Clinical and Practical Psychopharmacology

Antipsychotic Drugs in Schizophrenia:
Relative Effects in Patients With and Without Treatment Resistance

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Each month in his online column, Dr Andrade considers theoretical and practical ideas in clinical psychopharmacology with a view to update the knowledge and skills of medical practitioners who treat patients with psychiatric conditions.

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ABSTRACT

How antipsychotic drugs compare in schizophrenia, and especially in medication-refractory schizophrenia, is a subject of considerable interest. Two network meta-analyses and 1 direct comparison meta-analysis recently compared antipsychotics in schizophrenia patients with and without documented treatment resistance. One network meta-analysis of antipsychotic drugs in non-refractory patients found clear efficacy advantages for clozapine, amisulpride, olanzapine, and risperidone. One network meta-analysis of antipsychotic drugs in refractory patients found a clear efficacy advantage for olanzapine; surprisingly, in this meta-analysis, clozapine was superior to first-generation but not second-generation antipsychotics. One direct comparison meta-analysis found clozapine generally superior to first- and second-generation antipsychotics, with advantages more clearly apparent in studies that were 3 months in duration or less. Drug discontinuation and adverse effect data from these meta-analyses are presented, and issues arising from the results are briefly discussed. At the risk of oversimplification, it appears that clozapine retains its preeminence in medication-refractory schizophrenia and that clozapine and olanzapine are both associated with superior efficacy outcomes in non-refractory patients. Interestingly, haloperidol, generally considered a reference neuroleptic and a reference comparator drug, fared poorly in most comparisons.

Introduction

A large number of typical and atypical antipsychotics are available around the world, offering psychiatrists a choice of plenty for the treatment of schizophrenia. How do these drugs compare in their efficacy and adverse effect profile? Three recent meta-analyses[1–3] addressed the subject from different angles. These meta-analyses are rather detailed and contain some unexpected findings. The present article therefore summarizes the findings of these meta-analyses and offers the reader a critical perspective.

A Comparison of Antipsychotic Drugs in Non-Refractory Schizophrenia

Leucht et al[1] described a Bayesian-framework, multiple-treatments meta-analysis that utilized both direct and indirect comparisons to create a hierarchy for efficacy (based on psychopathology ratings) along with 6 other outcome measures. The authors searched computerized databases and other sources and identified 212 placebo-controlled, short-term (4–12 weeks), blinded randomized controlled trials (RCTs) (pooled N = 43,049) of 15 antipsychotic drugs administered as monotherapy in acute schizophrenia, schizoaffective disorder, schizophreniform disorder, and related psychotic conditions, as diagnosed using any criteria. Trials were excluded if they were conducted in stable patients, in those with predominantly negative symptoms, in those with concurrent medical illness, and in those with refractory illness.

The largest quantity of data was available for haloperidol, olanzapine, and risperidone. The mean age of the patients in the RCTs was about 38 years, and the mean duration of illness was about 12 years. Two-thirds (n = 144) of the studies were industry-driven. Only 9 studies were conducted in first-episode patients.

Psychopathology ratings. All 15 antipsychotic drugs outperformed placebo on the Positive and Negative Syndrome Scale (PANSS) or Brief Psychiatric Rating Scale. The effect size was large for clozapine (standardized mean difference [SMD], 0.88); intermediate for amisulpride, olanzapine, risperidone, and paliperidone (SMDs between 0.50 and 0.66); and small for zotepine, haloperidol, quetiapine, aripiprazole, sertindole, ziprasidone, chlorpromazine, asenapine, lurasidone, and iloperidone (SMDs between 0.33 and 0.49) (Table 1). The number needed to treat (NNT) favoring medication ranged from 6 with amisulpride to 20 with haloperidol.

The network meta-analysis identified substantial differences in efficacy between the different drugs. Clozapine emerged as the best antipsychotic in the hierarchy, followed by amisulpride, olanzapine, and risperidone (Table 2).

