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Therapeutic value of anti-psychotic drugs: A critical analysis of Cochrane meta-analyses of the therapeutic value of anti-psychotic drugs

Søren Ventegodt, MD, MMedSci, MSc*[1,2,3,4,5], Trine Flensborg-Madsen, MSc, PhD[6], Niels Jørgen Andersen, MSc[4,7], Bjarne Øwre Svanberg, BSc[1], Flemming Struve, MSc[1,2,3,5], Christian Endler, MSc, PhD[5] and Joav Merrick, MD, MMedSci, DMSc[8,9,10]

[1]The Quality of Life Research Center, Copenhagen, Denmark; [2]Research Clinic for Holistic Medicine, Copenhagen, Denmark; [3]Nordic School of Holistic Medicine, Copenhagen, Denmark; [4]Scandinavian Foundation for Holistic Medicine, Sandvika, Norway; [5]Interuniversity College, Graz, Austria; 6National Institute of Public Health, Centre of Alcohol Research, Southern University of Denmark, Copenhagen, Denmark; [7]Norwegian School of Management, Sandvika, Norway; [8]National Institute of Child Health and Human Development, [9]Office of the Medical Director, Division for Mental Retardation, Ministry of Social Affairs, Jerusalem, Israel and [10]Kentucky Children's Hospital, University of Kentucky, Lexington, United States

Abstract

About 5% of people in the developed world are prescribed anti-psychotic drugs. The scope of this study is to evaluate the positive and negative effects of anti-psychotic drugs, when treating the psychotic, mentally ill patient in comparison with placebo. Methods: Meta-analysis of the Cochrane protocols on anti-psychotic drugs. The study included all randomized clinical trials, where anti-psychotics have been tested in comparison with placebo. The primary outcomes of treatment of interest to the study were: Mental health (or "mental state"), cooperativeness (or "behaviour"), a hybrid measure of mental health, cooperativeness and hallucinatory behaviour (or "global state"), relapse of primarily un-cooperativeness or hallucinatory behaviour (or "relapse") as well as adverse effects. The study included analyses of dichotomous data using fixed effects relative risk (RR), an estimation of the 95% confidence interval (CI) as well as a calculation of the number needed to treat (NNT) and the number needed to harm (NNH). All significant NNHs were summed to estimate the sum of total NNH. Findings: The results showed, that anti-psychotic drugs improved mental health (NNT=50). It was also found that uncooperative behaviour (NNT=4) and "relapse" (NNT=4) was reduced, and that "global state" was improved (NNT=7). Anti-psychotic drugs were shown to have many adverse effects (total NNH=0.67) and the different types of anti-psychotic drugs had similar positive and negative effects. Anti-psychotic drugs did not cure mental health for patients with psychotic or mental illness, as the small, positive effect found could be explained by the bias. The drugs have many severe adverse effects.

Keywords: Cochrane, meta-analysis, psychiatry, psychotropic drugs.

Introduction

According to the World Health Organization (WHO), 400 million people suffer from a severe mental illness (1). In Denmark, the yearly consumption of anti-

* **Correspondence:** Søren Ventegodt, MD, MMedSci, MSc, Director, Quality of Life Research Center, Classensgade 11C, 1 sal, DK-2100 Copenhagen O, Denmark. Tel: +45-33-141113. E-mail: ventegodt@livskvalitet.org

psychotic drugs equals 6% of the population or about 300,000 people with an annual expense of 122 million EURO (2).

Some studies have recently shown that anti-psychotic drugs are of miniature efficiency, when treating children, patients with learning disabilities, as well as other groups of patients (3-5). Alongside these findings, a tendency towards attributing an increase of importance to patient narratives concerning a less positive impression of the treatment with anti-psychotic drugs has emerged (6,7) and mentally ill patients are known to frequently have discontinued the treatment. A significant part of the explanation is the patients' experiences of the treatment with anti-psychotic drugs as being less than perfect (8,9). Some researchers have even suggested that anti-psychotic drugs mainly work by reducing salience of ideas and perceptions, and thus doubt the positive effect of the drugs on the patient's mental health (10). Other researchers have suggested that non-drug therapy might be better for the patients in the long run (11). All of this has created an interest to re-evaluate the positive and negative effects of anti-psychotic drugs.

The ideal study would be an all-including meta-analysis of the positive and negative effects of all the anti-psychotic drugs in the treatment of the psychotic mental illnesses in general. But such a study has been considered difficult to complete, among other reasons due to the non-uniform quality of many of the studies, and because of the diversity of effect and adverse effects among the different types of anti-psychotic drugs.

