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Are Second Generation Antipsychotics a Distinct Class?

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Abstract

Introduction—Second generation antipsychotic medications have become synonymous with “atypicality.” To support the clinical lore of equivalent efficacy with reduced risk of extrapyramidal symptoms, clinical trials have overwhelmingly chosen a high-potency first-generation antipsychotic (e.g., haloperidol) as a comparator. Very few clinical trials have compared a second-generation antipsychotic with a low- or mid-potency first-generation antipsychotic medication.

Methods—We identified eight completed, published, double-blind, randomized clinical trials that compared a second-generation antipsychotic with a low- or mid-potency first-generation antipsychotic and reviewed outcome measures for efficacy and extrapyramidal symptoms; 1,241 patients were represented in these eight trials.

Results—Although data are very limited, mid- and low-potency first-generation antipsychotics show efficacy and extrapyramidal side effects that are comparable to those of second-generation antipsychotics.

Conclusion—Aside from clozapine, first-generation and second-generation antipsychotics represent a diverse group of medications that have heterogeneous receptor profiles and side effects but comparable clinical efficacy and potential to cause extrapyramidal symptoms. Clinicians may provide better treatment for patients by considering the unique pharmacological and side-effect profile of each particular antipsychotic independent of its classification as a first- or second-generation agent.

Keywords

schizophrenia; antipsychotics; atypical antipsychotic; first-generation antipsychotic; second-generation antipsychotic; efficacy; extrapyramidal symptoms; negative symptoms; neurocognitive effects; quality of life

In 1964, the National Mental Health Psychopharmacology Service Center compared the efficacy and side-effect profiles of three phenothiazines (chlorpromazine, fluphenazine, and thioridazine) against each other and placebo.¹ Each medication was more efficacious than placebo, but, despite using twenty-five different measures of clinical efficacy, no single phenothiazine showed a significant clinical advantage over another. The authors concluded that differences in “clinical efficacy between these three drugs, if present at all, are neither striking nor obvious.” Their analysis of the side-effect profiles of the agents did confirm that fluphenazine, a high potency antipsychotic, produced significantly more neurological side effects such as muscle rigidity, akathisia, dystonia, and oculogyric crisis. Patients in the fluphenazine group were also more likely to use anti-parkinsonian medications. In addition,

perhaps because of thioridazine's anticholinergic activity, this low potency phenothiazine produced a rate of extrapyramidal symptoms (EPS) that was comparable to placebo. This study demonstrated that antipsychotics from the same therapeutic class had equivalent efficacy but differed in their side-effect profiles.

In the 1960s, researchers hypothesized that, to be clinically effective, antipsychotics must have a catalep-togenic effect and apomorphine antagonism. Because of clozapine's inability to induce catalepsy in laboratory animals, researchers labeled clozapine "atypical" or "defective."^{2,3} However, clinical studies later established clozapine as the medication of choice for treatment-resistant schizophrenia due to its unparalleled efficacy and reduced rates of EPS.^{4,5} This led to the development of the group of agents that are collectively referred to as atypical or "second-generation" antipsychotics (SGAs), in contrast to the "first-generation" antipsychotics (FGAs). As a more diverse group of agents has been included in the "atypical" class of antipsychotics, the molecular definition of atypicality has become increasingly broad and is generally now considered to include relatively stronger serotonin (5-HT_{2A}) than dopamine (D₂) antagonism,⁶ "fast dissociation" from the D₂ receptor,⁷ moderate D₂ receptor occupancy,⁸ and extrastriatal D₂ occupancy.⁹ To date, there is no consensus on a clinical or molecular definition for atypicality in antipsychotics. The SGAs include amisulpride, aripiprazole, olanzapine, paliperidone, quetiapine, risperidone, ziprasidone, and zotepine. As a group, the SGAs promised improved functioning and reduced risk of EPS in the management of schizophrenia.^{10,11}

Several recent meta-analyses have challenged this premise of superior efficacy. These analyses either used haloperidol as the comparator FGA or did not differentiate the type of FGA comparator (although typically haloperidol and chlorpromazine were used). Haloperidol is a high potency FGA, and studies have shown that it causes high rates of EPS.¹² Geddes et al.¹³ found that the SGAs had similar efficacy and tolerability when compared with haloperidol. Leucht et al.¹⁴ found that quetiapine had similar efficacy to haloperidol, while other SGAs were superior. Geddes et al.¹⁵ re-analyzed the same data as Leucht et al.¹⁴ using different statistical principles. In their re-analysis, they found no significant difference between SGAs and low potency FGAs. Based on a meta-analysis, Davis et al.¹⁶ found that zotepine, aripiprazole, sertindole, quetiapine, and ziprasidone were similar in efficacy to haloperidol, while clozapine, amisulpride, risperidone, and olanzapine had superior efficacy. Thus, with respect to efficacy, the results of these meta-analyses suggested that significant heterogeneity exists among the SGAs.

