Antipsychotics in the Treatment of Schizophrenia: An Overview

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Schizophrenia is characterized by positive, negative, cognitive, disorganization, and mood symptoms. Antipsychotics are the mainstay in the pharmacologic 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. Although second-generation antipsychotics (SGAs) have generally been believed to be associated with a lower risk of EPS but a higher risk of metabolic adverse effects than first-generation agents (FGAs), the substantial variation in these and other side effects among agents within both classes indicates that it is not clinically useful to make a categorical distinction between FGAs and SGAs. 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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Schizophrenia is a chronic remitting and relapsing psychotic disorder associated with significant impairment in social and vocational functioning[1–3] and an average reduction in lifespan of 15 to 25 years.[3–5] Treatment includes medication and a range of psychosocial interventions.[6] The objectives of treatment are to reduce frequency and severity of psychotic exacerbation, ameliorate a broad range of symptoms, and improve functional capacity and quality of life. Until the introduction of antipsychotic medications a half-century ago, standard treatment for schizophrenia consisted of providing patients with a safe and supportive environment in a long-stay psychiatric hospital. The introduction of chlorpromazine, the first antipsychotic medication, sparked a revolution in the pharmacotherapy of schizophrenia.[7] Since that time, antipsychotics have become the cornerstone of pharmacologic treatment for schizophrenia.

PHARMACOLOGY OF ANTIPSYCHOTIC AGENTS

More than 60 antipsychotic medications have been developed over the past half-century, 20 of which are currently available in the United States (Figure 1). Antipsychotics have traditionally been classified into 2 major groups: first-generation (conventional) agents (FGAs) and second-generation (atypical) agents (SGAs). The one pharmacologic property shared by all available antipsychotics is blockade of the dopamine D_2 receptor (eg, antagonism or, in the case of aripiprazole, partial agonism).[8,9] Both direct blockade of the D_2 receptor and secondary depolarization blockade appear relevant to antipsychotic action.[10] Thus, these agents have their onset of action within a few days and then achieve much of their antipsychotic effect over several weeks.[11,12] However, the currently available antipsychotics differ in the extent to which they block the D_2 receptor at clinically relevant doses (indicated by percentage of receptor occupancy), which has implications for their clinical attributes. For example, 60% receptor occupancy is believed to be needed for antipsychotic effect, 70% occupancy is associated with elevated prolactin levels, and 80% occupancy is associated with extrapyramidal side effects (EPS).[8,9] There are also significant differences among available agents in affinity for other neuroreceptors, helping to explain differences in their side effect profiles.[13]

COMPARATIVE EFFECTIVENESS

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 (eg, hallucinations, delusions), but are only minimally effective for negative and cognitive symptoms, which contribute to much of the disability associated with schizophrenia.[3] FGAs are also associated with serious treatment burdens, including acute EPS and tardive dyskinesia (TD).[14]

Clozapine, the first so-called "atypical" or SGA, was introduced in the late 1960s. The introduction of clozapine discredited the belief that EPS are an unavoidable accompaniment of antipsychotic efficacy.[9] Although clozapine does not cause EPS or TD, its other adverse effects, in particular agranulocytosis, have substantially limited its use and prevented it from being approved for clinical use in most parts of the world until the past 2 decades (clozapine became available in the United States in 1990). When clozapine was found to be more effective than the FGAs in treatment-

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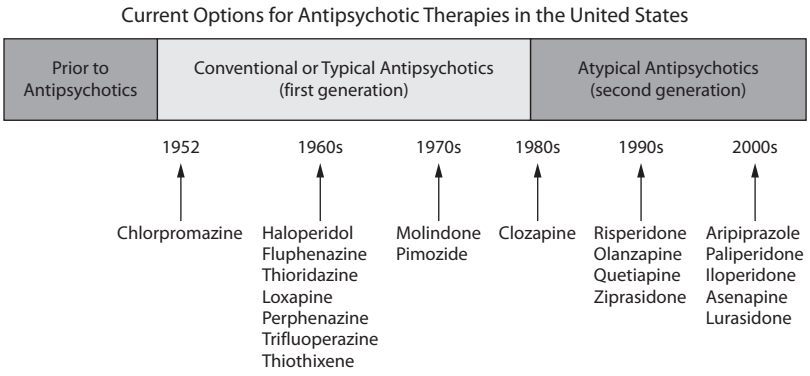
Figure 1. Historical Development of Antipsychotic Medications



