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The therapeutic value of antipsychotic drugs: A critical analysis of cochrane meta-analyses of the therapeutic value of anti-psychotic drugs used in Denmark

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Abstract

A rough estimate of the therapeutic value of a drug can be established from the ratio "Number Needed to Treat to Harm/Number Needed to Treat to Benefit" (NNH/NNT or NNtH/NNtB). The ratio illuminate the degree to which the treatment with the drug respects the ethical rule of "first do no harm"; if the ratio is >1 the drug helps more than it harms and is thus primarily beneficial. We need to compare the upper confidence limit of the NNtB with the lower confidence limit of the NNtH to assure that a drug helps and does not harm the patient.

Methods: We compare NNH/NNT ratio from the Cochrane meta-analyses of the commonly used antipsychotic drugs in Denmark.

Results: All antipsychotic drugs used in Denmark had a NNH/NNB< 1, and often 1/5 and 1/10, meaning that the drugs are likely to harm many more patients than they help. Antipsychotic drugs are known to have not only physical adverse effects, but also mental, existential, social and sexual side effects that are seldom included in the studies, giving a strong bias in favor of the drugs. Important factors that are often ignored in the studies were: suicides from drug-induced depression, suicide attempts and their consequences, spontaneous drug-induced death, drug-induced self-molestation, damage to learning and working ability, sexual function, social function, self-esteem and self-confidence, and cognitive factors.

Conclusions: Antipsychotic drugs on the Danish market today have a very low therapeutic value and seems to be primarily harmful to the patients. From an ethical perspective antipsychotic drugs can therefore not be used as a standard treatment for any mental illness. Further scientific investigation into the significance of this finding is urgently needed. Antipsychotic drugs might still be justified in the treatment of specific subgroups of patients like violent and sexually aggressive, acute psychotic, schizophrenic patients.

Keywords: Therapeutic value, psychiatry, psychotherapy, antipsychotic medicine, adverse effects, Cochrane meta-analysis, ethics, evidence-based medicine, suicide, global quality of life.

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Introduction

From the days of Hippocrates in 300 BCE medical ethics has stressed the importance of avoiding harm to your patient: "primum non nocere" – first do no harm. To serve the patient's best interest a physician must be certain that the drugs are helping and not causing harm to the patient. Most patients will accept mild adverse effects, and serious adverse effects can be tolerated if they are rare and the drugs is useful, but it is unethical to give drugs that severely harm a substantial fraction of the patients, and it becomes a really serious ethical problem if a drug harms more patients than it helps.

In medical science today we use the concept "Number Needed to Treat to Benefit" (NNT or NNtB) about the number of patients that must be treated for one to be helped, and the Number Needed to Treat to Harm (NNtH or NNH) to tell the number of patients that must be treated for one to be harmed. NNtB and NNtH are measured with an uncertainty (CI means confidence interval at p=.05), so there are always a highest and a lowest value for each NNT measure. To be sure that a drug really helps and does not harm we need to compare the lowest empirically supported value (i.e., the upper confidence limit, or pessimistic harms assessment) with the highest empirically supported value of the Number Needed to Treat to Benefit (NNtB), i.e. a pessimist's assessment of benefits. In principle the NNtH/NNtB ratio can be calculated better, if all positive and negative effects were added up to one number; the importance of each treatment effect factor should be multiplied with its likelihood before taken into the addition, and a negative effect should be given negative value. The problem with such a "smart" strategy is that the result will be totally dependent on the number of included factors – what makes it less smart than it appears at first glance.

Methods

We have compared the Cochrane meta-analyses of the commonly used antipsychotic drugs in Denmark (1-27) (see table 1). Surprisingly we found that almost all the drugs were harming more patients than they were helping, and often five or even 10 times more. We typically found NNtB to be 5-20 and NNtH 2-5. Just using a drug, which needs 10 patients treated for one to be helped, seems highly unethical, if a large fraction of the patients are harmed. Another serious problem is that the placebo effect is included in the results, making many drugs look active, when they are only slightly more effective that placebo.

