

Commentary

Expert Consensus Guidelines for Optimizing Pharmacologic Treatment of Psychotic Disorders

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The clinical trials literature provides guidance concerning a relatively small portion of the decision-making process clinicians face in practice. The *Expert Consensus Guidelines* employ a quantified methodology for measuring expert opinion as a means of filling the gap in areas where the clinical trial literature is scant, conflicting, or unclear. A key goal of the *Expert Consensus Guidelines for Optimizing Pharmacologic Treatment of Psychotic Disorders* was to address issues that have become increasingly complicated in the face of a growing class of antipsychotics, such as dosage, titration, sequencing of medications, and integration of new treatments into the existing armamentarium. The *Guidelines* were developed based on responses to a written questionnaire that was completed by leading American experts on the treatment of psychotic disorders. This commentary reviews key points discussed in the *Guidelines* and highlights interesting responses to the survey.

TREATMENT SELECTION AND DOSAGE

The experts overwhelmingly endorsed the atypical antipsychotics for the treatment of psychotic disorders. Risperidone was the top choice for first-episode and multi-episode patients, with the other newer atypicals rated first-line or high second-line depending on the clinical situation. Clozapine and a long-acting injectable atypical antipsychotic (when available) were other high second-line options for multi-episode patients (Guidelines 1A and 1B). The experts' dosing recommendations were relatively consistent with the package labeling for the drugs, al-

though the experts indicated that, for olanzapine and quetiapine, they would use somewhat higher doses than those recommended by the manufacturer for acute usage (Guideline 2).

The responses concerning maintenance treatment and dose adjustments were especially interesting. In some cases, the experts recommended a lower dose for maintenance treatment than for acute treatment, but in other cases, they did not necessarily feel that the dose had to be lowered. The experts were more inclined to use lower doses during maintenance treatment with conventional antipsychotics, probably because of concern about the risk of tardive dyskinesia, while with the newer generation drugs, they were less concerned about tardive dyskinesia and may have felt less compelled to reduce dosage (Guideline 2). The experts' estimates of dose equivalency among the different antipsychotics were also relatively consistent with the labeling for the drugs and followed a linear pattern (Guidelines 5A and 5B).

With regard to dose adjustments when there is an inadequate response, many experts recommended increasing the dose, despite the fact that few data suggest that a dose increase is likely to enhance response. If there is an inadequate response, over 90% of the experts would increase the dose of clozapine and olanzapine, over 80% would increase the dose of quetiapine and risperidone, and approximately 60% would increase the dose of aripiprazole, ziprasidone, and the decanoate formulations of fluphenazine and haloperidol before switching to a different agent (Guideline 7).

TRIAL LENGTH

Drug trial duration is an important issue: we still have few valid data concerning the length of an adequate trial of antipsychotics. The experts indicated that an adequate trial duration in patients who are showing little or no response to initial antipsychotic treatment would be 3 to 6 weeks. If a patient had a partial response, the experts would be likely to wait somewhat longer—4 to 10 weeks—before considering another antipsychotic treatment (Guideline 4).

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SWITCHING STRATEGIES

Most experts recommended increasing the dose of a medication before switching to another treatment. If it is decided to switch to a different antipsychotic, the experts were consistent in recommending cross-titration when switching between the oral antipsychotics.

Cross-titration was a first-line recommendation when switching to clozapine and a high second-line option, along with overlap and taper, when switching to another oral atypical antipsychotic (Guideline 7D). Whenever possible, cross-titration is preferable to rapid discontinuation or rapid initiation. Some patients may have withdrawal effects that could be subtle or could be misdiagnosed, and clinicians should try to be cautious and discontinue any psychotropic drug slowly. In switching to a long-acting injectable antipsychotic, the experts recommended continuing treatment with the oral antipsychotic, either at the same dose or at a gradually tapered dose, until therapeutic levels of the injectable agent are reached, to ensure continuous medication coverage.

USE OF THERAPEUTIC DRUG MONITORING

Monitoring of plasma levels is used fairly common with clozapine and haloperidol, but not with the other antipsychotics. When asked for which antipsychotics plasma levels were available to the respondents and how they used such levels to adjust dosing, over 50% of respondents said that plasma levels for clozapine, haloperidol, and haloperidol decanoate were available to them, and over 50% used these levels to monitor compliance; 88% of the experts used plasma levels of clozapine and over 50% used levels of haloperidol to adjust dose levels in patients with inadequate response or problematic side effects (Guideline 3).