refractory schizophrenia[15] and in reducing suicidality[16] and to be relatively devoid of significant short- and long-term motor side effects, this spurred research to develop more effective and safer antipsychotics. These efforts to develop "a safer clozapine" have led to the approval of 9 additional SGAs (Figure 1) in the United States over the past 15 years. Initially believed to be more efficacious and tolerable than the 10 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 1 FGA (perphenazine) and 4 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.[17,18] (Note, however, that CATIE excluded patients with a history of significant EPS from the group receiving perphenazine; thus, the results are primarily applicable to patients with low vulnerability for EPS.[19]) 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.[20] Research continues to compare the effectiveness of currently available antipsychotics. In this article, we summarize data on comparative efficacy, side effects, and impact on overall outcomes.[21,22]

Efficacy

Antipsychotics have consistently been found superior to placebo in reducing overall symptoms and risk of relapse in schizophrenia.[23,24] 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.[25] Although this observation may be partly explained by differences in the haloperidol dose used in the various trials,[26] this modest differential efficacy cannot be completely accounted for as a methodological artifact.[27] In contrast, no major differences in efficacy among various antipsychotics have been observed in meta-analyses of placebo-controlled studies,[28] 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.[15] Finally, direct comparisons between various SGAs reveal inconsistent differences in efficacy, except for an advantage for clozapine in treatment-refractory schizophrenia[29,30] and greater treatment persistence with olanzapine in chronic schizophrenia.[17,31] Comparative studies in the early stages of schizophrenia have also found no significant differences in efficacy among antipsychotics.[32]

Positive symptoms and disorganization. All available antipsychotics block the D_2 receptor and have robust efficacy for positive symptoms and disorganization,[3,28] 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.[33] However, the maximum effect 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.[30]

Negative symptoms. 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.[34,35] 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.[34]

Depressive symptoms. Similarly, antipsychotics can ameliorate depressive symptoms in conjunction with producing improvement in positive symptoms, but can also cause "neuroleptic dysphoria" associated with EPS.[36]

Cognitive symptoms. Although antipsychotics can improve attention in patients with schizophrenia, findings concerning their effects on other cognitive impairments are inconsistent and may include worsening.[37] No consistent differences have been found among antipsychotics in effects on neurocognitive dysfunction,[18] 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.

Relapse prevention. Antipsychotic medications substantially decrease likelihood of relapse in schizophrenia,[24] 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.[38]

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Safety and Tolerability

Adverse effects. Antipsychotic medications cause a range of neurologic, metabolic, cardiovascular, gastrointestinal, hematologic, genitourinary, musculoskeletal, endocrine, and other side effects.[39–47] 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 pharmacologic 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.[44,48] The 20 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 and the SGAs for each of these effects, without any definitive categorical separation between the 2 classes.

Patient vulnerability. 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 (eg, dose, titration method, in combination with what other agents), and the patient's vulnerability.

Impact on Overall Outcome

Untreated schizophrenia is associated with increased mortality, poor vocational and social functioning, and reduced quality of life.[3,4] Although antipsychotics ameliorate a range of symptoms and reduce the likelihood of relapse in schizophrenia, the extent to which treatment improves lifespan and psychosocial functioning is less clear. Despite use of FGAs and SGAs, the mortality gap has increased for patients with schizophrenia[4] and recent studies of mortality in schizophrenia have yielded mixed results.[49–51] Whereas Ren et al[49] observed no differences in mortality between treated and never-treated patients with schizophrenia, Tiihonen et al[50] observed lower mortality rates in association with long-term antipsychotic use. They also found different mortality rates with different agents, with clozapine associated with substantially lower mortality than other antipsychotics. Given clozapine's greater risk of adverse effects that would be expected to increase mortality risk (eg, agranulocytosis, seizures, metabolic syndrome), this finding is puzzling. Although the study had some notable methodological limitations,[51] the authors believed this finding was related to better symptom control and treatment adherence with clozapine.[52]

The impact of antipsychotic treatment on social functioning and quality of life in schizophrenia has not been well defined. Although beneficial effects on employment and reductions in disability have been reported,[53] such effects have been inconsistently documented. As a consequence, increasing research efforts are focused on developing new agents with efficacy for treating the cognitive and negative symptoms of schizophrenia.[6]