However during the last decade, many studies of the positive and negative effects of the anti-psychotic drugs vs. placebo have been thoroughly analyzed in a large number of Cochrane meta-analyses (12-88). Moreover, recently a large Cochrane study documented that all the different types of anti-psychotic drugs shared similar qualities in regards to beneficence, non-beneficence or even harmful qualities (13). As an effect of that, a significant step towards overcoming the obstacles hindering such a general meta-analysis seems to have been taken, thus making this current study possible.

The present study is a meta-analysis of the effect on anti-psychotic drugs in general for the psychotic mental illnesses in general. As the recent Cochrane study on the effects of the different antipsychotic drugs indicated that mental health ("mental state") did not improve significantly (13), a central research question of interest is therefore, if there is a positive treatment effect on mental health with the use of anti-psychotic drugs.

Methods

Cochrane Collaboration software for preparing and maintaining Cochrane reviews (Review Manager), and the basic review and meta-analysis principles recommended by the Cochrane Collaboration (89,90,91) were used in this study. The methodological quality of the studies was independently assessed by at least two authors. The data was extracted by two reviewers.

We searched Medline/PubMed and the Cochrane Library (CENTRAL) for all Cochrane reviews including studies investigating the effects of anti-psychotic drugs versus placebo for all illnesses, and these studies formed the basis of the study at hand. Only randomized controlled trials were included, while quasi-randomized studies were excluded. All participants were people with a diagnosis of schizophrenia or other types of psychotic mental illness, irrespective of age, sex or severity of illness.

The search allowed us to include data from 127 studies on the positive effect of anti-psychotic drugs including 16,646 patients and data from 556 studies on the adverse effects, which included 74,369 patients in the present analysis. As inclusion necessitated at least a Category B on The Cochrane Handbook rating of allocation, a similar number of studies were excluded. The reason for reviewing studies based on quantitative methods only was the lack of quantitative research in the field.

Types of intervention

1. Any of the following: High dose (Chlorpromazine, Thioridazine), middle dose (Zuclupenthixol, Peraphenazine), low-dose (Fluphenazine, Haloperidole, Sulpiride, Pimozide, Penfluridol), or atypical, (Risperidone, Aripiprazole, Quetiapine, Amisulpride, Olanzapine, Sertindole,

Ziprasidone). Thus including any dose or mode of administration (oral or by injection).
2. Any dose or mode of inactive placebo.

Types of outcome measures

1. Mental health (psychotic symptoms or "mental state"): Clinical significant response (short and medium term: 0 days – 6 month)
2. Behaviour (un-cooperative/disturbed/ deteriorated/hallucinatory): Clinical significant response (medium term: 6 weeks – 6 month)
3. Global state (Hybrid measures of mental health and uncooperative or hallucinatory behaviour): Clinical significant response (short and medium term: 0 days – 6 month)
4. Relapse (as defined in the clinical trials, often of un-cooperative or hallucinatory behaviour): Clinical significant response (long term: 6 month to 2 years)
5. Adverse effects (see Table 2): (short and medium term: 0 days – 6 month)

Methodological quality

1. Randomization

A fairly low percentage (about 10% of the studies) described the methods used to generate random allocation. For most studies, it did not seem completely clear that bias was minimized during the allocation procedure. About 40% reported that the participants allocated to each treatment group were estimated to be similar.

2. Blinding

About 50% gave a description of their attempts to make the investigation double-blind.

3. Treatment withdrawals

The description of those who left the study early was in general unclear or sometimes absent.

4. Outcome reporting

Studies frequently presented both dichotomous and continuous data in graphs, or reported statistical measures of probability (p-values). This diminished the possibility to acquire raw data for a synthesis. It was also common to use p-values as a measure of association between intervention and outcomes instead of showing the strength of the association. Although p-values are influenced by the strength of the association, they also depend on the sample size of the groups. Frequently, continuous data were presented without providing standard deviations/errors (about 60% of trials) or no data were presented at all (about 20% of trials). Thus a lot of possibly informative data were not at hand; we estimated that half of the information was lost here. Many studies used the the Brief Psychiatric Rating Scale (BPRS) that contains data related to quality of life like "anxiety", "emotional withdrawal", "guilt feelings", "blunted affect", "depression", "tension" and "anergia", but these subjective data were not analysed in any Cochrane studies, and is therefore not included in the present study.

5. Overall quality

The quality of trials as measured in the previous version of the review varied (mean using the Jadad Scale was about 3.5). Inclusion necessitated at least a Category B on the Cochrane Handbook rating of allocation. Practically no studies reached Category A, so all data must be considered to be prone to a moderate degree of bias.

