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Debate: Is the long term use of psychiatric drugs harmful?

The controversial topic will be discussed by leading experts at the Maudsley Debate, King's College London

The benefits of psychiatric drugs have been exaggerated and the harms underplayed due to poor trial designs, argues one expert in **The BMJ**. But another expert and a patient contend that the evidence supports the use of these drugs.

More than half a million people aged above 65 years die from the use of psychiatric drugs every year in the Western world and the benefits would need to be "colossal" to justify these "immensely harmful" treatments, argues Peter Gøtzsche, professor and director of the Nordic Cochrane Centre, Denmark.

But benefits are "minimal", he explains, adding that these treatments should "almost exclusively be used in acute situations". New guidelines should support this change as well as widespread withdrawal clinics to help many patients gradually come off these medications.

Benefits have been overemphasised and harms understated, he says, because randomised controlled trials have been biased, not blinded appropriately, have not fully evaluated the effects of these drugs and deaths have gone under reported.

For example, the majority of studies have included patients already using a psychiatric drug and such patients may undergo abstinence and suffer from withdrawal symptoms. As a result, this study design exaggerates benefits and increases harms, and has even driven some patients to suicide, he explains.

Industry funded trials have under reported deaths, he adds, estimating that there have probably been 15 times more suicides among people taking antidepressants than reported by the US Food and Drug Administration (FDA).

He calculates that deaths from three classes of drugs – anttipsychotics, benzodiazepines and similar drugs, and antidepressants were responsible for 3693 deaths every year in Denmark. This number corresponds to 539,000 deaths in the United States and European Union combined.

The effects of psychiatric drugs are so small, he says, and that it would be possible to lower current use by 98%. He recommends stopping the use of all antidepressant, ADHD and dementia drugs, and prescribing only 6% of antipsychotics and benzodiazepines.

But Allan H Young, a professor of mood disorders at King's College London, and John Crace, a psychiatric patient, argue that research supports the use of psychiatric drugs which are just as beneficial and efficacious as treatments for other common, complex conditions.

These drugs are needed, they insist, to reduce the long term harms of psychiatric conditions, which are the fifth leading cause of disability worldwide. Most patients suffer from co-existing health conditions, they add, a primary cause of death among this group.

They explain that psychiatric drugs are rigorously examined for efficacy and safety and while the evidence base is “imperfect”, research shows that psychiatric drugs are more beneficial than harmful.

Careful evaluation of these drugs is undertaken before and after regulatory approval, they explain, and that post surveillance after a drug is licensed can include safety of a medication in the general population, which unlike study populations, includes people with varied medical conditions.

Yet concerns persist and many are “overinflated”, they add, and list recent studies supporting the use of lithium, once labelled a "toxic placebo", and antipsychotics, and treatments for mood disorders.

But as with any drug treatment, the harms and benefits need to be evaluated from group data in trials, and be applied to individual patients whose subjective experiences are important to consider, they argue.

[Ends]

Notes to Editors:
The authors are taking part in the 52nd Maudsley debate to be held at King's College London on 13 May.

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Head To Head Maudsley Debate

Does long term use of psychiatric drugs cause more harm than good?

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Re: Does long term use of psychiatric drugs cause more harm than good?

We are a group of Cochrane editors who are responsible for the Cochrane Reviews that relate to mental health. Like Peter Gøtzsche we are writing in our personal capacity. Cochrane does not, and should not, have an agreed policy on the prescribing of psychotropic medicines.

We recognise that Peter has an important record as a renowned methodologist studying questions of bias, and as a researcher conducting systematic reviews. Therefore his interpretation of the evidence commands respect. However, we are concerned that in this article he steps beyond the accepted role of an independent researcher by appearing to recommend a course of action, and that this could, if acted upon, lead to patient harm.

We agree with Peter that the benefits of psychotropic drugs have long been exaggerated, or that harms (including suicide) have been underestimated. Peter is one of the many researchers that deserve credit for uncovering how the effects of bias, most notably selective outcome reporting, have created this distorted picture. We also agree that such overly optimistic interpretations lead to patient harm.