PSYCHOSOCIAL TREATMENTS

Although this overview focuses on pharmacologic treatment, a variety of psychological and social interventions are needed to optimize recovery and should constitute an essential part of treatment for schizophrenia.[6] Research on psychosocial approaches has demonstrated the efficacy of cognitive-behavioral therapy, social skills training, family psychoeducation, assertive community treatment, and supported employment,[6] and these approaches are recommended in the recent publication on psychosocial interventions by the Schizophrenia Patient Outcomes Research Team (PORT).[54]

OPTIMIZING OUTCOMES FOR PERSONS WITH SCHIZOPHRENIA

"Atypicality," or the ability of antipsychotics to produce a potent antipsychotic effect without EPS and the need for concomitant anticholinergic therapy, yields multiple therapeutic benefits[6,13] and varies substantially across patients and different agents. Although SGAs are generally more likely than FGAs to produce this effect consistently in a larger proportion of patients,[22] given the substantial variation among individual FGAs and SGAs in EPS liability, the formal FGA-SGA dichotomy is not useful.[6,25,48]

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 (Table 1). Nevertheless, just as it is important not to exaggerate what existing treatments for schizophrenia can offer, it is equally important not to discount what they can do. Both the initial introduction of the FGAs in the 1950s and the subsequent introduction of the SGAs in the 1990s represented meaningful steps in our efforts to provide effective treatment for individuals with schizophrenia.

CONCLUSION

Evolving pharmacologic and psychosocial treatments for schizophrenia have generated great excitement over the past 2 decades but only modest improvements in the lives of people with schizophrenia. Available treatments are only partially effective and are associated with a range of adverse effects. While the limitations in our current therapeutic

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Table 1. 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
Switching is risky so it is important to try to select the right first agent
Best outcomes achieved by matching patient's side effect vulnerabilities to the agent's pharmacologic profile
2. Proper Antipsychotic Trial Sequence
Begin with systematic 6- to 10-week trial of 1 antipsychotic with optimal dosing
If inadequate response, follow with systematic trial of monotherapy with 1 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 (eg, antipsychotic polypharmacy)[a]
3. Good Practice Guidelines for Ongoing Antipsychotic Treatment
Measurement-based individualized care
Ongoing careful monitoring essential
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 (eg, of the American Diabetes Association et al[56])
Standard protocols customized to individual vulnerabilities/needs and specific agent
Ongoing collaboration with patient in decision making

[a]Given limitations of antipsychotics for treating the various symptom domains of schizophrenia, clinicians often use combinations of antipsychotics and adjunctive treatment with other agents, but evidence of the effectiveness of these approaches for schizophrenia is generally weak at best.[55]

armamentarium are obvious, it is also clear that "usual treatment" generally falls far short of what can be achieved. The difficulty of translating the range of pharmacologic and psychosocial evidence-based treatments for schizophrenia into better outcomes for persons with schizophrenia is underscored by the marked variation in treatment practices and patient outcomes across different systems of care.

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.[22] 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. Key practices that can help reduce the efficacy-effectiveness gap include the following:

1. Being aware of what different treatments can and cannot do.
2. Practicing evidence-based medicine.[22,57]
3. Precisely defining treatment targets for patients based on informed personal preferences, individual vulnerabilities, and needs (eg, taking into account goals important to the specific patient, such as being able to go to school, work, stay off substances).[6,57]
4. Measuring the full impact (benefit-to-risk ratio) of individual treatments in each patient using measurement-based care in conjunction with a protocol-based approach to such measurement.[6,58]
5. Using collaborative informed decision-making on an ongoing basis, evaluating patient needs and preferences, measured effects of current treatments, and available treatment options at each stage.[6]

Even as we await development of more efficacious treatments with fewer adverse effects in the future, today we can do a much better job of utilizing existing treatments to optimize individual outcomes and reduce the considerable morbidity and mortality associated with schizophrenia.

Drug names: aripiprazole (Abilify), asenapine (Saphris), clozapine (Clozaril, FazaClo, and others), haloperidol (Haldol and others), iloperidone (Fanapt), lurasidone (Latuda), molindone (Moban), olanzapine (Zyprexa), pimozide (Orap), paliperidone (Invega), quetiapine (Seroquel), risperidone (Risperdal and others), thiothixene (Navane and others), ziprasidone (Geodon).

