Recent Advances in the Antipsychotic Treatment of Schizophrenia

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The primary objectives in the treatment of schizophrenia are to reduce frequency and severity of psychotic exacerbation, ameliorate a broad range of symptoms, and improve functional capacity and quality of life. Treatment includes medication and a range of psychosocial interventions. Antipsychotics are the cornerstone of pharmacological treatment for schizophrenia. The nineteen antipsychotics available in our country have traditionally been classified into two major groups: first-generation (conventional) agents (FGAs) and second-generation (atypical) agents (SGAs). The one pharmacological property shared by all available antipsychotics is blockade of the dopamine D2 receptor that is considered relevant to antipsychotic action. There are significant differences among available agents in affinity for other neuroreceptors, helping to explain differences in their side-effect profiles.

Efficacy

Schizophrenia is characterized by positive (reality distortion and disorganization), negative, cognitive, and mood symptoms, with the types and severity of symptoms differing among patients and over the course of the illness. FGAs are effective in reducing positive symptoms (e.g., hallucinations, delusions), but are only minimally effective for negative and cognitive symptoms that contribute to much of the disability associated with schizophrenia. FGAs are also associated with serious treatment burdens, including acute EPS and tardive dyskinesia (TD). Since 1990, ten SGAs have been introduced into clinical practice and these were initially believed to be more efficacious and tolerable than the nine available FGAs. The SGAs rapidly displaced the FGAs and became the standard of care—currently over 90% of the antipsychotics used to treat schizophrenia belong to this group. However, results of recent large-scale studies, such as the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study, which compared one FGA (perphenazine) and four SGAs (olanzapine, quetiapine, risperidone, and ziprasidone), appeared to indicate that the SGAs may be no more effective than the FGAs and may not be associated with better cognitive or social outcomes. The European First Episode Schizophrenia Trial, which compared open-label treatment with haloperidol, amisulpride, olanzapine, quetiapine, or ziprasidone in first-episode schizophrenia, also suggested the absence of significant benefits for SGAs over FGAs.

Antipsychotics have consistently been found superior to placebo in reducing overall symptoms and risk of relapse in schizophrenia. A meta-analysis of haloperidol-controlled trials indicated that some SGAs (notably clozapine, olanzapine, amisulpride, and risperidone) but not others were more effective than haloperidol. Although this observation may be partly explained by differences in the haloperidol dose used in the different trials, this modest differential efficacy cannot be completely accounted for as a methodological artifact. In contrast, no major differences in efficacy among various antipsychotics have been observed in meta-analyses of placebo-controlled studies, with haloperidol found to have efficacy similar to the SGAs. While limited, comparisons of SGAs with low- and mid-potency FGAs and comparisons among the FGAs suggest no consistent differences in efficacy, except for clozapine's superiority in treatment-refractory schizophrenia. Finally, direct comparisons between various SGAs reveal inconsistent differences in efficacy,

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except for an advantage for clozapine in treatment-refractory schizophrenia. Comparative studies in the early stages of schizophrenia have also found no significant differences in efficacy among antipsychotics.

All available antipsychotics block the D2 receptor and have robust efficacy for positive symptoms and disorganization, with no consistent differences found in efficacy for these domains. Response over the first 2-4 weeks of antipsychotic therapy is highly predictive of long-term response. The maximum effect, however, may not be achieved for several months, and trajectories of response vary considerably across patients. Responsiveness to antipsychotics also varies as a function of stage of illness, with first-episode patients responding faster and at a higher rate than those at later stages of the illness. Antipsychotics are less consistently effective in reducing negative symptoms and much of their effect on negative symptoms may be associated with reduction in positive symptoms. While antipsychotics ameliorate negative symptoms linked with positive symptoms, they can worsen negative symptoms associated with EPS. Consequently, the net effect of an antipsychotic on negative symptoms is generally determined by the extent to which it reduces negative symptoms associated with positive symptoms and triggers negative symptoms related to EPS. Antipsychotic agents have no demonstrable efficacy against primary enduring ("deficit") negative symptoms. Similarly, antipsychotics can ameliorate depressive symptoms in conjunction with producing improvement in positive symptoms, but can also cause "neuroleptic dysphoria" associated with EPS. Although antipsychotics can improve attention in patients with schizophrenia, findings concerning their effects on other cognitive impairments are inconsistent and may include worsening. No consistent differences have been found among antipsychotics in effects on neurocognitive dysfunction, with net impact determined by the agent's beneficial effects on attention and deleterious effects due to EPS and anticholinergic activity of the antipsychotic and of anticholinergic agents used to treat EPS. Antipsychotic medications substantially decrease likelihood of relapse in schizophrenia, without any consistent differences among agents. Since medication nonadherence is common in schizophrenia, long-acting injectable antipsychotics may have an advantage over oral treatment in reducing relapse rates.

Safety and Tolerability

Antipsychotic medications cause a range of neurological, metabolic, cardiovascular, gastrointestinal, hematological, genitourinary, musculoskeletal, endocrine, and other side-effects. In contrast to their broadly similar efficacy, antipsychotics differ markedly in adverse-effect profiles. Compared with the FGAs, the SGAs have generally been believed to have a lower risk of EPS but a higher risk of metabolic adverse effects. However, due to differences in pharmacological profiles within the FGA and SGA classes, there is substantial variation within both classes in their propensity to cause EPS and metabolic adverse effects. Thus, no categorical distinction can be made between so-called FGAs and SGAs with regard to these risks. The 19 antipsychotic medications available in the United States also differ in their propensity to cause other side effects, such as sedation, hypotension, cardiac arrhythmias, prolactin elevation and related sexual dysfunction, and anticholinergic effects, with substantial variation within both the FGAs

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and the SGAs for each of these effects, without any definitive categorical separation between the two classes. Patients with schizophrenia also vary in their vulnerability to develop various adverse effects with different agents. The likelihood that a patient will develop a particular side effect thus depends on the agent selected, how that agent is used (e.g., dose, titration method, in combination with what other agents), and the patient's vulnerability.