Discussion

A serious problem with the data is that they are provided by the industry, which has an interest in marketing their products. We found that most of the trials reviewed of the pharmaceuticals were designed to be very kind to the drugs. Only a small improvement of psychotic symptoms is often taken as help for the patient, in spite of the sad fact that these drugs rarely cure any patient for any disease. On the other hand the industry-imposed design has looked mostly at short-term physical adverse effects and often many extremely serious mental (28), social, existential, sexual, financial and other adverse effects and side effects were not included in the studies. Among some of the important factors often ignored in the studies were: suicides from drug-induced depression (28,39), suicide attempts and their consequences or spontaneous drug-induces death (4,30), drug-induced self-molestation (cutting etc), damage to learning and working ability, sexual function, social function, self-esteem, self-confidence and quality of life (4), notably including some adverse phenomena which physicians, and even psychiatric investigators, rarely have been trained to probe into. Other important biases have also been found (31). All this makes the NNtH likely to be systematically much too large and the NNtB likely to be systematically much too small, giving a very severe bias in favor of the drugs in the pharmaceutical studies, and most unfortunately also to the Cochrane meta-analyses re-using these data most often without any chance of mounting the appropriate critique. We definitely need to collect this information for the drugs being used to day. It has been argued that the positive effects are qualitatively more important than the negative effects of the drugs, but we have analyzed this and found that both positive and negative changes were registered, when they were clinically noticeable.

Table 1. NNH/NNB ratios for the antipsychotic drugs used in Denmark (1-23) are when calculated as described below always smaller than one, often 1/5 and sometimes less than 1/10, implying that many more patients are harmed than benefited by the antipsychotic drugs, making them unethical to use. NNH/NNT is calculated here according to the principles of securing a positive effect for the patient, see text; if calculated without this principle the NNtH/NNtB ratio will still often be less than one. The list of drugs is found in (31)

