I. MEDICATION SELECTION, DOSING, AND DOSE EQUIVALENCE

Guideline 1: Selecting Initial Pharmacologic Treatment for a Psychotic Disorder[Questions 1–3]

1A. First-Episode Patient

For ***a first-episode patient with predominantly positive symptoms***, the experts consider oral risperidone the treatment of choice. Other recommended medications for this clinical situation are aripiprazole, olanzapine, ziprasidone, and quetiapine (although the first two were rated first line and the second two high second line, these options clustered together and all were rated first line by approximately two-thirds of the experts).

For ***a first-episode patient with predominantly negative symptoms***, the experts recommend one of the newer oral atypical antipsychotics. Risperidone and aripiprazole received first line ratings, and the other three were rated high second line; however, all the options clustered together with only small differences in their confidence intervals.

For ***a first-episode patient with both prominent positive and negative symptoms***, the experts prefer oral risperidone. Other recommended medications for this clinical situation are aripiprazole, ziprasidone, olanzapine, and quetiapine (again these four options clustered together with only small differences in their confidence intervals).

The experts as a group varied in their ratings of using a long-acting injectable atypical antipsychotic for a first-episode patient to such an extent that there was no consensus on this item (with approximately a quarter of the experts rating it first line and approximately a third giving it third line ratings). The experts did not recommend the use of either oral or depot conventional antipsychotics for a first-episode patient (conventional antipsychotics received third line ratings in every case).

(***bold italics*** = treatment of choice)

Presentation	First Line*	High Second Line	Other Second Line
Predominantly ***positive*** psychopathology	***Risperidone*** Aripiprazole Olanzapine	Ziprasidone Quetiapine	Long-acting injectable atypical†
Predominantly ***negative*** psychopathology	Risperidone Aripiprazole	Ziprasidone Olanzapine Quetiapine	Long-acting injectable atypical
Both prominent positive and negative symptomatology	Risperidone Aripiprazole Ziprasidone	Olanzapine Quetiapine	Long-acting injectable atypical

*In this survey, we asked only about oral and long-acting injectable formulations of antipsychotics. Unless otherwise specified, all medications listed in the tables refer to the oral formulation.

†At the time of this survey, a long-acting injectable atypical antipsychotic was not available in the United States, although it was available in several other countries. In the survey, we asked the experts to rate how they would use such a formulation if it were available.

1B. Multi-Episode Patient

For ***a multi-episode patient with predominantly positive symptoms***, the experts consider oral risperidone the treatment of choice. Other recommended first line medications for this clinical situation are aripiprazole, ziprasidone, olanzapine, and quetiapine and a long-acting atypical antipsychotic. Clozapine was rated high second line. Other lower rated second line options were a long-acting conventional antipsychotic (depot) and an oral high-potency conventional.

For ***a multi-episode patient with predominantly negative symptoms***, risperidone, aripiprazole, and ziprasidone were rated first line; high second line choices were olanzapine, quetiapine, a long-acting atypical antipsychotic, and clozapine. (It should be noted that all these options tended to cluster together, with only small differences in their confidence intervals.) A long-acting conventional antipsychotic was a lower rated second line option.

For ***a multi-episode patient with both prominent positive and negative symptoms***, the experts preferred risperidone followed by aripiprazole. Other first line options were ziprasidone and olanzapine. High second line choices were a long-acting atypical antipsychotic, quetiapine, and clozapine. (Ratings for most of these options tended to cluster together with only small differences in their confidence intervals.) Other lower rated second line options were a long-acting depot conventional antipsychotic and an oral high-potency conventional.

The experts are clearly more willing to consider using clozapine or a long-acting injectable antipsychotic in a patient with a history of previous psychotic episodes. The experts did not recommend the use of mid- or low-potency conventional antipsychotics and gave only very limited support to the use of oral high-potency conventionals.

(***bold italics*** = treatment of choice)

Presentation	First Line	High Second Line	Other Second Line
Predominantly ***positive*** psychopathology	***Risperidone*** Aripiprazole Ziprasidone Olanzapine Long-acting injectable atypical Quetiapine	Clozapine	Long-acting conventional (depot) Oral high-potency conventional
Predominantly ***negative*** psychopathology	Risperidone Aripiprazole Ziprasidone	Olanzapine Quetiapine Long-acting injectable atypical Clozapine	Long-acting conventional
Both prominent positive and negative symptomatology	Risperidone Aripiprazole Ziprasidone Olanzapine	Long-acting injectable atypical Quetiapine Clozapine	Long-acting conventional Oral high-potency conventional

Guideline 2: Adequate Dose of Antipsychotics[Questions 4 & 6]

We asked the experts to write-in doses of conventional and atypical antipsychotics that they would recommend in different treatment situations. We used the mean and standard deviations of their responses to generate real-world doses rounded to currently available pill strengths. The experts' dosing recommendations generally agree closely with recommended doses given in the package labeling. For olanzapine and quetiapine, their recommendations for highest acute dose are somewhat higher than the highest doses for which safety data from clinical trials are available (20 mg of olanzapine and 800 mg of quetiapine). The panel would generally use higher doses for a patient who had had multiple episodes of psychosis than for a first-episode patient. The recommended dose ranges for maintenance treatment are also slightly lower than for acute treatment.

	First-episode patient		Multi-episode patient		
Medication	**Acute treatment (mg/day)***	**Maintenance treatment (mg/day)**	**Acute treatment (mg/day)***	**Maintenance treatment (mg/day)**	**Highest final acute dose (mg/day)**
Atypicals					
Aripiprazole	10–20	10–20	15–30	15–20	30
Clozapine	300–500	250–500	400–600	300–550	850
Olanzapine	10–20	10–20	15–25	12.5–22.5	40†
Quetiapine	350–700	300–600	500–800	400–750	950†
Risperidone	2.5–5.0	2.0–4.5	4.0–6.5	3.5–5.5	10.5
Ziprasidone	100–160	80–160	140–180	120–180	180
Conventionals					
Chlorpromazine	200–650	150–600	400–800	250–750	950
Fluphenazine	2.5–15.0	2.5–12.5	5.0–22.5	5.0–15.0	25.0
Haloperidol	3.0–13.5	1.5–10.5	7.0–18.5	6.0–13.5	25.0
Perphenazine	8–38	6–36	16–48	12–42	56
Thioridazine‡	225–550	150–500	350–650	250–550	650
Thiothixene	5–30	2–30	10–40	10–35	40
Trifluoperazine	5–30	2–20	10–35	10–30	40
Fluphenazine decanoate (mg/2–3 wk)	12.5–37.5	6.25–37.5	12.5–62.5	12.5–50.0	50.0
Haloperidol decanoate (mg/4 wk)	50–200	50–200	100–250	100–200	250

*In beginning treatment with an oral antipsychotic for which titration is not required or with a long-acting injectable antipsychotic, the experts recommend either starting with a low dose and increasing the dose based on level of response and side effects, or starting with a moderate dose. The experts do not recommend starting with a relatively high dose and then decreasing it if possible.[Questions 10 & 11]

†Safety of doses of olanzapine > 20 mg/day and of quetiapine > 800 mg/day have not been evaluated in clinical trials.

‡The package labeling for thioridazine includes a black box warning stating that this agent "has been shown to prolong the QTc interval in a dose related manner, and drugs with this potential, including thioridazine, have been associated with torsades de pointes-type arrhythmias and sudden death. Due to its potential for significant, possibly life-threatening, proarrhythmic effects, thioridazine should be reserved for use in the treatment of schizophrenic patients who fail to show an acceptable response to adequate courses of treatment with other antipsychotic drugs."