Despite this we make the following observations:

• The motion of the debate refers to “long term” use of psychiatric drugs, however Peter’s article appears to consider all use. This should have been clarified in the article, and failing to distinguish between short-, medium and long-term use for different types of patients does not facilitate the reader’s understanding.
• Psychotropic drugs and the patients for whom they are prescribed differ widely. Treating them as a homogenous whole is not helpful within such a concise article, given that there will be very different benefits and harms in different populations and with different drugs.
• The central argument Peter makes – that 98% of psychotropic drugs could be stopped without causing harm – is potentially damaging to patient well being, and is not justified within the article. In many cases the citations provided lead either to his own unpublished book or those of others, rather than scientific study reports. Thus it is hard or impossible for the reader to check their veracity.
• The data on suicide related to the use of antidepressants are central to Peter’s argument, and yet the only citation is to his own unpublished book. It is unclear in this section whether the figures presented relate to total suicides in the studies, total suicides in those taking antidepressants, or additional suicides in people taking antidepressants compared with those not taking them. This is an important distinction, and gets to the

heart of how many of these suicides can be attributed to the antidepressants. The same is true for the estimates of total deaths: the data as presented are simply insufficient to justify the confident conclusions and precise estimates reported.

• In the Cochrane Review cited (tricyclic antidepressants versus active placebo), Peter merely states that the "review did not find any meaningful effect". This over simplifies the findings of the review, which is now substantially out of date, identified scarce and heterogeneous data from old studies and led the authors to describe their findings as uncertain or "tentative".

In summary, we are concerned that the picture painted by Professor Gøtzsche may be a partial one, and that the extreme recommendations he makes based on his interpretation of the published research are inappropriate, and insufficiently justified by the scientific literature presented, to guide decision making in practice or health policy.

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Re: Does long term use of psychiatric drugs cause more harm than good?

Four of my Cochrane colleagues, the editor-in-chief and the editors responsible for reviews of antidepressants, antipsychotics and ADHD drugs, agree with me that the benefits of psychotropic drugs are exaggerated and the harms (including suicide) underestimated (1).

They are concerned, however, that my recommendation that we only need 2% of the drugs we currently use (1,2) could lead to patient harm. As they didn't explain how, this is a remarkably evidence-free postulate, particularly considering that I documented that psychiatric drugs kill more than half a million people every year in the United States and Europe (1,2). My recommendations would lead to healthier and more long lived populations and would spare tens of millions of people from becoming mentally crippled (2).

The Cochrane editors say that my recommendations are based on inappropriate interpretation of the published research and lament that some of my references are to my upcoming book. As they haven't read my book, they cannot know whether my interpretation of the science is appropriate. My book is evidence-based and has hundreds of relevant references.

The Cochrane editors are concerned that I step "beyond the accepted role of an independent researcher by appearing to recommend a course of action." I disagree vehemently. When doctors see harm on a massive scale, they have a duty to inform the public about it, and if they can suggest a solution, it is even better. It appears to me that by their non-evidence based attack on the messenger, the Cochrane editors protect psychiatry's guild interests rather than the patients.

The Cochrane editors say they cannot see what my estimates for total deaths and suicides refer to. However, I did use the term excess deaths (1). I also made the suicides clear: "there are likely to have been 15 times more suicides among people taking antidepressants than reported by the FDA" (1). I have several references for this estimate in my book and the studies are remarkably consistent (2). Here is one revealing observation (2). Thomas Laughren was responsible for the FDA's huge meta-anaysis of the randomised trials, which reported only 5 suicides in 52,960 patients on SSRIs, or one per 10,000 (3). Five years earlier, Laughren reported on 22 suicides in 22,062 patients randomised to antidepressants using FDA data, which is 10 per 10,000 (4), or 10 times as many as he reported five years later! There were only 2 suicides in 8,692 patients on placebo (4), which Laughren interpreted thus: "There is obviously no suggestion of an excess suicide risk in placebo-treated patients." No, but why didn't Laughren comment on the fact that flies in the face, namely that there were four times as many suicides on antidepressants as on placebo, which was statistically significant (P = 0.03, my calculation)? When Laughren left the FDA, he established the Laughren Psychopharm Consulting with himself as director to help the drug industry with getting their drugs approved (2).

