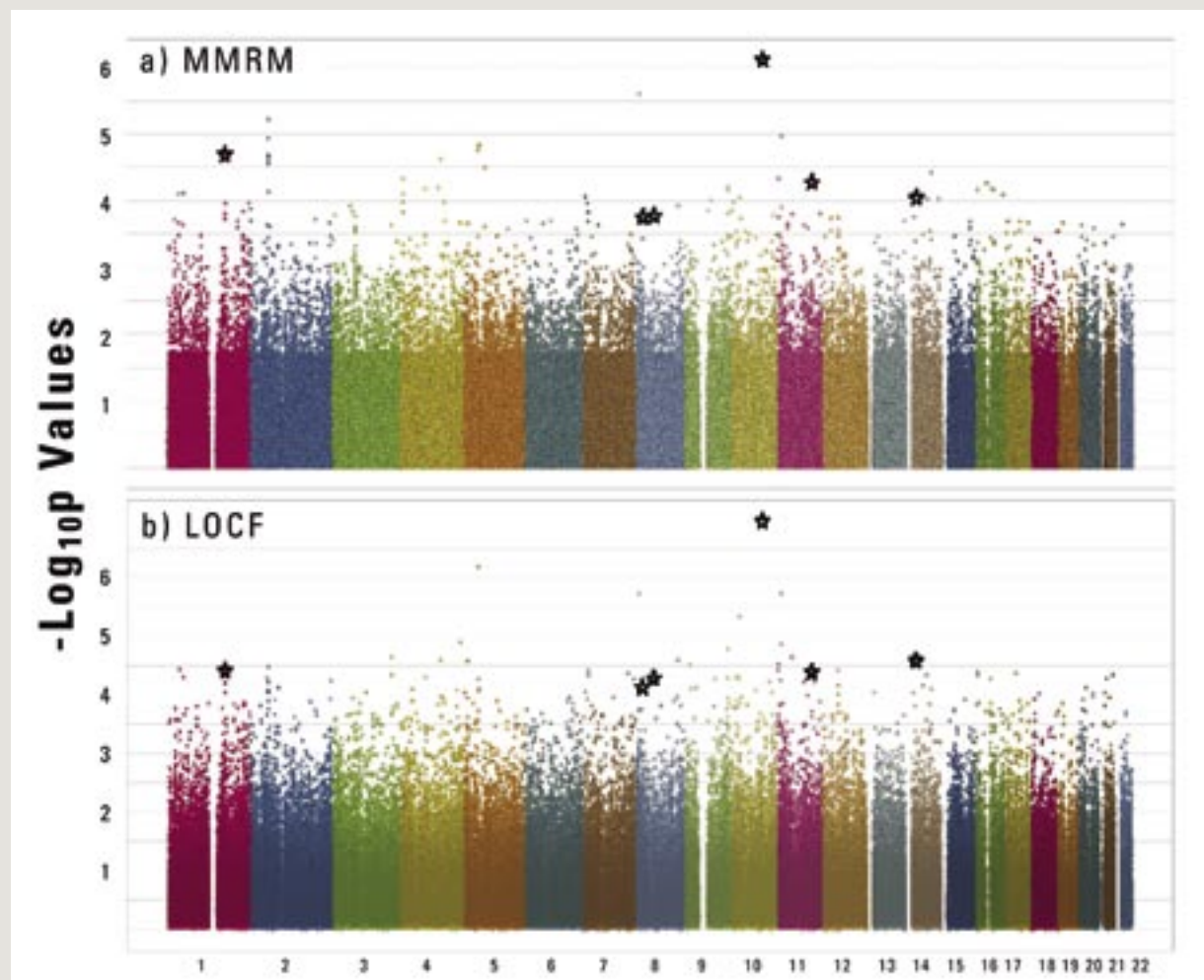
Challenges to Implementation

Several challenges currently stand in the way of implementing pharmacogenetics as a standard in psychiatric practice. Probably most pressing is the present lack of data. There is a need to confirm preliminary results in studies that have found associations between genes and drug response; few to no replication studies have been undertaken. There is also a need to evaluate the usefulness of implementing such findings into practice. It is not currently known whether genetic evaluation will actually be clinically useful or cost-effective or whether findings will be otherwise useful in the context of medical, personal, or public health.

