

Editorial

Are all antipsychotic drugs
the same?[†]

Stefan Leucht and John M. Davis

**Summary**

The classification system of atypical and typical antipsychotics has created a lot of confusion and might be abandoned. Nevertheless, to say that all drugs are the same and that therefore it does not matter which drug is given is wrong. Both typical and atypical antipsychotics differ in side-effects, mechanisms of action, cost and efficacy. The available choice of antipsychotics should be adapted to individual patients in a shared decision-making process.

Declaration of interest

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Girgis and colleagues present a unique 9-year naturalistic follow-up of an initially randomised clozapine *v.* chlorpromazine trial in first-episode schizophrenia.¹ Very few such long antipsychotic drug follow-ups have been published and the trial team must be lauded for their enormous efforts.

First-episode studies find little difference among antipsychotic drugs because there are ceiling effects due to high rates of remission – 78% in Girgis *et al.*'s study. A considerable number of patients with first-episode schizophrenia remitted without drug treatment in the pre-antipsychotic era,² and approximately 20% will not have a second episode.³

Nowadays, long-term studies (such as the study by Girgis *et al.*) are analysed by including all patients, whether they remained on their original drug, were switched to another drug or were drug-free. We have likened this approach to an automobile race between Alaska to Argentina where drivers were randomised to very expensive BMWs or the cheapest Ford.⁴ If the car broke down during the race, the driver could choose either a BMW (disclosure: BMW is a funder of the Technische Universität München) or a Ford as a replacement car. Many Fords quickly broke down, and the drivers invariably replaced them with BMWs. That only 29 (18%) out of 160 randomised participants remained in Girgis *et al.*'s study in the groups they were originally designated may have diluted the initial drugs' effects. This said, it is disappointing that even the most efficacious antipsychotic clozapine failed to produce a long-lasting benefit.

Historical perspective

We try to put this editorial in a historical perspective. All the previous 'chlorpromazine me too' antipsychotics had roughly equal efficacy, and the low-potency antipsychotics were advertised

as having few extrapyramidal side-effects (EPS), the high-potency ones as having minimal sedation so you could use them in high doses. The high-potency drug won the media war, the patients losing because the high-potency antipsychotics led to more EPS. The revival of clozapine in 1988 by the landmark study of Kane and colleagues,⁵ who found that 30% of treatment-resistant patients responded to clozapine *v.* 5% to chlorpromazine, led to enormous enthusiasm about the development of new antipsychotic drugs.

Twenty years later the evidence shows a much more sobering picture: initially, drug companies advertised their drugs as 'clozapine-like', i.e. EPS-free, more efficacious for general and treatment-resistant illness, and especially effective for negative symptoms. They promoted these drugs as being 5-HT₂ (serotonin) receptor blockers, like clozapine, using this pharmacological property as a justification for calling the drugs 'atypicals'. We have analysed the degree of dopamine and serotonin blockade in positron emission tomography or single-photon emission computed tomography studies, and found all the antipsychotics to be potent D₂ (dopamine receptor) blockers;⁶ however, most of the atypical antipsychotics which are potent 5-HT₂ blockers are no more efficacious than the 'typical' antipsychotics, and amisulpride, which is more effective,^{4,7} has no propensity to block 5-HT₂ receptors. The pharmaceutical companies also charged very high prices for these drugs, a worldwide market expected to reach \$20.8 billion in 2011 (www.reportlinker.com/p0236244/Antipsychotic-Drugs-Technologies-and-Global-Markets.html), cost being the key driver of the debate.

Antipsychotic drugs differ in many respects

Unfortunately, from the first randomised controlled trials onwards, most of the so-called atypicals had about equal efficacy to typicals, even for negative symptoms, and none of those few atypicals with superior efficacy to first-generation antipsychotics reached clozapine's efficacy.^{4,7} Nevertheless, the classification of atypical *v.* typical antipsychotics obscured differences, because meta-analyses based on hundreds of studies consistently found certain new drugs (e.g. amisulpride, olanzapine, risperidone) to be significantly better than older drugs, although these differences were small (clearly smaller than most differences in side-effects), and there is a debate about the effects of high haloperidol doses in comparator groups.^{4,7}

[†]See pp. 281–288, this issue.

Initially, the field was not aware of the weight gain problem, probably due to the preoccupation with EPS and tardive dyskinesia in the 1970s/1980s. But it had been known that low-potency typicals such as chlorpromazine caused weight gain. In the early papers on clozapine in the 1970s, it was reported that clozapine was associated with weight gain but it was not of great concern, although it should have been owing to its serious medical complications. The weight gain problem received more attention partly due to 'counter-marketing' (companies highlighting the problems of their competitor drugs) and the excessive weight gain associated with olanzapine and clozapine. However, some of the atypical drugs cause moderate weight gain (e.g. risperidone, quetiapine) and others minor amounts of weight gain (e.g. ziprasidone, aripiprazole, amisulpride).⁷ Here again, the over-generalisation of atypicals and typicals created the confusing misinterpretation that all old antipsychotics do not and all new antipsychotics do produce weight gain.

