

A Roadmap to Key Pharmacologic Principles in Using Antipsychotics: Application in Clinical Practice

The case examples and discussions in this ACADEMIC HIGHLIGHTS section were developed by Sheldon H. Preskorn, M.D., one of the editors of the Roadmap Project, to illustrate how to apply the pharmacologic principles concerning antipsychotic use outlined in the Roadmap to the types of cases clinicians are likely to encounter in real-world treatment settings. The recommendations in this article are based in part on those previously published in a supplement on antipsychotic use by Peter J. Weiden, M.D.; Sheldon H. Preskorn, M.D.; Peter A. Fahnstock, M.D.; Daniel Carpenter, Ph.D.; Ruth Ross, M.A.; and John P. Docherty, M.D., titled *Translating the Psychopharmacology of Antipsychotics to Individualized Treatment for Severe Mental Illness: A Roadmap*.¹ Dr. Preskorn acknowledges the other authors of that supplement and the Roadmap Editorial Board (Shitij Kapur, M.D., Ph.D., F.R.C.P.C.; David C. Mamo, M.D., M.Sc., F.R.C.P.C.; Stephen R. Marder, M.D.; Joseph P. McEvoy, M.D.; John W. Newcomer, M.D.; and Gary S. Sachs, M.D.), the experts who completed the survey, and Paola Vega of Expert Knowledge Systems for their invaluable help. The author is particularly appreciative of the editorial assistance of Ruth Ross, without whom this article would not have been produced. Support for this project was provided by an educational grant from Bristol-Myers Squibb, Inc.

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The publication *Translating the Psychopharmacology of Antipsychotics to Individualized Treatment for Severe Mental Illness: A Roadmap*¹ outlined key pharmacologic principles concerning the use of antipsychotics. In keeping with the recommendation of the President's New Freedom Commission on Mental Health² to incorporate the latest scientific information into mainstream health care as rapidly as possible, the Roadmap drew on clinical trial data, information on antipsychotic pharmacology, practice guidelines,³⁻⁶ consensus statements,⁷ and expert opinion to develop recommendations for achieving best outcomes for individual patients. Expert opinion was sampled using an initial survey and roundtable meeting of 10 experts and a follow-up survey of 27 experts who reached a

high level of consensus on many key questions not adequately addressed by the literature. (For a description of the survey methodology and respondents, see the Roadmap supplement.¹) The Roadmap presents recommendations to help clinicians make informed decisions about medication choice, dosing, and switching strategies based on (1) pharmacodynamic and pharmacokinetic properties of antipsychotics; (2) diagnosis, prominent symptoms, and treatment history; (3) demographic characteristics; and (4) medical conditions, including those related to antipsychotic treatment. The purpose of this article is to present a series of cases that illustrate how to apply these principles in the treatment of the types of patients clinicians are likely to encounter in daily practice.

Overview of Antipsychotic Psychopharmacology

Clinicians generally choose medications based on "therapeutic" class (the conditions a drug is approved to treat). Antipsychotics are a therapeutic class of medications with known efficacy for treatment of psychotic symptoms in schizophrenia and a labeled indication for this use. However, therapeutic class, while a starting point, may tell little about what a drug does in the body. Another approach is to consider the underlying properties of medications—their effects on target receptors (pharmacodynamics) and how they are metabolized (pharmacokinetics). Pharmacodynamics and pharmacokinetics ultimately determine the effect(s)—both good and bad—a drug will produce in an individual. Therefore, we asked the experts about the role of these factors in

guiding medication choices over and above data provided by clinical trials. These questions are particularly relevant for antipsychotics, which, despite sharing the same therapeutic indication, differ considerably in other pharmacologic properties.

