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Are antipsychotic drugs effective against acute psychosis?

PERSPECTIVES

TROND F. AARRE

trond.aarre@helse-forde.no
Trond F. Aarre, specialist in drug and addiction medicine and psychiatry. Head of Department at Nordfjord Psychiatric Centre and medical director of Mental Health Care, Førde Hospital Trust.
The author has completed the ICMJE form and declares no conflict of interests.

The scientific evidence suggests that the efficacy of antipsychotic drugs against acute psychosis is so marginal that they hardly deserve their name.

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In January 2025, the Norwegian Directorate of Health published their guidelines for psychopharmacological treatment of psychosis (1). They write: 'Experience tells us that refusal to offer antipsychotics is felt to be irresponsible'. The reason why they say '*is felt* to be irresponsible' rather than '*is* irresponsible' may well be that the evidence to support this treatment is weaker than one would think. Although the treatment of acute psychosis with antipsychotic drugs is considered routine, or even an obligatory course of action, research shows that few patients benefit significantly from these drugs (2–6).

Knowledge about the benefits of antipsychotics is essential. These drugs are even used for coercive treatment. For that to be acceptable, we need to impose particularly high evidential requirements and be particularly well informed about the evidence.

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The recommendations issued by the Directorate of Health

The Directorate of Health recommend antipsychotic drugs for any first-episode psychosis, although they admit that there are no placebo-controlled trials to support this recommendation. 'Historically, randomisation to placebo has been seen as ethically questionable for people with a first-episode psychosis because trials that involve groups with recurring psychotic episodes have showed that antipsychotics are clearly effective. In practice, placebo groups would therefore have their effective treatment delayed, and this was considered to be ethically problematic vis-a-vis patients who experience the onset of a serious mental disorder' (1). In other words, the Directorate believe that while there is no empirical support for their recommendation, such support is not required because the effect is likely to be as good for first-episode psychoses as for subsequent episodes. I will go on to demonstrate that the efficacy of the drugs in treating recurring episodes of psychosis is not as unequivocal as the Directorate maintain.

Methodology problems

Randomised trials have a number of inclusion and exclusion criteria. For instance, the criteria may exclude people who also meet the criteria for other mental health or substance use disorders, and this will systematically increase the probability of the drugs being effective or reduce the rate of improvement in the placebo group (7).

A more serious problem is that trial participants will normally be taking an antipsychotic drug to start with. In order to be eligible for the trial, they will need to suddenly come off these drugs (8), which is not a recommended course of action in clinical practice. It can be difficult to 'differentiate between symptoms that are caused by reducing or discontinuing a treatment and symptoms of a relapse or new psychotic episodes. There may also be a rebound effect or even a withdrawal syndrome at play' (9). In cases of randomisation to placebo, sudden discontinuation can trigger worsening of the condition, which increases the difference between the placebo group and the medication group (8).

Such methodological problems can lead to exaggerated perceived benefits of the drugs. The efficacy of antipsychotic drugs in controlled trials is greater than in clinical practice (10).

What is meaningful improvement?

I believe that for a therapeutic effect to be meaningful, it needs to be greater than the placebo effect. The difference must be of a certain size to be of clinical interest. If neither the doctor nor the patient can discern the difference, it is of little value.

Efficacy tends to be rated on the symptom rating scale referred to as PANSS (Positive and Negative Syndrome Scale). Analyses of the correlation between PANSS scores and symptom improvement have concluded that: Minimal improvement, which is far less than what we are looking for in clinical practice (11), equates to a 20 % reduction in the PANSS score or at least a 15-point decrease. If there is a reduction in the PANSS score of 50 % or more, or a decrease of at least 33 points, the patient is considered to be 'much improved' (12).

Improvement in the placebo groups

Many get better without antipsychotics. We see improvements in the placebo groups because a crisis often passes with time, and because life events may intervene to ease the problems, irrespective of the treatment. Additionally, the participants receive attention from dedicated professionals who communicate an explanation to their problems, boost the hope of improvement and provide systematic follow-up and emotional support. These non-specific effects produce improvement in both the placebo and the medication groups. Only approximately 40 % of the improvement we see with antipsychotics stems from their active substance (13).

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In a meta-analysis, placebo had an effect size of 0.59 for schizophrenia, which is considerably higher than the effect of adding antipsychotics: 'Pre-post effect sizes, whether for placebo or active treatments, are in *a different order of magnitude* than effect sizes resulting from the comparison of an intervention group with a control group' (14).

How many experience meaningful effect?