RELAPSE

Unfortunately, drug research often stops after determining whether an antipsychotic is efficacious in reducing acute positive symptoms. Few data are available concerning sequential treatment steps, including management of relapse. Given the lack of available data concerning managing relapse, the opinions of experts are highly relevant. However, clinicians often seem uncertain when deciding how to treat someone who relapses despite taking medication.

Concern remains as to how adequately clinicians can determine the level of a patient's compliance prior to relapse. Although the experts' responses clearly indicate that they believe long-acting injectable antipsychotics have an important role in the management of relapse, the editors note that such agents may come to play an even more prominent role in long-term management. Long-

acting injectable atypical antipsychotics were recommended as a low second-line option when treating a compliant patient who relapses. However, for patients about whose compliance clinicians are unsure of or who are noncompliant, the experts consider switching to a long-acting atypical antipsychotic as a first-line treatment recommendation (Guideline 8).

SWITCHING ANTIPSYCHOTICS

Few data address alternatives when switching antipsychotics. Although the experts certainly confirm the value of clozapine, there was some disparity in how many different medications from which classes they would try before switching a patient to clozapine. There still may be too much hesitancy to use clozapine. The most appropriate point at which to switch to clozapine remains controversial, and clinicians may want to consider fewer trials of other agents before switching patients to clozapine.

Risperidone was overwhelmingly listed as the top drug that clinicians would switch to after an inadequate response (Guideline 7B). Clozapine and olanzapine were listed as top choices when trying a second medication.

MONITORING FOR COMORBID CONDITIONS AND RISK FACTORS

Obesity is commonly associated with schizophrenia,¹ and patients with schizophrenia also appear to have an increased risk of diabetes. Given the fact that many antipsychotics can contribute to weight gain² and considering the lipophilic nature of many antipsychotics, clinicians should pay close attention to weight gain and lipid levels in patients with schizophrenia being treated with antipsychotics. Obesity and diabetes were considered the most important conditions to monitor for, followed by cardiovascular problems, HIV risk behavior, substance abuse, smoking, hypertension, and amenorrhea.

NONCOMPLIANCE

Clinicians rated the compliance levels of their own patients as substantially higher (43%) than that of patients reported in the literature (28%) (Guideline 11B). It is typical for us as clinicians to assume that our patients are more compliant than other patients, but these results show how easily clinicians can overestimate compliance in their patients. Compliance was defined as when a patient misses fewer than 20% of his or her medication doses, although the respondents preferred using a definition of missing less than 25% (Guideline 11A).

For patients who are perceived to be partially compliant, the experts consider psychosocial interventions the first choice. For patients who show evidence of noncompliance, the experts consider pharmacologic interventions

the first choice. Preferred psychosocial interventions were defined as patient education, family education and support, medication monitoring, and compliance therapy, which consisted of focused cognitive-behavioral therapy targeting compliance issues. Symptom and side effect monitoring and individual and group psychotherapy were also listed as options to be considered (Guideline 14B). The first-line pharmacologic strategy for partially compliant and noncompliant patients was switching to a long-acting atypical antipsychotic (Guideline 14C). It would be our preference to combine both psychosocial and pharmacologic interventions whenever possible, no matter what the level of compliance.

AGGRESSION, VIOLENCE, AND SUBSTANCE ABUSE

Aggression, violence, and substance abuse can complicate the course of mental illness. Although the experts seemed to assume that those complications were not due to noncompliance, this is an assumption that physicians should not necessarily make. Given the very strong possibility that partial compliance may be contributing to the emergence of aggressive or violent behavior, we would have liked to see long-acting injectable drugs play more of a role in the management of these problems, even though long-acting injectable atypical antipsychotics and olanzapine were only rated as high second-line options for aggression and violence. Clozapine and risperidone were the first-line choices for aggression and violence (Guideline 10A). Valproate and lithium were rated high second-line as adjunctive treatments for aggression and violence (Guideline 10B).