The panel endorsed clinical trial data as the most important consideration in medication decisions. Nevertheless, a majority felt that, when trials show roughly equal efficacy, pharmacodynamics can be important in selecting the most appropriate agent and avoiding withdrawal and additive effects when switching antipsychotics. Thus, even if antipsychotics have similar efficacy on average, prescribers may be able to achieve better than average results by considering other drug properties in selecting a specific drug

Figure 1. Three Variables That Determine Response to Any Drug^a

Clinical response	=	Affinity for and intrinsic activity on the site of action (pharmacodynamics)	×	Drug concentration at site of action (pharmacokinetics) (ADME)	×	Underlying biology of patient (GADE)
				<ul style="list-style-type: none"> • Absorption • Distribution • Metabolism • Elimination 		<ul style="list-style-type: none"> • Genetics • Age • Disease • Environment

^aReprinted with permission from Preskorn.⁸

Table 1. Binding Affinity of Selected Antipsychotics for Specific Neuroreceptors^{a,b}

Antipsychotic	D ₂	5-HT _{1A}	5-HT _{2A}	5-HT _{2C}	α ₁	H ₁	M ₁
Aripiprazole	0.34 ^c	1.7 ^c	3.4 ^c	15	57	61 ^c	> 1000
Clozapine	126	875	16	16	7	6	1.9
Haloperidol	0.7	1100	45	> 10,000	6	440	> 1500
Olanzapine	11	> 10,000	4	23	19	7	1.9
Quetiapine	160	2800	295	1500	7	11	120
Risperidone	4	210	0.5	25	0.7	20	> 10,000
Ziprasidone	5	3	0.4	1	11	50	> 1000

^aFrom Preskorn,⁹ with permission, based on Richelson,¹⁰ Abilify package insert,¹¹ Arnt and Skarsfeldt,¹² Bymaster et al.,¹³ and Seeger et al.¹⁴
^bData represented as K_i (nM).
^cData with cloned human receptors.
 Abbreviations: 5-HT = serotonin, α₁ = alpha-1 norepinephrine, D = dopamine, H₁ = histamine 1, M₁ = muscarinic acetylcholine-1.

Table 2. Common Adverse Effects Caused by Receptor Blockade^a

Receptors	Effects
Histamine H ₁	Sedation, weight gain, postural dizziness
α ₁ -Adrenergic	Hypotension
M ₁	Deficits in memory and cognition, dry mouth, constipation, tachycardia, blurred vision, urinary retention
Dopamine D ₂	Extrapyramidal side effects, prolactin elevation

^aBased on Gardner et al.¹⁵
 Abbreviations: α₁ = alpha-1 norepinephrine, M₁ = muscarinic acetylcholine-1.

for a specific patient. Moreover, given the frequency of medication changes and the current trend to combine psychiatric medications, these differences can be important in understanding and predicting what may happen when drugs are titrated, tapered, or added to each other.

Determinants of Clinical Response

The equation in Figure 1 shows the 3 major variables that determine a drug’s effect in a specific patient.

Pharmacodynamic factors. A drug’s effects are a function of how much of the agent binds to the receptors it affects and its intrinsic action (e.g., agonism, antagonism, inverse agonism) on those receptors. Agonists act like the endogenous neurotransmitter to fully activate a receptor. Antago-

nists produce no activation, taking the receptor “out of play.” Inverse agonists shift the receptor in the reverse direction of its normal state (to date, inverse agonists have generally had little clinical utility). Drugs can also fall between these reference points (e.g., partial agonists). A drug can affect just 1 site of action (i.e., be selective) at clinically relevant concentrations or more than 1 site of action as a function of its relative binding affinity.

All currently available antipsychotics block dopamine-2 (D₂) receptors to some extent but vary in the degree to which they affect the D₂ receptor relative to other clinically meaningful receptors. These differences in receptor binding affinities (Table 1) generally explain differences

in the clinical profiles (e.g., side effects) of these drugs (Table 2).¹⁵

Tables 1 and 2, taken together, provide guidance about the effects that can be expected at different doses of different antipsychotics. It should be noted that the Roadmap panel expressed more confidence about the role of dopamine, histamine, muscarinic, and α-adrenergic than serotonin receptors in the effects of antipsychotics. While full or partial D₂ receptor antagonism or blockade appears to be a universal characteristic of marketed antipsychotics and necessary for antipsychotic efficacy, there was no consensus among the experts on what role, if any, full or partial antagonism of specific serotonin receptor subtypes (e.g., 5-HT_{1A}) plays in antipsychotic efficacy.¹

In the Roadmap survey, the experts were asked about the relative importance of pharmacodynamic differences in choice of medication, side effect management, withdrawal effects during medication discontinuation, and cross-titration techniques when switching from one antipsychotic to another. Their recommendations are incorporated in the case discussions that follow.