Guideline 3: Therapeutic Drug Monitoring (Using Plasma Levels)[Question 5]

Over 50% of the experts reported that plasma level assays were available to them only for clozapine, haloperidol, and haloperidol decanoate. Clozapine was the agent for which the experts considered plasma levels most clinically useful. Over half the experts use plasma levels of clozapine and haloperidol to monitor compliance; 88% of the experts use clozapine levels to adjust dose, primarily if there has been an inadequate response or side effects are a problem. 50% of the experts use plasma levels of haloperidol (oral or decanoate) to adjust dose levels if the patient has an inadequate response or problematic side effects.

Guideline 4: Duration of an Adequate Trial[Question 13]

If a patient is having little or no response to the initial or to the second antipsychotic that is tried, the experts recommend waiting a minimum of 3 weeks and a maximum of 6 weeks before making a major change in treatment regimen. If the patient is showing a partial response to treatment, the experts would extend the duration of the trial somewhat, waiting 4–10 weeks before making a change for the initial antipsychotic and 5–11 weeks for the second antipsychotic. A major change in treatment regimen could mean either a significant dose increase or switching to a different agent. Note that the experts would wait longer if the patient is having a partial response, especially in the second trial. Although the differences were not dramatic, they are interesting, particularly given the lack of data from controlled trials addressing these issues. These results are similar to those from the 1996 *Expert Consensus Guidelines on the Treatment of Schizophrenia,** which recommended waiting 3–8 weeks if there is no response and 5–12 weeks if there is a partial response before switching to another pharmacologic strategy.

4A. Inadequate Response to Initial Antipsychotic

	Minimum number of weeks to wait	Maximum number of weeks to wait
Little or no response to treatment	3	6
Partial response to treatment	4	10

4B. Inadequate Response to Second Antipsychotic

	Minimum number of weeks to wait	Maximum number of weeks to wait
Little or no response to treatment	3	6
Partial response to treatment	5	11

* McEvoy JP, Weiden PJ, Smith TE, et al. The expert consensus guideline series: treatment of schizophrenia. J Clin Psychiatry 1996;57(suppl 12b):1–58

Guideline 5: Dose Equivalency

5A. To Haloperidol[Question 7]

We asked the experts to write-in doses of conventional and atypical antipsychotics that they would consider equivalent to a range of haloperidol doses. We used the mean and standard deviations of their responses to generate real-world doses rounded to currently available pill strengths. The goal was to obtain a better sense of the equivalency between the older conventional antipsychotics and the new generation of atypical antipsychotics. In general, the experts' responses followed a very linear pattern, indicating that it would probably be possible to use linear formulas to calculate dose equivalency. It is interesting to note that, in every case, the dose the experts consider equivalent to 30 mg of haloperidol is higher than the highest acute dose the experts indicated they would usually use (see Guideline 2).

Haloperidol	1 mg	5 mg	10 mg	20 mg	30 mg
Atypicals					
Aripiprazole	5	10	20	30	35
Clozapine	75	250	425	675	900
Olanzapine	2.5	10	20	30	45
Quetiapine	100	325	600	900	1200
Risperidone	1.0	3.0	5.5	10.5	15.0
Ziprasidone	40	100	140	180	240
Conventionals					
Chlorpromazine	60	250	500	900	1300
Fluphenazine	1	5	10	20	30
Perphenazine	4	16	32	64	88
Thioridazine	50	200	450	750	1000
Thiothixene	3	12	25	40	60
Trifluoperazine	3	12	25	40	55
Fluphenazine decanoate* (mg/2–3 wk)	6.25	12.5	25	50	75
Haloperidol decanoate* (mg/4 wk)	25	100	150	250	300

*For fluphenazine decanoate and haloperidol decanoate, the experts were asked to indicate the dosage they consider equivalent to that dose of oral haloperidol being given daily on an ongoing basis.

5B. To Risperidone[Question 8]

We asked the experts to write-in doses of conventional and atypical antipsychotics that they would consider equivalent to a range of risperidone doses. We used the mean ± the standard deviation of their responses to generate real-world doses rounded to currently available pill strengths. The goal here was to obtain a better sense of the equivalency of doses among the new generation of atypical antipsychotics. Again, the experts' responses generally followed a very linear pattern, indicating that it would probably be possible to use linear formulas to calculate dose equivalency. It is interesting to note that the doses the experts consider equivalent to 10 mg of risperidone are closest to those they consider equivalent to 20 mg of haloperidol (as would be expected since they indicated that they considered 10.5 mg of risperidone to be equivalent to 20 mg of haloperidol, see Guideline 5A).

Risperidone	1 mg	2 mg	4 mg	6 mg	10 mg
Atypicals					
Aripiprazole	5	10	15	25	30
Clozapine	75	175	350	500	700
Olanzapine	5	7.5	15	20	30
Quetiapine	100	225	450	600	825
Ziprasidone	40	60	120	160	200
Conventionals					
Chlorpromazine	80	175	350	550	800
Fluphenazine	1	5	7.5	12.5	15
Haloperidol	1.5	3.5	7.5	11.5	17
Perphenazine	6	12	24	40	54
Thioridazine	75	150	300	475	650
Thiothixene	4	8	17	25	35
Trifluoperazine	4	10	15	25	35
Fluphenazine decanoate* (mg/2–3 wk)	6.25	12.5	25	37.5	50
Haloperidol decanoate* (mg/4 wk)	25	50	100	150	225

*For fluphenazine decanoate and haloperidol decanoate, the experts were asked to indicate the dosage that they consider equivalent to that dose of oral risperidone being given daily on an ongoing basis.

Guideline 6: Dose Adjustment

6A. Factors to Consider in Dose Adjustment[Question 9]

The experts considered the use of concomitant medications, the patient's age, and the presence of hepatic disease the most important factors to consider in adjusting the acute antipsychotic dose. The priority given to the use of concomitant medications reflects our expanding knowledge of drug-drug interactions and their potential consequences. Other important factors to consider are the presence of cardiovascular or renal disease, whether or not the patient smokes, and the patient's weight. There was no consensus about the importance of the patient's sex, with 30% of the experts saying they would nearly always consider the patient's sex in dose adjustment and 23% saying they would rarely or never consider it. It is surprising that many of the experts (45%) would only sometimes consider the patient's weight in adjusting the dose. This is consistent with the observation that the determination of psychiatric drug dosage is infrequently influenced by the patient's weight, despite the fact that (given the highly lipophilic nature of these compounds) blood levels may ultimately be influenced by body mass. It may also reflect the pharmaceutical industry's desire to simplify dosage determination in the treatment of psychiatric disorders.

Always consider	**Sometimes consider**
Use of concomitant medications	Presence of cardiovascular disease*
Patient's age	Presence of renal disease
Presence of hepatic disease	Whether or not the patient smokes
	Patient's weight
	Patient's sex

*Very high second line

6B. Dose Selection for Special Populations[Question 12]

Dose Selection for Children and Adolescents. A majority of the experts would not generally use the following medications in children with a psychotic disorder who are 12 years of age or younger: aripiprazole, clozapine, chlorpromazine, fluphenazine, perphenazine, thioridazine, thiothixene, trifluoperazine, fluphenazine decanoate, and haloperidol decanoate. A majority of the experts would not generally use the following medications in an adolescent (13–18 years old) with a psychotic disorder: chlorpromazine, perphenazine, thioridazine, thiothixene, trifluoperazine. The doses recommended for pediatric patients are generally much lower than those given for adult patients (see Guideline 2), while the doses recommended for adolescents are only somewhat lower than those recommended for adults. These results underscore the need for more data on optimum dosing for children and adolescents.

Dose Selection for Elderly Patients. The experts generally recommend using lower doses in elderly patients than in younger adults. This probably reflects concerns about slower metabolism and greater sensitivity to adverse effects in older patients. Older patients are also more likely to have comorbid medical conditions and to be taking multiple medications, increasing the risk for adverse effects and drug-drug interactions. The experts generally recommend using much lower doses in elderly patients with dementia than in those with a psychotic disorder. The majority of the experts would not generally use the following medications in an elderly patient with a psychotic disorder or with dementia: chlorpromazine, thioridazine, thiothixene, trifluoperazine; 70% would also avoid haloperidol or fluphenazine decanoate in elderly patients with dementia.