Meta-analytical calculations

The meta-analysis was done in line with recommendations from the Cochrane Collaboration and the Quality of Reporting of Meta-analyses guidelines (89,90,91). The randomized-analysed endpoints used in the Cochrane reviews were used to group studies according to the above-mentioned outcomes. Funnel plots were made for each outcome and to summarize the effect, relative risks (RR) and risk differences (RD) were calculated, and the number needed to treat (NNT) and number needed to harm

(NNH) was calculated from RDs. To combine data in this meta-analysis the fixed effects model was used.

We did not apply weighting for study quality, since we did not have any empirical basis for doing so. The pooled NNH that combined all adverse effects into one measure was calculated as the inverse of the added inverse NNHs of all significant adverse effects (see Table 2). We avoided counting the same adverse effect twice, by grouping similar side effects into one group.

Results

Positive effects

Adding together all anti-psychotic drugs into the same meta-analysis (see table 1) we found data to favour anti-psychotic drugs according to: mental health (clinical significant response on psychotic symptoms or mental state) (n=8,407, 53 RCTs, RR 0.87, CI 0.81-0.94), NNT 50; cooperativeness (n=1085, 9 RCTs, RR 0.52, CI 0.45-0.61), NNT 4; clinical significant response in "global impression" (n=5,453, 47 RCTs, RR 0.76, CI 0.73-0.80), NNT 7; and long-term relapse (primarily of hallucinatory or un-cooperative behaviour) (n=1,701, 18 RCTs, RR 0.58, CI 0.53-0.64), NNT 4.

The NNT estimates varied substantially according to the different outcomes. Hence, the NNT for relapse and cooperativeness were 4 and 4 respectively, while the NNT for a clinical significant response to mental health (psychotic symptoms or mental state) was 50. Sub-dividing the meta-analysis into different categories of drugs showed the same pattern, with relapse and cooperativeness being the outcomes with the lowest NNT for all kinds of drugs and clinical significant responses to mental health (psychotic symptoms or mental state) having a substantially higher NNT (see Table 1).

Adverse effects

Adding together all anti-psychotic drugs we found data to favour placebo treatment according to a number of adverse effects. Table 2 shows the adverse effects that we found statistically significant for at least one group of antipsychotic drugs. It is important to notice that while most of the adverse effects might be seen as less burdensome than the mental illness they intent to cure, i.e. weight gain, some of the adverse effects must be considered serious threats to the patients health, like liver problems, Parkinsonism, and general movement disorders. Adding up all side effects showed a NNH of 0.67 (0.49-1.09), meaning that every patient treated with an antipsychotic drug was likely to get adverse effects. High-dose typicals (NNH=0.60; 0.43-0.98) and low-dose typicals (NNH=0.58; 0.38-1.23) showed similar low NNHs; an estimation of the total NNH of middle-dose typicals and atypicals was not possible due to lack of data.

Table 1. Number Needed to Treat (NNT) according to type of anti-psychotic drug and outcome

d	NNT High-dose typicals	NNT Low-dose typicals	NNT Atypicals	NNT All anti-psychoticdrugs
Mental health (psychotic symptoms or mental state not improved)	**No significant improvement**	**No significant improvement**	**237.7 (42.7 - ∞)**	**50.2 (26.4-519.8)**
Cooperativeness (lack of hallucinatory or uncooperative behavior)	**3.5 (2.9-4.4)**	**No studies**	**No studies**	**3.5 (2.9-4.4)**
"Global impression" (mental health and hallucinatory behavior not improved)	**5.3 (4.3-6.9)**	**3.9 (3.1-5.4)**	**12.7 (9.1-21.0)**	**6.8 (5.7-8.3)**
"Relapse" (primarily of hallucinatory and uncooperative behavior)	**3.2 (2.5-4.3)**	**3.2 (2.5-4.3)**	**4.9 (3.5-8.1)**	**3.7 (3.1-4.4)**

Table 2. Number needed to harm (NNH) according to type of antipsychotic drug and adverse effects. (Estimation of the NNHs of middle-dose typicals and atypicals was not possible due to lack of data)

