Comparative effectiveness of antipsychotic drugs in schizophrenia

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Chlorpromazine, which was discovered in 1952, has an exhaustively characterized efficacy/safety profile comprising serious limitations: effectiveness in the field failing to match efficacy in trials, residual symptoms in 50% of patients, a 20% relapse rate in compliant patients, and worrisome extrapyramidal side effects, including tardive dyskinesia in 5% per year. Second-generation "atypical" antipsychotics bypass these effects by having less affinity for the dopamine D_2 receptor and affinities for other neuroreceptors. Clozapine, the lead atypical antipsychotic, was followed in the mid 1990s by risperidone, olanzapine, and quetiapine, which now account for over half of new antipsychotic prescriptions in North America. The debate over their relative efficacy involves the potential well-being of millions of schizophrenics and billions of dollars. Atypical antipsychotics are considerably more expensive; evidence for their superiority is highly variable and often inadequate, largely confined to short-term regulatory studies. Their effects on long-term outcome (particularly negative symptoms), relapse prevention, social and vocational functioning, suicide prevention and quality of life, and family and caregiver burden are largely unknown. The National Institute of Mental Health's Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) project is a combined efficacy–effectiveness trial that aims to answer these questions in a broad range of patients with schizophrenia and Alzheimer's disease.

The modern era of treating psychotic disorders began in 1952 with the discovery that the compound chlorpromazine possessed antipsychotic properties and produced symptomatic improvement in patients with schizophrenia. Initially, chlorpromazine was termed a neuroleptic drug (derived from the Greek *neuron* and *lepsis*, meaning to "take hold of the nervous system") to describe its effects of psychomotor immobilization. The implication was that the therapeutic antipsychotic properties and adverse motor effects were inextricably linked. Thus, chlorpromazine and the numerous antipsychotic compounds that followed were initially considered to belong to a class of neuroleptic drugs in which therapeutic effects were inseparable from the extrapyramidal side effects (EPSs) they produced.[1]

Conventional antipsychotic drugs

Conventional antipsychotic drugs or neuroleptics are known to be efficacious in treating psychotic symptoms. However, almost half a century of experience with conventional antipsychotic drugs has revealed their substantial limitations. To varying degrees, all conventional antipsychotics carry the risk of side effects, including EPSs, hyperprolactinemia, and the neuroleptic malignant syndrome.[2] The most worrisome form of EPS, tardive dyskinesia (TD), can be irreversible and its incidence has been estimated at about 5% a year.[3] These medication

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side effects contribute to treatment nonadherence, which, in turn, leads to relapse and rehospitalization. Efforts to minimize EPSs have revealed that lowering the dose decreases side effects, but risks decreased efficacy and relapse.[4] In addition, the traditional antipsychotics do not alleviate all of the symptoms and disability caused by schizophrenia; at least 50% of patients have persisting or residual symptoms and disability despite treatment,[5] and at least 20% of patients relapse despite taking adequate doses of medication.[6,7] A substantial proportion of patients continue to be severely disabled and relapse frequently, due to either treatment nonadherence or ineffective treatment.[8-10] The hospitalizations and rehospitalizations that result from relapse produce substantial human suffering and significant financial costs to mental health systems.[11-16]

Thus, despite substantial data from controlled trials that support the efficacy of conventional antipsychotic medications for the positive symptoms of schizophrenia, the effectiveness of these agents in everyday practice is substantially less than their efficacy as determined in carefully controlled clinical trials. Although many factors may be involved, we do not know all the causes of this efficacy–effectiveness gap.[17] We do know, however, that the scientific and clinical promises of antipsychotic therapy have not been fully realized, and patients with schizophrenia remain vulnerable to a downward spiral of hospitalization, noncompliance, relapse, rehospitalization, and persistent disability.

Atypical antipsychotic drugs

The advent of the second generation of antipsychotic drugs has changed the risk/benefit profile of these medications. Clozapine was the prototype of the second generation of antipsychotics, and it has shifted the emphasis of drug development toward the search for drugs that have the same beneficial effects, without the risk of agranulocytosis caused by clozapine and without the EPSs that accompany treatment with the first-generation antipsychotics. Some of the newer medications, like olanzapine and quetiapine, are structurally similar to clozapine, while others, such as risperidone and ziprasidone, have a different structure, but share some of its key pharmacological features.