Pharmacokinetic factors refers to the pharmac in which drugs enter and leave the biological sites they affect. All antipsychotics have to cross the blood-brain barrier and find their way to the synapse; they are then eventually cleared from the synapse and eventually cleared from the body. The experts were asked about a number of clinical situations in which pharmacokinetic differences would be relevant, including use of long-acting medications, the effects of other co-prescribed medications on drug clearance, and how quickly to cross-taper agents when switching antipsychotics.

Biological variability in response. There is significant variation among individuals in the effects of all medications. Some variation is predictable on the basis of factors such as age or genetics. Other medications a person is taking are another source of variation in response, since such concomitant

medications can lead to drug-drug interactions as a result of pharmacodynamic or pharmacokinetic mechanisms. The Roadmap survey asked how factors such as age, genetics, and concomitant medications might influence decisions about use of antipsychotics. Of course, some variations in response cannot be predicted given the current level of knowledge about the individual patient receiving treatment (e.g., clinically important but currently unknown genetic differences), although tests for some variations in drug-metabolizing enzymes have become available.¹⁶

Cases in Which Pharmacodynamic Issues Play a Key Role

Case 1: How the Brain Reacts to Receptor Effects

Mr. A, a 34-year-old man with schizophrenia, has been treated with haloperidol for a number of years. The haloperidol controlled his florid psychotic symptoms (hallucinations and delusions), but the patient had significant negative symptoms that made it impossible for him to work. Mr. A and his family asked his primary care doctor, who managed Mr. A's medications, about trying a different agent to see if Mr. A might be able to take a job in the local sheltered workshop. The doctor therefore discontinued haloperidol and switched the patient to ziprasidone, 20 mg b.i.d., using a rapid crossover that lasted only 1 week. The patient returns for a follow-up visit after 1 week on monotherapy with ziprasidone, when he presents with dyskinesic movements that he and his family find very upsetting. The patient also appears to possibly be experiencing the early phases of a psychotic relapse. For these reasons, the patient and family ask if he should stop the new medication and go back to haloperidol. The primary care doctor consults you about what to do next.

What might have caused the patient to become agitated and restless?

The brain adapts to the presence of many psychiatric medications as a result of compensatory mechanisms (e.g., up-regulation of receptors in response to a drug that antagonizes that receptor; down-regulation in response to an agonist for that receptor). If such adaptation is not considered when changing drugs, withdrawal effects may occur. Chronic treatment with a D₂ antagonist can lead to up-regulation of D₂ receptors so that patients may develop distressing withdrawal dyskinesia when D₂ receptor blockade is reduced. Such a reduction in D₂ blockade can occur when a patient discontinues a potent D₂ blocker and switches to a drug with lower D₂ occupancy. This is most likely what happened in this case, as Mr. A rapidly discontinued the potent D₂ antagonist haloperidol and started treatment with ziprasidone, which produces minimal D₂ receptor blockade in most patients at a dose of 40 mg/day. Clinicians should be aware that such withdrawal effects can also occur when a patient switches from a full D₂ antagonist to a partial D₂ agonist (e.g., aripiprazole).

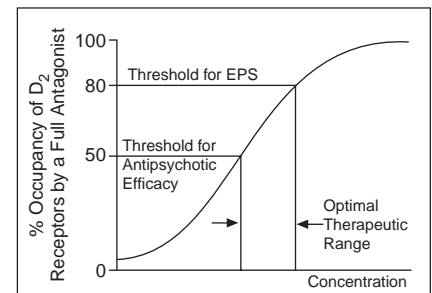
What would you recommend for Mr. A at this point?

If withdrawal effects are erroneously attributed to a new antipsychotic, patients may lose the opportunity for an adequate trial of that agent. Given that the dyskinesia appears likely to be a withdrawal effect and because the patient appears to be having some exacerbation of his psychotic symptoms, you advise the physician to increase the dose of ziprasidone to at least 120 mg/day, and ideally 160 mg/day, since this dose range has been shown, on average, to produce the minimum threshold of D₂ receptor occupancy needed for antipsychotic effect (e.g., approximately 60%).