Medication	Children with a psychotic disorder	Adolescents with a psychotic disorder	Elderly Patients with	
			Psychotic disorder	Dementia with behavioral disturbance and/or psychosis
Atypicals				
Aripiprazole	(10–15)*	10–20	10–15	10–15
Clozapine	(100–350)*	225–450	175–375	50–175
Olanzapine	5–10	10–15	5–15	5–10
Quetiapine	150–400	250–550	225–450	75–300
Risperidone	1.0–2.0	2.5–4.0	1.5–3.5	1.0–3.0
Ziprasidone	40–100	80–140	80–140	40–100
Conventionals				
Chlorpromazine	(150–200)*	(225–375)*	(150–300)*	(75–150)*
Fluphenazine	(1.5–5.0)*	2.5–10.0	2.5–7.5	1.0–5.0
Haloperidol	1.0–4.0	2.0–9.0	2.0–6.0	1.0–3.5
Perphenazine	(6–12)*	(12–22)*	6–24	2–14
Thioridazine	(100–250)*	(225–325)*	(150–300)*	(50–125)*
Thiothixene	(4–7)*	(4–20)*	(2–20)*	(1–11)*
Trifluoperazine	(2–10)*	(6–15)*	(4–15)*	(3–10)*
Fluphenazine decanoate	(6.25–12.5)*	12.5–25.0	6.25–25.0	(6.25–12.5)*
Haloperidol decanoate	(15–50)*,†	50–150	25–100	(15–100)*,†

*A majority of the experts would not generally use this medication in this population.

†Although with current formulations it would be difficult to administer 15 mg of haloperidol decanoate, this low mean suggests that the experts would be very cautious in dosing if it is decided to use this medication in children or elderly patients with dementia.

Guideline 7: Strategies When There Is an Inadequate Response

7A. When to Switch Antipsychotics[Question 14]

For each antipsychotic, we asked the experts whether they would increase the dose or switch to another agent if a multi-episode patient was having an inadequate response to the average target dose of the medication (see Guideline 2 for recommended target doses). Over 90% of the experts would first increase the dose of clozapine and olanzapine before switching, going as high as 850 mg/day of clozapine and 40 mg/day of olanzapine. Over 80% would increase the dose of quetiapine and risperidone before switching, going as high as 1100 mg/day of quetiapine and 10 mg/day of risperidone. Approximately 60% or more of the experts would also increase the dose of aripiprazole, ziprasidone, and the decanoate formulations of fluphenazine and haloperidol. The experts are divided fairly evenly as to whether increasing the dose or switching is the best strategy if a patient is having an inadequate response to the recommended target dose of one of the conventional oral antipsychotics, except for thioridazine, where 67% would switch to another agent. The experts may be less willing to increase the dose of the conventional oral medications because of concern about side effects, especially EPS and TD, at higher doses.

Inadequate response to adequate dose of	**Strategy**		
Atypicals	**Increase dose (% of experts)**	**Target dose (mg/day)**	**Switch medications (% of experts)**
Aripiprazole	68%	30–35	32%
Clozapine	93%	600–850	7%
Olanzapine	93%	25–40	7%
Quetiapine	84%	650–1100	16%
Risperidone	84%	6–10	16%
Ziprasidone	57%	160–220	43%
Conventionals			
Chlorpromazine	56%	550–1300	44%
Fluphenazine	55%	10–30	45%
Haloperidol	52%	10–30	48%
Perphenazine	51%	24–64	49%
Thioridazine	33%	500–800	67%
Thiothixene	49%	25–50	51%
Trifluoperazine	53%	20–55	47%
Fluphenazine decanoate	64%	37.5–62.5 mg/2–3 wk	36%
Haloperidol decanoate	64%	125–325 mg/4 wk	36%

7B. Switching Antipsychotics: Selecting the Next Agent[Question 15]

We asked the experts to indicate the first and second antipsychotics they would try after an inadequate response to the initial medication. The table lists those agents written in by 10% or more of the experts in Question 15. Note that, after trials of two atypical antipsychotics, 30% or more of the experts would switch to clozapine; this was recommended as a first line strategy in this situation by 70% of the experts in Question 18. The discrepancy between the responses in Questions 15 and 18 probably reflects differences in the way the question was posed as well as lack of certainty in the field as to the most appropriate place for clozapine in the treatment algorithm. The editors would endorse the response given in question 18, where approximately three quarters of the experts recommend switching to clozapine after inadequate response to two atypical antipsychotics (see Guideline 7G). For patients who had started with a conventional antipsychotic, the experts are more likely to try two other atypical antipsychotics before moving on to clozapine.

Inadequate response to:	First medication you would switch to*	(%)	Second medication you would switch to	(%)
Aripiprazole	Risperidone	(54%)	Clozapine	(39%)
	Olanzapine	(19%)	Olanzapine	(25%)
	Ziprasidone	(16%)	Risperidone	(19%)
Clozapine	Risperidone	(34%)	Olanzapine	(23%)
	Aripiprazole	(25%)	Quetiapine	(17%)
			Aripiprazole	(13%)
			Risperidone	(13%)
			Ziprasidone	(10%)
Olanzapine	Risperidone	(60%)	Clozapine	(43%)
	Aripiprazole	(12%)	Aripiprazole	(21%)
	Ziprasidone	(12%)	Quetiapine	(12%)
			Risperidone	(10%)
Quetiapine	Risperidone	(64%)	Olanzapine	(38%)
	Olanzapine	(14%)	Clozapine	(31%)
	Aripiprazole	(12%)	Aripiprazole	(14%)
Risperidone	Olanzapine	(50%)	Clozapine	(35%)
	Aripiprazole	(19%)	Aripiprazole	(25%)
	Clozapine	(12%)	Quetiapine	(13%)
	Quetiapine	(10%)		
	Ziprasidone	(10%)		
Ziprasidone	Risperidone	(44%)	Clozapine	(34%)
	Aripiprazole	(21%)	Olanzapine	(29%)
	Olanzapine	(21%)	Aripiprazole	(16%)
	Quetiapine	(10%)	Risperidone	(13%)
Chlorpromazine	Risperidone	(64%)	Olanzapine	(35%)
	Olanzapine	(18%)	Clozapine	(19%)
			Quetiapine	(14%)
			Aripiprazole	(11%)
			Risperidone	(11%)
			Ziprasidone	(11%)
Fluphenazine	Risperidone	(62%)	Olanzapine	(29%)
	Olanzapine	(16%)	Clozapine	(18%)
	Aripiprazole	(11%)	Quetiapine	(15%)
			Risperidone	(15%)
			Aripiprazole	(12%)
			Ziprasidone	(12%)

