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How effective are antidepressants for depression over the long term? A critical review of relapse prevention trials and the issue of withdrawal confounding

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***Abstract*:** The aim of this article is to discuss the validity of relapse prevention trials and the issue of withdrawal confounding in these trials. Recommendations for long-term antidepressant treatment are based almost exclusively on discontinuation trials. In these relapse prevention trials, participants with remitted depression are randomised either to have the antidepressant abruptly discontinued and replaced by inert placebo or to continue active treatment. The drug–placebo difference in relapse rates at the end of the maintenance phase is then interpreted as a prophylactic drug effect. These trials consistently produce remarkable benefits for maintenance treatment. However, the internal validity of this trial protocol is compromised, as research has shown that abruptly stopping antidepressants can cause severe withdrawal reactions that lead to (or manifest as) depression relapses. That is, there is substantial withdrawal confounding in discontinuation trials, which renders their findings uninterpretable. It is not clear to what degree the drug–placebo separation in relapse prevention (discontinuation) trials is due to withdrawal reactions, but various estimations suggest that it is presumably the majority. A review of findings based on other methodologies, including real-world long-term effectiveness trials like STAR*D and various naturalistic cohort studies, do not indicate that antidepressants have considerable prophylactic effects. As absence of evidence does not imply evidence of absence, no definitive conclusions can be drawn from the literature. To enable a thorough risk–benefit evaluation, real-world effectiveness trials should not only focus on relapse prevention, but also assess antidepressants' long-term effects on social functioning and quality of life. Thus far, reliable long-term data on these outcome domains are lacking.

Keywords: antidepressant, discontinuation, long-term, prevention, relapse, withdrawal

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Introduction

Treatment guidelines like those published by National Institute for Health and Care Excellence (NICE) or the American Psychiatric Association (APA) strongly recommend long-term maintenance treatment in people with (or at risk of) recurrent depression to prevent relapses.[1,2] In accordance with these recommendations, the rate and duration of antidepressant use is steadily increasing in the general population,[3–6] but this trend has stirred considerable controversy.[7,8] It has been suggested that long-term antidepressant treatment should be revisited,[9–11] and research indicates that many patients in receipt of long-term antidepressant medication do not necessarily require maintenance treatment.[12–14] Some authors cautioned that long-term antidepressant use may be largely ineffective, or even harmful.[10,11,15,16] One possible driver of unnecessary long-term prescriptions could be the propensity of antidepressants to cause dependence and withdrawal reactions.[17–22] This notion is often met

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with disbelief, and sometimes it is fiercely dismissed by leading academics as it stands in sharp contrast to the consistently positive findings from dozens of relapse prevention trials.[23–27] In this article, I will ponder these seemingly contradictory findings and critically discuss major issues that may resolve the conflicting literature on the benefits of long-term antidepressant treatment. To that end, I will focus mostly on antidepressants' prophylactic effects, as relapse prevention is the main indication for long-term antidepressant use in people with (recurrent) depressive disorders. A critical discussion of potential adverse effects of long-term use is important to consider but beyond the scope of the present article. For tolerability and safety issues, interested readers are referred to the pertinent literature.[28–30]

Relapse prevention trials: too good to be true?

The scientific evidence in support of long-term maintenance antidepressant treatment is based almost exclusively on relapse prevention trials.[1,2,31] These long-term studies are basically discontinuation trials, where antidepressant users in (stable) remission are randomised to either have the antidepressant abruptly stopped and replaced by inert placebo or to continue active treatment. The difference in relapse rates between the antidepressant and the placebo arm at the end of the maintenance phase is then assumed to reflect a prophylactic drug effect. As stated above, the results of these trials are unequivocally positive and consistently show that, after about 12 months, the relapse rate is roughly 40% for those participants who were abruptly switched to placebo and 20% for those maintained on active treatment, which results in a relative risk of 2 and a number needed to treat (NNT) of 5.[25–27]

