The Roadmap for Antipsychotic Psychopharmacology: An Overview

This ACADEMIC HIGHLIGHTS section presents highlights from a recently published supplement by Peter J. Weiden, M.D.; Sheldon H. Preskorn, M.D.; Peter A. Fahnestock, 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] *The authors thank the Roadmap Editorial Board (George S. Alexopoulos, M.D.; 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. Support for this project was provided by an educational grant from Bristol-Myers Squibb, Inc.*

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I. Introduction

This article summarizes recommendations from a recently published supplement, *Translating the Psychopharmacology of Antipsychotics to Individualized Treatment for Severe Mental Illness: A Roadmap*.[1] The President's New Freedom Commission on Mental Health[2] stressed the importance of incorporating the latest scientific information into mainstream health care as rapidly as possible. In keeping with this goal, 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. Respondents understood the survey would not be used to create guidelines but to supplement evidence-based recommendations. For a description of 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.

II. Aligning Pharmacologic Decisions With Objectives

The Roadmap recommendations are presented in the context of 2 theoretical models often used by clinicians who treat severe mental illness. The *maintenance model* emphasizes achieving and maintaining stability and preventing relapse. It is based on the assumption that the natural course of schizophrenia is to get worse. When response is maintained, it is considered a good outcome. In this model, stability is generally not jeopardized in an attempt to further reduce symptoms or side effects (although the level of continuing symptoms clinicians may consider acceptable will vary depending on the situation).

The *recovery model* places more emphasis on achieving further gains in mental, physical, and emotional health once stability is achieved.[8] It reflects a belief that schizophrenia symptoms often improve over time and that achieving stability is only the first step in a treatment plan that endeavors to achieve continued symptomatic and functional improvement. In this model, pharmacologic interventions are used to pursue improvement over and above the current level of symptoms or side effects. While advantages of the recovery model seem self-evident, it may be more complicated to implement, and additional risks may be associated with the more aggressive pharmacologic and/or psychosocial interventions involved.

Many pharmacologic decisions depend greatly on which treatment approach is emphasized. The developers of this Roadmap were interested in eliciting recommendations from the experts in situations in which multiple objectives may be competing or prioritizing one goal over another is necessary. For example, in deciding to switch antipsychotics in a "stable" but symptomatic patient, the clinician must consider the competing goals of a desire for continued improvement versus concern about triggering relapse. Similar issues arise for a patient who has responded well to an antipsychotic but gained significant weight or developed dyslipidemia. We present recommendations for such situations based on clinical trial data, expert opinion, and the pharmacology of the different agents.

III. Psychopharmacology

Clinicians generally choose medications based on "therapeutic" class (the conditions a drug is approved to treat).

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

Clinical response	=	Affinity for the site of action (pharmacodynamics)	×	Drug concentration at site of action (pharmacokinetics) (ADME)	×	Underlying biology of patient (GADE)
				• Absorption • Distribution • Metabolism • Elimination		• Genetics • Age • Disease • Environment

[a]Reprinted with permission from Preskorn.[9]

Table 1. Common Adverse Effects of Receptor Antagonism[a]

Receptor	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

[a]Based on Gardner et al.[11]
Abbreviations: α = alpha-1 norepinephrine, M_1 = muscarinic acetylcholine-1.

Antipsychotics are a therapeutic class of medications with known efficacy for 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 underlying properties of medications—effects on target receptors (pharmacodynamics) and metabolism (pharmacokinetics). Pharmacodynamics and pharmacokinetics ultimately determine the good and bad effect(s) a drug will produce in an individual. We asked the experts about the role of these factors in guiding medication choices over and above data from clinical trials. These questions are particularly relevant for antipsychotics, which, despite sharing the same therapeutic indication, differ considerably in other pharmacologic properties.