Drug discontinuation. The overall all-cause discontinuation rate was 35%. Among patients who discontinued treatment, the commonest reason for discontinuation was treatment inefficacy (40%). Adverse events were responsible for only 17% of dropouts. Olanzapine, amisulpride, and clozapine were associated with the most favorable all-cause discontinuation profiles. Importantly, almost all antipsychotic

Chittaranjan Andrade

- In schizophrenia patients who are not refractory to medications, clozapine and amisulpride are associated with the best efficacy outcomes. However, olanzapine and risperidone are also associated with more favorable efficacy outcomes than many other antipsychotic drugs.
- Clozapine and olanzapine are associated with the best efficacy outcomes in medication-refractory schizophrenia.
- Haloperidol is associated with poorer outcomes than many other antipsychotic drugs in both non-refractory and refractory schizophrenia.

Table 1. Magnitude of Reduction in Schizophrenia Psychopathology Ratings With Antipsychotic Drugs Relative to Placebo[a]

Drug	SMD	95% CI
Clozapine	0.88	0.73–1.03
Amisulpride	0.66	0.53–0.78
Olanzapine	0.59	0.53–0.65
Risperidone	0.56	0.50–0.63
Paliperidone	0.50	0.39–0.60
Zotepine	0.49	0.31–0.66
Haloperidol	0.45	0.39–0.51
Quetiapine	0.44	0.35–0.52
Aripiprazole	0.43	0.34–0.52
Sertindole	0.39	0.26–0.52
Ziprasidone	0.39	0.30–0.49
Chlorpromazine	0.38	0.23–0.54
Asenapine	0.38	0.25–0.51
Lurasidone	0.33	0.21–0.45
Iloperidone	0.33	0.22–0.43

[a]Data from the network meta-analysis of Leucht et al.[1] Drugs are listed in order of effect size, from largest to smallest.
Abbreviations: CI = credible interval, SMD = standardized mean difference.

drugs were associated with a lower all cause discontinuation rate than placebo (Table 3).

Weight gain. All antipsychotics were associated with significant weight gain relative to placebo, except for haloperidol, ziprasidone, and lurasidone; iloperidone, clozapine, zotepine, and olanzapine were associated with the greatest weight gain (SMDs, 0.62 to 0.74). These data were summarized in an earlier article in this column and are therefore not repeated here.[4]

Extrapyramidal adverse effects. The risk of extrapyramidal adverse effects, as compared with placebo, and operationalized by the use of antiparkinsonian drugs, was lowest with clozapine (odds ratio [OR], 0.30) and highest with haloperidol (OR, 4.76) (Table 4).

Sedation. Amisulpride, paliperidone, sertindole, and iloperidone were not associated with statistically significant sedation, although the ORs and especially the 95% confidence intervals (CIs) did imply likelihood of risk. There was significant risk of sedation with the remaining drugs in the following order of lowest to highest: aripiprazole (OR, 1.84), lurasidone (OR, 2.45), risperidone (OR, 2.45), haloperidol (OR, 2.76), asenapine (OR, 3.28), olanzapine (OR, 3.34), quetiapine (OR, 3.76), ziprasidone (OR, 3.80), chlorpromazine (OR, 7.56), zotepine (OR, 8.15), and clozapine (OR, 8.82).

Table 2. Relative Efficacy of Different Antipsychotic Drugs in Schizophrenia[a]

1. Clozapine was superior to all the other antipsychotics, with SMDs ranging from 0.22 to 0.55.
2. Amisulpride was superior to all the other antipsychotics (SMDs, 0.16 to 0.33) except clozapine, olanzapine, risperidone, and zotepine.
3. Olanzapine was superior to all the other antipsychotics (SMDs, 0.14 to 0.26) except clozapine, amisulpride, risperidone, paliperidone, and zotepine.
4. Risperidone was superior to all the other antipsychotics (SMDs, 0.11 to 0.24) except clozapine, amisulpride, olanzapine, paliperidone, and zotepine.
5. Paliperidone was superior to lurasidone and iloperidone only (both SMDs 0.17).
6. Haloperidol was superior to iloperidone only (SMD, 0.12).
7. Differences in the remaining antipsychotic drug pairwise comparisons were not statistically significant. These drugs, occupying the bottom of the hierarchy, were quetiapine, aripiprazole, sertindole, ziprasidone, chlorpromazine, asenapine, lurasidone, and iloperidone.