7B. *continued*

Inadequate response to:	First medication you would switch to*	(%)	Second medication you would switch to	(%)
Haloperidol	Risperidone	(59%)	Olanzapine	(28%)
	Olanzapine	(18%)	Clozapine	(19%)
	Aripiprazole	(13%)	Quetiapine	(14%)
			Risperidone	(14%)
			Ziprasidone	(14%)
			Aripiprazole	(11%)
Perphenazine	Risperidone	(62%)	Olanzapine	(29%)
	Olanzapine	(14%)	Clozapine	(18%)
	Aripiprazole	(11%)	Quetiapine	(15%)
	Ziprasidone	(11%)	Risperidone	(15%)
			Aripiprazole	(12%)
			Ziprasidone	(12%)
Thioridazine	Risperidone	(68%)	Olanzapine	(29%)
	Olanzapine	(14%)	Clozapine	(18%)
			Aripiprazole	(15%)
			Risperidone	(15%)
			Quetiapine	(12%)
			Ziprasidone	(12%)
Thiothixene	Risperidone	(64%)	Olanzapine	(30%)
	Olanzapine	(14%)	Clozapine	(18%)
	Aripiprazole	(11%)	Risperidone	(15%)
			Aripiprazole	(12%)
			Quetiapine	(12%)
			Ziprasidone	(12%)
Trifluoperazine	Risperidone	(61%)	Olanzapine	(27%)
	Olanzapine	(17%)	Clozapine	(18%)
	Aripiprazole	(11%)	Risperidone	(15%)
			Ziprasidone	(15%)
			Aripiprazole	(12%)
			Quetiapine	(12%)
Long-acting injectable atypical	Clozapine	(27%)	Clozapine	(40%)
	Risperidone	(24%)	Olanzapine	(17%)
	Haloperidol decanoate	(15%)	Aripiprazole	(10%)
			Ziprasidone	(10%)
Injectable fluphenazine decanoate	Long-acting injectable atypical	(38%)	Clozapine	(41%)
	Risperidone	(24%)	Olanzapine	(21%)
Injectable haloperidol decanoate	Long-acting injectable atypical	(39%)	Clozapine	(45%)
	Risperidone	(22%)	Olanzapine	(15%)

*If the patient did not respond to the initial antipsychotic you tried and you have switched to another antipsychotic, the experts recommend waiting 3–6 weeks before making a major change in treatment regimen (e.g., switching to yet another antipsychotic) if the patient is having little or no response to treatment, and waiting 5–11 weeks if the patient is having a partial response to treatment.[Question 13]

7C. Switching Antipsychotics: Target Doses[Question 15]

The recommended target doses for the second and third antipsychotics the experts would try are, for the most part, consistent with the acute target doses shown in Guideline 2, although there is a tendency to consider using doses at the higher end of the range, especially for the third medication tried.

	Dosing of first switch (mg/day)	Dosing of second switch (mg/day)
Atypicals		
Aripiprazole	20–30	15–30
Clozapine	350–450	350–500
Olanzapine	15–30	15–25
Quetiapine	550–750	500–800
Risperidone	3.5–7	4.5–8
Ziprasidone	120–160	120–180
Long-acting injectable atypical (risperidone)	37.5–50 mg/2 wk	50 mg/2 wk*
Conventionals		
Fluphenazine	—	50*
Haloperidol	10*	10–20
Fluphenazine decanoate	6.25–62.5 mg/2–3 wk	75 mg/2–3 wk*
Haloperidol decanoate	100–250 mg/4 wk	100–450 mg/4 wk

*Only one write in.

7D. Preferred Switching Strategies for Oral Antipsychotics[Question 16]

We asked the experts what strategy they would use in switching to each of the oral atypical antipsychotics, assuming that the first antipsychotic does not require tapering before discontinuation. In switching to any of the oral atypicals except clozapine, the experts recommend using cross-titration (gradually tapering the dose of the first antipsychotic while gradually increasing the dose of the second) or overlap and taper (continuing the same dose of the first antipsychotic while gradually increasing the second to a therapeutic level and then tapering the first). For each drug, a larger percentage of the experts considered cross-titration first line. In switching to clozapine, the experts recommend using cross-titration, probably reflecting the need to institute clozapine treatment gradually and not to withdraw the previous medication abruptly or prematurely. They would also consider using overlap and taper in switching to clozapine (rated high second line). The experts do not recommend strategies that involve stopping the first antipsychotic before beginning the second.

When switching to:	First Line	High Second Line
Oral atypical antipsychotic other than clozapine		Cross-titration Overlap and taper
Clozapine	Cross-titration	Overlap and taper

7E. Preferred Switching Strategies for Injectable Antipsychotics[Question 17]

In switching to a depot conventional antipsychotic, the experts recommend either continuing the oral antipsychotic at the same dose until therapeutic drug levels of the injectable antipsychotic are achieved and then gradually tapering the oral antipsychotic or else beginning to taper the oral antipsychotic gradually after giving the first injection, with a larger percentage of the experts favoring the first strategy. Some experts would consider discontinuing the oral antipsychotic immediately once therapeutic levels of the injectable antipsychotic are achieved.

The experts' recommendations for switching to a long-acting atypical antipsychotic are similar, except that there is stronger support for continuing the oral antipsychotic at the same dose until therapeutic drug levels of the injectable antipsychotic are achieved and then gradually tapering the oral antipsychotic compared with the other options.

It should be noted that the experts definitely do not recommend stopping the oral antipsychotic when the first long-acting injection is given, since this would leave the patient without adequate antipsychotic coverage during the switchover and potentially increase the risk of relapse.

When switching to:	First Line	High Second Line	Other Second Line
Depot conventional		Continue oral antipsychotic at same dose until patient achieves therapeutic blood levels of the injectable antipsychotic and then gradually taper the oral antipsychotic Taper the oral antipsychotic gradually after giving the first long-acting injection	Continue oral antipsychotic at same dose until patient achieves therapeutic blood levels of the injectable antipsychotic and then immediately discontinue the oral antipsychotic
Long-acting injectable atypical		Continue oral antipsychotic at same dose until patient achieves therapeutic blood levels of the injectable antipsychotic and then gradually taper the oral antipsychotic	Taper the oral antipsychotic gradually after giving the first long-acting injection Continue oral antipsychotic at same dose until patient achieves therapeutic blood levels of the injectable antipsychotic and then immediately discontinue the oral antipsychotic

7F. Strategies When There Is a Partial Response[Question 19]

We asked the experts about the appropriateness of a number of strategies to try to improve response in a patient who is having a partial but still inadequate response (e.g., a patient with some persisting positive symptoms). The experts gave only limited support to any of the options and rated many of them third line, probably reflecting the lack of empirical data concerning these strategies.

If partial response to:	First Line	High Second Line	Other Second Line
Oral conventional			Add a long-acting injectable atypical antipsychotic Add an oral atypical antipsychotic Add valproate Add a benzodiazepine
Oral atypical			Add a long-acting injectable atypical antipsychotic Add valproate Add an oral atypical antipsychotic Add a benzodiazepine Add lithium Add ECT
Depot conventional			Add an oral atypical antipsychotic Add valproate

7G. When to Switch to Clozapine[Question 18]

Clozapine is indicated for treatment-refractory schizophrenia. However, clinicians vary in how they define treatment-refractory illness and there are no universally accepted criteria for treatment-refractoriness in schizophrenia. We therefore asked the experts in what clinical situations they would be most likely to consider a switch to clozapine. The experts consider a trial of clozapine a strategy of choice for a patient who has failed to respond to adequate trials of one or more conventional antipsychotics and two atypical antipsychotics. They would also consider it a strategy of choice for a patient who had failed to respond to trials of one or more conventionals and all the atypicals. However, 13% of the experts rated this option third line, probably because there would be no advantage in trying all the other five atypical antipsychotics before going to clozapine. The experts also consider a trial of clozapine a first line option for patients who have failed to respond to trials of two or three atypicals or trials of one or more conventionals and one atypical. Although some experts would consider clozapine for patients who have not responded to two conventionals or one atypical, there was much less support for these options. When it is most appropriate to switch to clozapine remains an area of controversy with few data to inform clinical practice. We may in fact be doing our patients a disservice by trying multiple drugs before going to clozapine.

(***bold italics*** = indications receiving the highest rating from at least 50% of the experts)

First Line	High Second Line	Other Second Line
Trials of one or more conventional antipsychotics and two atypical antipsychotics		Trials of two conventional antipsychotics Trial of one atypical antipsychotic
Trials of one or more conventional antipsychotics and all of the other atypical antipsychotics		
Trials of three atypical antipsychotics		
Trials of two atypical antipsychotics		
Trials of one or more conventional antipsychotics and one atypical antipsychotic		

Guideline 8: Pharmacologic Strategies for Managing Relapse

8A. Relapse When Taking an Oral Antipsychotic[Questions 20–22]

If a patient relapses whom the clinician believes is compliant with medication based on all available evidence (e.g., family report, plasma levels), the experts recommend (high second line ratings) either switching to a different oral antipsychotic or increasing the dose of the current medication. Another second line option the experts would consider is switching to a long-acting injectable antipsychotic. This probably reflects concerns that the patient may not actually be compliant, since studies have found that clinicians are often incorrect in their assessment of patients' compliance. It may also reflect concerns about absorption problems with the oral formulations.