The other reported advantage of SGAs over FGAs was the relative absence of EPS. To compare the risk of EPS with SGAs and low-potency FGAs, Leucht et al.¹⁷ quantified EPS rates as the primary outcome measure and efficacy as a secondary measure. Only 31 trials were identified that met the authors' strict inclusion criteria. The results suggested that low-potency FGAs might have a comparable risk of EPS compared with SGAs, but that the SGAs were moderately more effective. Two important caveats should be noted before generalizing from these results. First, of the 31 studies, 15 used clozapine as the SGA. Clozapine has superior efficacy to other antipsychotics in treatment-refractory schizophrenia; therefore, the inclusion of clozapine among the SGAs positively skewed the results for the SGAs as a group.^{4,18} In addition, 3 of the studies used very low doses of low-potency FGAs (less than or equal to 300 mg/day chlorpromazine equivalent). The inclusion of these studies may have contributed to the finding of reduced efficacy among the FGAs.

The results of the recent Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) trial were surprising, with perphenazine, a mid-potency FGA, producing similar rates of effectiveness and adverse events compared with olanzapine, quetiapine, risperidone, and ziprasidone.¹⁹ In his commentary on the CATIE study, Lieberman mentioned that this

finding might have been the result of excluding patients with tardive dyskinesia from the perphenazine group, but he also suggested that the finding may reflect the fact that perphenazine is a mid-potency antipsychotic. He noted that most previous comparisons between FGAs and SGAs have used haloperidol at relatively high doses.²⁰ The CATIE results re-ignited the debate concerning the comparative superiority of the SGAs. Given the considerable cost of the newer medications, recent studies have questioned the relative efficacy of these medications by looking at quality of life years and predicted cost-effectiveness.^{21,22} The Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS 1), which was based in the United Kingdom, deliberately excluded clozapine. This study found no differences in Heinrich's Quality of Life Scale,²³ total cost of service use and medication, symptom scales, or EPS ratings between subjects taking an FGA compared with those taking an SGA.²¹ Similarly, in an analysis of the CATIE data, Rosenheck et al. found that perphenazine was associated with a lower total overall cost than the SGA comparators and tended to be associated with improved Quality Adjusted Life Year (QALY) ratings in contrast to the SGAs included in this study.²²

Since this debate is likely to continue, it is helpful to re-examine the comparative efficacy and side-effect profiles of available antipsychotic medications. One clinical definition of an atypical antipsychotic is "low EPS relative to haloperidol at clinically effective doses."²⁴ Using this definition, would some low- or mid-potency FGAs qualify as "atypical"? As a group, are the SGAs "atypical" antipsychotics? Apart from clozapine, are SGAs superior to low- or mid-potency FGAs in terms of efficacy or EPS? The purpose of this review is to examine studies that compared SGAs (excluding clozapine) with low- or mid-potency FGAs with respect to efficacy and EPS.

METHODS

We conducted a rigorous PubMed search for articles in English involving schizophrenia and every permutation of SGAs that were available at the time the search was done (amisulpride, aripiprazole, olanzapine, quetiapine, risperidone, ziprasidone, zotepine) in comparison with low- and mid-potency FGAs (amoxapine, chlorpromazine, methotrimeprazine, loxapine, mesoridazine, molindone, perazine, perphenazine, prochlorperazine, promazine, thioridazine, triflupromazine). We also expanded the search to include websites of pharmaceutical companies, the websites clinicaltrials.gov and clinicalstudiesresults.org, the Cochrane database, and relevant bibliographies. We selected published, double-blind, randomized clinical trials that compared an SGA with a low- or mid-potency FGA and that included measures of efficacy and/or EPS. We excluded trials that did not separate high-potency from low- or mid-potency comparators. For our analyses, we used the a priori primary efficacy measure defined by the investigator for each study. As an outcome measure of EPS rates, we used the results of the Barnes Akathisia Scale (BAS),²⁵ the Simpson Angus Scale (SAS),²⁶ the Extrapyramidal Symptom Rating Scale (ESRS),²⁷ and the Abnormal Involuntary Movement Scale (AIMS).²⁸