[a]Data from the network meta-analysis of Leucht et al[1] that compared amisulpride, aripiprazole, asenapine, chlorpromazine, clozapine, haloperidol, iloperidone, lurasidone, olanzapine, paliperidone, quetiapine, risperidone, sertindole, ziprasidone, and zotepine.
Abbreviation: SMD = standardized mean difference.

Table 3. Relative All-Cause Discontinuation Rates for Different Antipsychotic Drugs in Schizophrenia[a]

1. Olanzapine was associated with a lower discontinuation rate than all other drugs except clozapine, amisulpride, risperidone, paliperidone, and zotepine (ORs, 0.58–0.76).
2. Amisulpride was associated with a lower discontinuation rate than all other drugs except clozapine, olanzapine, risperidone, paliperidone, and zotepine (ORs, 0.53–0.71).
3. Clozapine was associated with a lower discontinuation rate than haloperidol, sertindole, ziprasidone, lurasidone, and iloperidone (ORs, 0.57–0.67).
4. Paliperidone was associated with a lower discontinuation rate than haloperidol, sertindole, ziprasidone, asenapine, lurasidone, and iloperidone (ORs, 0.60–0.71).
5. Risperidone was associated with a lower discontinuation rate than haloperidol, sertindole, ziprasidone, lurasidone, and iloperidone (ORs, 0.66–0.78).
6. Quetiapine and aripiprazole were each associated with a lower discontinuation rate than haloperidol (ORs, 0.77–0.78).
7. Other differences in pairwise comparisons between antipsychotic drugs were not statistically significant.
8. Haloperidol, sertindole, lurasidone, and ziprasidone were associated with the highest discontinuation rates.
9. All antipsychotic drugs (except zotepine) were associated with a lower all-cause discontinuation rate than placebo (ORs, 0.43–0.80).

[a]Data from the network meta-analysis of Leucht et al[1] that compared amisulpride, aripiprazole, asenapine, chlorpromazine, clozapine, haloperidol, iloperidone, lurasidone, olanzapine, paliperidone, quetiapine, risperidone, sertindole, ziprasidone, and zotepine.
Abbreviation: OR = odds ratio.

Serum prolactin elevation. No drug significantly lowered serum prolactin; the benefits of aripiprazole, in this regard, narrowly missed statistical significance (SMD, −0.22). Relative to placebo, increase in serum prolactin was not statistically significant for quetiapine, asenapine, chlorpromazine, and iloperidone. Seven antipsychotics significantly raised serum prolactin; from least increase to greatest increase, these were olanzapine (SMD, 0.16), ziprasidone (SMD, 0.25), lurasidone (SMD, 0.34), sertindole (SMD, 0.45), haloperidol (SMD, 0.70), risperidone (SMD, 1.23), and paliperidone (SMD,

Table 4. Extrapyramidal Side Effects Associated With Antipsychotic Drugs in Schizophrenia[a]

1. The risk of EPS was significantly lower with clozapine than with placebo (OR, 0.30).

2. The risk of EPS was not significantly elevated with sertindole, olanzapine, quetiapine, aripiprazole, iloperidone, amisulpride, and asenapine.

3. From lowest to highest risk, extrapyramidal side effects were significantly more likely with ziprasidone (OR, 1.61), paliperidone (OR, 1.81), risperidone (OR, 2.09), lurasidone (OR, 2.46), chlorpromazine (OR, 2.65), zotepine (OR, 3.01), and haloperidol (OR, 4.76) than with placebo.