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REFERENCES

1. Tandon R, Keshavan MS, Nasrallah HA. Schizophrenia, "just the facts": what we know in 2008, pt 1: overview. *Schizophr Res*. 2008;100(1–3):4–19.
2. Hegarty JD, Baldessarini RJ, Tohen M, et al. One hundred years of schizophrenia: a meta-analysis of the outcome literature. *Am J Psychiatry*. 1994;151(10):1409–1416.
3. Tandon R, Nasrallah HA, Keshavan MS. Schizophrenia, "just the facts," 4: clinical features and conceptualization. *Schizophr Res*. 2009;110(1–3):1–23.
4. Saha S, Chant D, McGrath J. A systematic review of mortality in schizophrenia: is the differential mortality gap worsening over time? *Arch Gen Psychiatry*. 2007;64(10):1123–1131.
5. Tandon R, Keshavan MS, Nasrallah HA. Schizophrenia, "just the facts," 1: what we know in 2008, 2: epidemiology and etiology. *Schizophr Res*. 2008;102(1–3):1–18.
6. Tandon R, Nasrallah HA, Keshavan MS. Schizophrenia, "just the facts," 5: treatment and prevention: past, present, and future. *Schizophr Res*. 2010;122(1–3):1–23.
7. Delay J, Deniker P, Karl J. Traitement des etats d'excitation et d'agitation par une methode medicamenteuse derive de l'hibernotherapie. *Ann Medicopsychol*. 1952;119:267–273.
8. Kapur S, Remington G. Dopamine D(2) receptors and their role in atypical antipsychotic action: still necessary and may even be sufficient. *Biol Psychiatry*. 2001;50(11):873–883.
9. Kapur S, Zipursky R, Jones C, et al. Relationship between dopamine D(2) occupancy, clinical response, and side effects: a double-blind PET study of first-episode schizophrenia. *Am J Psychiatry*. 2000;157(4):514–520.
10. Kapur S, Mizrahi R, Li M. From dopamine to salience to psychosis—linking biology, pharmacology and phenomenology of psychosis. *Schizophr Res*. 2005;79(1):59–68.
11. Emsley R, Rabinowitz J, Medori R. Time course for antipsychotic treatment response in first-episode schizophrenia. *Am J Psychiatry*. 2006;163(4):743–745.
12. Leucht S, Busch R, Hamann J, et al. Early-onset hypothesis of antipsychotic drug action: a hypothesis tested, confirmed and extended. *Biol Psychiatry*. 2005;57(12):1543–1549.