Cases 2 and 3: Effects of Dose and D₂ Antagonism

To achieve the best outcomes for the individual patient, clinicians often have to carefully titrate the dosage of an antipsychotic to achieve the right balance

Figure 2. Narrow Range Between Efficacy and Behavioral Toxicity With D₂ Receptor Antagonists^{a,b}



^aReprinted with permission from Preskorn.¹⁷

^bD₂ antagonism ≥ 50% appears needed for antipsychotic efficacy, while antagonism > 80% is associated with increased risk of acute extrapyramidal side effects (EPS).¹⁸ This curve explains the narrow window between efficacy and EPS with full D₂ antagonists (note the curve would differ for partial D₂ agonists).

of receptor effects, as illustrated in the following 2 cases.

Case 2: Effect of a dose increase.

Mr. B, a patient with schizophrenia, has not achieved a satisfactory response with 10 mg/day of olanzapine. When the doctor increases the dose to 20 mg, the patient's response improves markedly, with no occurrence of extrapyramidal side effects (EPS).

Case 3: Effect of a dose reduction.

Ms. C, a patient with schizophrenia, has experienced good amelioration of psychotic symptoms but has developed distressing EPS on treatment with 6 mg/day of risperidone. When the doctor lowers the dose to 4 mg/day, the patient's response in terms of psychotic symptoms is maintained and the EPS resolve.

How would you explain the clinical effects in these two cases in terms of each patient's individual brain receptors?

Figure 2 shows that a minimum threshold of 50%–60% antagonism or blockade of the D₂ receptor appears to be required for antipsychotic efficacy, while blockade above 80% is associated with an increased risk of acute EPS. This figure explains the relatively narrow window between antipsychotic efficacy and risk of acute EPS associated with D₂ antagonism.

Many patients who are taking 10 mg/day of olanzapine are in the correct range to achieve antipsychotic efficacy without EPS, but a sizable percentage fall below the minimum threshold of 50%–60% blockade that is generally considered necessary for antipsychotic efficacy and need a higher dose to achieve satisfactory antipsychotic response. In Case 2, Mr. B fell below the 60% threshold on 10 mg/day but achieved approximately 60%–80% D₂ receptor blockade on 20 mg/day and experienced a good response.

In Case 3, Ms. C was above the 80% threshold for EPS at 6 mg/day of risperidone; when the dose was lowered, receptor blockade went down to approximately 70%—achieving D₂ receptor occupancy above the minimum threshold needed for efficacy but below that for EPS.

While these cases illustrate the general principle presented in Figure 2, not all patients will experience a good response just because they achieve 50%–80% D₂ receptor blockade. Some patients may need an alternative treatment that involves additional mechanisms besides D₂ blockade. In essence, optimal clinical management involves the prescriber's making these decisions based on a careful assessment of the patient and his or her response to treatment.

Case 4: Prolactin-Related Side Effects

Ms. D is a 25-year-old woman with schizophrenia who has responded well to treatment with risperidone 6 mg/day. However, Ms. D's periods have stopped and she is distressed by this.

What is likely to be the cause of Ms. D's amenorrhea?

Some antipsychotics induce prolactin elevation because of potent D₂ effects.¹⁹ While hyperprolactinemia can be asymptomatic, it can also cause amenorrhea and galactorrhea in women and gynecomastia and sexual dysfunction in men. The first-generation antipsychotics (e.g., haloperidol) and risperidone are most likely to be associated with this adverse effect,

while aripiprazole, clozapine, and quetiapine are associated with the least prolactin elevation (some studies report lowering of prolactin levels with aripiprazole) and ziprasidone and olanzapine fall in between.^{19–21} Female patients taking antipsychotics should be asked about changes in menstrual pattern, libido, and galactorrhea, and male patients should be asked about libido and erectile and ejaculatory function.²¹ If hyperprolactinemia is suspected, serum prolactin levels can be measured to confirm the cause of the symptoms. Female patients should tell their gynecologist or primary care doctor that they are taking an antipsychotic that can cause hyperprolactinemia to avoid needless workups for pituitary abnormalities.