RESULTS

Efficacy

We identified eight completed, published randomized, controlled trials (RCTs) that compared the efficacy of SGAs with a low- or mid-potency FGA (Table 1). The CATIE trial is an antipsychotic effectiveness trial with a complex outcome design—it is not an efficacy trial.²⁰ Therefore, the CATIE study was not included in this analysis. We also located four relevant abstracts^{39–42} and a single RCT with 10 subjects that was terminated prior to completion.⁴³ Because these five publications did not report adequate information about antipsychotic dosages or anticholinergic use, we did not include them in Table 1. Only

two^{29,31} of the eight studies we identified showed a significant difference in efficacy favoring the SGA. Neither of these studies had a sample size over 100. The six studies that did not show a significant difference in efficacy had a wide range of sample sizes (ranging from 43 to 306).^{33–38}

Rates of EPS

Three studies indicated that the rate of EPS was increased on at least one measure among patients treated with FGAs compared with SGAs.^{31,33,35} Seven studies showed no statistically significant differences in the use of anticholinergics. Conley et al.³⁴ used a scheduled dose of benztropine, which may have masked some EPS.

DISCUSSION

Are SGAs More Efficacious Than Low- and Mid-Potency FGAs?

Based on the available evidence, it is not possible to draw a meaningful conclusion. The trials are limited by small sample size, short duration, some high drop-out rates, and the lack of placebo controls, except in the zotepine study.³¹ The results of the RCTs we identified did not show evidence favoring the efficacy of SGAs as a class over low- and mid-potency FGAs. Unfortunately, the considerable heterogeneity of the reported data would not allow for a systematic meta-analysis or calculation of effect sizes.

Interest in the comparative efficacy of the SGAs and the FGAs continues, and the issue is far from resolved. In response to findings in the CATIE trial, Ascher-Svanum et al.⁴⁴ conducted a large ($N = 2,327$), 3-year, naturalistic trial using the same primary outcome as in the CATIE trial, time to discontinuation. As a group, SGAs were associated with a longer time to discontinuation than FGAs. However, of the five SGAs examined in this study, only clozapine and olanzapine were associated with a longer time to discontinuation compared with perphenazine. The authors concluded that the SGAs represent a heterogeneous group.

Are Low- and Mid-Potency FGAs Associated with More EPS than SGAs?

Again, it is not possible to draw a firm conclusion about the propensity of these different medications to cause EPS. Our ability to assess an increased risk for EPS in short-term trials is limited, especially since these trials tend to involve small numbers of patients and lack statistical power to adequately detect meaningful differences in rates of EPS. Despite these barriers to arriving at a definitive conclusion, the eight RCTs we identified did not show evidence that the FGAs as a group produced higher rates of EPS than the SGAs.

The short duration of these eight studies also limited the ability to draw any conclusions about rates of tardive dyskinesia with low- and mid-potency FGAs. A 2004 review of studies of at least 12 months duration suggested that the rate of tardive dyskinesia was higher with FGAs than SGAs.⁴⁵ However, all of the studies that were included in that review used haloperidol as the FGA comparator. The rates of tardive dyskinesia with low- and mid-potency FGAs have not been determined, but earlier work suggested that haloperidol was associated with a higher odds ratio of developing tardive dyskinesia than phenothiazines.⁴⁶

Recent studies comparing antipsychotics, including the CATIE trial, have not been designed with the aim of capturing differences in rates of tardive dyskinesia. The CATIE trial leaves this question unanswered since subjects with a history of tardive dyskinesia were excluded from randomization to the FGA arm.²⁰ This difference may have introduced potential confounders.⁴⁷ The long-term naturalistic study conducted by Ascher-Svanum et al.⁴⁴ did

not attempt to capture reasons for discontinuation and specifically did not measure rates of tardive dyskinesia.