This, in short, is the scientific evidence on which treatment guidelines largely base their recommendation for long-term antidepressant treatment.[1,2,31] At first glance, this evidence base indeed appears impressive, and, without a critical look at the methodology of these trials, which number in dozens, one is understandably tempted to conclude that antidepressants have 'remarkable' long-term efficacy.[32] Based on evidence from relapse prevention (discontinuation) trials, it was even claimed that antidepressants are 'one of the most effective of all drugs'.[23] However, as I already pointed out in previous articles,[10,33] the validity of these trials, and hence the interpretation of their findings, cannot be accepted at face value. As researchers, we should not be seduced into believing that a drug is highly effective simply because a specific trial protocol has consistently produced impressive treatment effects, as these effects could be the result of a flawed trial protocol.[34] Such systematic bias in clinical trials is also referred to as 'hard-wired bias'.[35]

The persistent superiority of antidepressants over placebo in relapse prevention (discontinuation) trials is a peculiar finding, given that only about 50% of acute treatment trials are positive,[36,37] which results in a disappointingly small average treatment effect,[38,39] and a NNT of about 9.[40,41] This recently led researchers from the Nordic Cochrane Center to state that 'Taken together, the evidence does not support definitive conclusions regarding the efficacy of antidepressants for depression in adults, including whether they are more efficacious than placebo for depression' (p. 8).[39] Moreover, it is important to note that trial protocols other than discontinuation trials failed to find reliable evidence of remarkable long-term benefits.[42–44] This prompted SN Ghaemi, a leading psychiatric researcher from Tufts Medical Center in Boston, MA, to conclude that '(Antidepressants') long-term prophylactic effectiveness in recurrent unipolar major depression remains uncertain' (p. 957).[16] In this respect, the evidence from relapse prevention (discontinuation) trials indeed appears too good to be true.[34] How could a drug that has very limited efficacy in the acute and long-term treatment of depression symptoms possibly have such impressive prophylactic effects? We therefore need to consider that the strong and consistent effects produced in relapse prevention (discontinuation) trials are possibly a methodological artefact. I will now explain how this impressive drug-placebo separation could come about.

Withdrawal confounding in relapse prevention trials

Relapse prevention (discontinuation) trials are very popular in psychiatry but have a bad reputation among critics. According to various authors, their validity is poor and findings hence difficult to interpret.[34,42,45,46] Issues discussed in the literature include, among others, poor representativity and generalisability of results (findings apply only to a subset of users who responded particularly well to the drugs), inflated effect size estimates (treatment responders are assessed for treatment

response, which is tautological) and unblinding effects (participants who have their active treatment abruptly discontinued may notice it). Here, I will focus on one particular issue, that is, withdrawal confounding.[46]

Various authors have stressed that prolonged antidepressant use can cause neurochemical adaptations (physical dependence) and corresponding withdrawal reactions upon dose reduction or discontinuation comparable with other central nervous system (CNS) drugs like benzodiazepines, stimulants or opioides.[18,22,47,48] There is now compelling evidence from clinical trials, observational studies and user surveys that stopping antidepressants can cause severe and persistent withdrawal reactions in a substantial portion of users.[49,50] Withdrawal symptoms include, among others, anxiety, panic, irritability, aggression, lethargy, flu-like symptoms, electric-shock sensations (brain zaps), fatigue, dizziness, tremor, dysphoria, bouts of crying, suicidality, insomnia, anorexia and nausea. Many of these symptoms are, therefore, easily misdiagnosed as a depression relapse when relapses are assessed *via* symptom rating scales such as the Hamilton Depression Rating Scale that cannot differentiate withdrawal from relapse.[51,52]

