BMJ 2015;349:h2435 doi: 10.1136/bmj.h2435 (Published 12 May 2015)

HEAD TO HEAD

MAUDSLEY DEBATE

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

We could stop almost all 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 of treatment and increases the harms in the placebo group, 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]

Correspondence to: P C Gøtzsche pcg@cochrane.dk, A H Young allan.young@kcl.ac.uk

For personal use only: See rights and reprints http://www.bmj.com/permissions Subscribe: http://www.bmj.com/subscribe

A meta-analysis of trials of fluoxetine and venlafaxine in severe depression showed that it takes only a few days longer before 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 almost all 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 a fraction 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 declare the following interest: AHY has done paid lectures or been on advisory boards for all major companies producing drugs used in affective and related disorders. He was the lead investigator for Embolden Study (AstraZeneca), BCI neuroplasticity

For personal use only: See rights and reprints http://www.bmj.com/permissions Subscribe: http://www.bmj.com/subscribe

study, and Aripiprazole Mania Study, and received funds for investigator initiated studies from AstraZeneca, Eli Lilly, Lundbeck, Wyeth. He has received research grants from NIMH (USA); CIHR (Canada); NARSAD (USA); Stanley Medical Research Institute (USA); MRC (UK); Wellcome Trust (UK); Royal College of Physicians (Edinburgh); BMA; UBC-VGH Foundation (Canada); WEDC (Canada); CCS Depression Research Fund (Canada); MSFHR (Canada); and NIHR (UK).

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.

Provenance and peer review: Commissioned; externally peer reviewed.