Studies of longer duration could provide more information about EPS. The longer term studies available in the literature included a mixture of low- and high-potency FGAs, and EPS was not a primary outcome measure. One 6-month trial that included the SAS and the AIMS as secondary outcome measures found no significant differences on these scales.⁴⁸ Researchers from the Netherlands analyzed a large database of outpatient prescriptions to measure the rate of anticholinergic medication use associated with different classes of antipsychotics. As expected, the high potency FGAs were associated with a higher rate of anticholinergic use, but no differences existed when SGAs were compared with all FGAs.⁴⁹ A further analysis of a smaller sample indicated that risperidone was not associated with any more anticholinergic prescriptions than low potency FGAs.⁵⁰

Negative Symptoms

Given clozapine's efficacy in producing greater improvement in negative symptoms,⁴ investigators have hoped that other SGAs could offer improved treatment for the deficit syndrome of schizophrenia. However, it is difficult to draw any meaningful conclusions about changes on negative symptom subscales based on results of short-term trials in patients with acute psychosis. It is possible that an improvement in psychotic symptoms will also produce a corresponding improvement in the negative subscores that may not reflect a long-term change. Of the eight trials discussed in this paper, only one trial found that the SGA was associated with a significant improvement on the PANSS negative scale.³⁵

Quality of Life

In an effort to measure "drug effectiveness" it is increasingly recognized that psychosocial functioning and quality of life are important measures to consider in schizophrenia treatment studies,⁵¹ and there is some suggestion that SGAs are associated with improved quality of life compared with FGAs.⁵² Of the eight trials discussed in this paper, only one study included a measure of psychosocial functioning (20% change in Quality of Life scale),²³ on which no statistically significant difference was found in the two treatment arms comparing perphenazine and aripiprazole.³³ None of the eight trials included any other measure of psychosocial functioning, such as return to employment, independent living, or a measure of interpersonal relationships.

Neurocognition

An important issue in selecting antipsychotic treatment is the question of neurocognitive effects. None of the eight trials discussed in this paper included any measure of neurocognition. Previous work has suggested that the SGAs may produce improved neurocognitive functioning in comparison with the FGAs.⁵³ It was therefore a surprise when no differences in neurocognitive effects between the mid-potency FGA perphenazine and the SGA comparators were detected in the CATIE study.⁵⁴ The authors of the CATIE analysis suggested that the earlier findings of a class difference in neurocognitive effects might be due to the high doses of haloperidol and anticholinergic medications used in other trials. This important question clearly deserves further study.

CONCLUSION

Our most remarkable finding was that very few studies have compared low- and mid-potency FGAs with SGAs. This finding was confirmed in a recent meta-analysis from the Cochrane database, which reported that 68% of the trials of atypical antipsychotics published since 1990 used haloperidol as the comparator.⁵⁵ This trend is surprising

considering Kane's selection of chlorpromazine as the comparator in the seminal 1988 study which identified clozapine as the treatment of choice for treatment-resistant schizophrenia. Kane selected chlorpromazine for use in this study because its side-effect profile most closely resembled clozapine, which therefore enhanced the blinding.⁴

While it may be premature to conclude that certain FGAs are equally efficacious and have similar risks of EPS relative to SGAs, the available evidence does not support the superiority of the SGAs as a class. The SGAs are derived from several different classes of compounds and arguably do not have an "independent" identity.⁵⁶ As seen in other reviews and meta-analyses, the SGAs are associated with superior outcomes only when they are grouped with clozapine. While antihistaminic and anticholinergic adverse effects are common with FGAs such as chlorpromazine and thioridazine, they are even more common with the SGAs. In a comprehensive review of the neuroreceptor pharmacology of antipsychotics, Richelson reported affinity data that indicate that olanzapine is associated with high rates of antihistaminic effects, risperidone with alpha-2 antagonism, ziprasidone with alpha-1 antagonism at rates similar to those seen with chlorpromazine, and clozapine with anti-muscarinic antagonism.⁵⁷ The adverse metabolic side effects associated with some of the SGAs have also been well described.⁵⁸

As our review demonstrates longer, higher quality studies are needed to fully assess the efficacy and side effects of SGAs compared with low- and mid-potency FGAs. Antipsychotics are best viewed on a continuum of efficacy and potential to cause EPS, with clozapine perhaps being the unique outlier and true "atypical" agent. Currently the SGAs have approximately a 90% share of the U.S. market.⁵⁹ The evidence to support this disproportionate use of SGAs is minimal at best. When selecting medications for a particular patient, the clinician's choice should be guided by the unique clinical properties and side-effect profile of each medication rather than by artificial and ill-defined distinctions between SGAs and FGAs.