When the clinician is unsure of the level of compliance or there is clear evidence of noncompliance, the experts' first line recommendation is to switch to a long-acting injectable atypical. They would also consider a long-acting conventional depot antipsychotic (high second line). If the clinician is unsure of the level of compliance, the experts would also consider adding a long-acting atypical to the oral antipsychotic.

Relapse	First Line	High Second Line	Other Second Line
Despite compliance		Switch to a different oral antipsychotic Increase the dose of the current antipsychotic	Switch to long-acting injectable atypical antipsychotic Add an adjunctive agent Add a long-acting injectable atypical antipsychotic Add another oral antipsychotic Switch to long-acting conventional depot
When unsure of level of compliance	Switch to long-acting injectable atypical antipsychotic*	Switch to long-acting conventional depot Add a long-acting injectable atypical antipsychotic	Switch to a different oral antipsychotic Add a long-acting conventional depot Add an adjunctive agent
When noncompliant	Switch to long-acting injectable atypical antipsychotic	Switch to long-acting conventional depot	Switch to a different oral antipsychotic

*At the time of this survey, a long-acting injectable atypical antipsychotic was not available in the United States, although it was available in several other countries. In the survey we asked the experts to rate how they would use such a formulation if it were available.

8B. Relapse on a Long-Acting Injectable Antipsychotic[Questions 23, 54]

If a patient relapses when receiving a long-acting conventional antipsychotic (depot), the experts' first line recommendation is to switch to a long-acting injectable atypical antipsychotic. They would also consider increasing the dose or the frequency of injections of the long-acting conventional (high second line options).

If a patient relapses when receiving a long-acting injectable atypical antipsychotic, the experts' first line recommendation is to increase the dose of the injectable antipsychotic. They would also strongly consider adding the oral form of the injectable antipsychotic to try to boost response (very high second line). The experts do not recommend switching to a conventional depot antipsychotic (third line rating).

Current Treatment	First Line	High Second Line	Other Second Line
Long-acting depot conventional antipsychotic	Switch to long-acting injectable atypical antipsychotic*	Increase the dose of the long-acting conventional antipsychotic Increase the frequency of injections of the long-acting conventional antipsychotic	Add an oral antipsychotic Obtain plasma levels Add an adjunctive agent Switch to a different oral antipsychotic Switch to a different conventional depot agent if not previously tried
Long-acting injectable atypical antipsychotic	Increase the dose of the long-acting injectable atypical	Add the oral form of the long-acting injectable atypical	Add an adjunctive agent Obtain plasma levels Add a different oral antipsychotic Switch to a different oral antipsychotic

*At the time of this survey, a long-acting injectable atypical antipsychotic was not available in the United States, although it was available in several other countries. In the survey we asked the experts to rate how they would use such a formulation if it were available.

Guideline 9: Dose Adjustment in Stable Patients[Question 24]

If the patient is being treated with an atypical antipsychotics or with fluphenazine or haloperidol decanoate, the majority of the experts would continue maintenance treatment with the same dose that was effective acutely, although over 40% would lower the dose of olanzapine or risperidone. A majority of the experts said they would lower the dose of an oral conventional antipsychotic for maintenance treatment; however, the percentages are very close, with 40% or more of the experts recommending continuing the acute dose of the conventional antipsychotic. The uncertainties shown in this area are consistent with a lack of information concerning optimum doses for maintenance treatment with both conventional and atypical antipsychotics.

Medications to continue at acute dose during maintenance treatment	
	% of experts endorsing this strategy
Aripiprazole	78%
Clozapine	66%
Olanzapine	59%
Quetiapine	71%
Risperidone	51%
Ziprasidone	72%
Fluphenazine decanoate	59%
Haloperidol decanoate	58%

Medications	**Target maintenance dose if it is decided to lower dose***
Atypicals	
Aripiprazole	(10–15)†
Clozapine	(225–375)†
Olanzapine	(7.5–15.0)†
Quetiapine	(250–500)†
Risperidone	(2.5–4.0)†
Ziprasidone	(60–120)†
Conventionals	
Chlorpromazine	175–425
Fluphenazine	3.5–10
Haloperidol	3–8
Perphenazine	8–24
Thioridazine	150–350
Thiothixene	7–20
Trifluoperazine	5–20
Fluphenazine decanoate	(6.25–25)†
Haloperidol decanoate	(50–125)†

*The experts recommend waiting at least 6 months and preferably a year after a patient has become stable before lowering the dose of the antipsychotic.[Question 25]

†The majority of the experts would not lower the dose of this medication during maintenance treatment.

Guideline 10: Managing Complicating Problems

10A. Selecting Antipsychotics for Patients With Complicating Problems[Question 26]

The experts consider clozapine the treatment of choice for patients who present with suicidal behavior. This is consistent with a new indication for clozapine for "reducing the risk of recurrent suicidal behavior." Clozapine is also the top choice for aggression and violence. Other highly rated options for aggression and violence are risperidone (rated first line), olanzapine, and a long-acting injectable atypical (both rated high second line). There were no first line recommendations for the other problems we asked about—dysphoria/depression, cognitive problems, and substance abuse—for which all of the oral atypical antipsychotics as well as a long-acting injectable atypical received second line ratings. The experts would also consider a long-acting depot conventional for a patient with substance abuse. The lack of first line consensus on these items probably reflects the fact that, although an increasing number of studies have looked at the effects of atypical antipsychotics on mood, cognition, and substance use, the data are not yet sufficiently consistent or dramatic to influence clinical practice. It is interesting that the experts would not recommend oral conventional antipsychotics for patients with any of the problems that we asked about, except aggression/violence, for which conventional orals were second line options. It is possible that these complicating problems may be caused or exacerbated by noncompliance. Therefore, it is not surprising that a long-acting atypical antipsychotic was a prominent alternative, especially for aggression/violence and substance-abuse problems.

(***bold italics*** = treatments of choice)

Complicating problem	First Line*	High Second Line	Other Second Line
Aggression/violence	Clozapine Risperidone	Olanzapine Long-acting injectable atypical	Quetiapine Ziprasidone Aripiprazole Long-acting depot conventional Conventional
Suicidal behavior	***Clozapine***	Risperidone Olanzapine Ziprasidone	Aripiprazole Quetiapine Long-acting injectable atypical Long-acting depot conventional
Dysphoria/depression		Olanzapine Clozapine Aripiprazole Risperidone Ziprasidone	Quetiapine Long-acting injectable atypical
Cognitive problems		Risperidone Aripiprazole Olanzapine Ziprasidone Clozapine	Quetiapine Long-acting injectable atypical
Substance abuse		Clozapine Risperidone Long-acting injectable atypical Aripiprazole Olanzapine	Quetiapine Ziprasidone Long-acting depot conventional

*In this survey, we asked only about oral and long-acting injectable formulations of antipsychotics. Unless otherwise specified, all medications listed in the tables refer to the oral formulation.

10B. Selecting Adjunctive Treatments for Patients With Complicating Problems[Questions 27–30]

When we asked about a number of adjunctive medications that are commonly used in clinical practice to treat a variety of complicating problems in patients with schizophrenia, the experts as a group had few strong recommendations, probably reflecting the lack of decisive empirical data in this area. The only first line recommendation was a selective serotonin reuptake inhibitor (SSRI) for dysphoria/depression, reflecting studies showing that antidepressants can be helpful for patients with comorbid depression. Venlafaxine was a very high second line for dysphoria/depression. For aggression and violence, valproate and lithium received high second line ratings. For suicidal behavior, the same two antidepressants recommended for dysphoria/depression received high second line ratings, with ECT another high second line option. The question of how to treat persisting negative symptoms has long been a difficult issue in the field. Although there was no consensus on any of the adjunctive treatments which were rated second line for negative symptoms, it should be noted that approximately a quarter of the experts or more rated the following options first line: a glutaminergic agent, an SSRI, another antipsychotic, or venlafaxine.