It is widely accepted that the actions of typical antipsychotics involve their ability to block the dopamine D_2 receptors in the limbic system and striatum. It is thought that the blockade of receptors in the limbic system is the basis for the antipsychotic action; the reduction in the activity of the striatum contributes to the EPSs (and possibly the development of TD); and the D_2 blockade of the hypothalamic–pituitary axis leads to hyperprolactinemia. The new drugs differ pharmacologically from conventional antipsychotics principally in their lower affinity for the D_2 receptor and relatively greater affinities for other neuroreceptors, including those for serotonin ($5\text{-}HT_{1A}$, $5\text{-}HT_{2A}$, $5\text{-}HT_{2C}$, $5\text{-}HT_3$, $5\text{-}HT_6$, and $5\text{-}HT_7$) and norepinephrine (α_1 and α_2 subtypes), and in their ability to modulate glutamate receptor–mediated functions and behaviors.[18] A pharmacological property that has been emphasized as critical for conferring atypical activity is the ratio between D_2 and $5\text{-}HT_{2A}$ receptor antagonism; a low ratio is characteristic of the new agents.[19] In addition, they appear to exhibit some degree of regional anatomic specificity, altering neurochemical activity in the limbic and frontal cortical regions, while having very little effect on the corpus striatum.[20]

A variety of characteristics in addition to neuroreceptor affinities, including effects in animal models, potentially greater efficacy in treating negative, cognitive, and mood symptoms, and lower propensity to cause EPSs, have been used to identify and define the new antipsychotics.[18,21] In this article, "atypical antipsychotic" refers to clozapine, olanzapine, quetiapine, risperidone, and ziprasidone. Amisulpride has also been proposed as an atypical antipsychotic. However, because of its more traditional mechanism of action, we have not included it in this discussion. However, this does not negate the possibility that it may warrant inclusion as a second generation of atypical antipsychotic. Sertindole is not included because it is no longer available for clinical use. Because clozapine is the prototype and has unique risks and benefits, the others will be referred to as "newer" atypical antipsychotics. Conventional antipsychotic drugs—typified by low-potency chlorpromazine, intermediate-potency perphenazine, and high-potency haloperidol—are those introduced before 1990.

Comparison of conventional and atypical antipsychotic drugs

Various claims have been made with regard to the superiority in efficacy and safety of the atypical antipsychotics relative to the conventional drugs. This has precipitated an important debate that is now underway

regarding the appropriate role of the second-generation or atypical antipsychotic drugs in treating schizophrenia. At issue are the potential well-being of millions of persons with schizophrenia and billions of dollars. The debate concerns the relative efficacy of atypical and conventional antipsychotic drugs, their side effects, their effectiveness for patients in everyday settings, and their cost-effectiveness. The atypical antipsychotics cost considerably more than the conventional drugs they may replace. If the additional costs of atypical antipsychotics are not justified by their benefits, this information could significantly influence clinicians and policy makers in resource allocation decisions. For example, in the USA, where the dissemination of medical technology is largely determined by market forces, atypical antipsychotics are widely used, while countries with more systematic health care planning and budgeting have been more deliberate in adopting these new products.

Although a variety of claims of efficacy and safety of atypical antipsychotics compared with conventional agents have been made, the evidence is highly variable and in many cases inadequate. Some questions can be answered from the available literature and data from studies presented at scientific meetings, but many more cannot. There is now strong evidence that atypical antipsychotics are efficacious in schizophrenia, and that they are associated with a lower risk of EPSs than conventional antipsychotic drugs.[22] However, a comprehensive understanding of the nature and extent of any clinical advantages of the atypical antipsychotics over their conventional counterparts is not available. The advantages of the atypical antipsychotics regarding EPSs and TD may be offset by disadvantages in terms of other side effects. For example, it appears that the atypical antipsychotics as a class produce substantial weight gain to a greater degree than conventional antipsychotics. Clinical trials of the efficacy and safety of the atypical antipsychotics show weight gain in as many as 50% to 80% of study subjects.[23] Although these reports indicate that weight gain is an effect shared by the atypical antipsychotics, the individual drugs may vary in the magnitude of this effect. Clozapine and olanzapine have been associated with the most dramatic weight gain, while ziprasidone may produce the least weight gain of the atypical antipsychotics examined for this effect thus far.[24] The physiological mechanism of weight gain is unknown. Also unknown are consequences of the weight effects. These could range in severity from mild cosmetic changes to significant disfigurement to increased rates of cardiovascular disease, diabetes, and mortality.

