

Do Large Scale Studies of the Use of Antipsychotics Help Us Choose the Most Effective Treatments for Schizophrenia?

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Abstract.

A number of large-scale antipsychotic studies have been carried out in recent years.

Before the introduction of atypical antipsychotics, all antipsychotics were considered to act on the D2 receptor and all appeared to have equal efficacy. The new generation of antipsychotics all act on multiple receptors and each has a different receptor profile, hence there have been many queries about which of these medications is most effective for the treatment of schizophrenia. The large scale studies were intended to compare the first generation antipsychotics to each of the second generation [or atypical] ones, thus enabling decisions to be made as to which were the most effective. This article reviews these studies and assesses the utility of their conclusions.

Key words: antipsychotics – effectiveness – efficacy – recovery – schizophrenia - First Episode Psychosis

Introduction.

Primary and secondary care teams are required to manage patients with first-episode psychosis, chronic schizophrenia, relapsing episodes and treatment resistant schizophrenia. Recent restructuring and movement towards shared care of patients with mental illness has meant that more patients will be cared for in primary rather than secondary care. This means that much prescribing of anti-psychotic medication will be carried out in primary care.

Before the introduction of atypical antipsychotics, all antipsychotics were considered to act on the D2 receptor and all appeared to have equal efficacy. The new generation of anti psychotics all act on multiple receptors and each has a different receptor profile, hence there have been many queries about which of these medications is most effective for the treatment of schizophrenia. Two questions arise; are there advantages in using atypical anti psychotics as opposed to typical ones, and , if so, which are the most effective and safe atypical anti psychotics to use.

Hence, a number of large scale anti psychotic studies have been carried out in recent years to compare different anti psychotics. These large scale studies were intended to compare the first generation antipsychotics to each of the second generation [or atypical] ones, thus enabling decisions to be made as to which were the most effective.

In the first place it is worth stating what the difference is between typical and atypical anti psychotics. Typical anti psychotics, such as chlorpromazine or haloperidol work on the D2 receptor, and over the years are of proven efficacy in dealing with positive symptoms of schizophrenia, that is, hallucinations, delusions, and thought disorder. The most important adverse effects of the typical anti psychotics are extra-pyramidal neurological adverse effects. Atypical anti psychotics work on other receptors as well as D2, notably 5HT receptors, and each of these drugs has a different profile of receptors on which it works. Atypical anti psychotics in usual dosage do not usually cause extra-pyramidal adverse effects (although some, such as risperidone, do in higher dosage). It has been hoped that atypical anti psychotics would be more effective than typical anti psychotics in treating negative symptoms, however many atypical anti psychotics tend to cause the development of metabolic syndrome

including weight gain and diabetogenesis as adverse effects.

Five major studies comparing antipsychotic efficacy have been identified as important large scale studies which may give us information on comparative efficacy of antipsychotics.

The studies were as follows.

CUTLASS (Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia study) (1,2).

CATIE (Clinical Antipsychotic Trials of Intervention Effectiveness study) (3,4).

SOHO (Schizophrenia outpatients Health Outcomes study) (5-8).

CAFÉ (Comparison of Atypicals in First Episode study) (9,10).

EUFEST (European First Episode Schizophrenia Trial) (11).

Our group have reviewed these studies elsewhere (12), and we can only review them briefly in this paper.

CAFÉ, EUFEST, and a Subset of SOHO studied patients with first episode psychosis. The larger part of SOHO, CATIE and CUTLASS studied Chronic Patients. A sub group of SOHO, CAFE, and EUFEST studied First Episode Patients.

We will discuss these studies on the premise that we wish to use them, as large scale studies in as close to 'real world' conditions, in order to decide whether a typical anti psychotic, such as haloperidol, is as appropriate to use in either first episode or chronic schizophrenia, and whether the most appropriate atypical antipsychotic treatment is risperidone, olanzapine, or quetiapine. Ziprasidone is included in some of the studies, but is unavailable in the UK, while the partial dopamine agonist aripiprazole was introduced too late to participate.

If we assess the trials one by one, what we find is the following;

CAFE - standing for Comparison of Atypicals in First Episode, (9,10) was a 52- week randomized, double-blind, flexible-dose, multicenter study which evaluated the overall effectiveness (as measured by treatment discontinuation rates) of olanzapine, quetiapine, and risperidone in patients early in the course of psychotic illness (9). The trial, although well randomised and blinded, uses discontinuation as a primary endpoint - this is hard to draw conclusions from: patients may discontinue due to adverse effects, due to lack of efficacy or against medical advice for a multitude of reasons. (9,10) As a secondary endpoint, the study does make use of a PANSS scoring system to measure efficacy, adding some weight to the conclusion that olanzapine, quetiapine and risperidone in early psychosis patients have equivalent efficacies.