Complicating problem	First Line	High Second Line	Other Second Line
Aggression/violence		Valproate Lithium	Carbamazepine Beta-blocker Benzodiazepine Gabapentin ECT Lamotrigine Topiramate
Suicidal behavior		Selective serotonin reuptake inhibitor (SSRI) Electroconvulsive therapy (ECT) Venlafaxine	Mirtazapine Lithium Valproate Bupropion Nefazodone Lamotrigine
Dysphoria/depression	SSRI	Venlafaxine	ECT Mirtazapine Bupropion Nefazodone Lithium Tricyclic antidepressant Valproate Lamotrigine Trazodone
Persisting negative symptoms			A glutamatergic agent (e.g., glycine, cyclo-serine) SSRI Another antipsychotic Venlafaxine A stimulant

10C. Strategies for a Patient With Clinically Significant Obesity[Questions 31, 32]

There is increasing concern about long-term medical problems in patients with schizophrenia, especially obesity and its complications. Many antipsychotics can contribute to weight gain and clinicians face difficult clinical dilemmas when a patient with clinically significant obesity (BMI ≥ 30) responds well to a medication that is likely to be contributing to the patient's weight problem. If a patient with clinically significant obesity has responded to an antipsychotic other than clozapine, the experts recommend a trial of a different antipsychotic with less weight gain liability combined with nutritional and exercise counseling if possible. They would also consider (high second line) continuing the same antipsychotic and providing nutritional and exercise counseling to try to help the patient lose weight. However, reflecting the fact that most patients receiving clozapine have already failed to respond to other agents, the experts would continue clozapine in this situation and try to address the weight problem with nutritional and exercise counseling. Although the experts gave a high second line rating to lowering the dose of clozapine in this situation, clinical studies have found that weight gain does not appear to be a dose-related effect. It is interesting that the experts gave second line ratings to the addition of topiramate. Although there have been case reports of weight loss with this agent in schizophrenia, there are no controlled studies supporting this practice. The experts did not recommend the use of weight loss medications (orlistat, sibutramine) or surgical treatment of obesity in this population.

Clinical presentation	First Line	High Second Line	Other Second Line
Patient who has responded well to an antipsychotic other than clozapine	Switch to a different antipsychotic with less weight gain liability and provide nutritional and exercise counseling	Switch to a different antipsychotic with less weight gain liability Continue treatment with the same antipsychotic at the same dose and provide nutritional and exercise counseling	Lower the dose of the current antipsychotic and provide nutritional and exercise counseling Add topiramate and provide nutritional and exercise counseling
Patient with treatment resistant illness who has responded well to clozapine	Continue treatment with clozapine at the same dose and provide nutritional and exercise counseling	Lower the clozapine dose and provide nutritional and exercise counseling	Switch to a different antipsychotic with less weight gain liability and provide nutritional and exercise counseling Add topiramate and provide nutritional and exercise counseling

10D. Monitoring for Comorbid Conditions and Risk Factors[Question 33]

Many patients with schizophrenia rely on their psychiatric care provider for general medical care. With the improving outcomes being achieved with the newer atypical antipsychotics, more attention is being focused on short- and long-term health and wellness in this population. We asked the experts which conditions and risk factors they felt it was ***most important*** to monitor. We also asked which ones it was feasible to monitor in a psychiatric treatment setting. The experts felt that it was important to monitor for all the conditions we asked about, with obesity and diabetes considered the most important (rated 9 by 60% and 56% of the experts, respectively). The experts' ratings of feasibility reflect the relative difficulty of the assessments involved (e.g., it is relatively simple to monitor weight and blood pressure, but much harder to evaluate osteoporosis). Although we did not ask about obtaining lipid profiles, the editors note that clinicians should also obtain lipid levels on a regular basis, because some antipsychotics are associated with hyperlipidemia. A recent expert conference concluded that, as part of routine care, a lipid panel should be obtained if one is not available. Given that individuals with schizophrenia, as a group, are considered to be at high risk for coronary heart disease, lipid screening should be carried out at least once every 5 years and more often when there is evidence of lipid levels that approach those that would lead to treatment.* The same conference also recommended that clinicians should be aware of, and monitor regularly for, symptoms of increased prolactin. If clinically indicated, prolactin should be measured, and, if elevated, a work-up for the cause of the elevation should be initiated. Consideration should also be given to switching to a prolactin-sparing medication—if the symptoms disappear and prolactin levels fall to normal, an endocrine work-up can then be avoided. Recommendations on other complicating conditions, such as cardiac problems (QTc prolongation and myocarditis), cataracts, and EPS will also be included in the Mount Sinai guideline when it is published.

(***bold italics*** = conditions receiving the highest rating from at least 50% of the experts)

Conditions and risk factors to monitor for	First Line	Second Line
Most important	***Obesity*** ***Diabetes*** Cardiovascular problems HIV risk behavior Medical complications of substance abuse Heavy smoking Hypertension Amenorrhea	Galactorrhea Osteoporosis
Most feasible for psychiatric treatment team to monitor	***Obesity*** ***Hypertension*** Amenorrhea Diabetes Heavy smoking Galactorrhea Cardiovascular problems	HIV risk behavior Medical complications of substance abuse Osteoporosis

*Marder SR, Essock SM, Miller AL, et al. The Mount Sinai Conference on the Health Monitoring of Patients with Schizophrenia. Am J Psychiatry (submitted)

II. COMPLIANCE (ADHERENCE)

Guideline 11: Levels of Compliance

11A. Defining Levels of Compliance[Question 36]

We provided the experts with the definitions of compliance given below to use as benchmarks in answering a series of questions about the assessment and management of compliance problems. We also asked them to tell us how they would define levels of compliance. On average, the expert panel would set a higher threshold for compliance, as shown below, and would consider a patient who missed more than 65% of his or her medication noncompliant.

Level of compliance	Definitions provided in the survey	Average of experts' preferred definitions
Compliant	Misses < 20% of medication	Misses < 25% of medication
Partially compliant	Misses 20%–80% of medication	Misses 25%–65% of medication
Noncompliant	Misses > 80% of medication	Misses > 65% of medication

11B. Reported Extent of Compliance[Questions 34 & 35]

Not surprisingly, the experts report that their patients show higher levels of compliance than are generally reported in the literature.

Level of compliance	Levels reported in the literature	Experts' estimate of compliance levels in their patients
Compliant (misses < 20% of medication)	28%	43%
Partially compliant (misses 20%–80% of medication)	46%	38%
Noncompliant (misses > 80% of medication)	26%	19%

Guideline 12: Assessing Compliance[Question 37]

The experts consider asking the caregiver or patient first line strategies for assessing compliance; they would also consider pill counts, obtaining blood levels, and using self-rating scales. They did not consider routine use of urine tests appropriate.

Preferred strategies	Also consider
Asking relative or caregiver	Pill counts
Asking patient	Blood levels
	Self-rating scale for compliance

Guideline 13: When to Intervene for Compliance Problems[Question 38]

The experts were unanimous about the need to intervene if a patient is missing more than 80% of medication. They would usually intervene if a patient is missing approximately 50% of prescribed medication (91% would usually intervene). The majority of the experts (52%) would also usually intervene when a patient is missing approximately 20% of medication. There was less agreement about whether to intervene if a patient is only missing occasional doses (13% would usually intervene, 39% would sometimes intervene, and 48% would generally not intervene).