Another challenge on the road to putting pharmacogenetics into practice is the limited catalogue of functional variants. In other words, we do not know what to look for. Although projects such as HapMap are presently developing large databanks of publicly accessible

FIGURE 6

View of Whole Genome in a Genome-Wide Association Study of Response to Iloperidone in the Treatment of Patients with Schizophrenia⁸⁴



Shown here are the association results for analysis of each chromosome. Points represent P values (y axis) and genomic location (x axis) of single nucleotide polymorphisms (SNPs), illustrating the degree to which each SNP is associated with change in Positive and Negative Symptoms Scale Total. Associations identified through this study were weak but the method employed is one of the first of its kind, representing a potentially promising future for genomic analysis in psychiatry.

MMRM=mixed-effects model repeated measures; LOCF=last observation carried forward

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SNPs and haplotypes, still only a fraction of markers have been well-characterized as affecting the function of genes and when such variants are identified, as in the case of CYP, they generally only account for a very small percentage of the population with that disorder.

Finally, the issue of drug response heterogeneity extends beyond genetic variation. Factors such as age, smoking, diet, and compliance with prescription regimen affect drug response at least as much as genetic variation, albeit through different mechanisms. Additionally, cultural and environmental differences present as very difficult variables to control for. These factors may not only confound the role of genetic heterogeneity but might also make the task of measuring and cultivating useful information from genetic screening quite difficult.

The ultimate goal of pharmacogenetics is the development of individualized treatment plans on the basis of genetic evaluation. Upon diagnosis, clinicians may some day hypothetically be able to use a patient's DNA sample to predict treatment outcome and optimum dosage. Perhaps what psychiatry has lacked most acutely is a reliable set of predictors for how drugs work. Ideally such a method would eliminate the need for trial-and-error prescribing, reduce side effects, and increase both treatment response and patient compliance. For example, prescribers would potentially benefit from being able to predict whether olanzapine or clozapine might be tolerated earlier in treatment for severe cases or whether an individual will respond to lower or higher doses of quetiapine. As the field awaits such progress, patients in the meantime must rely on the knowledge and good judgement of their health-care providers; clinicians must capitalize on available knowledge to make informed prescribing decisions.

Conclusion

Psychiatry has a great need for the development of novel agents to target symptoms of psychosis and mood disorders and for the development of novel methods to identify optimum individualized treatment plans. Although current atypical antipsychotics differ in their binding affinities, as a whole this is a relatively homogenous class of drugs. Remission rates for the most prevalent psychiatric disorders are discouragingly low. Few strategies exist for treatment-refractory patients; healthcare providers find themselves prescribing full doses of several drugs, recognizing that symptoms are being chased with inadequate tools. Further understanding the pathophysiology of psychotic disorders will aid in the ability to develop novel treatments. Healthcare providers can benefit from understanding this pathophysiology, too, and apply this knowledge to optimize use of agents that are currently available.

There does exist a need for fixed-dose trials that can more accurately predict how new agents will be used in practice. However, much of the discrepancy observed between trials and practice is difficult to control for in relatively small trials that aim to predict population-wide uses. Disease severity, symptoms, and drug tolerance vary greatly among individuals and in different populations. Family history of disease and treatment response can also inform diagnosis and symptom profiles and, potentially, treat-

ment response. Prescribers must trust their observations, questioning reasons for a drug not working at a dose in which it is expected to work. Dosing is therefore as much art as science in clinical practice.

Finally, it is important to treat not only symptoms but also patients. The benefits of psychosocial and psychotherapeutic components of treatment can sometimes be forgotten among the complexity of pharmacologics. Psychiatric drugs are not magic bullets; even patients with the best responses still require other types of intervention to optimize quality of life. Prescribers have great influence not only on the treatment of symptoms but also on patient awareness, knowledge, social functioning, and overall quality of life. Recalling a wholistic approach to prescribing and treating in combination with a comprehensive understanding of drug-brain-body interactions will appreciably improve patient care.