CATIE - **CATIE** was a randomised study lasting only 18 months. It included olanzapine, perphenazine, quetiapine, risperidone, with ziprasidone being added on later (3). This trial was a comparative study, and so lacked a control arm and used discontinuation of medication as an inverse measure of efficacy - an easily quantifiable event, but making for difficult interpretation. However most criticism has been directed at the unusually low (quetiapine, ziprasidone) and high (olanzapine and perphenazine) doses of drug used, which were reflected in their differing rates of efficacy. It appears in this study that olanzapine was the more efficacious than the other drugs as assessed by rates of discontinuation, but in fact, it seems that there was little difference between the rates of discontinuation of olanzapine and perphenazine, thus suggesting little significant difference between typical and atypical medications in terms of efficacy. Also, at all events, the rates of discontinuation for all medications were surprisingly high (3).

CutLASS The Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS 1) (1) was a study which aimed to compare the cost utility of first generation antipsychotics to that of second generation antipsychotics in chronic patients. Thus its aim was different from the other four trials. This trial allows for less generalisation of its findings to the general population as it makes use of a specific subpopulation (those switching from one medication to another after a period of treatment). It has been argued that the trial design allowed observer bias, because randomisation was only to first or

second generation medications, with the very similar sulpiride and amisulpride in the first and second generation groups respectively. Also some patients were prescribed oral medications and some depot injections - making comparisons difficult due to possible differences in compliance. Given these issues with the design, it is not surprising that the outcome of the study was that there was no difference between the cost efficacy of the two groups of medications.

EUFEST, The European First Episode Schizophrenia Trial (11), aimed to compare the effectiveness of second-generation antipsychotic drugs with that of a low dose of haloperidol, in first-episode schizophrenia (11). It was an open randomised controlled trial of haloperidol versus second generation antipsychotic drugs which took place in 50 sites, in 14 countries (8). This trial makes use of discontinuation as an endpoint with the weaknesses we have described. Treatment of first episodes of psychosis is shown to be feasible, but it could not suggest if haloperidol or second generation drugs may be more efficacious. The medications used were haloperidol, amisulpride, olanzapine, quetiapine or ziprasidone. One problem with EUFEST was that risperidone was not included in the study, so this trial cannot be used to decide the relative merits of olanzapine, risperidone and quetiapine.

SOHO – This study compared olanzapine, clozapine, amisulpride, risperidone, quetiapine, and typical antipsychotics (oral, depot). These were the antipsychotics available when the study was designed. It is an observational study, and as such, it has been able to provide three year data. This trial was hindered by the observational design of the study and small numbers reaching the primary end point (4%). Caution should be exercised in the conclusion that olanzapine is superior to risperidone, quetiapine or typical antipsychotics. A similar result was found both in the full study and the subgroup of first episode patients. (5-8)

Conclusion

There is much information useful for clinical practice to be gathered from the results of these major studies; however, interpretation is hampered by both variations and weakness in study design. CUTLASS and CATIE have led to NICE revising its guidelines so that there is no longer advice that first episode patients should always be started on an atypical medication; instead, typical and atypicals may now be equally used in these patients. However, on balance it does appear that different antipsychotics possess differing efficacy, but also of relevance to the development of sound clinical guidelines is their differing adverse effects profile. Thus, the increased propensity of atypical medications to raise lipids, increase weight gain, and cause diabetogenesis (4,13) must be balanced against the increased extrapyramidal adverse effects of the typical medications, while aripiprazole has a low incidence of both groups of adverse effects, but may be less effective on balance (14). It needs to be remembered that the atypical were preferred to the typical in the IRIS first episode guidelines (15) because patients were less likely to complain of sedation and extrapyramidal effects, and hence were more likely to engage with services after the acute episode was over. This advice remains valid despite changes suggested by NICE and the recent studies, since engagement is key to successful long term treatment of schizophrenia.

There is other evidence which needs to be taken into account when deciding which atypical antipsychotic to use. Metanalyses by Davis (16) and Lucht (17) suggest that atypical antipsychotics can be divided into two groups regarding efficacy; a more efficacious group of olanzapine, risperidone, and amisulpride, and a group of rather lower efficacy including quetiapine, aripiprazole and ziprasidone. This suggestion confirms the results, taken together, of the large studies described above. Finally, it is worthwhile describing the place of clozapine in the treatment of schizophrenia. Clozapine was the first atypical antipsychotic but its adverse effect of agranulocytosis means that it is only used in severe schizophrenia which is resistant to other medications. At least two antipsychotics should have been used at full dosage for at least six weeks each before clozapine is considered, and other causes of refractory schizophrenia, such as use of cannabis, need to be excluded (NICE (18)). The position of clozapine as a treatment for resistant schizophrenia has been confirmed by a second CUTLASS study (2), which has shown that it is more cost efficacious than other antipsychotic medications.

To conclude, major clinical studies do give us useful comparative data to decide which antipsychotics should be chosen in treating schizophrenia; however, interpretation is hampered by both variations and weakness in study design. In these circumstances, the choice of antipsychotic must depend on efficacy, adverse effects, and the preference of patients.

GP comment

What have I learned from this paper?

1. Recent evidence suggests that most atypical antipsychotics are probably not more effective than the older “typical” antipsychotics but at least some of them have a better adverse effect profile.
2. Although large-scale studies have provided some information, there are difficulties in interpreting the data with certainty.
3. The evidence continues to show that clozapine is effective in resistant schizophrenia but it should only be prescribed in specialist centres after the failure of two other antipsychotic drugs because of the risk of serious adverse effects.

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