Withdrawal reactions can be so severe that they classify as a depression relapse in up to 27% of users within 5–8 days of double-blind placebo-controlled treatment interruption.[53] That is, abrupt discontinuation of antidepressants relates to significantly higher rate of new depression episodes.[53,54] This increased risk is not necessarily due to misclassification of acute withdrawal symptoms, yet is likely caused by withdrawal reactions, for example, neurochemical adaptations suddenly unopposed.[55,56] These types of withdrawal reactions are commonly defined as rebound disorders (rapid return of original symptoms at greater intensity) and persistent (protracted) post-acute withdrawal disorders (return of persistent original symptoms at greater intensity and/or symptoms related to new emerging disorders).[50] While rebound disorders usually occur within a few days after drug discontinuation, and resolve spontaneously within up to 6 weeks, persistent post-acute withdrawal disorders may also have a delayed onset and last for several months or, occasionally, even years.[47,57,58] Rebound disorders and persistent post-acute withdrawal disorders have also been described with various other CNS drugs, including opioids, benzodiazepines, stimulants, antipsychotics and lithium.[48,59]

According to two placebo-controlled trials, abrupt discontinuation of antidepressants can lead to a significant decline in social functioning within a few days, with further progression of impairments very likely.[60,61] These functional impairments that come along with withdrawal symptoms may cause stress that can trigger or precipitate a depression relapse.[62,63] The link between withdrawal-related functional impairments and depression relapse has never been examined directly,[60,61] but is indirectly supported by robust epidemiological findings that social functioning deficits, for example, due to job strain,[64,65] relate prospectively to increased risk of depression.[66] Finally, there is evidence that the more users had previously been exposed to and the longer they had been on antidepressants, the higher the risk of severe withdrawal reactions.[17,50,67,68] Thus, as cumulative exposure to antidepressants appears to influence the incidence and severity of withdrawal reactions,[50,67] discontinuation trials with a longer pre-randomization (stabilization) phase may thus have more confounded results. Moreover, it is important to note that a majority of participants who enter a relapse prevention (discontinuation) trial had already been on antidepressants and other psychotropic drugs for a long time. In the lead-in (washout) phase, these participants may thus already undergo withdrawal, and then again in the space of a few weeks if randomised to the discontinuation (placebo) arm. For someone who has been on prescribed psychotropics for years, this may cause no small degree of disturbance both psychologically and physiologically.[45,62]

In sum, abruptly stopping antidepressants can cause various types of withdrawal reactions that meet diagnostic criteria of a new depression episode, including rebound disorders and persistent post-acute withdrawal disorders.[47,48,50] Moreover, acute withdrawal symptoms can be misdiagnosed as depression relapse or may trigger a relapse due to withdrawal-related functional impairments.[51,52,62] It follows that a significant portion (possibly even a majority) of events recorded as depression relapses in the discontinuation arm of maintenance studies are in fact due to withdrawal reactions.[69,70] When we examine the survival curves in relapse prevention (discontinuation) trials, we easily see that the drug–placebo separation occurs almost completely within the first 12 weeks (see for instance the graphs presented in the FDA review[25]). That is,

antidepressants appear to exert a 'prophylactic' effect for the first 12 weeks only; thereafter, the drugs do not protect any better against relapse than a placebo pill. This has been noted by various authors and is empirically well established. [10,70–72] The findings detailed above hence indeed question the validity of relapse prevention (discontinuation) trials, of which the vast majority, noteworthy, does not attempt to differentiate relapse from withdrawal.[46,69] Of course genuine depression relapses also occur in the discontinuation (placebo) arm, but this is not the point. The fundamental issue is that events recorded as relapses could very well be, and in many cases certainly are, the result of withdrawal reactions. Therefore, the internal validity of relapse prevention (discontinuation) trials is compromised.[34,46,73] Given that the outcome in these maintenance studies is confounded, we must acknowledge that they are uninterpretable and cannot serve as a valid evidence base for long-term maintenance treatment. The next question hence is whether there is evidence of prophylactic effects from studies with other methodologies that would support long-term antidepressant treatment.

Extension trials and longitudinal observational studies: do they concur with relapse prevention trials?