"Atypical" antipsychotics
Sertindole (N05AE03) [1] NNtB: 'very much improved' as compared to those taking placebo NNT 7.9, CI 4.3 to 41.1 NNtH: almost as haloperidol. Akathisia - 8mg: 1 study, n=245, RR 0.2, CI 0.1 to 0.5, NNH 6.0, CI 4.1 to 11.2; 16mg: 1 study, n=252, RR 0.1, CI 0.0 to 0.3, NNH 5.4, CI 3.9- 9.0; 20mg: 1 study, n=253, RR 0.3, CI 0.2 to 0.7, NNH 7.3, CI 4.6 to 17.9; 24mg: 2 studies, n=524, RR 0.5, CI 0.3 to 0.7, NNH 8.6, CI 5.6 to 18.3. Tremor - 8mg: 1 study, n=245, RR 0.3, CI 0.1 to 0.7, NNH 8.5, CI 5.2 to 24.0; 16mg: 1 study, n=252, RR 0.2, CI 0.1 to 0.5, NNH 7.3, 4.8 to 15.6; 20mg: 1 study, n=253, RR 0.2, CI 0.1 to 0.6, NNH 7.8, CI 4.9 to 18.1; 24mg: 2 studies, n=524, RR 0.4, CI 0.2 to 0.6, NNH 8.2, CI 5.6 to 15.3. For Hypertonic - 24mg: 2 studies, n=524, RR 0.5, CI 0.3 to 0.8, NNH 12.4, CI 7.5 to 35.0. NNtH/NNtB=4/41.1= 0.097 Ziprasidone (N05AE04) [2] NNtB: As haloperidol. NNtH: Not calculated; almost as haloperidol. Clozapin (N05AH02), No Cochrane study found Olanzapine (N05AH03) [3] NNtB: 'no important clinical response' NNT 8 CI 5 to 27 NNtH: weight gain NNH 5 CI 4 to 7). Insufficient data. NNtH/NNtB=4/27= 0.15 Quetiapine (N05AH04) [4] NNtB 11 CI 7 to 55. NNtH: Movement disorders NNH 4 CI 4 to 5. Dry mouth NNH 17 CI 7 to 65. Sleepiness NNH 18 CI 8 to 181. NNtH/NNtB=7/55= 0.13. No summarized data of spontaneous patient death (4 of 728 died in one RCT, 2 of 618 died in an other RCT). Amisulpride (N05AL05) [5] NNtB not specified: NNT 3 CI 3 to 7. NNtH: Need for antiparkinson drugs: NNH 4 CI 3 to 6. Agitation NNH 11 CI 6 to 50. NNtH/NNtB=3/7= 0.43 (Chlorpromazine used as reference´). Risperidone (N05AX08)[6,7] NNtB: As Olanzapine. NNtH: sexual dysfunction abnormal ejaculation NNH 20 CI 6 to 176. Impotence RR 2.43 CI 0.24 to 24.07. One third of people given either drug experienced some extrapyramidal symptoms (n=893, 3 RCTs, RR 1.18 CI 0.75 to 1.88) but 25% of people using risperidone require medication to alleviate extrapyramidal adverse effects (n=419, 2 RCTs, RR 1.76 CI 1.25 to 2.48, NNH 8 CI 4 to 25). Weight gain: NNH 7 CI 6 to 10). NNtH/NNtB=4/27= 0.15 Aripiprazole (N05AX12) [8] NNtB: NNT 5 CI 4 to 8. NNtH: Need for antiparkinson drugs NNtH 4 CI 3 to 5. (Previous study included NNtH: Insomnia NNH 4 CI 3 to 9.) NNtH/NNtB=3/8= 0.37
High-dose typical antipsychotics
Chlorpromazine (N05AA01) [9] NNtB: Prevents relapse, longer term data: NNT 4 CI 3 to 5. Improves symptoms and functioning NNT 6 CI 5 to 8. NNtH: Sedation: NNH 5 CI 4 to 8. Acute movement disorder NNH 32 CI 11 to 154. Need for antiparkinson drugs NNH 14 CI 9 to 28. Lowering of blood pressure with accompanying dizziness NNH 11 CI 7 to 21. Considerable weight gain NNH 2 CI 2 to 3. NNtH/NNtB=2/5= 0.15 Levomepromazine (N05AA02). No Cochrane study found Promazine (N05AA03). No Cochrane study found Thioridazine (N05AC02)[10] NNtB: "global state outcomes" NNT of 2 CI 2 to 3; NNtH: Sedation NNH 4 CI 2 to 74. Cardiac adverse effects NNH 3 CI 2 to 5. NNTH/NNTB=2/3= 0.67 Melperone (N05AD03), No Cochrane study found Pipamperone (N05AD05) No Cochrane study found Chlorprothixene (N05AF03)No Cochrane study found
Middle-dose typical antipsychotics
Perphenazine (N05AB03) [11]NNtB: 2 CI 1 to 20. NNtH: invalid data. Depot perphenazine decanoate[12]: NNtB as clopenthixol decanoate and other antipsychotic drugs. Need for anticholinergic drugs (one RTC NNtH 4 and another NNtH 10), movement disorders (RR 1.36, CI 1.1 to 1.8

Table 1. (Continued)