What remained was a clear advantage of the new drugs in terms of EPS, which with some restrictions is still true. A drug with a high EPS risk would probably nowadays no longer get approved. Of course, most studies used the high-potency typical antipsychotic haloperidol as a comparator. This drug, however, produced more EPS than atypicals even in low doses below 5 mg/day (see discussions in Leucht *et al.*⁷). The EPS risk of the various atypicals differs (e.g. risperidone produces more EPS than most other second-generation antipsychotics⁸), but these differences are relatively small. Low-potency typical antipsychotics also produce relatively few EPS and not necessarily more than atypicals,⁷ but they are all sedating. There are a few old drugs such as sulpiride and some old mid-potency antipsychotics such as perphenazine, which clinically surprisingly did not produce more EPS than quetiapine in the CATIE (Clinical Antipsychotic Trials of Intervention Effectiveness) study.⁹ Some atypical antipsychotics (e.g. amisulpride, risperidone) increase prolactin levels more than typical antipsychotics, but almost all other atypicals increase prolactin levels less than typicals. Some atypicals (e.g. sertindole, ziprasidone) and some typicals (e.g. thioridazine, pimozide) prolong the QTc interval. There are differences in sedation, as well.

CATIE, CUTLASS and EUFEST

Finally, the controversial effectiveness studies CATIE,⁹ Cost Utility of the Latest Antipsychotic drugs in Schizophrenia Study (CUTLASS)¹⁰ and European First-Episode Schizophrenia Trial (EUFEST)¹¹ fuelled the discussion, because they were again interpreted as showing no differences, although the side-effect results were virtually the same as in the previous meta-analyses: even concerning efficacy we see a similar pattern (for discussion, see Leucht *et al.*⁴). The CUTLASS¹⁰ trial is an extreme case because groups of drugs were compared assuming that all atypical drugs were similar. The EUFEST¹¹ study found a markedly lower rate of treatment discontinuation with amisulpride and olanzapine and in the last observation carried forward results of the Positive and Negative Syndrome Scale (PANSS) compared with haloperidol. These results may be clouded by bias present in open studies.⁷ The CATIE study found olanzapine was the most effective in terms of rates of discontinuation (hazard ratios between 0.41 to 0.59) and time to good response,⁹ although other statistical analyses failed to find differences in efficacy. High discontinuation rates (e.g. 74% in CATIE), which differ in amount and reasons between groups, are an important problem of many long-term studies. At some degree of attrition due to poor efficacy, patients are no longer randomised and even the best statistical

method cannot account for these enormous discontinuation rates. Although we have shown that pharmaceutical companies often put spin on the interpretation of their studies,¹² two analyses did not detect a sponsor bias in the actual efficacy data.^{7,13}

Personal interpretation

Our personal interpretation of this debate is that the classification of antipsychotics into atypical and typical has led to a lot of confusion because these drugs differ in many properties such as efficacy, side-effects and cost (some are now generic), mechanism of action (amisulpride is a selective dopamine antagonist and aripiprazole is a partial dopamine agonist), and therefore the classification might be abandoned. We agree that apart from clozapine no new drug was a breakthrough in efficacy. Their (amisulpride, olanzapine, risperidone) effect sizes compared with typical antipsychotics were small (between 0.13 and 0.31), although the numbers needed to treat for one additional responder were actually not bad (between 6 and 15).⁷ But to say that all drugs are the same and that therefore it does not matter which drug is given to the patient is wrong, and reverting back to high-dose haloperidol, the previous primary treatment in many countries, would not help patients.

We feel, as there are many real differences among drugs, that the physician should adapt the treatment accordingly to the individual patient through a shared decision-making process. Patients have different preferences and at the end it is they who must take the medication. Some patients want to avoid weight gain or EPS or sexual side-effects, and others want to receive the most efficacious compound. The best antipsychotic drug will not work if the patient does not take it, so there is a role for depot formulations. We feel it is important to empower the patient to make informed decisions about which drug and dose to take as well as the route of delivery, which may lead to better feedback and adherence, and although evidence is not perfect (in some cases only suggestive), we think the cumulative effect would be to get a better result with more patients.

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poems
by
doctors

Rosiglitazone and Other Bitter Pills

Bob Adams

I saw her across the aliskiren lawn
her depakote fastened at the neck
Macroliding gently on abstral plane
she entered my life

Boarding jet nebulisers we
pirouetted to nexium
No astringents here
Everything was dream skin silk

It was evening and primroses swayed
gently from their castor oil beds and
acylovirs passed on the ultrabase
Hormones raged and I exjaded . . .

'You are marvelon, are you varenicline
Do you favism, ergot abilify?
Manuka honey, my belladonna menopur
yasmin, can we menjugate tonight?'

All went quetiapine, from losartan to
highsartan. Curse my lustral that night.
How crassly salicylic, how did I know
she was a one touch product with domperidone?

Mercilon was her reply. No sublimaze
No interferon at the eleventh hour
No lipitor, no calcichew.
Pergoliding like a pseudo ephedrine

was the only way to get fibrelief. But
she was no lamotrigine. Mercurially diuretic
with tremendous menorrhagia, she had
zybaned all hope with sevikar flagyl

Later, in javlor, there was no ritalin.
I had taken risperdal and it could
have worked. Warfarin could have been
avoided if I had used my tegritol

Rosiglitazone my regal princess
You promised so much, now
waxing lyrica is all that remains
No Viagra no pregaday, just mogadon

Drug Count 53. There are no competing interests. Dr Adams does not do any work for drug companies.