	NNH High-dose typicals	NNH Low-dose typicals	NNH All antipsychotic drugs
1. Photosensitivity	7.9 (6.2-11.0)	No studies	7.9 (6.2-11.0)
2. Eye problems	6.5 (4.9-9.8)	Not significant	6.5 (4.9-9.6)
3. Low blood pressure	10.2 (7.7-15.4)	Not significant	14.6 (11.6-19.8)
4. Constipation	18.5 (12.2-38.7)	8.8 (4.6-96.9)	26.0 (17.9-47.5)
5. Dry mouth	9.5 (7.5-13.1)	8.5 (5.0-26.3)	10.8 (9.1-13.3)
6. Weight gain	3.6 (2.4-5.4)	9.1 (5.7-22.3)	14.9 (11.6-20.7)
7. Salivation and drooling	40.7 (24.4-132.6)	13.9 (8.9-32.2)	40.9 (27.3-80.7)
8. Peripheral oedema	No studies	No studies	9.4 (5.7-26.9)
9. Dystonia	25.7 (17.3-49.7)	8.3 (5.0-25.4)	21.9 (14.9-41.3)
10. Parkinsonism	8.8 (6.8-12.7)	3.1 (2.4-4.4)	13.4 (9.8-21.2)
11. Tremor	15.8 (9.5-48.3)	9.6 (6.6-17.7)	21.2 (16.3-30.4)
12. Rigidity	12.0 (7.8-26.4)	3.7 (2.9-5.3)	11.1 (8.3-17.0)
13. Weakness including asthenia	6.1 (4.0-12.9)	No studies	13.8 (9.6-24.5)
14. Sleepiness and sedation	4.2 (3.7-5.0)	7.7 (5.5-12.0)	7.0 (6.3-7.9)
15. Fits (loss of consciousness)	38.2 (19.0 - ∞)	Not significant	35.8 (18.8-389.2)
16. Liver problems	11.8 (7.2-31.9)	Not significant	9.9 (6.3-23.9)
17, Urinary problems	52.1 (26.2-3977.3)	Not significant	25.5 (17.7-45.8)
18. Blurred vision	Not significant	12.0 (7.0-40.7)	62.4 (27.7-247.4)
19. Thick speech or speech disorder	Not significant	Not significant	15.3 (9.9-33.9)
20. General movement disorder	Not significant	7.0 (3.5-292.6)	24.3 (17.4-39.9)
21. Dizziness	No studies	Not significant	20.8 (14.4-37.6)
22. Akathisia	Not significant	7.8 (5.2-15.5)	Not significant
ALL (added together)	0.60 (0,43-0.98)	0.58 (0.38-1.23)	0.67 (0.49-1.09)

Heterogeneity

The studies varied regarding type of inclusion criteria, anti-psychotic drugs and outcomes. In order to reduce the heterogeneity, it is common practice in Cochrane studies to exclude trials that differ much. In this study we included all studies irrespective of the heterogeneity in order to avoid bias. In addition to fixed effect model we also used a random effects model, but this did not change the results much.

Discussion

Two percent of the mentally ill patients treated with anti-psychotic drugs improved their mental health ("mental state") (NNT=50); as we included all studies the effect tested for was a small, but significant clinical effect. A signicant bias of all data can easily explain this small effect, Therefore it is not correct to claim based on these data that mentally ill patients can be cured. Uncooperative behaviour and relapse of hallucinatory behaviour was significantly reduced in a quarter of the patients prescribed anti-psychotic drugs (NNT=4), but this is likely to be due to a passifying effect of the drug, in a way poisoning the patients. In accordance with this interpretations we found adverse effects to be very common (total NNH=0.67).

We aimed to use long-term data for the effects of anti-psychotic drugs, as many patients have them prescribed for a relatively long period (sometimes several years). Long-term data for "relapse" was found, but very few long-term studies were found in order to investigate the other outcomes. For "behaviour" and "global impression", only short- and medium-term data was found, and for "mental state" and "adverse effect" a finding of primarily short-term data complemented with little medium-term data took place. In order to make the present analysis it was

necessary to include short, medium and long-term data in order to uphold the validity of this study, There are some indications that the positive effects diminish over time; "global impression" thus falls from NNT=4 (short-term) to NNT=7 (middle-term) (4), but there were no long-term data. Based on the experience gained from performing this study, the research group recommend that long-term data should be collected in future testing of anti-psychotic drugs. In addition, many of the original outcome measures of the studies were non-theory-based hybrid measures that included both mental health and behaviour (i.e. the Brief Psychiatric Rating Scale, BPRS). These hybrid measures have been grouped together and relabelled "global impression" in the Cochrane studies, but their significance is not clear.