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13. Tandon R, Jibson MD. Efficacy of newer generation antipsychotics in the treatment of schizophrenia. *Psychoneuroendocrinology*. 2003;28(suppl 1): 9–26.
14. Nasrallah HA, Tandon R. Classic antipsychotic medications. In: Nemeroff C, Schatzberg A, eds. *American Psychiatric Press Textbook of Psychopharmacology*. 4th ed. Washington, DC: American Psychiatric Press; 2009:533–554.
15. 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(9):789–796.
16. Meltzer HY, Alphs L, Green AI, et al; International Suicide Prevention Trial Study Group. Clozapine treatment for suicidality in schizophrenia: International Suicide Prevention Trial (InterSePT). *Arch Gen Psychiatry*. 2003;60(1):82–91.
17. Lieberman JA, Stroup TS, McEvoy JP, et al; Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Investigators. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *N Engl J Med*. 2005;353(12):1209–1223.
18. Keefe RS, Bilder RM, Davis SM, et al; Neurocognitive Working Group. Neurocognitive effects of antipsychotic medications in patients with chronic schizophrenia in the CATIE Trial. *Arch Gen Psychiatry*. 2007; 64(6):633–647.
19. Rankupalli B, Tandon R. Practicing evidence-based psychiatry, 1: applying a study's findings: the threats to validity approach. *Asian J Psychiatr*. 2010;3(1):35–40.
20. Kahn RS, Fleischhacker WW, Boter H, et al; EUFEST study group. Effectiveness of antipsychotic drugs in first-episode schizophrenia and schizophreniform disorder: an open randomised clinical trial. *Lancet*. 2008;371(9618):1085–1097.
21. Kane JM, Leucht S, Carpenter D, et al; Expert Consensus Panel for Optimizing Pharmacologic Treatment of Psychotic Disorders. The Expert Consensus Guideline Series. Optimizing pharmacologic treatment of psychotic disorders. Introduction: methods, commentary, and summary. *J Clin Psychiatry*. 2003;64(suppl 12):5–19.
22. Tandon R, Belmaker RH, Gattaz WF, et al; Section of Pharmacopsychiatry, World Psychiatric Association. World Psychiatric Association Pharmacopsychiatry Section statement on comparative effectiveness of antipsychotics in the treatment of schizophrenia. *Schizophr Res*. 2008;100(1–3):20–38.
23. Adams CE, Coutinho E, Davis JM, et al. Cochrane Schizophrenia Group publications. *The Cochrane Library.* Chichester, United Kingdom: John Wiley and Sons; 2009 (szg.cochrane.org, accessed July 19, 2011).
24. Leucht S, Barnes TRE, Kissling W, et al. Relapse prevention in schizophrenia with new-generation antipsychotics: a systematic review and exploratory meta-analysis of randomized, controlled trials. *Am J Psychiatry*. 2003;160(7):1209–1222.
25. Leucht S, Corves C, Arbter D, et al. Second-generation versus first-generation antipsychotic drugs for schizophrenia: a meta-analysis. *Lancet*. 2009;373(9657):31–41.
26. Hugenholtz GW, Heerdink ER, Stolker JJ, et al. Haloperidol dose when used as active comparator in randomized controlled trials with atypical antipsychotics in schizophrenia: comparison with officially recommended doses. *J Clin Psychiatry*. 2006;67(6):897–903.
27. Haj-Ibrahim J, Tandon R. Practicing evidence-based psychiatry, 2: interpreting integrative literature: systematic reviews and meta-analyses. *Asian J Psychiatr*. 2011;4(1):80–85.
28. Leucht S, Arbter D, Engel RR, et al. How effective are second-generation antipsychotic drugs? a meta-analysis of placebo-controlled trials. *Mol Psychiatry*. 2009;14(4):429–447.
29. McEvoy JP, Lieberman JA, Stroup TS, et al; CATIE Investigators. Effectiveness of clozapine versus olanzapine, quetiapine, and risperidone in patients with chronic schizophrenia who did not respond to prior atypical antipsychotic treatment. *Am J Psychiatry*. 2006;163(4):600–610.
30. Chakos M, Lieberman J, Hoffman E, et al. Effectiveness of second-generation antipsychotics in patients with treatment-resistant schizophrenia: a review and meta-analysis of randomized trials. *Am J Psychiatry*. 2001;158(4):518–526.
31. Leucht S, Komossa K, Rummel-Kluge C, et al. A meta-analysis of head-to-head comparisons of second-generation antipsychotics in the treatment of schizophrenia. *Am J Psychiatry*. 2009;166(2):152–163.
32. Salimi K, Jarskog LF, Lieberman JA. Antipsychotic drugs for first-episode schizophrenia: a comparative review. *CNS Drugs*. 2009;23(10): 837–855.
33. Kinon BJ, Chen L, Ascher-Svanum H, et al. Early response to antipsychotic drug therapy as a clinical marker of subsequent response in the treatment of schizophrenia. *Neuropsychopharmacology*. 2010; 35(2):581–590.