While the panel overwhelmingly endorsed clinical trial data as most important in medication decisions, 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. Even if antipsychotics have similar efficacy *on average* or the *average* optimal dose is known, we may be able to achieve better than average results by considering other drug properties in making decisions for the specific patient. Given the frequency of medication changes and the current trend to combine psychiatric medications, these differences can be very 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 which site(s) of action it affects, how many sites it occupies, and its actions at the site(s) (e.g., agonism, antagonism, inverse agonism). *Agonists* act like the endogenous neurotransmitter to fully activate a receptor. *Antagonists* produce no activation, taking the receptor "out of play." *Inverse agonists* shift the receptor in the reverse direction of normal (these have generally had little clinical utility). Drugs can also fall between these reference points (e.g., partial agonists). A drug can affect just one site of action (i.e., be selective) at clinically relevant concentrations or more than one site of action as a function of its relative binding affinity for more than one regulatory protein. When a drug affects *multiple* receptors, its pharmacology can change with its dose, as the drug sequentially engages different target receptors in a dose-dependent, concentration-dependent manner.[10] Binding affinity does not indicate the effect (e.g., agonism or antagonism) a drug has on its target.

The relationship between receptor binding profiles and adverse effects is better understood than the effect of receptor binding profiles on efficacy. All available antipsychotics block dopamine-2 (D_2) receptors to some extent but vary in the degree to which they affect the D_2 receptor relative to other clinically meaningful receptors. These differences in receptor binding affinities generally explain differences in the clinical profile of these drugs (e.g., side effects)[11] (Table 1). We asked the panel about the importance of pharmacodynamic differences in choice of medication, side effects, withdrawal effects, and cross-titration techniques when switching. The panel expressed more confidence about the role of dopamine, histamine, muscarinic, and α-adrenergic than serotonin receptors in the effects of antipsychotics. While D_2 receptor antagonism or blockade appears to be a universal characteristic of marketed antipsychotics and necessary for antipsychotic efficacy, there was no consensus on what role, if any, specific serotonin receptor subtypes play in antipsychotic efficacy.

Pharmacokinetic factors refer to the ways in which drugs enter and leave the body and hence 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 from the body. The experts were asked about clinical situations in which pharmacokinetic differences would be relevant, including use of long-acting medications, effects of coprescribed medications on clearance, and how quickly to cross-taper agents when switching.

Biological variability in response. There is significant variation among individuals in the effects of all medications. Some variation is predictable based on factors such as age or gender. Other medications are another source of variation in response, since these can lead to drug-drug interactions. The sur-

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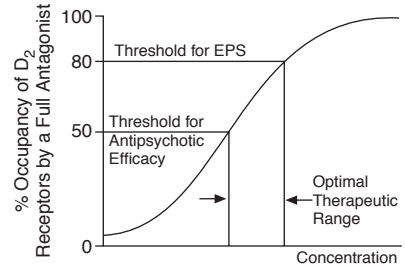
Figure 2. Narrow Range Between Efficacy and Behavioral Toxicity With D_2 Receptor Antagonists[a,b]



[a]Reprinted with permission from Preskorn.[12]
[b]D_2 antagonism ≥ 50% appears needed for antipsychotic efficacy, while antagonism > 80% is associated with increased risk of acute extrapyramidal side effects (EPS).[13] This curve explains the narrow window between efficacy and EPS with full D_2 antagonists (note the curve would differ for partial D_2 agonists).

Table 2. Binding Affinity of Selected Antipsychotics for Specific Neuroreceptors[a,b]

	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

[a]From Preskorn,[10] with permission, based on Richelson,[16] Abilify package insert,[14] Arnt and Skarsfeldt,[17] Bymaster et al.,[18] and Seeger et al.[19]
[b]Data represented as Ki (nM).
[c]Data with cloned human receptors.
Abbreviations: D = dopamine, 5-HT = serotonin, α_1 = alpha-1 norepinephrine, H_1 = histamine 1, M_1 = muscarinic acetylcholine-1.

vey asked how such factors might influence decisions about use of antipsychotics. Of course, some variations in response cannot be predicted given the current level of knowledge (e.g., clinically important but unknown genetic differences).

Effects of Dose and D_2 Antagonism

Figure 2 shows that a minimum threshold of 50% antagonism or blockade of the D_2 receptor appears to be required for antipsychotic efficacy, while blockade greater than 80% is associated with a markedly increased risk of acute extrapyramidal side effects (EPS). This figure explains the relatively narrow window between antipsychotic efficacy and risk of acute EPS associated with unopposed D_2 antagonism.