[a]Data from the network meta-analysis of Leucht et al.[1]
Abbreviations: EPS = extrapyramidal side effects, OR = odds ratio.

1.30). No RCT included in the meta-analysis provided data for clozapine, amisulpride, and zotepine comparisons. However, there is adequate evidence from outside this meta-analysis documenting increase in serum prolactin levels with amisulpride and zotepine and absence of increase with clozapine. Importantly, paliperidone and risperidone raised serum prolactin significantly more than did all other drugs, including haloperidol, and haloperidol increased serum prolactin significantly more than all the remaining drugs except chlorpromazine and sertindole.

QTc prolongation. QTc prolongation was not statistically significant for lurasidone, aripiprazole, paliperidone, and asenapine. QTc decrease with lurasidone and increase with asenapine narrowly missed statistical significance. There was a significant increase in QTc with the remaining drugs. Listed in increasing order, these were haloperidol (SMD, 0.11), quetiapine (SMD, 0.17), olanzapine (SMD, 0.22), risperidone (SMD, 0.25), iloperidone (SMD, 0.34), ziprasidone (SMD, 0.41), amisulpride (SMD, 0.66), and sertindole (SMD, 0.90). In these RCTs, QTc data were unavailable for clozapine, chlorpromazine, and zotepine.

Other issues. Meta-regression analyses were provided in the supplemental data. These showed, for example, that chlorpromazine doses above 600 mg/d were associated with greater efficacy without a corresponding increase in extrapyramidal side effects. In contrast, haloperidol doses below 12 mg/d (and even 7.5 mg/d) reduced extrapyramidal side effects without compromising efficacy.

Inconsistencies between direct and indirect estimates were few and did not influence the general results. The results were generally unchanged in the different sensitivity analyses conducted. The efficacy outcomes remained largely similar in analyses that removed the placebo or haloperidol groups and when dose, discontinuation rate, blinding, industry support, study duration, illness chronicity, and year of publication were examined in meta-regressions and sensitivity analyses. The overall findings of the meta-analysis are summarized in Table 5.

A Comparison of Antipsychotic Drugs in Refractory Schizophrenia

Samara et al[2] described a Bayesian-framework, network meta-analysis that utilized both direct and indirect comparisons of antipsychotic medications in patients with treatment-resistant schizophrenia. The authors searched

Table 5. General Conclusions That Emerge From the Meta-Analysis Comparing Antipsychotic Drugs in Non-Refractory Schizophrenia[a]

1. Antipsychotic drugs are not similar in efficacy. However, the differences between antipsychotics with regard to efficacy are rather small, whereas differences in various adverse effects can be quite large. The small differences in efficacy may nevertheless be clinically significant given that the differences in efficacy between drugs and placebo are not very much larger.

2. Clozapine and amisulpride are associated with the greatest efficacy, and lurasidone and iloperidone with the lowest efficacy. This advantage for clozapine emerged even though the patients in the RCTs in this meta-analysis were not medication-refractory.

3. Amisulpride, olanzapine, and clozapine are associated with the lowest all-cause discontinuation rate, and haloperidol, lurasidone, sertindole, and ziprasidone are associated with the highest all-cause discontinuation rate.

4. Weight gain is least with haloperidol, ziprasidone, and lurasidone and greatest with clozapine, zotepine, and olanzapine.

5. The need for antiparkinsonian medications is lowest with clozapine and highest with haloperidol and zotepine.

6. Increase in serum prolactin is least with aripiprazole and greatest with risperidone and paliperidone.

7. Sedation is least with amisulpride and greatest with clozapine, zotepine, and chlorpromazine.

8. QTc prolongation is least with lurasidone and greatest with sertindole and amisulpride.

[a]Data from the meta-analysis of Leucht et al.[1]
Abbreviation: RCT = randomized controlled trial.

computerized databases and other sources and identified 40 single- or double-blind RCTs (pooled N = 5,172) of 12 antipsychotic drugs administered as monotherapy.