Extension trials start as double-blind acute phase trials with a placebo and antidepressant arm. After the acute treatment phase, treatment responders continue on the same treatment they were initially randomised to. The advantage of extension trials over discontinuation trials is thus that they avoid withdrawal confounding, as acute treatment responders continue with the same treatment they were already on (i.e. the placebo arm is not a discontinuation arm). Unfortunately, there are only very few placebo-controlled extension trials. A systematic review and meta-analysis by Zimmerman *et al.* found only five small trials of 6–12 months duration.[74] They report an average relapse rate of 8% for active treatment and 25% for placebo. However, there are flaws in this meta-analysis. For instance, in one trial the reported relapse rate for placebo was not from the extension arm (that is, from participants who were treated with placebo during the acute phase), but from participants re-randomised from antidepressant to placebo (hence a typical discontinuation arm affected by withdrawal confounding).[75] In another trial,[76] the rates reported by Zimmerman *et al.* were actually not for relapses (new depression episodes; not reported in the target article), but for loss of response (<30% symptom reduction from baseline),[74] which is a different outcome. Due to these flaws, the results reported by Zimmerman *et al.* must be interpreted with caution.[74]

The National Institute of Mental Health (NIMH)-sponsored real-world effectiveness trial STAR*D also included a 12-month extension phase for treatment responders, but unfortunately it was not placebo-controlled.[77] Nevertheless, the results show that, when prophylactic effects are assessed *via* long-term follow up of continuously treated acute-phase responders (rather than *via* abrupt treatment discontinuation after the acute phase), then sustained remission with antidepressants is a rare event.[16,43] According to the intent-to-treat re-analysis by Pigott *et al.*,[43] the rate of sustained remission for participants who entered the extension phase in remission was only 6% at the final 12-month assessment. A similarly very low rate of sustained remission (only 11% over 12 months of treatment) was also reported in another NIMH-sponsored real-world effectiveness trial.[44] These publicly funded real-world trials based on representative outpatient samples indicate that the long-term benefits of antidepressants appear disappointingly poor once their prophylactic effects are assessed with protocols other than discontinuation trials. These findings are largely confirmed by the meta-analysis of classic long-term trials conducted by Deshauer *et al.*,[42] according to which there is no significant drug–placebo difference in remission rates after 6–8 months of treatment (drug: 45%, placebo: 38%).

I will now turn to a brief discussion of observational studies on relapse prevention. Eli Lilly, manufacturer of fluoxetine, published evidence from observational studies suggesting that short-term antidepressant use, relative to continued use, relates to higher relapse rates.[78,79] This was seen as a confirmation that long-term treatment is often necessary and beneficial. However, it was later demonstrated that these studies sponsored by Eli Lilly applied a flawed statistical method that systematically biases the results against short-term use.[80] In fact, when the observational data are analysed with an unbiased statistical method, then short-term antidepressant use is associated with lower relapse rates than continued use.[80–82] Systematic reviews of longitudinal cohort studies likewise do not indicate that antidepressant treatment prevents relapses, chronicity or clinical progression of depression.[83–85] Noteworthy, in the

most recent review of primary care and community studies, the authors stated that antidepressant use typically relates to similar or even worse outcomes than non-use.[86] Indeed, many observational studies point to the possibility that (long-term) antidepressant use may increase the risk of recurrent or persistent depression.[87–89] These findings are also supported by research on the pharmacodynamic mechanisms of tolerance and tachyphylaxis, which suggests that the more and the longer a person has been treated with antidepressants, the larger the risk of non-response, relapse and chronicity;[77,90,91] for a comprehensive review, see Fava and Offidani.[56]

Finally, the average rate of sustained recovery in patients with mood disorders was higher in the pre-treatment era (that is, before the widespread use of antidepressants) than in psychiatry's modern drug-centred treatment era, despite today's patients diagnosed with mood disorders being, on average, less severely ill.[92,93] Although the aim of this article is not to provide a comprehensive review of observational studies, it can be concluded from previous systematic reviews that antidepressant use does not, on average, relate to less relapses or sustained recovery in people with depression.[83,85] If anything, observational studies hint at increased risk of relapses and chronicity with long-term antidepressant use.[10,83,86,93] It must be borne in mind that the validity of observational studies is limited due to confounding by indication, so these studies cannot prove that long-term use is ineffective or harmful. However, taken together the findings from observational studies certainly do not indicate that long-term antidepressant use has remarkable benefits.