1 Gøtzsche PC. Deadly psychiatry and organised denial. People's Press (forthcoming).
2 Gøtzsche PC. Why I think antidepressants cause more harm than good. *Lancet Psychiatry* 2014;1:104-6.
3 Bola J, Kao D, Soydan H, et al. Antipsychotic medication for early episode schizophrenia. *Cochrane Database Syst Rev* 2011;6:CD006374.
4 Moncrieff J, Wessely S, Hardy R. Active placebos versus antidepressants for depression. *Cochrane Database Syst Rev* 2004;1:CD003012.
5 Khin NA, Chen YF, Yang Y, et al. Exploratory analyses of efficacy data from schizophrenia trials in support of new drug applications submitted to the US Food and Drug Administration. *J Clin Psychiatry* 2012;73:856-64.
6 Jensen PS, Arnold LE, Swanson JM, et al. 3-year follow-up of the NIMH MTA study. *J Am Acad Child Adolesc Psychiatry* 2007;46:989-1002.
7 Walsh BT, Seidman SN, Sysko R, et al. Placebo response in studies of major depression: variable, substantial, and growing. *JAMA* 2002;287:1840-7.
8 Whitaker R. Mad in America. Perseus Books, 2002.
9 Petersen M. Our daily meds. Sarah Crichton Books, 2008.
10 Whitaker R. Anatomy of an epidemic. Broadway Paperbacks, 2010.
11 Schneider LS, Dagerman KS, Insel P. Risk of death with atypical antipsychotic drug treatment for dementia: meta-analysis of randomized placebo-controlled trials. *JAMA* 2005;294:1934-43.
12 Tiihonen J, Lönnqvist J, Wahlbeck K, et al. 11-year follow-up of mortality in patients with schizophrenia: a population-based cohort study (FIN11 study). *Lancet* 2009;374:620-7.
13 De Hert M, Correll CU, Cohen D. Do antipsychotic medications reduce or increase mortality in schizophrenia? A critical appraisal of the FIN-11 study. *Schizophr Res* 2010;117:68-74.
14 Weich S, Pearce HL, Croft P, et al. Effect of anxiolytic and hypnotic drug prescriptions on mortality hazards: retrospective cohort study. *BMJ* 2014;348:g1996.
15 Coupland C, Dhiman P, Morriss R, et al. Antidepressant use and risk of adverse outcomes in older people: population based cohort study. *BMJ* 2011;343:d4551.
16 Leucht S, Fennema H, Engel R, et al. What does the HAMD mean? *J Affect Disord* 2013;148:243-8.
17 Gibbons RD, Hur K, Brown H, et al. Benefits from antidepressants: synthesis of 6-week patient-level outcomes from double-blind placebo-controlled randomized trials of fluoxetine and venlafaxine. *Arch Gen Psychiatry* 2012;69:572-9.
18 Hróbjartsson A, Gøtzsche PC. Placebo interventions for all clinical conditions. *Cochrane Database Syst Rev* 2010;1:CD003974.
19 Leucht S, Kane JM, Etschel E, et al. Linking the PANSS, BPRS, and CGI: clinical implications. *Neuropsychopharmacology* 2006;31:2318-25.
20 Molina BS, Hinshaw SP, Swanson JM, et al. The MTA at 8 years: prospective follow-up of children treated for combined-type ADHD in a multisite study. *J Am Acad Child Adolesc Psychiatry* 2009;48:484-500.
21 Marco E. Neurobehavioral adaptations to methylphenidate. *Neurosci Behav Rev* 2011;35:1722-39.
22 Breggin P. Psychiatric drug withdrawal: a guide for prescribers, therapists, patients, and their families. Springer, 2013.
23 Breggin PR. The rights of children and parents in regard to children receiving psychiatric diagnoses and drugs. *Children Soc* 2014;28:231-41.
24 Birks J. Cholinesterase inhibitors for Alzheimer's disease. *Cochrane Database Syst Rev* 2006;1:CD005593.
25 Nielsen M, Hansen EH, Gøtzsche PC. What is the difference between dependence and withdrawal reactions? A comparison of benzodiazepines and selective serotonin re-uptake inhibitors. *Addiction* 2012;107:900-8.
26 Das-Munshi J, Stewart R, Ismail K, Bebbington PE, Jenkins R, Prince MJ. Diabetes, common mental disorders, and disability: findings from the UK National Psychiatric Morbidity Survey. *Psychosom Med* 2007;69:543-50.
27 Fok ML, Hayes RD, Chang CK, Stewart R, Callard FJ, Moran P. Life expectancy at birth and all-cause mortality among people with personality disorder. *J Psychosom Res* 2012;73:104-7.
28 Rawlins MD. A population approach to the rational use of therapeutic interventions. *Clin Ther* 2013;35:1634-8.
29 Leucht S, Hierl S, Kissling W, Dold M, Davis JM. Putting the efficacy of psychiatric and general medicine medication into perspective: review of meta-analyses. *Br J Psychiatry* 2012;200:97-106.
30 Clinical Practice Research Datalink. *MHRA main activities.* www.cprd.com/contact/mhra.asp.
31 Shepherd M. Prophylactic lithium: another therapeutic myth? An examination of the evidence to date. *Lancet* 1968;1:968-71.
32 McKnight RF, Adida M, Budge K, Stockton S, Goodwin GM, Geddes JR. Lithium toxicity profile: a systematic review and meta-analysis. *Lancet* 2012;379:721-8.
33 Severus E, Taylor MJ, Sauer C, et al. Lithium for prevention of mood episodes in bipolar disorders: systematic review and meta-analysis. *Int J Bipolar Disord* 2014;2:15.
34 Aiff H, Attman PO, Aurell M, Bendz H, Schön S, Svedlund J. The impact of modern treatment principles may have eliminated lithium-induced renal failure. *J Psychopharmacol* 2014;28:151-4.
35 Cipriani A, Hawton K, Stockton S, Geddes JR. Lithium in the prevention of suicide in mood disorders: updated systematic review and meta-analysis. *BMJ* 2013;346:f3646.
36 Angst F, Stassen HH, Clayton PJ, Angst J. Mortality of patients with mood disorders: follow-up over 34-38 years. *J Affect Disord* 2002;68:167-81.

Cite this as: *BMJ* 2014;349:h2435

© BMJ Publishing Group Ltd 2015

For personal use only: See rights and reprints http://www.bmj.com/permissions Subscribe: http://www.bmj.com/subscribe