What I get out of the colossal underreporting is that SSRIs likely increase suicides in all ages. It is remarkable that it is so subjective how many suicides there are and also that several major drug companies have cheated with their reporting of suicides and suicide attempts (2). I doubt SSRIs are safe at any age, and they kill very many elderly patients by falls and hip fractures (2,6).

In contrast to what the Cochrane editors say, the Cochrane review of tricyclic antidepressants versus an active placebo containing atropine is not substantially out of date (7). It is from 2004, but according to Cochrane routines that doesn't make it out of date if no new relevant trials have been published, which is highly unlikely. The newest of the 9 included trials is from 1984. The drug industry doesn't use active placebos because then the whole world could see that the emperor has no clothes. It is also misleading when the editors say that the authors described their findings cautiously. Evidence-based medicine is about using the best available evidence, and this review is the most reliable evidence we have about the effect of antidepressant drugs (1,2). It didn't find any effect (1,2).

My interpretation of the science is shared by the patients who disagree strongly with the psychiatrists about psychiatric drugs, which they intensely dislike (2). It is telling that in meta-analyses of depression trials, both in children and in adults, the psychiatrists found effect sizes between 0.25 and 0.29 whereas there was no effect when the patients were asked (effect sizes 0.05 and 0.06) (2,8-10).
Surveys are similarly revealing. Although the psychiatrists deny it is a problem (2), about half the patients on antidepressants feel that the drugs change their personality (11,12). And in a large survey of 2,031 citizens from 1995, people thought that antidepressants, antipsychotics, electroshock and admission to a psychiatric ward were more often harmful than beneficial (13).

So whom should we believe? The psychiatrists who are often on industry payroll and know that if they report favourable results, they will be asked again? Or the patients?

The Cochrane editors think that my recommendations are extreme. I write about being extreme in my book: "Usually, people who are extreme are few in number but in this case, it is the vast majority of psychiatrists that are extreme. It is truly extreme that psychiatrists have built their specialty on a number of myths, lies and highly flawed research, which have harmed our nations to the extent we have seen. Marcia Angell [previously editor-in-chief of the New England Journal of Medicine] has noted that psychiatrists should consider that other medical specialists, unlike psychiatrists, would be very reluctant to offer long-term symptomatic treatment without knowing what lies behind the symptoms, e.g. if a patient suffers from nausea or headache" (2).

Stopping psychiatric drugs abruptly is dangerous, as it can lead to suicide and homicide because of withdrawal akathisia (2). We need widespread withdrawal clinics because many patients have become dependent on psychiatric drugs, including antidepressants, and need help to stop taking them slowly and safely (1).

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HEAD TO HEAD

MAUDSLEY DEBATE

Does long term use of psychiatric drugs cause more harm than good?

We could stop 98% of psychotropic drug use without deleterious effect, says **Peter C Gøtzsche**, questioning trial designs that underplay harms and overplay benefits. **Allan H Young** and **John Crace** disagree, arguing that evidence supports long term use

Peter C Gøtzsche *professor, Nordic Cochrane Centre, Rigshospitalet, DK-2100 Copenhagen, Denmark*, Allan H Young *professor of mood disorders, Institute of Psychiatry, Psychology and Neurosciences, King's College London, UK*, John Crace *psychiatric patient and parliamentary sketch writer, Guardian, London, UK*

Yes—Peter C Gøtzsche

Psychiatric drugs are responsible for the deaths of more than half a million people aged 65 and older each year in the Western world, as I show below.[1] Their benefits would need to be colossal to justify this, but they are minimal.[1-6]

Overstated benefits and understated deaths

The randomised trials that have been conducted do not properly evaluate the drugs' effects. Almost all of them are biased because they included patients already taking another psychiatric drug.[1 7-10] Patients, who after a short wash-out period are randomised to placebo, go "cold turkey" and often experience withdrawal symptoms. This design exaggerates the benefits and increases the harms, and it has driven patients taking placebo to suicide in trials in schizophrenia.[8]