34. Stahl SM, Buckley PF. Negative symptoms of schizophrenia: a problem that will not go away. *Acta Psychiatr Scand*. 2007;115(1):4–11.
35. Tandon R, Ribeiro SCM, DeQuardo JR, et al. Covariance of positive and negative symptoms during neuroleptic treatment in schizophrenia: a replication. *Biol Psychiatry*. 1993;34(7):495–497.
36. Voruganti L, Awad AG. Neuroleptic dysphoria: towards a new synthesis. *Psychopharmacology (Berl)*. 2004;171(2):121–132.
37. Hill SK, Bishop JR, Palumbo D, et al. Effect of second-generation antipsychotics on cognition: current issues and future challenges. *Expert Rev Neurother*. 2010;10(1):43–57.
38. Adams CE, Fenton MKP, Quraishi S, et al. Systematic meta-review of depot antipsychotic drugs for people with schizophrenia. *Br J Psychiatry*. 2001;179(4):290–299.
39. Allison DB, Mentore JL, Heo M, et al. Antipsychotic-induced weight gain: a comprehensive research synthesis. *Am J Psychiatry*. 1999;156(11): 1686–1696.
40. Glassman AH, Bigger JT Jr. Antipsychotic drugs: prolonged QTc interval, torsade de pointes, and sudden death. *Am J Psychiatry*. 2001; 158(11):1774–1782.
41. Haddad PM, Wieck A. Antipsychotic-induced hyperprolactinaemia: mechanisms, clinical features and management. *Drugs*. 2004;64(20): 2291–2314.
42. Kane JM. Tardive dyskinesia circa 2006. *Am J Psychiatry*. 2006;163(8): 1316–1318.
43. Newcomer JW, Haupt DW. The metabolic effects of antipsychotic medications. *Can J Psychiatry*. 2006;51(8):480–491.
44. Weiden PJ. EPS profiles: the atypical antipsychotics are not all the same. *J Psychiatr Pract*. 2007;13(1):13–24.
45. Smith M, Hopkins D, Peveler RC, et al. First- v second- generation antipsychotics and risk for diabetes in schizophrenia: systematic review and meta-analysis. *Br J Psychiatry*. 2008:192:406–411.
46. Ozbilen M, Adams CE. Systematic overview of Cochrane reviews for anticholinergic effects of antipsychotic drugs. *J Clin Psychopharmacol*. 2009;29(2):141–146.
47. Ray WA, Chung CP, Murray KT, et al. Atypical antipsychotic drugs and the risk of sudden cardiac death. *N Engl J Med*. 2009;360(3):225–235.
48. Fischer-Barnicol D, Lanquillon S, Haen E, et al; Working Group 'Drugs in Psychiatry.' Typical and atypical antipsychotics—the misleading dichotomy: results from the Working Group 'Drugs in Psychiatry' (AGATE). *Neuropsychobiology*. 2008;57(1–2):80–87.
49. Ran MS, Chan CL-W, Chen EY-H, et al. Differences in mortality and suicidal behaviour between treated and never-treated people with schizophrenia in rural China. *Br J Psychiatry*. 2009;195(2):126–131.
50. Tiihonen J, Lönnqvist J, Wahlbeck K, et al. 11-year follow-up of mortality in patients with schizophrenia: a population-based cohort study (FIN11 study). *Lancet*. 2009;374(9690):620–627.
51. De Hert M, Correll CU, Cohen D. Do antipsychotic medications reduce or increase mortality in schizophrenia? a critical appraisal of the FIN-11 study. *Schizophr Res*. 2010;117(1):68–74.
52. Tiihonen J, Wahlbeck K, Lonnqvist J, et al. Effectiveness of antipsychotic treatments in a nation-wide cohort of patients in community care after first hospitalisation due to schizophrenia and schizoaffective disorder: observational follow-up study. *BMJ*. 2006;333(7561):224.
53. Thirthalli J, Venkatesh BK, Kishorekumar KV, et al. Prospective comparison of course of disability in antipsychotic-treated and untreated schizophrenia patients. *Acta Psychiatr Scand*. 2009;119(3):209–217.
54. Dixon LB, Dickerson F, Bellack AS, et al; Schizophrenia Patient Outcomes Research Team (PORT). The 2009 schizophrenia PORT psychosocial treatment recommendations and summary statements. *Schizophr Bull*. 2010;36(1):48–70.
55. Correll CU, Rummel-Kluge C, Corves C, et al. Antipsychotic combinations vs monotherapy in schizophrenia: a meta-analysis of randomized controlled trials. *Schizophr Bull*. 2009;35(2):443–457.
56. American Diabetes Association, American Psychiatric Association, American Association of Clinical Endocrinologists, et al. Consensus development conference on antipsychotic drugs and obesity and diabetes. *J Clin Psychiatry*. 2004;65(2):267–272.
57. Tandon R, Targum SD, Nasrallah HA, et al; Treatment Effectiveness in Schizophrenia Consortium. Strategies for maximizing clinical effectiveness in the treatment of schizophrenia. *J Psychiatr Pract*. 2006;12(6):348–363.
58. Marder SR, Essock SM, Miller AL, et al. Physical health monitoring of patients with schizophrenia. *Am J Psychiatry*. 2004;161(8):1334–1349.