Atypical antipsychotic drugs have also been associated with alterations in glucose metabolism and with elevations of blood cholesterol and lipids.[24-26] Two recently published case series described 10 patients on atypical antipsychotics who either developed diabetes or had a significant exacerbation of existing disease.[25,26] Looking at both reports combined, weight gain occurred in 60% of subjects prior to the development of diabetes. The relationships between the atypical antipsychotic effects on weight gain and the effects on glucose, cholesterol, and lipids are not known. Also not known are the long-term medical consequences of all these effects. It is quite possible that the nutritional and metabolic effects of the atypical antipsychotics could pose safety problems that are as onerous to patients treated with them as TD was to patients treated with conventional antipsychotics.

Two meta-analyses of studies of atypical antipsychotics have recently received widespread attention. The first, by Leucht and colleagues, examined the safety and efficacy of olanzapine, quetiapine, and risperidone, from randomized controlled trials.[22] (Sertindole was also examined, but is not mentioned further here because it is no longer available due to alleged cardiac toxicity.) This meta-analysis evaluated the change in overall psychopathology to measure global efficacy, the change in negative symptoms, the use of antiparkinsonian medications as a measure of side effects, dropouts due to treatment failure, and dropouts due to adverse events. All the atypical antipsychotics and haloperidol were superior to placebo regarding global efficacy, with olanzapine and risperidone "very modestly" superior to haloperidol. Regarding negative symptoms, all the atypical antipsychotics and haloperidol were superior to placebo. The analyses showed olanzapine and risperidone as superior to haloperidol, and quetiapine as inferior to haloperidol in treating negative symptoms. However, when sub- and supratherapeutic doses were examined, quetiapine was just as effective as haloperidol in treating negative symptoms. All the newer atypical antipsychotics were better than haloperidol regarding the use of antiparkinsonian medications and were similar to each other. Risperidone was closer to haloperidol than the other newer atypical antipsychotics regarding the use of antiparkinsonian drugs.

Geddes and colleagues examined 52 randomized controlled trials that compared atypical antipsychotics (including amisulpride and sertindole) with conventional

antipsychotics or with other atypical antipsychotics.[21] Examined outcomes included symptom scores, dropout rates, and scores on measures of side effects. Overall, they found that atypical antipsychotics were slightly more effective and better tolerated than conventional antipsychotics. Thus, the conclusions of both major meta-analyses were consistent with regard to effectiveness and tolerability. However, Geddes and colleagues also noted that the advantage of atypical antipsychotics increased as the dose of the conventional comparator increased. They conducted additional analyses using only doses of conventional antipsychotics that did not exceed recommendations (haloperidol 12 mg daily or equivalent) and no longer found differences in dropout rates between the atypical and conventional antipsychotics. On the other hand, even when excessive doses of conventional antipsychotics were excluded from analyses, fewer EPSs occurred with atypical antipsychotics. Nevertheless, on the basis of the finding that many of the perceived benefits were due to excessive doses of the conventional comparator drugs, Geddes and colleagues found that the atypical antipsychotics have no clear advantage in terms of either efficacy or tolerability. They concluded that the atypical antipsychotics' apparent advantage in terms of EPSs was not enough to improve their overall tolerability or to warrant recommending them as first-line treatments.

To summarize the existing evidence, it is reasonably clear that atypical antipsychotics are at least as effective as the conventional antipsychotics in reducing positive symptoms in patients with schizophrenia. Claims that they are superior in reducing positive symptoms have not yet been proven.[21,22] Olanzapine and risperidone appear to be slightly more effective than conventional antipsychotics in reducing negative symptoms, but it is not clear whether this is due to a direct therapeutic effect or to less frequent EPSs or other secondary causes of negative symptoms.[21] Long-term trials of the effectiveness of atypical antipsychotics in reducing negative symptoms are needed.[7] Existing studies have found that atypical antipsychotics cause fewer EPSs than their conventional counterparts, especially when the conventional comparator is haloperidol. In spite of marketing claims, studies of effects on cognitive function are wholly inconclusive, as are studies of the effects on mood symptoms. The effects of these drugs on long-term outcome, relapse prevention, social and vocational functioning, suicide prevention, quality of life, and family and caregiver burden have just begun to be explored.