Under-reporting of deaths in industry funded trials is another major flaw. Based on some of the randomised trials that were included in a meta-analysis of 100 000 patients by the US Food and Drug Administration, I have estimated that there are likely to have been 15 times more suicides among people taking antidepressants than reported by the FDA—for example, there were 14 suicides in 9956 patients in trials with fluoxetine and paroxetine, whereas the FDA had only five suicides in 52 960 patients, partly because the FDA only included events up to 24 hours after patients stopped taking the drug.[1]

Estimate of total deaths

For antipsychotics, I used a meta-analysis of placebo controlled trials in patients with dementia because they would be less likely to have been receiving psychiatric drugs before randomisation. The absolute death rate was 1% higher in the treatment group.[11] The Finnish cohort study of mortality in patients with schizophrenia[12]—and all other such studies that support the idea that antipsychotics lower mortality—is unreliable. (The mortality in patients who were not taking drugs was very high and didn't concur with other Finnish data, and 64% of the deaths were not accounted for.[13])

A well conducted cohort study of patients of average age 55 found that benzodiazepines and similar drugs doubled the death rate; the excess death rate was about 1% a year.[14]

A cohort study of patients older than 65 who were their own control found that all cause mortality was 3.6% higher when patients were taking the newer antidepressants for one year than when they did not take antidepressants.[15]

I used Danish prescription statistics to estimate the number of deaths caused by these three classes of drugs. Because falls, which are much more common in older people, are an important cause of death in people taking psychotropic drugs,[1] I included only people at least 65 years of age and used conservative death rates: 1% for antipsychotics, 1% for benzodiazepines and similar drugs, and only 2% for antidepressants. The total number of deaths a year in Denmark (3693) when scaled up corresponded to 539 000 in the United States and European Union combined.[1]

What about the benefits?

The randomised trials are not only biased by the "cold turkey" design but also because they have not been adequately blinded. A Cochrane review of tricyclic antidepressants included only trials that had atropine in the placebo to prevent unblinding because of the conspicuous side effects of the drugs. This review did not find any meaningful effect[4]; the effect corresponded to only 1.3 points on the Hamilton scale,[1] and the smallest effect that can be perceived is 5-6 points.[16]

A meta-analysis of trials of fluoxetine and venlafaxine in severe depression showed that it takes only a few days longer before

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the Hamilton score in the placebo group drops by an additional 1.3 points.[17] Thus, if we wait a few days, we would get the same result if taking a placebo, or if the patients weren't treated at all, because what we see in a placebo group is not a placebo effect but mainly the spontaneous remission of the disease.[1 18] The modest observed effect of antidepressants on anxiety can also be explained by unblinding bias because it is similar to that reported for depression.[1]

Trials in schizophrenia are also disappointing. In newer submissions to the FDA, the effect on the positive and negative syndrome scale (PANSS) was only 6,[5] even though these trials were heavily biased by cold turkey and unblinding effects.[1 8] This is far below the minimally clinically relevant effect, which is about 15.[19]

The benefits of drugs for attention deficit hyperactivity disorder (ADHD) are also uncertain.[6 9 10] The short term relief seems to be replaced by long term harms,[10 20] and animal studies strongly suggest that these drugs can produce brain damage,[10 21] which is probably the case for all psychotropic drugs.[22 23]

Long term harm

Given their lack of benefit, I estimate we could stop 98% of psychotropic drugs without causing harm—by dropping all antidepressants, ADHD drugs, and dementia drugs (as the small effects are probably the result of unblinding bias)[1 24] and using only 6% of the antipsychotics and benzodiazepines we currently use.[1] This would lead to healthier and more long lived populations. Because psychotropic drugs are immensely harmful when used long term, they should almost exclusively be used in acute situations and always with a firm plan for tapering off, which can be difficult for many patients.[1 22]

We need new guidelines to reflect this. We also need widespread withdrawal clinics because many patients have become dependent on psychiatric drugs, including antidepressants,[1 25] and need help so that they can stop taking them slowly and safely.[22]