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Table 1

Studies comparing the efficacy of SGAs with a low- or mid-potency FGA

Comparator (study)	Study design	Subjects (initial→ endpoint)	Medication regimen	Anti-cholinergics?	Primary efficacy variable	EPS
Studies favoring SGA efficacy for treatment of schizophrenia						
Risperidone versus methotrimiprazine (Blin et al. 1996) ²⁹	Two centers, randomized, double blind, 4-week study	Acute, risperidone: 21 → 17, methotrimiprazine: 21 → 14	Flexible dose, mean daily dose of risperidone: 8.6 mg, methotrimiprazine: 125 mg	No differences	20% reduction on PANSS ³⁰ ; significant improvement in risperidone arm	ESRS: no differences
Zotepine versus chlorpromazine (Cooper et al. 2000) ³¹ *	Multicenter, randomized, parallel group, double-blind, placebo controlled, 8-week study	Acute, zotepine: 53 → 34, chlorpromazine: 52 → 27, Placebo: 53 → 28	Fixed dose options zotepine: 150 or 300 mg, chlorpromazine: 300 or 600 mg;	No differences	BPRS ³² change from baseline; improvement in zotepine arm	AIMS: no differences; SAS worse in chlorpromazine group;
Studies finding no significant difference in efficacy for treatment of schizophrenia						
Aripiprazole versus perphenazine (Kane et al. 2007) ³³ *	Multicenter, randomized, double-blind, 6-week study	Treatment-resistant, aripiprazole: 154 → 150; perphenazine: 146 → 144	Flexible dose aripiprazole (15–30 mg), perphenazine (8–64 mg), mean doses not recorded	No differences	Total PANSS change from baseline; no difference	BAS, AIMS: no differences; SAS lower in aripiprazole group
Olanzapine versus chlorpromazine (Conley 1998) ³⁴ *	Multicenter, randomized, double-blind, 8-week study	Treatment-resistant, olanzapine: 42 → 42, chlorpromazine: 42 → 39	Fixed dose: olanzapine 25 mg, chlorpromazine 1,200 mg	Chlorpromazine group received fixed dose (4 mg) benztropine	Total BPRS: no difference	SAS, BAS: no differences
Quetiapine versus chlorpromazine (Peuskens and Link 1997) ³⁵	Multicenter, double-blind, parallel group, 8-week study	Acute, quetiapine: 101 → 70, chlorpromazine 100 → 66	Flexible dose, mean daily dose at end of study quetiapine: 407 mg, chlorpromazine: 384 mg	No differences	BPRS, CGI: no difference	SAS, AIMS: no differences; BAS lower in quetiapine group
Risperidone versus perphenazine (Hoyberg et al. 1993) ³⁶	Multicenter, parallel group, double-blind, 8-week study	Acute, risperidone: 55 → 41, perphenazine: 52 → 37	Flexible dose, mean daily dose at end of study risperidone: 8.5 mg, perphenazine: 28 mg	No differences	20% reduction on total PANSS: no differences	ESRS: no differences
Risperidone versus amoxapine (Apiquian et al. 2005) ³⁷ *	Two centers, randomized, double-blind, 6-week study	Acute, risperidone: 21 → 20, amoxapine 22 → 19	Flexible dose, mean daily dose at study end risperidone: 4.5 mg, amoxapine: 228 mg	No differences	30% reduction on PANSS: no difference	BAS, AIMS, and SAS: no differences
Ziprasidone versus chlorpromazine (Kane et al. 2006) ³⁸ *	Multicenter, randomized, double-blind, 12-week study	Treatment-resistant, ziprasidone: 152 → 136, chlorpromazine: 154 → 135	Flexible dose, mean daily dose at study end ziprasidone 153.8 mg, chlorpromazine 743.6 mg	No differences	BPRS, CGI: no difference	BAS, SAS: no differences; AIMS significant increase in ziprasidone group

* Analyses performed using last observation carried forward (LOCF) and intent to treat (ITT). EPS: extrapyramidal symptoms; PANSS: Positive and Negative Syndrome Scale; BPRS: Brief Psychiatric Rating Scale; CGI: Clinical Global Impressions Scale; SAS: Simpson-Angus Scale (rating of extrapyramidal symptoms); BAS: Barnes Akathisia Scale; AIMS: Abnormal Involuntary Movement Scale; ESRS: Extrapyramidal Symptom Rating Scale