Ms. D's doctor obtains a laboratory workup that shows elevated serum prolactin levels.

What can the doctor do to address the problem?

If prolactin is elevated and the patient is distressed by the symptoms, the doctor can consider lowering the dose of the current medication, if possible, or changing to a medication less likely to elevate prolactin.⁴ If hyperprolactinemia does not resolve with a medication change, medical follow-up should be obtained to rule out a medical problem (e.g., pituitary tumor).²¹

The doctor lowers the dose of risperidone to 4 mg/day, which continues to provide good symptomatic control, but Ms. D's periods do not resume. The doctor then decides to switch Ms. D to aripiprazole.

What should her doctor tell Ms. D about this change of medication?

Female patients switched to an antipsychotic less likely to elevate prolactin should be counseled that their menses are likely to resume in a few weeks to months and to use appropriate birth control if they are sexually active.

Cases 5–7: Drugs That Bind to Multiple Receptors: Impact of Dosing and Vulnerability for Side Effects

Taken together, Tables 1 and 2 and the equation in Figure 1 provide guid-

ance about the types of side effects that may occur with different doses of different antipsychotics. The equation shows that variable 1 (affinity for and intrinsic activity at its site[s] of action) × variable 2 (concentration) determines a drug's usual effect at a given dose. When a drug affects multiple receptors, its pharmacology can change with its dose. Thus, as dose and hence concentration increase, the drug's effects can change as the drug sequentially engages different target receptors in a dose-dependent, concentration-dependent manner.⁹ (Note that binding affinity does not indicate the specific effect, such as agonism or antagonism, that a drug has on that target.) The following cases illustrate the importance of understanding how the effect of antipsychotics can change as the dose changes and different receptors are affected. Note that the relationship between receptor binding profiles and adverse effects is better understood than the effect of receptor binding profiles on efficacy.

Case 5: Managing agitation with aripiprazole. *Ms. E is a 34-year-old married woman with bipolar disorder who was not able to tolerate lithium and gained significant weight on divalproex. She stopped the divalproex against medical advice. Although she was able to lose weight off medication, she experienced a destructive manic episode for which she was hospitalized 18 months ago. During that hospitalization, Ms. E was switched to quetiapine. She has remained symptomatically stable on quetiapine 600 mg/day but has gained 25 pounds. She is very distressed by this weight gain, which she has not been able to manage despite trying many different diets. Her doctor therefore suggests that Ms. E consider switching to aripiprazole.*

What was the rationale for trying aripiprazole in this case?

Among the second-generation antipsychotics, the greatest weight gain occurs with clozapine and olanzapine, and the least with ziprasidone and aripiprazole.^{22–26} Unfortunately, weight gain is a side effect that is not likely to

respond to a dose reduction. Therefore, if a stable patient is unable to continue treatment with the current antipsychotic because of excessive weight gain, and diet and lifestyle changes have been ineffective, the Roadmap panel recommended switching to an antipsychotic that is less likely to cause weight gain (aripiprazole and ziprasidone, followed by risperidone).¹ Ms. E has bipolar disorder, and only 3 of the currently available second-generation antipsychotics, aripiprazole, olanzapine, and quetiapine, have been approved for the maintenance treatment of this disorder. Therefore, given the patient's problems with weight gain, aripiprazole appeared to be the most appropriate option to try.

Ms. E's doctor cross-titrates the 2 drugs. After 2 weeks, Ms. E has discontinued quetiapine and is at a dose of 25 mg/day of aripiprazole. At this point, Ms. E's husband calls her primary care physician to report that he is concerned that Ms. E might be developing a manic episode since she "is not sleeping well and seems agitated." Her doctor calls you for a consultation at this point.

What would you suggest as the next step for Ms. E?

