Risk of relapse after antidepressant discontinuation in anxiety disorders, obsessive-compulsive disorders, and post-traumatic stress disorder

Batelaan NM, Bosman RC, Muntingh A, et al
Cite this as: BMJ 2017;358:j3927
Find this at: http://dx.doi.org/10.1136/bmj.j3927

Study question What are the risks of relapse and time to relapse following discontinuation of antidepressants in patients with anxiety disorder who responded to antidepressants?

Methods The results of 28 relapse prevention trials, including a total of 5233 patients, were summarised in a meta-analysis. Studies were included if they focused on patients with anxiety disorder who responded to antidepressants, if they randomised patients to either discontinuing antidepressants or switching to placebo, and if they compared relapse rates or time to relapse between patients who continued antidepressants and patients who discontinued antidepressants.

Study answer and limitations Summary relapse prevalences were 36.4% (95% confidence interval 30.8% to 42.1%) for the placebo group and 16.4% (12.6% to 20.1%) for the antidepressant group. Compared with placebo, a clear benefit of continuing antidepressants for at least a year after response to treatment was seen for both relapse and time to relapse. No evidence was found that type of anxiety disorder, duration of previous treatment, duration of follow-up, mode of discontinuation, or whether concurrent psychotherapy was allowed influenced the risk of relapse. Studies with a treatment duration of more than one year were not available, so no advice can be provided for treatment continuation after one year.

What this study adds Among clinical trial participants with an initial response to the drug, a third relapse if treatment is discontinued after a year. The lack of evidence after this period should not be interpreted as an explicit advice to discontinue antidepressants after one year. Decisions about whether to continue or withdraw treatment should consider the relapse risk in relation to adverse effects of the treatment and patient preferences.

Funding, competing interests, data sharing No funding was received for this study, the authors have no competing interests, and no additional data are available.
Screening for glaucoma using intraocular pressure alone

**ORIGINAL RESEARCH** Cross sectional study

**Glaucma and intraocular pressure in EPIC-Norfolk Eye Study**

Chan MPY, Broadway DC, Khawaja AP, et al

Cite this as: BMJ 2017;358:j3889

Find this at: http://dx.doi.org/10.1136/bmj.j3889

**Study question** What is the current burden of definite and suspected glaucoma in the UK, and is measurement of intraocular pressure (IOP) a viable method of identifying affected patients?

**Methods** This community based cross sectional observational study examined members of the EPIC-Norfolk cohort in Norwich and the surrounding rural and urban areas. A total of 8623 participants aged 48-92 recruited from the community underwent ocular examination to identify glaucoma, including visual acuity and field, tonometry, and assessment of the optic disc. The performance of IOP as a case finding tool was examined, with sensitivity and specificity.

**Study answers and limitations** Established glaucoma (presence of characteristic structural abnormalities of the optic disc and visual field loss, with no other explanations for the disc and field appearances) was identified in 363 participants (4%), 314 (87%) of whom had primary open angle glaucoma. A further 607 (7%) were classified as having suspected glaucoma (presence of early or minor glaucomatous disc features, associated with a normal visual field or the absence of visual field data) and 863 (10%) had ocular hypertension (IOP >21 mm Hg, the current threshold). Of the 107 participants with newly diagnosed primary open angle glaucoma, 81 (76%) had a mean IOP below 21 mm Hg. Measurement of IOP did not offer a viable combination of good sensitivity and specificity for glaucoma case finding at any referral threshold. Although this study examined people recruited from the community, it does not constitute a representative population sample, and hence precise rates of disease must be treated with caution. It is likely that these findings represent a conservative estimate.

**COMMENTARY** An outdated concept that should be abandoned

In the linked paper, Chan and colleagues report the distribution of intraocular pressure (IOP) and the frequency of glaucoma in the EPIC-Norfolk cohort, a community based cross sectional study of a UK population.1 With knowledge of both the distribution of IOP and the frequency of glaucoma, the authors determined that the diagnostic capability of IOP alone to detect glaucoma is poor. This conclusion is important because “Glaucma and suspected glaucoma combined account for the sixth largest share of NHS outpatient attendances…”2 Since guidelines from the National Institute for Health and Care Excellence3 describe one of the features of chronic open angle glaucoma as “IOP in either eye exceeding 21 mm Hg,” referrals solely on the basis of IOP may be contributing to resource overuse.

**Leading cause of blindness**

Glaucma, an optic neuropathy with a characteristic appearance of the optic disc and progressive vision loss, is a leading cause of blindness worldwide.4 The authors’ findings of a prevalence of 3%-4% in a population aged 48 years or more, a preponderance of open angle glaucoma, and increasing prevalence with age have been frequently seen in other, similar studies.4-5 Readers should be aware that the population studied was almost entirely white. Open angle glaucoma is much more prevalent in people of African descent,6 and angle closure glaucoma is more prevalent in people of Asian descent, particularly those from China.7

That vision loss from glaucoma can be reduced by treatment to lower the IOP and that glaucoma is largely asymptomatic until there is noticeable damage to the optic
What this study adds In this British community, cases of glaucoma, suspected glaucoma, and ocular hypertension represent a large number of potential referrals to the hospital eye service. An important new finding was that although most (67%) cases of glaucoma had been previously diagnosed, the bulk (76%) of unidentified disease was classified as normal pressure glaucoma. The use of IOP alone in glaucoma case finding is probably not viable. There is a need to re-examine the policy of referral to hospital for eye examination based on IOP measurements alone.