Although first introduced only in the mid-1990s, risperidone, olanzapine, and quetiapine now account for more than half the new antipsychotic prescriptions in the USA and Canada. The rates of usage vary in Europe, Asia, and South America from as low as 5% to as much as 40%. Patients who had inadequate therapeutic responses to conventional antipsychotics or who suffered problematic side effects were the first to be switched to the atypical antipsychotics. Now, however, many newly diagnosed or first-episode patients are initially prescribed these newer agents with the hope (not yet backed by evidence) of giving them every early advantage.[27] Worldwide, many patients with schizophrenia continue treatment with the conventional antipsychotics. Because there are no long-acting atypical preparations yet available, conventional antipsychotics in a long-acting injectable form retain an important role for patients who cannot adhere to oral regimens. (At the beginning of 2001, a long-acting version of risperidone was in phase 2 trials.)

Atypical antipsychotic medications are several times more expensive than conventional antipsychotics in the USA, averaging $5000 or more per patient per year. Thus, these medications have substantial potential for influencing the use of scarce resources. While their high cost may discourage their use, they have the potential to generate substantial savings in health and non–health care resources if they are more cost-effective than other available treatments. Even if atypical antipsychotic drugs do not decrease the overall costs of care, their use may be warranted if their benefits are judged to be substantial enough to justify the increased expenditure. The clinical and public policy decision to supplant conventional with atypical antipsychotic treatment requires empirical evidence. This is important because the spending of large sums of money on treatments that are less cost-effective than available alternatives may result in needless waste of scarce resources and deprive some patients of clinical benefits to which they would otherwise have access.

The evidence to support the superior effectiveness of atypical antipsychotics over conventional antipsychotics is currently limited and predominantly based on short-term efficacy studies. Existing evidence does not adequately address long-term effectiveness and cost issues. The studies to date, which were for the most part sponsored by pharmaceutical companies and designed to achieve regulatory approval based on evidence of efficacy and safety, are largely short term (6–8 weeks),

involve initially hospitalized patients, and focus mainly on the core psychopathology of schizophrenia and well-known side effects (eg, EPSs). These studies do not definitively demonstrate the "real world" effects of the newer atypical antipsychotics, nor do they adequately examine the broad range of side effects that may occur. At the same time, however, these studies provide evidence of greater safety for these medications, at least in terms of rates of EPSs and TD, and the possibility of superior therapeutic benefits in psychopathologic and functional domains that have not, as yet, been adequately or fully evaluated.

Conclusion

Existing evidence suggests some, albeit inconsistent, advantages in efficacy and tolerability for the newer atypical antipsychotics over the conventional antipsychotics for patients with schizophrenia. However, the limited types of assessment measures used and the short study durations do not provide adequate information about treatment for this highly variable and chronic condition. Moreover, the patient samples involved in these studies and the conditions imposed by the restrictions of the protocols limit the generalizability of the results. Additional information, from studies not sponsored by pharmaceutical companies, is needed to inform clinicians and policy makers about appropriate role of atypical antipsychotics.

Several studies are currently ongoing or in preparation to examine the comparative effectiveness of atypical antipsychotics. The one with which we are most familiar is the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) project, a major research initiative in the USA by the National Institute of Mental Health, which will assess the effectiveness of the second-generation antipsychotics in a broad range of patients with schizophrenia and in patients with Alzheimer's disease. The CATIE trial in schizophrenia combines elements of efficacy and effectiveness trials. Medications will be randomly assigned on a double-blind basis. Follow-up will be up to 2 years. The primary outcome will be all-cause treatment discontinuation, and this will be validated by measures of symptoms, side effects, quality of life, and costs. The study will examine strategies for what to do when a patient fails an initial trial of an atypical antipsychotic drug. For example, should a second newer atypical antipsychotic be prescribed or is clozapine the best choice? In addition, the trial seeks to avoid some of the problems that have been criticized in earlier trials. Instead of high-potency haloperidol, medium-potency perphenazine is the conventional comparator. The dose of the conventional comparator will not be excessive. Cost–effectiveness and cost–benefit analyses will be conducted to help identify the value of any advantages that atypical antipsychotics may have over conventional antipsychotics or over each other. Ultimately, the CATIE trial in schizophrenia seeks to provide crucial information regarding the role of atypical antipsychotic medications for patients with schizophrenia. In addition to the CATIE Project, the Medical Networks in Medicine (MEDNET) is examining the comparative effectiveness of different drug groups in their indicated disorders in Germany (W. Gaebel, H. J. Moller, personal communication). At the same time, in many countries, investigators have no government support for research on mental disorders and their treatment. An alternative approach is to utilize funding from a consortium of pharmaceutical companies to support investigator-initiated clinical trials, such as was done by the European First-Episode Treatment Study in Schizophrenia (EUFEST) group (W. Fleischhacker, R. Kahn, personal communication).