Aripiprazole, the first partial agonist approved by the U.S. Food and Drug Administration, has 30% of dopamine's intrinsic activity at the D₂ receptor. Hence, it cannot exceed the equivalent of 70% blockade (antagonism) of D₂ receptors even if it occupies 100% of those receptors. This profile is confirmed by clinical studies that have not found a dose-response effect for parkinsonian EPS with this agent.¹¹ Nevertheless, some effects of partial agonists are dose related. For example, the "activation" sometimes reported when initiating aripiprazole is more likely to occur at higher doses that produce relatively more dopamine agonism (particularly in individuals with D₂ receptor supersensitivity due to chronic treatment with a D₂ antagonist). Switching abruptly from an antipsychotic with more potent antihistaminic properties (e.g., quetiapine, olanzapine) to one that does not

block histamine receptors (e.g., aripiprazole, ziprasidone) may also cause "activation."

Given this information, you advise the doctor that the agitation Ms. E is experiencing could be due to excessive dopamine agonism at this relatively high dose of aripiprazole and/or could be due to abrupt withdrawal of olanzapine, which is more sedating than aripiprazole. You also acknowledge the need for careful monitoring to be sure a new manic episode is not developing. Because aripiprazole on average appears to have a "flat" dose-response curve between 15 and 30 mg/day, you suggest that, as the first step, the doctor lower the dose of the aripiprazole to see if these symptoms might represent early activation that could be minimized by using a lower dose.²⁷ You also suggest that the doctor prescribe a benzodiazepine to help Ms. E sleep over the next few weeks.

Case 6: Managing agitation with ziprasidone. *Mr. F is a 31-year-old man with schizophrenia who has done well symptomatically but has gained a significant amount of weight on olanzapine; his most recent laboratory results also indicated elevations in his lipid levels. Mr. F lives with his grandparents, who are concerned about his general health and have been encouraging him to watch his diet and to exercise more. Unfortunately, Mr. F has still been unable to lose weight. His primary care physician suggests that Mr. F consider switching to ziprasidone. Mr. F and his grandparents agree, and his doctor cross-titrates the 2 drugs, beginning with 10 mg b.i.d. of ziprasidone. After 2 weeks, Mr. F has discontinued olanzapine and is at a dose of 40 mg b.i.d. of ziprasidone. At this point, Mr. F's grandmother calls the doctor to report that her grandson "seems agitated and has been getting up repeatedly at night and disturbing the household."*

What strategy would you suggest to manage Mr. F's agitation and insomnia?

Although early "activation" can occur with both aripiprazole and ziprasidone,

the strategies for addressing this problem are not the same for the 2 drugs. Whereas using the lowest possible effective dose of aripiprazole is recommended to minimize activation (see case of Ms. E), going up to a relatively high dose is the most helpful strategy to minimize activation with ziprasidone. Ziprasidone's affinity for the 5-HT_{2A} receptor is 10 times more potent than its affinity for the D₂ receptor. Thus, low doses (e.g., 40 mg/day) block 5-HT_{2A} receptors but have little D₂ receptor antagonism. On average, sufficient antagonism of D₂ receptors for antipsychotic efficacy does not occur with ziprasidone until the dose reaches 120–160 mg/day. The differences in relative engagement of serotonin and dopamine receptors at different doses may explain why early "activation" with ziprasidone is associated with lower doses (because blockade of 5-HT_{2A} receptors can cause the release of dopamine in the brain) and then abates at higher doses (e.g., 120 mg/day) when that effect is mitigated by D₂ receptor antagonism.²⁷

The doctor reassures the patient and his grandparents that the agitation and insomnia Mr. F is experiencing are likely to be a transient side effect that can be managed by raising the dose of the ziprasidone and adding a mild sedative at bedtime for the next several weeks. She increases the dose of ziprasidone to 60 and then 80 mg b.i.d. and prescribes a low-dose benzodiazepine for the patient to take at bedtime. At a follow-up appointment 2 weeks later, Mr. F's grandmother reports that he has been sleeping better and seems calmer.