Summary and conclusion

Relapse prevention (discontinuation) trials have produced strong and consistent evidence of drug–placebo separation during the first 12 weeks of treatment; thereafter, treatment effects remain constant for at least 12 months.[26,27,72] The common interpretation of these findings is that antidepressants have strong prophylactic effects, and that they effectively prevent depression relapses.[1,2,23,31] This interpretation is challenged by research on antidepressant withdrawal reactions, which also emerge within days or a few weeks after treatment discontinuation (or dose reduction), and which can be severe and persistent.[21,50,94] Clinical trials and observational studies have shown that when antidepressants are abruptly (or rapidly) stopped, patients are at increased risk of relapse.[53,54] Severe withdrawal symptoms and related functional impairments may develop within a few days in patients who were in stable remission,[53,61] but late onset and slow but persistent progression of symptoms is also possible.[47,48,51] Withdrawal reactions comprise not only acute withdrawal symptoms, but also rebound disorders and persistent post-acute withdrawal disorders.[47,48,50] This makes the differentiation between withdrawal and relapse even more challenging for an assessor in a clinical trial. For the vivid personal account of a psychiatrist with lived experience, see Stockmann.[95] Hundreds of individual case reports are posted on SurvivingAntidepressants.org.

It is difficult to quantify the extent to which events recorded as depression relapse in maintenance studies are related to withdrawal reactions, but different estimations suggest that it is presumably the majority.[46,69,70] These findings indicate that there is substantial withdrawal confounding in relapse prevention (discontinuation) trials and that the internal validity of these studies is compromised. It follows that the results of these trials are uninterpretable. Publicly funded real-world long-term effectiveness trials like STAR*D showed that the benefits of continued antidepressant use are disappointingly poor.[16,43,77] The results of longitudinal observational studies likewise do not indicate that (long-term) antidepressant use prevents relapses or chronicity.[83–85] If anything, it appears that long-term antidepressant treatment, compared with short-term use or non-use, relates to worse outcomes.[10,15,81] More research is urgently needed to explain how such findings come about, but the pharmacodynamic mechanisms of tolerance and tachyphylaxis are probably a good starting point.[56,96]

This article concurs with a growing number of physicians and researchers who caution against indiscriminate long-term antidepressant treatment.[8–11,55] Currently, there is no reliable evidence that long-term antidepressant treatment is beneficial and there are legitimate concerns that it may be largely ineffective or even harmful in a substantial portion of users.[10,11,16,55,96] It is particularly problematic that we have almost no data on antidepressants' long-term effects on objective measures of social functioning (e.g. employment and disability rates) and patient-oriented outcomes such as quality of life. A critical reappraisal of current treatment guidelines along these lines is required. However, in keeping with the logical

principle of 'absence of evidence is not evidence of absence' we must remain mindful that long-term antidepressant use may be useful to some patients.[97] It is therefore important to conduct large real-world effectiveness trials that can adequately evaluate antidepressants' long-term effects on depression symptoms, social functioning and quality of life. Classic long-term parallel-arm placebo-controlled trials are the preferred methodology. Discontinuation trials should be avoided unless they apply very slow and individually tailored tapers and carefully discriminate withdrawal reactions from genuine depression relapses. Finally, it would also be worthwhile to focus more generally on influences of industry-sponsorship and authors' conflicts of interest,[10,98] as these may systematically bias the literature on the risks and benefits of antidepressants.[36,99–102]

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