(***bold italics*** = over 50% of the experts gave the highest rating to intervention)

Usually intervene	Sometimes intervene
Patient missing more than 80% of medication doses or has stopped medication completely	Patient missing occasional doses
Patient missing approximately 50% of medication	
Patient missing approximately 20% of medication*	

*High second line

Guideline 14: Strategies for Addressing Compliance Problems

14A. Selecting Initial Strategies[Questions 39 & 40]

We asked the experts about the appropriateness of three different types of strategies that have been used to address compliance problems:

- Pharmacologic interventions (e.g., switching to a long-acting medication)
- Psychosocial interventions (e.g., patient education, compliance therapy [focused cognitive-behavioral therapy targeting compliance issues])
- Programmatic interventions (e.g., intensive case management, assertive community treatment)

The experts gave first line ratings to all three types of interventions. The editors note that clinicians should generally employ a combination of strategies tailored to the specific needs of the patient. The experts gave the highest ratings to psychosocial interventions for patients who are partially compliant, probably reflecting findings that such interventions can improve compliance levels. Psychopharmacologic interventions received the highest ratings for noncompliant patients, probably reflecting the fact that patients who are not taking their medication are at the highest risk for relapse and it is especially important to try to get the patient back on medication as quickly as possible.

(***bold italics*** = intervention of choice)

Clinical presentation	Preferred interventions to improve compliance
Partially compliant	***Psychosocial interventions***
	Pharmacologic interventions
	Programmatic interventions
Noncompliant	***Pharmacologic interventions***
	Programmatic interventions
	Psychosocial interventions

14B. Psychosocial and Programmatic Interventions to Improve Compliance[Questions 41 & 42]

Among psychosocial interventions for improving compliance, the experts gave the highest ratings to patient/family education, medication monitoring, and compliance therapy. Their ratings agree with research findings concerning the efficacy of these strategies in improving compliance. Findings concerning the efficacy of group and individual psychotherapy in improving compliance are equivocal, as shown by the lower ratings given to these options.

Among programmatic interventions the experts recommend assertive community treatment (ACT), ensuring continuity of treatment provider across treatment settings, and intensive case management services. These recommendations reflect findings in the literature that intensive case management, in particular the kind of assistance provided by ACT programs, can significantly improve compliance levels. Lack of continuity in care providers can lead to serious compliance problems, since patients may be continued on an ineffective or difficult-to-tolerate treatment regimen or may not receive continuing medication coverage after discharge. The experts also considered supervised residential services, partial hospitalization, rehabilitation services, and involuntary outpatient commitment useful options for improving compliance.

Psychosocial interventions		**Programmatic interventions**	
Preferred	**Also consider**	**Preferred**	**Also consider**
Patient education Family education and support Medication monitoring Compliance therapy (focused cognitive-behavioral therapy targeting compliance issues)	Symptom and side effect monitoring Individual or group psychotherapy	Assertive community treatment (ACT) Continuity of primary clinician across treatment modalities (e.g., inpatient, outpatient, and residential programs) Intensive services (e.g., contact 1–5 times weekly or more frequently as needed)	Supervised residential services Partial hospitalization services Rehabilitation services Involuntary outpatient commitment

14C. Pharmacologic Strategies for Addressing Compliance Problems[Questions 43 & 44]

There was strong agreement among the experts that the first line pharmacologic strategy for addressing compliance problems is to switch the patient to a long-acting injectable atypical antipsychotic once this option is available (rated first line for partially compliant patients and treatment of choice for noncompliant patients). High second line options are to switch to a long-acting depot conventional or add a long-acting injectable atypical. Another high second line option for a patient who is partially compliant is to continue the same pharmacotherapy and intensify psychosocial interventions to improve compliance. However, the experts do not recommend this strategy for a patient who is noncompliant.

(***bold italics*** = treatment of choice)

Clinical presentation	First Line	High Second Line	Other Second Line
Partially compliant	Switch to a long-acting atypical antipsychotic*	Switch to a long-acting conventional depot antipsychotic Add a long-acting injectable atypical antipsychotic No change in pharmacotherapy; intensify psychosocial treatment	Switch to a different oral antipsychotic that has not previously been used Regular monitoring of plasma levels Add a long-acting conventional depot antipsychotic
Noncompliant	***Switch to a long-acting atypical antipsychotic***	Switch to a long-acting conventional depot antipsychotic Add a long-acting injectable atypical antipsychotic	Add a long-acting conventional depot antipsychotic Regular monitoring of plasma levels Switch to a different oral antipsychotic that has not previously been used

*At the time of this survey, a long-acting injectable atypical antipsychotic was not available in the United States, although it was available in several other countries. In the survey we asked the experts to rate how they would use such a formulation if it were available.

III. LONG-ACTING INJECTABLE ANTIPSYCHOTICS

Guideline 15: Benefits of Long-Acting Injectable Antipsychotics[Question 45]

The experts consider the greatest benefit of a long-acting injectable antipsychotic to be assured medication delivery. Other important advantages are the ability to know immediately when a patient misses medication and the fact that the patient continues to have some medication in his or her system even after a missed dose. Additional advantages are the reduced risk of relapse associated with continuous medication, and the ability to know that relapse, if it occurs, is not the result of compliance problems.

(***bold italics*** = benefits receiving the highest rating from at least 50% of the experts)

Most important	Somewhat important
Assured medication delivery	Regular contact with patient
Knowing immediately when medication is missed	Convenience for patient
Reduced risk of relapse	Ability to use lower effective dose
Some continuing medication coverage after a missed dose	
Knowing that relapse has occurred despite adequate pharmacotherapy	

Guideline 16: Potential Disadvantages of Long-Acting Injectable Antipsychotics[Question 46]

The experts consider lack of patient acceptance the most important potential disadvantage of long-acting injectable antipsychotics. To some extent, this response probably reflects an assumption that patients will not accept the idea of continuing injections. However, once they try a long-acting medication, many patients are surprised to find how easy it is to tolerate receiving medication in this way. Although lack of patient autonomy is another potential concern that is sometimes mentioned, patient surveys do not support this as being a major factor. Although the experts said that they considered inability to stop medication immediately should side effects become a problem somewhat important as a potential disadvantage, the editors were hard pressed to find examples of situations in which immediate discontinuation of an antipsychotic in a long-acting formulation was a medical necessity. Even in neuroleptic malignant syndrome, there is no evidence that mortality rates are higher among patients receiving a long-acting injectable antipsychotic than in those receiving an oral medication (assuming that the condition is identified and appropriately treated).

Most important	Somewhat important	Not too important
Lack of patient acceptance	Logistical issues	Reimbursement issues
	Inability to stop medication immediately should side effects become a problem	Inadequately established benefit
	Negative physician perceptions	
	Stigma associated with injections or depot clinics	
	Inadequately appreciated benefit	
	Local effects of repeated injections	

Guideline 17: Factors Favoring Use of Long-Acting Injectable Antipsychotics[Question 47]

In deciding whether to use a long-acting injectable antipsychotic, 96% of the experts consider the availability of an atypical antipsychotic in such a formulation very important. This probably reflects concerns about side effects associated with the conventional depot antipsychotics. Other factors that the experts consider very important in deciding to use a long-acting injectable are good patient acceptance of the injection, evidence that the rate of relapses and side effects will be lower than with oral equivalents, better quality of life for their patients, and ease of administration.