Case 7: Identifying a therapeutic dose of quetiapine. *Mr. G is a 24-year-old man with a new onset of psychotic symptoms, primarily paranoid hallucinations about strangers from the government following him and sending hostile messages through the radio. His doctor has diagnosed schizophreniform disorder. Mr. G is agitated and has been having difficulty sleeping because he feels that "they will come and get me in my sleep." The*

family has been informed about the different medication choices. The clinician did not recommend beginning with aripiprazole or ziprasidone because of the patient's current level of agitation. The family did not want to try olanzapine because of its metabolic effects or risperidone because of the increased risk of EPS compared with the other newer agents. The clinician therefore suggests that they begin the patient on quetiapine, especially given its sedating effects. The patient is started on treatment with 150 mg/day of quetiapine, and the dose is then increased to 300 mg/day. After 1 week, the patient is calmer and sleeping better but is still hallucinating and paranoid. The clinician suggests the need

to continue increasing the dose to achieve antipsychotic effects, but the family is scared to go to "such a high dose."

Why would it make sense to go to a higher dose, and how can you help the patient and family understand the idea of relative potency?

Quetiapine binds most potently to H_1 and α_1 receptors. To achieve D_2 occupancy, the dose and hence concentration of quetiapine must be increased to a level 10 times higher than is needed to affect the H_1 and α_1 receptors.^{1,15} This is consistent with the observation that 50 mg of quetiapine is effective as a sedative for many patients but 400–600 mg is usually needed for antipsychotic effect.²⁸

This case illustrates the importance of considering the other medications a patient is taking when adding, changing, or adjusting the dose of psychiatric medications.²⁹ If Ms. H's doctor had been aware of the potential for this type of interaction, he could have chosen a different antidepressant that is not a substantial inhibitor of CYP2D6 (e.g., sertraline, citalopram). This case also illustrates the importance of informing patients about potential side effects and advising them to contact their doctor if they develop such problems rather than stopping their medication on their own. For detailed information on potential drug-drug interactions involving psychiatric drugs, see the 2006 Guide to Psychiatric Drug Interactions.³¹

Cases in Which Pharmacokinetic Factors Play a Key Role

How drugs are metabolized and cleared from the body will affect the levels available at their site of action and thus their efficacy and side effects in a given patient. The following cases illustrate how important it is for clinicians to be aware of how pharmacokinetics (how drugs are metabolized and cleared) and pharmacodynamics (the effects the drugs have in the body) can interact to produce unexpected effects in individual patients.

Case 8: Drug-Drug Interactions

Ms. H is a 37-year-old woman with schizoaffective disorder. The patient has been maintained on risperidone 6 mg/day for several years with good symptomatic control. However, she recently developed a depressive episode, and her doctor added paroxetine 20 mg/day. Three weeks later, the patient's mother calls the doctor to report that Ms. H has been hospitalized with an acute psychotic episode. Ms. H's doctor contacts the attending psychiatrist on the inpatient ward and learns that Ms. H apparently developed distressing EPS shortly after starting the paroxetine and decided to stop taking all of her medications.

Why did Ms. H suddenly develop EPS after being able to tolerate risperidone treatment for several years?

Drugs are an important cause of acquired biological variance (Figure 1) that can change a patient's response to concomitantly prescribed drugs.²⁹ Drugs can interact with one another pharmacodynamically (e.g., EPS due to additive effects such as can occur with the ingestion of 2 D_2 receptor blockers) and/or pharmacokinetically (e.g., effects on metabolism and/or clearance that can affect the accumulation of a coprescribed drug). The most common pharmacokinetic drug-drug interaction involves effects on phase one (oxidative) metabolism via the cytochrome P450 (CYP) enzymes responsible for drug biotransformation and hence elimination.²⁹ For example, coadministration of a substantial CYP2D6 inhibitor (bupropion, fluoxetine, or paroxetine) can increase risk of acute EPS in patients treated with risperidone by transforming patients who are genetically normal metabolizers into phenocopies of individuals who are functionally deficient in CYP2D6-mediated drug metabolism.³⁰ This is apparently what happened in this case of Ms. H.