Case 1. Effect of a dose increase. Mr. R, a patient with schizophrenia, had not achieved a satisfactory response with 10 mg of olanzapine. When the dose was raised to 20 mg, response improved markedly without EPS.

A majority of patients on 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% blockade and need a higher dose to achieve satisfactory antipsychotic response. Mr. R fell below the 50% threshold on 10 mg/day but achieved approximately 60% D_2 receptor blockade and a good response on 20 mg/day.

Case 2. Effect of a dose reduction. Ms. M, a patient with schizophrenia, experienced good amelioration of psychotic symptoms but developed distressing EPS on 6 mg/day of risperidone. When the dose was lowered to 4 mg/day, her response was maintained and the EPS resolved. At 6 mg/day, Ms. M was above the 80% threshold for EPS; when the dose was lowered, receptor blockade went down to approximately 60%—above the threshold for efficacy but below that for EPS.

While these cases illustrate the principle in Figure 2, not all patients experience a good response just because they achieve 60%–80% D_2 receptor blockade. Some may need treatment that involves additional mechanisms besides D_2 blockade.

Effects of D_2 Partial Agonism

Until the introduction of the class of D_2 partial agonists, all available antipsychotics were D_2 antagonists. Because clinicians may not be as familiar with partial agonism, it may be helpful to clarify how partial agonists affect the D_2 receptor. As an example, aripiprazole, the first partial agonist approved by the U.S. Food and Drug Administration, has 30% of dopamine's intrinsic activity at the D_2 receptor. Hence, it cannot exceed the equivalent of 70% blockade (antagonism) of D_2 receptors even if it occupies 100% of those receptors. This profile is confirmed by studies that show that doses of aripiprazole that produce 95% occupancy of D_2 receptors in the striatum are not associated with an increased risk of EPS.[14]

Some effects of partial agonists *are* dose related. For example; the "activation" sometimes reported when initiating aripiprazole is more likely at higher doses that produce relatively more dopamine agonism (this effect could be more pronounced in individuals with D_2 receptor supersensitivity due to chronic treatment with a D_2 antagonist). Since aripiprazole appears to have a "flat" dose-response curve between 15 and 30 mg/day in terms of antipsychotic efficacy when treating populations of patients, such early activation can be minimized by aiming for a target dose at the lower end of that range.[15] (Note that flat dose-response curves in populations of patients do not mean that an individual patient may not benefit from a higher or lower dose. Activation occurring shortly after starting a nonsedating antipsychotic can also be due to withdrawal from a more sedating antipsychotic.)

Drugs That Bind to Multiple Receptors

Tables 1 and 2, taken together, provide guidance about side effects that may occur with different doses of different antipsychotics. For example, quetiapine binds most potently to H_1 and α_1 receptors. To achieve D_2 occupancy, the dose and hence concentration of quetiapine must typically be increased to a level 10 times higher than needed to affect the H_1 and α_1 receptors. This is consistent with the observation that 50 mg of quetiapine is effective as a sedative

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for many patients but 400–600 mg is usually needed for antipsychotic effect. With risperidone, the affinity for 5-HT_2 and D_2 receptors is closer, consistent with the increased incidence of EPS at doses above 6 mg/day. Ziprasidone's affinity for the 5-HT_{2A} receptor is 10 times more potent than for the D_2 receptor; thus, ziprasidone at low doses blocks 5-HT_{2A} receptors but has little effect on D_2 receptors until doses of 120–160 mg/day, at which point the concentration is typically sufficient to achieve at least 50% D_2 antagonism and antipsychotic efficacy for most patients. Differences in the relative engagement of serotonin and dopamine receptors may explain why early "activation" (thought to be mediated by serotonin mechanisms) with ziprasidone is associated with lower doses and abates at higher doses (e.g., 120 mg/day) when that effect is mitigated by D_2 receptor antagonism.[15]