The mean age of the pooled sample was about 39 years; the sample was 72% male. The mean duration of illness was about 16 years. Patients had had a mean of 7 previous hospitalizations. All RCTs were at least 3 weeks long; the median duration was 11 weeks. The mean dropout rate was 30%. Clozapine was represented in 20 RCTs, haloperidol in 15, olanzapine in 14, and risperidone in 12. Data for aripiprazole, perphenazine, and thiothixene could not be included because the data were not usable or were not connected to the network.

Efficacy. There were 9 antipsychotic drugs included in the network meta-analysis of psychopathology ratings; these were chlorpromazine, clozapine, fluphenazine, haloperidol, olanzapine, quetiapine, risperidone, sertindole, and ziprasidone. Olanzapine was superior to quetiapine, haloperidol, and sertindole (SMDs, 0.29 to 0.46, corresponding to 6–10 PANSS points); clozapine was superior to haloperidol and sertindole (SMDs, 0.22 to 0.40, corresponding to 5–8 PANSS points); and risperidone was superior to sertindole (SMD, 0.32, corresponding to 7 PANSS points). There were no significant differences in other comparisons between antipsychotics. Haloperidol, fluphenazine, and sertindole were lowest in the efficacy hierarchy.

In this network meta-analysis,[2] olanzapine, clozapine, and risperidone were superior to quetiapine for the attenuation of positive symptoms (SMDs, 0.33 to 0.43, corresponding to 2–3 PANSS points), and clozapine and risperidone were

Chittaranjan Andrade

Table 6. General Conclusions That Emerge From the Meta-Analysis Comparing Antipsychotic Drugs in Treatment-Resistant Schizophrenia[a]

1. Olanzapine, clozapine, and risperidone are mostly better than quetiapine, haloperidol, and sertindole for the attenuation of positive symptoms and overall psychopathology ratings; the effect sizes, however, are small.
2. Olanzapine is superior to many other typical and atypical antipsychotics (including clozapine) for the attenuation of negative symptoms.
3. Clozapine is superior in efficacy to haloperidol and chlorpromazine but is not better than other atypical antipsychotics.
4. Haloperidol, often considered as a reference neuroleptic, is associated with poor negative, positive, and overall outcomes relative to many atypical antipsychotics and with greater all-cause discontinuation relative to olanzapine.
5. Clozapine and olanzapine are associated with lower rates of discontinuation due to inefficacy relative to other antipsychotics.

[a]Data from the meta-analysis of Samara et al.[2]

Table 7. Clozapine vs Other Antipsychotics in Refractory Schizophrenia[a]

1. In short-term comparisons, clozapine was superior to comparator antipsychotics (20 comparisons; N = 1,312; SMD, 0.39; 95% CI, 0.17–0.61).
2. In long-term comparisons, clozapine was not significantly superior to comparatory antipsychotics (11 comparisons; N = 819; SMD, 0.11; 95% CI, −0.09 to 0.31).
3. In all studies and at the last time point at which data were available, clozapine was superior to comparator antipsychotics (24 comparisons; N = 1,858; SMD, 0.29; 95% CI, 0.09–0.49).
4. Clozapine attenuated positive symptoms significantly more than did the other antipsychotics in both short-term (8 comparisons; SMD, 0.27) and long-term (7 comparisons; SMD 0.25) comparisons.
5. Clozapine attenuated negative symptoms significantly more than did the other antipsychotics only in the short-term comparisons (7 comparisons; SMD, 0.25) and not in the long-term comparisons (8 comparisons).
6. Clozapine was associated with a higher response rate in short-term comparisons (8 comparisons; N = 1,218; R, 1.17; 95% CI, 1.07–2.73; NNT = 9) but not long-term comparisons (5 comparisons).
7. In meta-regression, greater baseline severity of illness predicted greater long-term response.