Case 9: Smoking and Drug Metabolism

Mr. I is a 38-year-old patient with schizophrenia who has been stable on clozapine 600 mg/day for several years, after repeated relapses on other antipsychotic medications. Mr. I was recently admitted to the hospital for back surgery, where he remained for 2 weeks. The hospital is a "no-smoking" facility, so that Mr. H, a heavy smoker, is forced to quit smoking during his admission. After 10 days, Mr. H has a seizure. He is confused and disoriented. Blood levels are obtained and show that Mr. H's clozapine levels are high (1250 ng/mL). The attending physician contacts Mr. I's psychiatrist, who reports that Mr. I had a clozapine level of 600 ng/mL at a dose of 600 mg/day while he was being treated as an outpatient. The attending physician therefore reduces the clozapine dose to 300 mg/day, which is proportional to how much the level has increased. The patient remains symptomatically stable during the rest of his hospitalization and subsequent admission to a rehabilitation center (also a no-smoking facility) for 2 weeks of intensive physical therapy. Mr. I is then discharged back to the group home where he lives. Mr. I resumes smoking upon discharge. Two weeks later, the

staff at the home call his psychiatrist to report that Mr. I has begun to display florid psychotic symptoms.

What caused these changes in symptomatic status, and what should the psychiatrist do at this point?

A high percentage of patients with schizophrenia and bipolar disorder smoke.³² Cigarette smoking can induce metabolism of CYP1A2 substrates such as clozapine and olanzapine and thus significantly decrease plasma levels of these drugs.^{33,34} (For a more detailed discussion of the role of therapeutic drug monitoring in the use of clozapine and the effect of smoking on plasma levels of clozapine, readers are referred to an article by Khan and Preskorn, "Examining Concentration-Dependent Toxicity of Clozapine."³⁵) The Roadmap panel suggested that clinicians consider using a higher dose of these antipsychotics and/or therapeutic drug monitoring in patients who smoke. In patients who quit smoking, doses may need to be lowered to avoid toxicity due to increased plasma levels as a result of the loss of induction. Conversely, patients stabilized on an antipsychotic during an inpatient stay on a nonsmoking unit may need a dose increase when they resume smoking upon discharge. Now that Mr. I has resumed smoking in the group home, his clozapine levels have probably decreased, accounting for the recurrence of psychotic symptoms.

Mr. I's psychiatrist increases the clozapine dose to the original pre-hospitalization level of 600 mg/day. A week later, the staff at the home report that Mr. I's symptoms have stabilized.

Conclusion

In selecting a pharmacologic strategy, clinicians must often do risk/benefit analyses and balance competing objectives (e.g., when a patient has a good symptomatic response to a medication but develops side effects that pose a risk to long-term health).

The Roadmap approach is based on the fact that an understanding of the pharmacodynamic and pharmacokinetic characteristics of antipsychotics can help guide treatment and dosing decisions and enable clinicians to minimize acute and long-term complications in order to achieve best outcomes for the individual patient. However, because pharmacologic principles can supplement—but not substitute for—evidence-based data, the Roadmap recommendations presented here are based on pharmacologic and clinical trial data as well as expert opinion about common clinical situations not adequately addressed in the literature. Although the focus of the Roadmap is pharmacologic treatment, clinicians should keep in mind that medication treatment alone is not sufficient to achieve the best outcomes in patients with psychosis. It is also important to provide patients and families/caregivers with psychoeducation, social support, and case management and to refer patients for appropriate treatment of associated problems (e.g., substance abuse, financial and housing problems) and vocational and rehabilitation services.

Finally, clinicians should remember that each patient is unique. As our treatments continue to improve, we will face new dilemmas and complex decisions. As much as possible, the best expert to consult is often your patient. Research increasingly supports the value of giving patients as great a role as possible in clinical decision making.³⁶ As stressed by the President's New Freedom Commission report,² a major component of the recovery model is actively involving patients in defining their own goals and working with them to achieve them.

Drug names: aripiprazole (Abilify), bupropion (Wellbutrin, and others), citalopram (Celexa), clozapine (FazaClo, Clozaril, and others), divalproex (Depakote), fluoxetine (Prozac and others), haloperidol (Haldol and others), lithium (Eskalith, Lithobid, and others), olanzapine (Zyprexa), paroxetine (Paxil and others), quetiapine (Seroquel), risperidone (Risperdal), sertraline (Zoloft and others), ziprasidone (Geodon).

Disclosure of off-label usage: The author has determined that, to the best of his knowledge, no investigational information about pharmaceutical agents that is outside US Food and Drug Administration–approved labeling has been presented in this article.

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