Funding, competing interests, data sharing Medical Research Council, Cancer Research UK, and the International Glaucoma Association. The clinic for the third health examination was funded by Research into Ageing. Two of the authors (DFG and PJF) have received commercial funding and grants unrelated to this research. The EPIC management committee will consider data requests on a case by case basis in line with MRC guidelines.

nerve, provide the rationale for screening for the presence of glaucoma in the community or in a primary care setting.

The designation “glaucoma” is now reserved for people with damage to the optic nerve, not a particular level of IOP. Screening strategies for glaucoma could potentially include: historical and demographic information, as glaucoma is more prevalent in older people, those of African origin, and those with a first degree relative with glaucoma; IOP measurement, as the prevalence of glaucoma increases as the IOP increases; imaging of the optic disc, retinal nerve fibre layer, and macula, because all these structures change with progressive optic nerve damage; and tests of visual function, particularly the visual field test.

Historically, IOP has been a common screening tool for glaucoma for several reasons. Firstly, the higher the IOP, the more likely it is that someone has glaucoma or will develop glaucoma. Secondly, much evidence has shown that a raised IOP is not only associated with glaucoma, but can cause glaucoma damage. Lastly, the measurement of IOP is simple, can be performed by non-specialists, and produces a single number that does not require sophisticated interpretation.

Well known deficiencies

The deficiencies of IOP as a standalone screening tool for glaucoma, however, have been known for decades. Chan and colleagues’ data from the EPIC-Norfolk cohort reaffirm that no IOP threshold reliably separates those with optic nerve damage from those without. We now know that approximately 50% of people with glaucoma (about 76% in the current study) have an IOP of less than 21 mm Hg and so would be missed by screening; furthermore, approximately 10% of people without glaucoma have an IOP of at least 21 mm Hg. Many of the latter will never develop the condition and would be overdiagnosed and potentially overtreated after screening.

The authors conclude that “The large number of people with confirmed glaucoma and intraocular pressure under the threshold for ocular hypertension (21 mm Hg) reinforces the weakness of reliance on this for detection of glaucoma,” but do not provide alternative solutions. Ideally, a screening test would actually detect the disease rather than simply identifying one of the risk factors. Two possible options are imaging the optic nerve and retina to detect any structural damage, or testing the function of the optic nerve. Both remain problematic.

Optical coherence tomography can rapidly image the optic nerve and retinal nerve fibre layer to identify structural damage. Although one preliminary clinic based report showed the high diagnostic accuracy of optical coherence tomography for diagnosing glaucoma, the test has yet to be evaluated for screening and the associated costs presently precludes widespread use in community or primary care settings. An analysis of data from the National Health and Nutrition Examination Survey revealed that functional testing of the optic nerve with frequency doubling technology perimetry was not sensitive or specific enough for population based screening. Unfortunately, currently no adequate screening test for glaucoma exists.

Instead of attempting to detect individual eye diseases it may be more cost effective to screen for all leading causes of vision loss at the same time: cataract, glaucoma, age related macular degeneration, and diabetic retinopathy. For example, a study of screening for diabetic retinopathy using a non-mydriatic camera with remote evaluation of images also found a glaucomatous appearing optic nerve in 10% of screened eyes, and age related macular degeneration in 9%. Researchers could usefully investigate combined approaches to screening in future studies. Reliable and timely detection of glaucoma, a common and treatable cause of blindness, is a public health priority.

Cite this as: BMJ 2017;358:j4160

Find the full version with references at http://dx.doi.org/10.1136/bmj.j4160
Multivariate and network meta-analysis of multiple outcomes and multiple treatments: rationale, concepts, and examples

Riley RD, Jackson D, Salanti G, et al

Cite this as: BMJ 2017;358:j3932
Find this at: http://dx.doi.org/10.1136/bmj.j3932

The majority of meta-analyses are based on combining results (eg, treatment effect estimates) extracted from study publications. Unfortunately, relevant studies may not evaluate the same sets of treatments and outcomes, which create problems for meta-analysis. For example, in a meta-analysis of 28 trials to compare eight thrombolytic treatments after acute myocardial infarction, it is unrealistic to expect every trial to compare all eight treatments; in fact a different set of treatments was examined in each trial, with the maximum number of trials per treatment only eight. Similarly, relevant clinical outcomes may not always be available. Studies that do not provide direct evidence about a particular outcome or treatment of interest are often excluded from a meta-analysis evaluating that outcome or treatment. This is unwelcome, especially if their participants are otherwise representative of the population, clinical settings, and condition of interest.

Riley and colleagues describe how statistical models for multivariate and network meta-analysis address this by simultaneously analysing multiple outcomes and multiple treatments, respectively. This allows more studies to contribute towards each outcome and treatment comparison. That is, in addition to using direct evidence, the summary result for each outcome now depends on correlated results from related outcomes, and the summary result for each treatment comparison now incorporates indirect evidence from related treatment comparisons. Thus extra information is gained, and the authors show how this can be quantified. Real examples are used to illustrate the methods, and a network meta-analysis is shown to provide a coherent framework for comparing and ranking multiple treatments. For example, in a network meta-analysis of the aforementioned eight thrombolytic treatments, the summary results suggest accelerated alteplase, tenecteplase, and urokinase are the top three ranked treatments for reducing risk of death by 30-35 days, based on the direct and indirect evidence. Assumptions, challenges, and novel extensions of the approaches are also outlined.

Plots of the ranking probability for each treatment considered in the thrombolytics network meta-analysis. (Top panel) the probability scale; (bottom panel) the cumulative probability scale.