NNT 5). NNtH/NNtB = 4/8 = 0.50 (Chlorpromazine used as reference). Zuclopenthixol (N05AF05) [13] NNtB: Patient not unchanged or worse: NNT 10 CI 6 to 131. NNtH: Extraparamydal symptoms NNH 2 CI 2 to 31. Need for antiparkinson drugs NNH 3 CI 3 to 17. NNtH/NNtB=3/131= 0.023 Zuclopenthixol decanoate [14] NNtB: Prevented or postponed relapses NNT 8, CI 5-53. NNtH: Adverse effects NNH 5, CI 3-31. NNtH/NNtB=3/53= 0.057
Low-dose typical antipsychotics
Fluphenazine (N05AB02) [15] NNtB: NNT= placebo (not effective). NNtH: Experiencing extrapyramidal effects such as akathisia NNH 13 CI 4 to 128. NNtH/NNtB=4/Infinite= 0.00 Haloperidol (N05AD01) [16] NNtB: NNT 3 CI 2 to 5/Global improvement NNT 3 CI 2.5 to 5. NNtH: Acute dystonia NNH 5 CI 3 to 9. Need for antiparkinson drugs NNH 3 CI 2 to 5. NNtH/NNtB=2/5= 0.40 Flupentixol (N05AF01) [17] NNtH/NNtB: as other depot antipsychotics. Pimozide (N05AG02) [18] NNtB: Prevents relapse NNT 4 CI 3 to 22. NNTH: Tremor NNH 6 CI 3 to 44- Need for antiparkinson drugs NNH 3 CI 2 to 5. NNtH/NNtB=2/22= 0.091 Penfluridole (N05AG03) [19] NNtB: 'improvement in global state' NNT 3 CI 2 to 10 – as chlorpromazine, fluphenazine, trifluoperazine, thioridazine, or thiothixene. NNtH as chlorpromazine, fluphenazine, trifluoperazine, thioridazine, or thiothixene. NNtH/NNtB=4/10= 0.40 Sulpiride (N05AL01) [20] NNtH/NNtB: evidence is limited and data relating to claims for its value against negative symptoms is not trial-based. New generation antipsychotics[21]**:** NNtH: Of the new generation drugs, only clozapine was associated with significantly fewer extrapyramidal side-effects (EPS) (RD=-0.15, 95% CI -0.26 to -0.4, p=0.008) and higher efficacy than low-potency conventional drugs. These findings might have been biased by the use of the high-potency antipsychotic haloperidol as a comparator in most of the trials. First episode schizophrenia[22]: NNH 3 CI 2 to 6 The results of this review are inconclusive. Antipsychotics in treatment of childhood onset psychoses[23]: NNtH/NNtB: There are few relevant trials and, presently, there is little conclusive evidence regarding the effects of antipsychotic medication for those with early onset schizophrenia. Some benefits were identified in using the atypical antipsychotic clozapine compared with haloperidol but the benefits were offset by an increased risk of serious adverse effects. Early intervention for psychosis[24]: NNtB: Six month follow up: less likely to develop psychosis at a six month follow up NNT 4 CI 2 to 20, 12 month follow up: Not significant! NNtH: Weight gain etc., insufficient data
Other drugs sometimes used against psychosis
prochlorperazine (N05AB04), No antipsychotic Cochrane study found periciazine (N05AC01), No Cochrane study found tetrabenazine (N05AK01) No antipsychotic Cochrane study found Litium (N05AN01) [25] NNTB: as placebo (not efficient). NNTH: Insufficient data. NNTH/NNTB=something/infinite<<1 Benzodiazepines [26] NNTB: NNT 3 CI 2 to 17. NNTH: Maybe worse than placebo. NNTH/NNTB= 100/17? Probably >1 Valproate [27] NNTB: Insufficient data. NNTH: Insufficient data acepromazine (N05AA04), No Cochrane study found

It therefore seems likely that NNtB and NNtH numbers build on equality noticeable phenomena, and therefore comparable. The fact that the antipsychotic drugs have highly unfavorable NNH/NNT ratios cannot be dismissed by the argument the positive effects of the drugs (i.e. the anti-hallucinating effect) are more important than the negative side effects (i.e. severe obesity). We found that there is not one single, antipsychotic, psychopharmacological drug that can be used without harming the patients more than benefiting them; NNH/NNT were always <1 (see table 1).

During the last 10 years the many Cochrane units all over the world have provided us with highly valuable meta-analyses. Because of this unique source of scientifically established high-level knowledge, we now in our opinion know that the ethical treatment of many psychiatric disorders is still psychotherapy, which on one hand in many studies has been documented to help and on the other never has been documented to harm the patients (see 32-34).