The interpretation of the NNH values found is debatable as the different types of anti-psychotic drugs have different profiles of adverse effects. The aim of the present analysis of the adverse effects was not to establish the single NNH numbers, which are better established in the tests of the different groups of anti-psychotic drugs one by one, but to establish the total NNH, which expresses the likelihood to get one or more side effects using any type of anti-psychotic drug. In spite of the different profiles, the non-beneficial or harmful effects of the different types of anti-psychotic drugs seem to be of similar intensity in this data interpretation. We do not know if some of the adverse effects are statistically correlated, but this is likely to be the case. If that is the case, then the total NNH is calculated too small. A moderate correlation of 0.1 would change the NNHt to about 1. There is an ongoing methodological debate about the concepts of "number needed to treat" and "number needed to harm" (92,93), but we do not find the arguments against these concepts presented convincing, and before better concepts are developed, we should not abandon the few effective tools we have to evaluate the clinical value of drugs. Abandoning the NNTs and NNHs would make it quite impossible to evaluate the products of the pharmaceutical industry in metaanalysis, which we obviously need to do, the antipsychotic drugs being an example of this urgent need.

There are several problems with the study inclusion criteria: a) Why look at only placebo controlled trials? Although active controlled trials are not that numerous in antipsychotic trials, nevertheless they would methodologically still provide usable comparisons between individual compounds. b) Why only look at randomised trials? - although they are accepted as the 'best design these trials will almost never be actually designed as safety trials, as they nearly always have efficacy as their primary objective. Often trials - even otherwise good ones - are poor at systematically reporting all safety data. They also tend not to be large enough to be powered to look at rare events, even when aggregated in a meta-analysis across studies. They are also known in many different clinical areas to generally select an atypical subset of the treatable population into the RCT. We found it problematic that many of the early studies did not allow the efficacy result from a study to be extracted (e.g. just a P-value was given). It is pointless having an optimized search algorithm, if then the data cannot be extracted. This might have serious implications for the robustness of the findings.

We found only 127 studies (~17,000 patients) to be of sufficient quality to be included, but 556 studies on adverse events (~70,000 patients). The reason for this is that the drugs four times as often are tested against each other than against placebo. This fact should not induce bias.

There was a 'general heterogeneity' in the old trials (different drugs, different designs, different adverse effects signals, different population, differing quality etc). One could fairly argue that the quality of the studies was so poor in general and bias so large that the "Cochrane-type metaanalysis" are in fact completely meaningless. This position might be philosophically correct, but will render us completely without tools for evaluating the therapeutic effects of any drugs, giving the pharmaceutical industry power to float the market with inefficient and harmful drugs, so we do not want to go there.

Research has not been thorough, when it comes to the studies of global quality of life, sexual or social functioning, so we have drawn our conclusions based on rather incomplete data. We have assumed that because the early studies of the effect of antipsychotic drugs showed that quality of life, social and sexual functioning were significantly reduced, the pharmaceutical industry simply avoided these measures in the later research, the same way as they avoided all long term measures for adverse effects,

This assumption might be wrong and we encourage researchers more resourceful than our group to investigate this.

The Cochrane studies did not test the effect of anti-psychotic drugs against "active placebo" (94), which is another more serious source of bias (95). We recommend that all future studies of mind-altering pharmaceutical drugs be tested this way, or even better against the optimal, alternative non-drug CAM treatment for the relevant disorder (96).

Conclusions

In this meta-analysis, data from 127 studies on the positive effect of anti-psychotic drugs including 16.646 patients has been interpreted in the first general meta-analysis on the effect of antipsychotic drugs. The statistical analysis showed, that the anti-psychotic drugs actually did improve mental health ("mental state") compared with placebo (NNT=50). As we have included all outcomes, large and small, we know that this effect is very small indeed, as one in fifty gets a small improvement. We also know that all data is moderately biased, but we find that the small effect can be easily explained by the bias. We therefore did not find the antipsychotic drugs to improve the mental state of mentally ill patients. The study showed that the patients' "behaviour" seems to be significantly improved due to a reduction in un-cooperativeness and "relapse" seems to improve due to less hallucinatory behaviour (NNT=4). These effects can be explained from a pacifying effect of the drugs coming from a general poisoning of the patient. "Global state", a hybrid measure of unclear significance, was also improved. The anti-psychotic drugs had many adverse effects (total NNH=0.67), but this should probably be corrected to total NNH=1 as we expect some correlation between adverse effects. All types of anti-psychotic drugs had in general similar levels of positive and negative effects. Thus an overall conclusion of this data interpretation is that the anti-psychotic drugs included in this study did not improve mental health. Taken together with the shown extent of the side effects following the use of such medicine, the treatment of psychotic, mentally ill patients with anti-psychotic drugs cannot be considered rational.

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