[a]Results of the meta-analysis by Siskind et al.[3] A 3-month cutoff separated short- and long-term studies. Data are reported for comparisons rather than studies because some studies included more than 1 comparator arm.
Abbreviations: CI = confidence interval, NNT = number needed to treat, SMD = standardized mean difference.

superior to haloperidol (SMDs, 0.27 to 0.29, corresponding to about 2 PANSS points). Olanzapine was superior to clozapine, risperidone, haloperidol, chlorpromazine, and sertindole for the attenuation of negative symptoms; the SMDs ranged from 0.14 to 0.44, corresponding to about 1.0 to 2.5 PANSS points. Ziprasidone was superior to both chlorpromazine and sertindole (SMDs, 0.26 to 0.44).

Risperidone, clozapine, and olanzapine were each associated with about doubled odds of treatment response relative to haloperidol; the corresponding NNTs were 7 to 8. Otherwise, there were no significant differences in the response rates in pairwise comparisons in the network meta-analysis.

Drug discontinuation. Olanzapine significantly reduced the odds of all-cause discontinuation relative to haloperidol (OR, 0.56) and fluphenazine (OR, 0.24); otherwise, the network meta-analysis found no significant differences in pairwise comparisons between antipsychotic drugs. Discontinuation due to inefficacy was significantly less likely with clozapine than with fluphenazine, haloperidol, quetiapine, and risperidone (ORs, 0.08 to 0.44; NNTs, 6–10), and, for this outcome, chlorpromazine and olanzapine were superior to haloperidol and fluphenazine (ORs, 0.04 to 0.27; NNTs, 5–7), and risperidone was superior to fluphenazine (OR, 0.19; NNT, 7).

A number of subgroup, sensitivity, and meta-regression analyses were conducted, including an inspection of outcomes in the context of varying degrees of treatment resistance; these yielded no fresh insights, perhaps because most of the analyses were underpowered. The findings of this meta-analysis are summarized in Table 6.

Clozapine vs Other Antipsychotics in Refractory Schizophrenia

Siskind et al[3] described a conventional meta-analysis of single- or double-blind, direct comparisons of clozapine with first- and second-generation antipsychotics in treatment-refractory schizophrenia. The authors searched computerized databases and other sources and identified 25 comparisons in 21 papers (pooled N = 2,364). The comparator drugs were

olanzapine (9 studies), risperidone (7 studies), haloperidol (5 studies), chlorpromazine (2 studies), and quetiapine and ziprasidone (1 study each).

Eight papers described studies that were funded by the manufacturer of the comparator antipsychotic, and 2 papers described studies funded by the manufacturer of clozapine. Data were reported for trial durations ranging from 6 to 78 weeks; with 3 months set as a cutoff, there were 21 short-term and 13 long-term comparisons.

Efficacy outcomes. Important efficacy outcomes are presented in Table 7. In summary, clozapine was superior to comparator antipsychotics for positive symptom outcomes, negative symptom outcomes, and overall psychopathology ratings; the benefits were clearer in the short-term comparisons.

Some interesting findings emerged in sensitivity analyses. The benefits of clozapine on psychopathology ratings were evident in both short- and long-term comparisons when industry-supported studies were excluded. Clozapine was generally underdosed relative to the comparator antipsychotics; when studies with less dosing imbalance were examined, the advantage for clozapine was enhanced. Clozapine was strongly superior to comparator drugs in pediatric trials (3 comparisons).

Excluding studies that included medication-intolerant patients and excluding single-blind studies did not change the findings. Similarly, an examination of clozapine vs first- and second-generation drugs separately did not change the findings. Clozapine was superior to olanzapine, haloperidol, and chlorpromazine in the short term. Clozapine was not superior to olanzapine in the long term and was not superior to risperidone in either short- or long-term comparisons.