How the Brain Adapts to Receptor Effects of Antipsychotic Medications

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 agonism of that receptor). If such adaptation is not considered when changing drugs, withdrawal effects may occur. Chronic treatment with a D_2 antagonist can lead to up-regulation of D_2 receptors so that patients may develop distressing withdrawal dyskinesia when D_2 receptor blockade is reduced (e.g., by stopping the D_2 blocker, switching to a drug with lower D_2 occupancy [e.g., low-dose ziprasidone] or from a full D_2 antagonist to a partial D_2 agonist [e.g., aripiprazole]). Switching abruptly from an antipsychotic with potent antihistaminic properties to one that does not block histamine receptors (e.g., aripiprazole, ziprasidone) may also cause "activation." Such withdrawal effect may be erroneously attributed to the new antipsychotic, so that the patient loses the opportunity for an adequate trial of that agent.

Drug-Drug Interactions

Drugs are an important cause of acquired biological variance (Figure 1) that can change a patient's response to concomitantly prescribed drugs.[20] Drugs can interact with one another pharmacodynamically (e.g., EPS due to additive effects of 2 D_2 receptor blockers) and/or pharmacokinetically (e.g., effects on metabolism and/or clearance and thus accumulation of another drug). The most common clinically important pharmacokinetic drug-drug interactions involve effects on phase one (oxidative) metabolism via the cytochrome P450 (CYP450) enzyme system, which is responsible for the clearance of most drugs.[20] For example, coadministration of a substantial CYP2D6 inhibitor (bupropion, fluoxetine, or paroxetine) can increase risk of acute EPS in patients treated with risperidone, by making genetically normal metabolizers functionally deficient in CYP2D6.[21] It is important to consider other medications a patient is taking when adding, changing, or adjusting the dose of psychiatric medications.[20] For information on drug-drug interactions involving psychiatric drugs, see *Guide to Psychiatric Drug Interactions*.[22]

IV. Disease and Symptom Factors

Before prescribing any medication, it is important to ensure that the diagnosis is accurate and take a history that includes current medications, history of response, adherence problems, persistent symptoms or side effects, and substance use.

Achieving Stability: Acute Treatment

The psychiatric diagnosis—schizophrenia, schizoaffective disorder, psychotic depression, or bipolar disorder—had little effect on the panel's ratings of antipsychotics to treat an acute psychotic episode. Consistent with published guidelines,[4–7] the experts preferred the non-clozapine second generation antipsychotics (SGAs) (aripiprazole, olanzapine, quetiapine, risperidone, ziprasidone) over first generation antipsychotics (FGAs) (e.g., haloperidol) as initial treatment for all of these diagnoses. There were no significant differences in ratings for different SGAs, as indicated by overlapping confidence intervals.

Because duration of untreated psychosis predicts poorer outcomes, it is important to provide effective treatment as early as possible for a first episode.[23] Before beginning medication, baseline weight, body mass index (BMI), and metabolic parameters should be recorded so that effects on these parameters can be monitored. In choosing an initial antipsychotic, it is important to minimize risk of unexpected adverse events that could lead to long-term medication avoidance. Consistent with treatment guidelines,[4,6] the panel recommended SGAs over FGAs for first-episode patients, with no consensus that any of the SGAs is preferable to the others for a first-episode, except that clozapine is reserved for patients who fail to respond to other agents or have active suicidal ideation. Dosing recommendations for a first-episode patient are shown in Table 3.

If a patient has failed to respond to adequate trials of 2 antipsychotics, the panel strongly supported switching to clozapine, as long as there are no problems with adherence or substance abuse. However, if the lack of response is due to poor adherence, the experts recommended switching to a long-acting SGA (e.g., long-acting injectable risperidone) and would consider a depot FGA. When lack of response occurs in the context of substance abuse, the panel also recommended a long-acting antipsychotic, probably reflecting concerns about adherence. Treatment guidelines also recommend integrated treatment programs for patients with serious mental illness complicated by substance abuse.[24]

"Stable" Patients With Persistent Symptoms or Side Effects

Before raising the dose or switching medications for persistent symptoms in a stable patient, it is important to consider whether the problem is likely to be