The question is whether the efficacy of antipsychotics is clinically interesting, rather than only statistically significant. In my opinion, minimal improvement is not good enough.

A meta-analysis of treatments for people with multiple psychotic episodes (167 trials, 28,102 patients) showed that approximately half saw at least a 20 % reduction in their PANSS score (minimally improved) (3). Only 23 % of the participants achieved a 50 % reduction (much improved). The 'number needed to treat' was five for minimal improvement and eleven for much improvement. Leichsenring et al. maintain that the effect sizes for most of the drugs in this meta-analysis were so small that they were likely to have no clinical significance (6).

In a meta-analysis of trials that compared olanzapine or amisulpride to other antipsychotic drugs or placebo (16 studies, 6221 patients), the condition of 20 % of the patients on antipsychotics remained unchanged or deteriorated (5). Even worse, 43 % of the patients did not even see a minimal improvement, and only a third were 'much improved'. The authors concluded that there is a high nonresponse rate when stringent criteria are set for improvement.

The Norwegian Directorate of Health state that in cases of first-episode psychosis, more than 80 % will have a response, defined as at least a 20 % improvement of the PANSS score (1). This equates to a 'minimal improvement'. A 50 % reduction, which means that the individual has much improved, was seen in approximately 50 % of participants. There were no placebo groups in the referenced study, so we do not know how much of this improvement was caused by the drugs (15).

Staff at the Food and Drug Administration (FDA), which approves new drugs for use in the US, have studied the size of the difference between antipsychotics and placebo. Trials conducted in North America between 1999 and 2007 showed, on average, a reduction in PANSS score that was only six points greater with medication than with placebo (4). In other words, this difference is not even considered a 'minimal improvement'. It is so minute that it would be difficult to perceive and hardly of clinical interest.

For schizophrenia, a standardised mean difference (SMD) in effect sizes between antipsychotics and placebo of 0.73 will equate to a minimal clinical improvement of 15 points on the PANSS score. In their analysis, Leichsenring et al. found a standardised mean difference of 0.38–0.45, which in their opinion cannot be detected by clinicians and therefore can have no clinical benefit (6).

Because there is only a minute effect, approximately 25 % of patients take more than one antipsychotic drug (16). Polypharmacy is associated with severe problems and poor outcomes, but does not resolve these problems. It is also associated with many undesirable effects and a higher mortality rate (16).

Good enough for coercive treatment?

It is clear from the Directorate of Health's comments on the mental healthcare legislation that 'for the expected impact of treatment, the probability of a positive response will have to be higher than usual. Additionally, it is a requirement that the treatment must lead to a considerable change in the patient's condition' (17). If more than minimal improvement is required, there

is a conspicuously large proportion of patients who see no meaningful effect from antipsychotic drugs. In my opinion, the higher-than-usual probability requirement for a positive response to coercive treatment, as set out in section 4 - 4 of the Mental Healthcare Act, is not met.

> ***«If more than minimal improvement is required, there is a conspicuously large proportion of patients who see no meaningful effect from antipsychotic drug»***

Nonetheless, some individuals undoubtedly have a manifest and worthwhile benefit from these drugs. While some have little effect against delusional thoughts and hallucinations, they have a favourable effect on irritability, aggressiveness and restlessness. Such improvements can decide whether an individual is a risk to themselves or others, and if the individual can receive the necessary assistance. Even partial efficacy may be what an individual needs to live a dignified life outside of an institution. These are factors we need to consider when we interpret the body of evidence.

Minimal efficacy in most cases

Low medication efficacy and high placebo efficacy suggest that we should continue to conduct placebo-controlled trials of antipsychotics. The disappointing findings of the scientific studies mean that we can no longer take for granted that the drugs have a meaningful effect in the majority of those who experience psychosis.

The problem is not a lack of evidence of effect, but evidence that a majority of patients experience no meaningful effect. The drugs have a series of adverse effects that will have to be balanced against their questionable benefits.

After more than 60 years of administering antipsychotic drugs, we have yet to demonstrate more than minimal efficacy in the majority of patients. Those who believe that antipsychotic drugs are more effective than this, should produce equally good or better studies that arrive at the opposite conclusion. It is no longer enough to wish or believe that these drugs work the way we want them to work. Time has come to *demonstrate* that they do. Until somebody is able to do that, I will stop referring to them as antipsychotics. Instead, I will use the name introduced by the pharmaceutical industry itself: neuroleptics. For there is reason to doubt their efficacy against acute psychosis.

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