Optimizing Individual Outcomes

Given the significant variability in drug pharmacokinetics and treatment responsivity in individual patients, it should be emphasized that broadly equivalent efficacy across patient groups does not translate into equal efficacy in individual patients. It is not currently possible to predict which antipsychotic may be optimal for a given patient. There is no best agent or best dose for all patients, although dose ranges for optimal effectiveness do appear to exist. Decisions about antipsychotic therapy therefore often entail a trial and error process involving careful monitoring of response and adverse effects, an ongoing risk-benefit assessment, and judicious switching if necessary. To achieve optimal therapy for schizophrenia, clinicians must balance efficacy benefits and side-effect costs of treatments in a way that is customized for the needs and vulnerabilities of the individual patient. The meticulous application of this approach can reduce the significant gap between what we know about best practices and the therapy that is actually provided for patients with schizophrenia.

TABLE

Summary

Schizophrenia is characterized by positive, negative, cognitive, disorganization, and mood symptoms. Antipsychotics are the mainstay of the pharmacological treatment of schizophrenia. Findings concerning efficacy for positive symptoms and disorganization suggest no consistent differences among available antipsychotics, with the exception of clozapine's superior efficacy for treatment-resistant schizophrenia. Efficacy for negative, depressive, and cognitive symptoms appears to be determined by 1) the extent to which reduction in positive symptoms brings about improvement in these other domains and 2) the extent to which extrapyramidal side effects (EPS) and anticholinergic effects (of the antipsychotic and of agents used to treat EPS) exacerbate them. Thus, the ability of antipsychotics to produce a potent antipsychotic effect without EPS and need for concomitant anticholinergic therapy yields multiple therapeutic benefits. In contrast to their broadly similar efficacy, antipsychotics differ markedly in their propensity to cause various adverse effects. Choice of antipsychotic medication should be based on individual preference, prior treatment response and side-effect experience, medical history and risk factors, and adherence history, with side-effect profile a major determinant of antipsychotic choice.

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References

1. Buchanan RW, Kreyenbuhl J, Kelly DL, et al. The 2009 Schizophrenia PORT psychopharmacological treatment recommendations and summary statements. Schizophr. *Bull.* 2010;**36** :71-93.
2. Kahn RS, Fleischhacker WW, Boter H, et al. Effectiveness of antipsychotic drugs in first-episode schizophrenia and schizophreniform disorder: an open randomized clinical trial. *Lancet.* 2008;**371**:1085–1097.
3. Kane J, Honigfeld G, Singer J, et al. Clozapine for the treatment-resistant schizophrenic: a double-blind comparison with chlorpromazine. *Arch. Gen Psychiatry.* 1988;**45**:789–796.
4. Leucht S, Corves C, Arbter D, et al. Second-generation versus first-generation antipsychotic drugs for schizophrenia: a meta-analysis. *Lancet.* 2009;**373**:31–41.
5. Lieberman JA, Stroup TS, McEvoy JP, et al. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *N Engl J Med* 2005;**353**:1209–1233.
6. Marder SR, Essock SM, Miller AM, et al. Physical health monitoring of patients with schizophrenia. *Am J Psychiatry.* 2004;**161**:1334–1349.
7. McEvoy JP, Lieberman JA, Stroup JP, et al. Effectiveness of clozapine versus olanzapine, quetiapine, and risperidone in patients with chronic schizophrenia who did not respond to prior antipsychotic treatment. *Am J Psychiatry.* 2006;**163**:600–610.
8. Tandon R, Nasrallah HA, Keshavan MS. Schizophrenia, "just the facts" 5. Treatment and prevention. *Schizophr Res.* 2010;122:1–23.
9. Tandon R, Moller H-J, Belmaker RH, et al. World Psychiatry Association Pharmacopsychiatry Section statement on comparative effectiveness of antipsychotics in the treatment of schizophrenia. *Schizophr Res.* 2008;**100**:20–38.

Steps to achieve optimum outcomes with currently available antipsychotics

1. Considerations in selecting the best antipsychotic for a particular patient

- Equivalent efficacy across agents
- Individual variability in response
- No good predictor of individual response to different agents
- Different agents have different side effects
- Different patients have different vulnerabilities and preferences

2. Proper antipsychotic trial sequence

- Begin with systematic 6-10 week trial of one antipsychotic with optimal dosing
- If inadequate response, follow with systematic trial of monotherapy with one or more other antipsychotics at adequate dose and duration
- If inadequate response, follow with a trial of clozapine or a long-acting antipsychotic
- Follow with a trial of clozapine, if not tried before
- Only then consider other strategies (e.g., antipsychotic polypharmacy)

3. Good practice guidelines for ongoing antipsychotic treatment

- Measurement-based individualized care
- Repeated assessment of efficacy using reliably defined treatment targets (facilitated by use of standard rating scales)
- Careful assessment of adverse effects
- Care consistent with health monitoring protocols
- Standard protocols customized to individual vulnerabilities/needs and specific agent
- Ongoing collaboration with patient in decision-making