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Table 3. Initial Dose and Titration Schedule for a First-Episode Patient With No Complicating Conditions Affecting Dosing[a]

Antipsychotic	Usual Starting Dose (mg/day) Avg (range)	Interval Between Dose Increases	Usual Dose Increment	Usual Initial Target Dose Range (mg/day)	
				Low Avg (range)	High Avg (range)
Aripiprazole	10 (5–15)	1 week	5 (or 10 mg)	10 (5–15)	25 (20–30)
Olanzapine	10 (5–15)	1 week	5 mg	10 (7.5–12.5)	22.5 (20–30)[b]
Quetiapine[c]	150 (50–250)	3 days (but wide range)	150 mg (but wide range)	300 (but wide range)	800 (600–1000)
Risperidone	1.5 (1–2)	1 week (but wide range)	1.5 mg (but wide range)	2 (1–3)	6 (5–8)
Ziprasidone	60 (40–100)[d]	4 days	40 or 60 mg	100 (60–140)	200 (160–240)
Haloperidol	3 (1–4)	1 week	2–4 mg	5 (2–8)	10 (10–15)

[a]The doses in this table are based on responses from the Roadmap expert survey with mean doses and standard deviations from survey results converted to "real world" doses. Note there are some differences from information in the package inserts for these agents.
[b]Safety of doses above 20 mg/day has not been evaluated in clinical trials.
[c]Package insert recommends the following: initial doses of 50 mg/day for bipolar depression, increasing to 300 mg by day 4; initial doses of 100 mg/day for bipolar mania increasing to 400 mg/day by day 4, with a final target dose of no higher than 800 mg/day; and initial doses of 50 mg/day for schizophrenia, increasing to 300–400 mg/day by day 4, with a final target dose of no higher than 750 mg/day.
[d]Package insert recommends initial dose of 40 mg/day for schizophrenia and 80 mg/day for bipolar mania.

amenable to a pharmacologic intervention or whether other problems (e.g., substance abuse, nonadherence) that may be better addressed nonpharmacologically are interfering with response.

In deciding to make an elective switch for side effects, it is important to differentiate between distressing but not dangerous side effects and those that pose a risk to the patient's future health. The panel's recommendations for managing side effects in stable patients are summarized in Table 4 (for weight and cardiometabolic issues, see below). Whether a dose adjustment or a change of antipsychotics is recommended depends on the side effect. Because EPS and sedation may respond to a dose adjustment, lowering the dose is the first recommendation for these problems, while switching antipsychotics is recommended for problems less likely to respond to a dose change (e.g., weight gain). When switching antipsychotics, it is also important to consider potential for long-term complications (EPS, tardive dyskinesia, weight gain, and metabolic abnormalities).[1]

The current medication should be considered in selecting dose and speed of the switch to minimize withdrawal or rebound effects. If a patient has a history of being very sensitive to side effects, the experts recommended switching more slowly and aiming for a lower target dose. If the patient has a history of responding only to very high doses, they would aim for a higher dose of the new agent. If the patient has had little or no response to the current medication or wants to stop immediately because of side effects, the majority would switch more quickly.

Table 4. Strategies for Managing Side Effects in Patients Who Are Stable

Side Effect	Recommended Strategies[a]
Parkinsonian symptoms or akathisia	Dose adjustment Add adjunctive medication Switch to different antipsychotic
Tardive dyskinesia	Switch to different antipsychotic Dose adjustment
Persistent sedation	Dose adjustment Switch to different antipsychotic
Persistent insomnia	Add adjunctive medication Dose adjustment Switch to different antipsychotic
Prolactin-related side effects (eg, amenorrhea, galactorrhea)	Dose adjustment Switch to different antipsychotic
Sexual difficulties judged to be due to the antipsychotic	Switch to different antipsychotic Dose adjustment
Anticholinergic side effects of antipsychotic	Dose adjustment Switch to different antipsychotic
Anticholinergic side effects related to adjunctive anticholinergic agent	Dose adjustment of anticholinergic Switch to antipsychotic with lower EPS liability with plan to then discontinue anticholinergic agent Dose adjustment of antipsychotic
Weight gain and cardiometabolic risk factors	Switch to different antipsychotic with lower weight gain liability and metabolic risk, if possible If switch not possible, encourage lifestyle changes (eg, diet, smoking cessation, exercise program)

[a]Strategies are listed in the order of their mean scores, with the highest rated options listed first. The decision to make a change in the treatment regimen because of side effects should be based on an assessment of the risks and benefits involved.