Other outcomes. Study completion was comparable in clozapine and comparator groups in both short-term and long-term comparisons. Adverse drug reactions corresponded to the known profile of the drugs.

General Comments

Many antipsychotic drugs were not represented in the meta-analyses. In some cases, such as for brexpiprazole and cariprazine, the probable explanation is that the data were unavailable at the time the meta-analyses were conducted. In some cases, such as for blonanserin, there may have been too few RCTs on the drug published in the English language. With other antipsychotics, such as perphenazine, sulpiride, levosulpiride, pimozide, penfluridol, trifluoperazine, and flupenthixol, the RCTs may not have met the defining criteria set by the authors.

A broad finding from the meta-analysis in non-refractory schizophrenia[1] was that amisulpride and olanzapine appeared to offer the best balance between high efficacy and a low all-cause discontinuation rate. Whereas this observation could influence prescribing practices, clinicians must realize that other matters should also be kept in mind, such as sensitivity to prolactin-related adverse effects with amisulpride (not shown in this meta-analysis), risk of sedation and weight gain associated with clozapine and olanzapine (the other 2 drugs that scored heavily on efficacy), and so on. Readers are reminded that most advantages for one antipsychotic over another were characterized by small effect sizes; therefore, at least for some drugs in some patients, it could make sense to consider the potential adverse effect burden as a concern that overrides an efficacy advantage. Individualized, informed decision-making is called for.

It is interesting that many of the more recently introduced antipsychotics (aripiprazole, quetiapine, ziprasidone, asenapine, iloperidone, and lurasidone) were ranked in the lower half of the efficacy hierarchy of treatments for non-refractory schizophrenia.[1] Paliperidone was an exception; so, the finding was probably not a cohort effect. Additionally, year of publication of RCT did not influence the results, as examined in a meta-regression analysis.[1]

Given that many of the newer antipsychotics (lurasidone, risperidone, paliperidone, ziprasidone) were associated with a significant risk of extrapyramidal adverse effects, it is a moot point whether the term *atypical antipsychotic* can be justifiably applied to these drugs. In support of the designation of atypicality, however, tardive dyskinesia is uncommon with the newer drugs.

The findings of the different meta-analyses cannot be generalized beyond the data from which they were generated. For example, the results of the meta-analysis on non-refractory schizophrenia[1] cannot be generalized to youth with schizophrenia, those with first-episode or negative symptom illness, those with significant medical comorbidities or refractory illness, and those with stable illness.

Specific Comments on the Place of Clozapine

Clozapine, globally considered the treatment of choice in patients with medication-refractory schizophrenia, was surprisingly not superior to any of the second-generation antipsychotics in one network meta-analysis of antipsychotic drugs in treatment-resistant schizophrenia.[2] This questions the special position that clozapine holds in the treatment of refractory schizophrenia.[5]

There are many possible explanations. Clozapine may have been underdosed in the included RCTs; dosing was certainly lower in the comparisons with second-generation antipsychotics relative to the comparisons with first-generation antipsychotics. Many important clozapine studies were excluded from this meta-analysis because the clozapine arms were not blinded. Patients who were markedly refractory may have been underrepresented in the RCTs. It must also be considered that clozapine has been associated with special benefits (eg, attenuation of aggression, a lower risk of rehospitalization, and a lower risk of suicide) that would not have been captured in the psychopathology ratings examined in the meta-analysis.[5–7] Reassuringly, the more inclusive, direct-comparison meta-analysis of clozapine in refractory schizophrenia clearly identified a preeminent position for this drug with regard to efficacy outcomes.[3]

Parting Notes

Tables 5–7 summarize the findings of the 3 meta-analyses examined in this article. At the risk of extreme oversimplification, it can be considered that clozapine and olanzapine are associated with the best efficacy outcomes in both refractory and non-refractory schizophrenia; clozapine remains a preeminent choice for refractory schizophrenia.

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