These studies will contribute to the body of evidence that is needed to definitively evaluate the effectiveness of the atypical antipsychotic drugs and determine their proper use. ❑

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Eficacia comparada de antipsicóticos en la esquizofrenia

La clorpromazina, que fue descubierta en 1952, tiene un perfil de eficacia / seguridad ampliamente caracterizado que incluye serias limitaciones: la eficacia en la práctica clínica es menor a la de los ensayos clínicos, hay síntomas residuales en el 50% de los pacientes, hay un 20% de recaídas en pacientes que están adheridos al tratamiento y se presentan desagradables efectos secundarios extrapiramidales, incluyendo la disquinesia tardía en un 5% por año. Los antipsicóticos "atípicos" evitan estos efectos al tener menos afinidad por el receptor D_2 de dopamina y sí afinidades por otros neurorreceptores. La clozapina, líder entre los antipsicóticos atípicos, fue seguida a mediados de la década de los 90 por risperidona, olanzapina y quetiapina, los que ahora dan cuenta de más de la mitad de las prescripciones de nuevos antipsicóticos en América del Norte. El debate acerca de su eficacia relativa involucra el potencial bienestar de millones de esquizofrénicos y billones de dólares. Los antipsicóticos atípicos de segunda generación son considerablemente más caros, las evidencias acerca de su superioridad son altamente variables y a menudo inadecuadas y se limitan a estudios de regulación de corta duración. Los efectos de la evolución a largo plazo (particularmente los síntomas negativos), la prevención de recaídas, el funcionamiento social y vocacional, la prevención de suicidios y la calidad de vida, y el costo para las familias y cuidadores son poco conocidos. El proyecto acerca de la eficacia de intervención de los ensayos clínicos de antipsicóticos del National Institute of Mental Health es un estudio de eficacia – eficiencia cuyo objetivo es responder a estas preguntas en una amplia población de pacientes con esquizofrenia y enfermedad de Alzheimer.

Efficacité comparative des traitements antipsychotiques dans la schizophrénie

La chlorpromazine, découverte en 1952, et dont les caractéristiques d'efficacité/sécurité d'emploi ont été dressées de façon exhaustive, comporte de sérieuses limitations. En effet, l'efficacité réelle de la chlorpromazine n'atteint pas celle déterminée dans les études, 50 % des patients souffrent de symptômes résiduels, 20 % des patients rechutent malgré une bonne observance. Par ailleurs, la chlorpromazine entraîne l'apparition d'effets secondaires extrapyramidaux préoccupants, telle la dyskinésie tardive dont l'incidence est de 5 % par an. Les antipsychotiques de seconde génération, dits "atypiques", évitent ces problèmes du fait qu'ils ont une affinité moindre pour les récepteurs dopaminergiques D_2, tout en possédant une affinité pour d'autres neurorécepteurs. La clozapine, chef de file des antipsychotiques atypiques, a été suivie dans le milieu des années 90 par la rispéridone, l'olanzapine et la quetiapine qui représentent à l'heure actuelle plus de la moitié des prescriptions d'antipsychotiques en Amérique du Nord. Le débat quant à leur efficacité relative intéresse le bien-être potentiel de millions de schizophrènes et un marché portant sur des milliards de dollars. Les nouveaux antipsychotiques coûtent en effet beaucoup plus cher et leur supériorité, très variable et souvent insuffisante, n'est confirmée que dans des essais à court terme à visée réglementaire. L'effet à long terme de ces médicaments sur le devenir de la maladie (en particulier sur les symptômes négatifs), la prévention des rechutes et des suicides, l'insertion sociale et professionnelle, la qualité de vie et la charge supportée par l'entourage familial et le personnel soignant sont autant d'inconnues. C'est pour élucider ces points que le projet CATIE (Clinical Antipsychotic Trials of Intervention Effectiveness), une étude d'efficacité/efficience, est actuellement mené sous l'égide du National Institute of Mental Health chez un grand nombre de patients atteints de schizophrénie et de la maladie d'Alzheimer.

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