V. Demographics

Age

Acute treatment. Only 4 FGAs and none of the SGAs have labeled FDA indications for pediatric patients, and empirical data in this population are limited.[25] The Roadmap panel gave similar ratings to the different antipsychotics for an adolescent with acute psychosis as for a healthy young adult with schizophrenia or other psychotic disorder, with aripiprazole, ziprasidone, and risperidone receiving highest ratings and little support for FGAs. There was somewhat less support for olanzapine in adolescents than adults, probably because pediatric patients appear more sensitive to side effects such as weight gain.[26] Careful monitoring of suicide risk, body

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weight, BMI, and metabolic status is recommended in adolescents receiving antipsychotics.[25]

The panel gave similar ratings to the different antipsychotics to treat acute psychosis in older patients as in healthy young adults, with all the nonclozapine SGAs favored over FGAs. Older patients are more likely to have comorbid medical conditions and to be taking multiple medications, which need to be considered in selecting an antipsychotic.[27,28] Labeling for all the SGAs contains a black box warning concerning increased mortality rates in elderly patients with dementia-related psychosis. Although none of the SGAs are approved for treatment of dementia-related psychosis, clinicians should keep this warning in mind when using these agents to treat other types of psychosis in the elderly.[29]

"Stable" patients. Two thirds of the experts would be *more* willing to make an elective change of antipsychotic in an adolescent than an adult, perhaps reflecting findings that early successful interventions in schizophrenia may lead to better long-term outcomes.[23] Consistent with guideline recommendations,[4] 85% of the Roadmap experts would use a lower target dose and slower titration schedule when switching antipsychotics in older patients.

Gender

Women may require lower antipsychotic doses than men and may be more vulnerable to weight gain, cardiometabolic side effects, and hyperprolactinemia.[4,30] It is important to be alert for prolactin-related effects on women's menstrual cycles and fertility.

VI. Common Comorbidity

Weight and Cardiometabolic Risk

Recent data show that U.S. patients with a major mental illness die 25–30 years earlier than the general population, with cardiovascular disease (CVD) the most frequent cause of death.[31] Patients with schizophrenia and bipolar disorder have elevated rates of CVD and CVD risk factors, many of which are modifiable (e.g., smoking, hypertension, overweight/obesity, dyslipidemia, and diabetes mellitus).[32–38] An elevated CVD risk was present even before the introduction of the SGAs,[32,33] and the problem has been compounded by the fact that some of the medications used to treat these illnesses can themselves cause weight gain and metabolic abnormalities. Although SGAs may directly contribute to insulin resistance, possibly by a direct effect on glucose transporters,[39,40] they increase cardiometabolic risk primarily through their differential tendency to cause weight gain.[41] Weight gain can lead to insulin resistance, which can develop into hyperglycemia, prediabetes, and eventually type 2 diabetes mellitus.[42] Among SGAs, the greatest weight gain occurs with clozapine and olanzapine, and the least with ziprasidone and aripiprazole.[32,43–46] (See the Roadmap supplement[1] for recommendations for monitoring metabolic parameters.)

Acute treatment. In choosing an antipsychotic for a patient who is overweight or obese or has 1 or more other CVD risk factors, the panel gave highest ratings to aripiprazole and ziprasidone, followed by risperidone, and would generally avoid olanzapine and low-potency conventional antipsychotics. If a patient has not responded to trials of several other antipsychotics or is at risk for suicide, the panel considered it appropriate to initiate clozapine even if the patient has weight problems or CVD risk factors, with somewhat less support for using clozapine in a patient who is obese or has multiple CVD risk factors or diabetes. When clozapine is used in such a patient, weight and metabolic parameters should be carefully monitored and interventions initiated to try to control weight and reduce CVD risk factors.