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An expert panel review of clinical challenges in psychiatry

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CME POSTTEST

To receive your certificate of CME credit or participation, please complete the posttest (you must score at least 70% to receive credit) and activity evaluation answer sheet found on page 16 and return it by mail or fax. Once received, your posttest will be graded and, along with your certificate (if a score of 70% or more was attained), returned to you by mail. Alternatively, you may complete these items online and immediately print your certificate at www.neiglobal.com/pt/08dosingmonograph. There is no fee for this activity.

Please select the single best choice (circle your answers on the next page):

1. When is the earliest point in treatment to make a switch-or-stay decision with reasonable predictive accuracy?

- A. At sign of first response
- B. One week
- C. Two weeks
- D. Four weeks
- E. Six weeks

2. Which might be clinically equivalent to clozapine (300–900 mg/day) in treatment-refractory schizophrenia patients?

- A. 16 mg/day risperidone
- B. 25–45 mg/day olanzapine
- C. 1,200 mg/day quetiapine
- D. 320 mg/day ziprasidone
- E. 30 mg/day aripiprazole

3. If not taken with food, ziprasidone:

- A. Cannot be absorbed effectively
- B. Metabolizes too quickly to be effective
- C. Absorbs more quickly, becoming effective faster
- D. Metabolizes more slowly, staying effective longer

4. Which of the following can be true regarding state-dependent dosing?

- A. Depression requires higher doses than mania
- B. Mania requires higher doses than depression
- C. Low-dose selective serotonin reuptake inhibitors can augment full-dose antipsychotics in treatment-resistant unipolar depression
- D. None of the above

5. What was the range of remission rates reported for recent large trials of the most common psychiatric disorders?

- A. 50% to 75%
- B. 10% to 25%
- C. 40% to 60%
- D. 25% to 60%

6. Which of the following is not likely to improve patient compliance?

- A. QD dosing
- B. Psychoeducation
- C. BID dosing
- D. Cognitive-behavioral therapy

7. What component of bipolar disorder is thought to be genetically associated?

- A. 30%
- B. 55%
- C. 67%
- D. 87%

8. Which of the following is not a function of postsynaptic serotonin receptors?

- A. Directing serotonin to presynaptic receptors
- B. Regulating hormones
- C. Regulating metabolism
- D. Inhibiting cortical pyramidal neurons

9. Which has the highest affinity for muscarinic-2 receptors as compared to dopamine-2 (D_2) receptors?

- A. Olanzapine
- B. Clozapine
- C. Quetiapine
- D. Ziprasidone
- E. Paliperidone

10. Which has the highest affinity for 5-HT_{2A} receptors as compared to D_2 receptors?

- A. Olanzapine
- B. Risperidone
- C. Aripiprazole
- D. Asenapine
- E. Iloperidone



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ACTIVITY EVALUATION

Please rate the following, using a scale of: 1-bad 2-below average 3-average 4-above average 5-excellent

1. The overall quality of the content was: 1 2 3 4 5
2. The relevance of the content to my professional needs was: 1 2 3 4 5
3. The level at which the following learning objective was met: Develop treatment selection and dosing strategies that are designed to maximize patient adherence 1 2 3 4 5
4. The level at which the following learning objective was met: Consider the impact of common antipsychotic side effects on patient functionality when selecting treatment options 1 2 3 4 5
5. The level at which the following learning objective was met: Integrate novel treatment tools into clinical practice as they become available 1 2 3 4 5
6. The level at which this activity was objective, scientifically balanced, and free of commercial bias was: 1 2 3 4 5
7. The overall quality of this activity was: 1 2 3 4 5
8. Based on my experience and knowledge, the level of this activity was: Too Basic Basic Appropriate Complex Too Complex
9. Based on the information presented in this activity, I will:

A. Change my practice	C. Do nothing as current practice reflects activity's recommendations
B. Seek additional information on this topic	D. Do nothing as the content was not convincing
10. What barriers might keep you from implementing changes in your practice you would like to make as a result of participating in this activity?

11. The following additional information about this topic would help me in my practice:

12. How could this activity have been improved?

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