No—Allan H Young, John Crace

Psychiatric conditions are common, complex, costly, and often long term illnesses. More than a fifth of all health related disability is caused by mental ill health, studies suggest, and people with poor mental health often have poor physical health and poorer (long term) outcomes in both aspects of health.[26]

Raised standardised mortality rates and reduced life expectancy have been reported in people with psychiatric disorders such as psychosis and mood and personality disorders.[27] These increased death rates are only partly because of suicide and mostly attributable to coexisting physical health disorders. There is thus a clear need for psychiatric disorders to be treated to attempt to reduce the long term harm associated with them. The key question is whether psychiatric drugs do more harm than good.

All therapeutic interventions may potentially do both good and harm, and thorough evaluation of the relative benefits and harms of a treatment should be done for psychiatric drugs no less than for any others.[28] These evaluations of benefits and harms are based on group data, which have to be applied to judgments for individual patients and can therefore be advisory only; the individual's subjective experience is crucially important to consider.

Psychiatric drugs are as beneficial as other treatments used for common, complex medical conditions. Leucht and colleagues reviewed the efficacy of psychiatric and general medicine drugs by analysing meta-analyses: they found that psychiatric drugs were generally as efficacious as other drugs.[29]

What about harms?

Worldwide, regulatory agencies are responsible for ensuring that drugs work and are acceptably safe. Postmarketing surveillance continues after drugs are licensed. This can further refine, or confirm or deny, the safety of a drug in the general population, which unlike study populations includes people with varied medical conditions. Several approaches are used to monitor the safety of licensed drugs, including spontaneous reporting databases, prescription event monitoring, electronic health records, patient registries, and record linkage between health databases.[30] These safeguards work to ensure drugs available do more good than harm.[30]

Nevertheless, many concerns have been expressed about psychiatric drugs, and for some critics the onus often seems to be on the drug needing to prove innocence from causing harm rather than a balanced approach to evaluating the available evidence.

Overinflated concerns

Whether concerns are genuine or an expression of prejudice is not clear, but over time many concerns have been found to be overinflated. A few examples may be illustrative. The efficacy and safety of lithium have long been questioned, echoing an early description of it being a "toxic placebo."[31] However, recent meta-analyses have confirmed lithium's efficacy and shown the adverse effects to be less than previously feared.[32 33] Of course, lithium needs to be used carefully, but recent Scandinavian data show that if guidelines are followed the long term harm is minimal,[34] and new benefits, such as reduction in suicide, have become apparent.[35]

Similar concerns were raised about atypical antipsychotics, particularly clozapine, with some doctors and patients fearing that these drugs would increase death rates because of side effects. However, recent long term data are reassuring and have shown an inverse correlation between mortality and cumulative use. Indeed, the authors of a pivotal study concluded: "Long-term treatment with antipsychotic drugs is associated with lower mortality compared with no antipsychotic use."[12] Similar findings were reported by Angst and colleagues, who studied the effects of treatment on the mortality of patients with mood disorders over decades.[36] A total of 406 patients with affective disorder were followed prospectively for 22 years or more. Mortality was then assessed for 99% of them after 34-38 years, at which time 76% had died. In all groups long term drug treatment significantly lowered suicide rates, these authors concluded, despite the fact that it was the more severely ill patients who were treated.

In summary, psychiatric drugs are rigorously examined for efficacy and safety, before and after regulatory approval. The long term studies discussed above are reassuring, although the evidence, as ever, is imperfect. Taking all this into account we contend that the motion that the long term use of psychiatric drugs is causing more meaningful harm than good is not correct and the evidence, such as it is, suggests the contrary.

Competing interests: All authors have read and understood BMJ policy on declaration of interests and have no relevant interests to declare.

The authors are taking part in the 52nd Maudsley debate, "This house believes that the long term use of psychiatric medications is causing more harm than good," to be held in London on 13 May 2015. A podcast

of the debate will be available at www.kcl.ac.uk/ioppn/news/special-events/maudsley-debates/index.aspx.

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