ADJUNCTIVE TREATMENT

Adjunctive treatment is an interesting topic because so many patients with psychotic disorders receive adjunctive treatments. However, the expert panel did not recommend any adjunctive treatments as first-line for complicating conditions, with the exception of selective serotonin reuptake inhibitors for dysphoria or depression.

CONCLUSION

Since the clinical trials literature can answer only some of the questions involved in the clinical decision-making process, *Expert Consensus Guidelines* can play an important role in filling in the gaps in the literature. The *Guidelines* also reveal expert opinions that are sometimes surprising concerning, for example, dosing and plasma levels, maintenance treatment, obesity, compliance, and the use of adjunctive treatment. We hope that the treatment recommendations presented in these *Guidelines*, which are based on an aggregate of expert opinion, when used in combination with the most up-to-date empirical data from clinical trials, will enable clinicians to provide the best treatment possible for their patients.

REFERENCES

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1. All of the following were recommended as first-line treatments for first-episode patients with predominantly positive symptoms *except*:
 - a. Risperidone
 - b. Olanzapine
 - c. Clozapine
 - d. Aripiprazole
2. For a first-episode patient with predominantly negative symptoms, the experts recommended use of oral conventional antipsychotics.
 - a. True
 - b. False
3. In a patient with a history of previous psychotic episodes, the experts did not recommend the use of _____ antipsychotics and gave only very limited support to the use of _____ antipsychotics.
 - a. Mid- or low-potency conventional; oral high-potency conventional
 - b. Oral atypical; mid- or low-potency conventional
 - c. Oral high-potency conventional; injectable atypical
 - d. Depot conventional; mid- or low-potency conventional
4. Clinicians recommended using slightly lower doses of antipsychotics during acute treatment than during maintenance treatment.
 - a. True
 - b. False
5. Over 50% of experts responded that they had plasma levels available to them only for:
 - a. Risperidone, ziprasidone, and haloperidol
 - b. Clozapine, quetiapine, and aripiprazole
 - c. Clozapine, haloperidol, and haloperidol decanoate
 - d. Aripiprazole, risperidone, and haloperidol decanoate
6. Adequate trial duration for a patient with little or no response to an initial antipsychotic was listed as:
 - a. 4 to 10 weeks
 - b. 1 to 2 weeks
 - c. 3 to 6 weeks
 - d. 5 to 11 weeks
7. Among clinicians, _____ would only sometimes consider a patient's weight in adjusting the dosage.
 - a. 75%
 - b. 45%
 - c. 15%
 - d. 89%
8. Before switching the antipsychotic, over 90% of experts said they would first increase doses of _____ and _____.
 - a. Clozapine and olanzapine
 - b. Quetiapine and risperidone
 - c. Aripiprazole and ziprasidone
 - d. Fluphenazine decanoate and haloperidol decanoate

9. All of the following were listed as the first medications that would be switched to after an inadequate response to another medication *except*:
- Risperidone
 - Olanzapine
 - Ziprasidone
 - Perphenazine
10. Overlap and taper was listed as a first-line recommendation when switching to clozapine from another oral antipsychotic agent.
- True
 - False
11. To manage relapse when the clinician has reason to believe the patient has been noncompliant with an oral antipsychotic regimen, the first-line recommendation is to:
- Switch to a long-acting conventional depot
 - Switch to a long-acting injectable atypical antipsychotic
 - Switch to a different oral antipsychotic
 - Add an adjunctive agent
12. In treating complicating problems such as aggression and violence, all of the following were listed as first-line and high second-line recommendations *except*:
- Haloperidol
 - Risperidone
 - A long-acting injectable atypical antipsychotic
 - Clozapine
13. In selecting adjunctive treatment for patients with complicating problems, physicians had no first-line treatment recommendations *except* _____ for depression:
- Electroconvulsive therapy
 - Glutamatergic agent
 - Selective serotonin reuptake inhibitor
 - Another antipsychotic
14. When asked to rate compliance (missing < 20% of medication doses), physicians often rated their own patients' compliance as substantially higher than that of patients reported in literature.
- True
 - False
15. Programmatic interventions were listed as the intervention of choice when treating noncompliant patients.
- True
 - False
16. Preferred programmatic or psychosocial interventions to improve compliance included all of the following *except*:
- Patient education
 - Family education and support
 - Supervised residential services
 - Medication monitoring

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