Stable patients. If a patient has responded well to an antipsychotic other than clozapine but has gained weight and/or developed metabolic abnormalities, the panel recommended trying a different antipsychotic with lower liability for causing these problems, with support for this strategy increasing as the number of risk factors increases.

Since patients on clozapine therapy have usually not responded to other antipsychotics or have an increased risk for suicide, the risk-benefit equation in deciding to make a change is more difficult. If a patient on clozapine gains significant weight and/or develops CVD risk factors, the experts would decide on a strategy based on the treatment history. If the person had only had trials of 2 of the older SGAs before clozapine or was able to live independently before beginning clozapine, they would consider a trial of one of the newer SGAs. If the patient was unable to live independently due to persistent psychosis or had a history of violence or frequent suicidal ideation before clozapine, they would continue clozapine and try to manage weight and metabolic problems with lifestyle changes and/or lipid-lowering medication.

Smoking

A high percentage of patients with schizophrenia and bipolar disorder smoke.[37] Cigarette smoking can induce metabolism of the CYP1A2 substrates clozapine and olanzapine.[47] 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. Conversely, patients stabilized on an antipsychotic during an inpatient stay may need a dose increase when they resume smoking upon discharge.

EPS and Tardive Dyskinesia

The SGAs, like the FGAs, affect D_2 receptors and can still cause EPS, although generally less frequent and severe.[43,48] Among the SGAs, risperidone is associated with the most and clozapine and quetiapine with the fewest EPS; the likelihood of EPS also depends on rapidity of dose escalation, target dose, and the patient's vulnerability.[48] SGAs have also been reported to have a lower risk of tardive dys-

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kinesia than the FGAs.[49] In selecting an antipsychotic for a patient with tardive dyskinesia or a history of EPS, if possible, choose an agent with low EPS liability.

Elevated Prolactin Levels

Some antipsychotics induce prolactin elevation because of potent D_2 effects.[50] While hyperprolactinemia can be asymptomatic, it can also cause amenorrhea and galactorrhea in women and gynecomastia and sexual dysfunction in men. The FGAs and risperidone are associated with the most and aripiprazole, clozapine, and quetiapine with the least prolactin elevation (some studies report lowering of prolactin levels with aripiprazole), while ziprasidone and olanzapine fall in between.[50–52] Female patients taking antipsychotics should be asked about changes in menstrual pattern, libido, and galactorrhea, and male patients about libido and erectile and ejaculatory function.[52] If hyperprolactinemia is suspected, serum prolactin levels should be measured. If elevated and the patient is distressed by the symptoms, consider lowering the dose, if possible, or changing to a medication less likely to elevate prolactin.[4] 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. 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).[52] 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 sexually active.

Other Comorbid Conditions

For a discussion of how comorbid infectious diseases (e.g., HIV, hepatitis) and chronic respiratory diseases (e.g., obstructive sleep apnea) can affect treatment decisions involving antipsychotic medications, see the full Roadmap supplement.[1]

Conclusion

In selecting a pharmacologic strategy, clinicians must often do risk/benefit analyses and balance competing objectives (e.g., a patient with good symptomatic response but side effects that pose a risk to long-term health). The Roadmap approach is based on the belief that an understanding of the pharmacodynamics and pharmacokinetics of antipsychotics can help guide treatment decisions and enable clinicians to minimize acute and long-term complications to achieve best outcomes for the individual patient. However, because pharmacologic principles can supplement—but not substitute for—evidence-based data from clinical trials, we integrated pharmacologic and clinical trial data in this publication 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 still more complex decisions. As much as possible, the best expert to consult is your patient. 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 to achieve them.

Off-label disclosure: In this ACADEMIC HIGHLIGHTS, faculty may be presenting investigational information about pharmaceutical agents that is outside U.S. Food and Drug Administration–approved labeling. This information is intended solely as continuing medical education and is not intended to promote off-label use of any of these medications. If you have questions, contact the medical affairs department of the manufacturer for the most recent prescribing information.

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