(***bold italics*** = factors receiving the highest rating from at least 50% of the experts)

Most important	Somewhat important
Availability of an atypical antipsychotic in a long-acting injectable formulation	Longer interval between injections
Good patient acceptance of injection	Demonstrated superior efficacy to oral equivalent
Demonstrated fewer relapses/hospital admissions than oral equivalent	Easy preparation of injection
Fewer side effects than oral medications	Little dose titration required with long-acting injectable formulation
Better quality of life/patients say they feel better	Easy dose conversion from oral equivalent
Easy administration of injection	Easy dose conversion from other oral antipsychotic agent

Guideline 18: Indications for Switching From an Oral Antipsychotic to a Long-Acting Injectable Atypical[Questions 48 & 49]

We asked the experts about the appropriateness of using a long-acting injectable atypical antipsychotic in a variety of clinical situations. The experts consider a long-acting atypical antipsychotic the treatment of choice for a patient who is taking an oral atypical and requests the long-acting formulation, for a patient who relapses because of noncompliance with an oral atypical antipsychotic, and for a patient who is experiencing EPS on a depot conventional antipsychotic. The experts consider a long-acting injectable atypical first line for a patient in involuntary outpatient commitment, for a patient who is chronically relapsing on an oral conventional, for a patient with lack of insight or denial of illness, for a patient taking an oral atypical antipsychotic who is relapsing for reasons that are unclear, and for a patient with a history of aggressive or violent behavior. It is interesting that the experts perceive a role for the use of long-acting injectable atypicals that goes well beyond treatment of patients with compliance problems (see the many other second line indications listed below). Of all the situations that we asked about, the only ones in which the experts would not generally consider a long-acting injectable atypical are a patient taking an oral atypical or conventional who is stable and not experiencing EPS or a patient who has been newly diagnosed with schizophrenia and has had no previous antipsychotic treatment.

Further recommendations: We asked the experts how concern about the potential for TD would affect their decision to switch to an injectable atypical antipsychotic. The majority of the experts would definitely switch if there is concern about TD in a patient who is experiencing EPS on a depot or oral conventional antipsychotic (96% and 73% first line, respectively). Even if the patient is not experiencing EPS, many of the experts would consider switching from a depot or oral conventional if there is concern about TD (49% and 38% first line, respectively). The editors were unsure on what basis a clinician would decide that there was in fact no or minimal risk of TD.[Question 50]

We asked the experts about the appropriateness of beginning treatment with a long-acting injectable atypical while the patient is hospitalized, given shorter lengths of hospital stays. This strategy was rated high second line by the expert panel, in order to ensure continuing medication coverage when the patient is discharged and to facilitate acceptance of an injectable medication in outpatient treatment. The experts also noted that this strategy may be helpful because patients are most vulnerable to relapse soon after discharge.[Questions 52 & 53]

(***bold italics*** = indications receiving the highest rating from at least 50% of the experts)

First Line	High Second Line	Other Second Line
Patient taking an* oral atypical antipsychotic *who requests a long-acting antipsychotic	History of or potential for suicidal behavior	Other severe psychosocial stressor
Patient taking an* oral atypical antipsychotic *who is experiencing relapse because he or she stopped taking medication	Homelessness	Early episode schizophrenia
Patient taking a* depot conventional antipsychotic *who is stable but experiencing EPS	Comorbid substance abuse problems	Patient taking a depot conventional antipsychotic who is stable and is not experiencing serous EPS
Involuntary outpatient commitment	Lack of social supports	Bipolar mania with psychosis
Patient taking an oral conventional antipsychotic who is chronically relapsing	Elderly patient taking an oral conventional antipsychotic who forgets to take medication	Dementia with psychosis
Persistent lack of insight/denial of illness	Patient taking an oral conventional antipsychotic who is stable but experiencing EPS	Elderly patient taking an oral conventional antipsychotic who is having troublesome side effects
Patient taking an oral atypical antipsychotic who is experiencing relapse for reasons that are unclear		A patient with treatment-refractory illness who is taking clozapine and having troublesome side effects
History of or potential for aggressive or violent behavior		

Guideline 19: Factors Motivating Patients to Return for Repeat Injections[Question 51]

The experts consider the influence of family/caregivers and physician/treatment team to be most important in motivating patients to return for repeat injections.

Most important	Somewhat important
Urging/insistence of family or caregivers	Involuntary outpatient commitment
Urging of physician/treatment team	Contact with treatment team
	Decreased risk of relapse
	Not having to remember to take oral medication
	Convenience
	Better efficacy

IV. DEFINING REMISSION AND RECOVERY

Guideline 20: Indicators of Remission and Recovery[Question 55]

With improving outcomes, research studies are now trying to evaluate the effectiveness of different antipsychotics not only in producing remission of symptoms but in promoting long-term recovery in patients with schizophrenia. However, as yet there is no general consensus on how best to define these terms. We therefore asked the experts to rate the appropriateness of a number of factors as indicators of remission and recovery. There was strong agreement that the level of positive symptoms is the single most important indicator of remission. High second line indicators are levels of cognitive/disorganized, negative, and depressive symptoms, reflecting studies that show that these associated symptoms contribute in a substantial way to the functional disability associated with schizophrenia. In defining recovery, however, the experts gave almost equal weight to all of the indicators that we asked about, indicating that recovery is a concept involving improvement in multiple domains.

Rank ordering of symptomatic indicators: When the experts were asked to rank order four key indicators of remission and recovery, their responses agreed very closely with those presented in the table below: 89% considered level of positive symptoms the most important indicator of remission, followed by cognitive/disorganized symptoms, negative symptoms, and depressive symptoms, all three of which were ranked similarly. However, there was less agreement on the most important indicator of recovery, with 41% considering level of positive symptoms most important, 33% giving the highest ranking to level of cognitive/disorganized symptoms, and 28% ranking level of negative symptoms as most important.[Question 56]

Rank ordering of functional outcomes. When asked to rank order three functional outcomes as indicators of remission, the experts were divided, with 45% considering independent living, 32% occupational/education functioning, and 20% peer relationships the most important functional indicator of remission. This division among the panel may reflect the fact that one is unlikely to see major changes in any of these areas in the shorter time frame that is usually used to measure remission (see Guideline 21). However, when asked about the same functional outcomes as indicators of recovery, the majority (64%) felt that occupational/educational functioning was the most important functional outcome in recovery, followed by peer relationships (considered most important by 20%) and independent living (considered most important by 18%). When asked about the most appropriate way of defining functional improvement in their patients, 86% of the experts considered relative rather than absolute change in the patient the most appropriate indicator.[Questions 57 & 58]

(***bold italics*** = indicators receiving the highest rating from at least 50% of the experts)

Remission			**Recovery**
First Line	**High second line**	**Other second line**	**First line**
Level of positive symptoms	Level of cognitive/ disorganized symptoms Level of negative symptoms Level of depressive symptoms	Meaningful peer relationships Ability to live independently Occupational/educational functioning	Occupational/educational functioning Meaningful peer relationships Level of negative symptoms Ability to live independently Level of positive symptoms Level of cognitive/disorganized symptoms Level of depressive symptoms

Guideline 21: Severity and Duration of Symptoms as Indicators of Remission and Recovery[Questions 59 & 60]

We asked the experts what levels of symptom severity were most appropriate to use in defining remission and recovery. Their ratings are presented in the bar charts below. The majority of the experts would consider a patient in remission who had mild levels of positive, cognitive/disorganized, negative, and depressive symptoms (62%, 69%, 62%, and 73% of the experts, respectively). However, a third of the experts felt that no positive symptoms should be present for a patient to be considered in remission.

The experts' ratings shifted to the left when asked about indicators for recovery, with a majority (62%) saying that there should be no positive symptoms for a patient to be considered in recovery. In terms of negative symptoms, 62% of the panel would consider a patient in recovery who had mild negative symptoms while 33% would look for no negative symptoms. The panel was more evenly split as to whether a patient could have mild cognitive or depressive symptoms and still be considered in recovery.

Duration of symptoms. The expert panel said that the improvement in symptomatic indicators should be maintained for at least 3 months for a patient to be considered in remission and for a year or more for a patient to be considered in recovery. The experts believe that improvement in functional indicators (occupational/vocational functioning, independent living, peer relationships) needs to be maintained for somewhat longer, 15–17 months, for the patient to be considered in recovery.

Severity of symptoms as indicators of remission and recovery