To compare NNtH and NNtB will always to some extend be comparing apples and pears; this problem can only be solved by measuring one integrated endpoint of both positive and negative effect like *global quality of life* (which can be measured with a simple questionnaire like the QOL1 with one questions on self-assessed global quality of life (35)), self-assessed physical and mental health, or self-assessed ability of functioning in a number of relevant domains (work, social life, family, sexuality). We recommend the use of a wise and balanced combination of self-assessed mental and physical health, global quality of life, and ability in general as the endpoints for any medical treatment. The low ratio NNH/NNT is the likely reason that the pharmaceutical industry systematically has avoided the use of such endpoint that illuminates the effect of the drugs on the whole person. It has also avoided long-term documentation of adverse effects, in spite of many physicians and patients have been asking for these data for years.

We suggest that we call the inverse number NNH/NNT for ”the ethical treatment value of the drug”. The way it is calculated is in a way “double pessimistic”; we estimate that a drug with NNH/NNT>10 has a 99% chance to be a primarily beneficial (valuable) drug, and a NNH/NNT value<1/10 signifies a 99% risk of being a primarily harmful drug. We suggest that the NNH/NNT value of ”penicillin in the treatment of syphilis” (about 100) can be a benchmark for a highly valuable drug.

If effects and side effects are mechanistically related, like the better mobility after curing a femural fracture leading to an increased future fracture rate, the above-mentioned “smart” formula must be used. The last important thing is that most symptoms and side effects are reversible, but brain damage, suicide and dead are not. Suicide is a negative effect that is much more difficult to tolerate that all other adverse effects and every study must therefore include a long-term survey of increased or diminished suicide rate.

The last thing to consider is that placebo often has a NNT=3; the difference between the antipsychotic drugs and placebo are therefore only marginal; an alternative explanation to a therapeutic effect is the fact that you can feel the drug in you brain, destroying the blindness of the study and creating an “active placebo” effect. If this is the case, we are actually only using placebo to treat, but with high risk of causing side effects and serious harm to the patients. This has never been investigated for the antipsychotic drugs neither by the pharmaceutical companies nor by neutral researchers, and this must urgently be done.

Conclusions

In conclusion, the NNH/NNT ratio might be the needed guideline for evaluating the therapeutic effect of drugs; when this analysis is carried out on the antipsychotic drug using the upper confidence limit of NNT and the lower confidence limit of NNH for the comparison, we find that all antipsychotic drugs used in Denmark are more harmful than beneficial.

We presume that the antipsychotic drugs on the market today in Denmark are very much the same as in all other countries, as the same drugs are used almost everywhere. The analysis indicates that the antipsychotic drugs are likely not to improve health and thus to be without any net therapeutic value; they are likely to be primarily harmful to the patients. This does not mean that the drugs cannot to be used for life-saving and other compelling reasons, like on extremely aggressive, patients that urgently needs to be calmed down, or on acute psychotic sexually

violent schizophrenic patients etc., but they can not be used ethically as a standard treatment for any kind of mental illness.

On the other hand recent research comparing psychotherapy with psychiatric treatment has documented psychotherapy to be helpful to many groups of patients (32-34), and also more helpful than the psychiatric standard treatment, without having the adverse effects of the anti-psychotic drugs.

We believe that the NNH/NNT ratio is the best indicator we have today of the total therapeutic value (benefit-vs.-harm) of a drug, but we must admit that it is a crude summary index of benefit-vs.-harm. For a better evaluation of a medical treatment we need to use a combined measure of *global quality of life* (like QOL1 and QOL5) (35), self-assesses health (36), and self-assessed ability (in a number of relevant domains) (36).

We need urgently - for the sake of all patients - to be able to estimate the total therapeutic value of a drug (or any other treatment) more accurate in the future, and recommend that all clinical trials in the future use *global QOL and self-assessed physical and mental health* as obligatory outcomes; long term studies including all relevant dimensions like *loss of working and studying ability, suicide, and spontaneous drug-induced death* are also absolutely necessary for an ethical evidence-based medicine in psychiatry.

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