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Antidepressants, withdrawal, and addiction; where are we now?

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Abstract

Controversy continues with regard to antidepressants and withdrawal. Recent debates have focused on the prevalence and length of withdrawal, and some continue to state that withdrawal from these compounds constitutes 'addiction'. In this editorial we examine the evidence underlying these recent debates. We acknowledge gaps in knowledge, and make suggestions for how the field can progress.

Keywords

Antidepressive agents; addiction; serotonin uptake inhibitors; paroxetine

Despite acknowledgement of antidepressant withdrawal syndromes dating back to the use of the first tricyclic antidepressant, imipramine (Mann and Macpherson, 1959), the topic remains controversial. A recent review, published in *Addictive Behaviours*, commissioned

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by the United Kingdom All Party Parliamentary Group for Prescribed Drug Dependence, has suggested that symptoms of antidepressant withdrawal are similar to those seen with drugs of dependence; that the prevalence is significantly higher than originally proposed (around 50%); that withdrawal is severe in nearly half of cases, and that symptoms can persist for years (Davies and Read, 2018). This review has been submitted to the National Institute for Health and Care Excellence (NICE), and Public Health England (PHE), who will appraise the evidence. When bold assertions (with potentially significant repercussions at societal level) are made, it is vital that they are correctly scrutinised on the basis of existing literature.

We therefore examine the conceptual basis of proposing antidepressants as 'addictive', withdrawal phenomena associated with antidepressants, how evidence has accumulated, gaps that exist in the literature and pharmacological considerations. We then use the example of the selective serotonin reuptake inhibitor (SSRI), paroxetine, to illustrate these points.

Are antidepressants addictive?

Conceptualising antidepressant withdrawal as 'addiction' is not new and has been debated before (Medawar, 1997; Nielsen et al., 2012; Nutt, 2003; Tyrer, 1999). The main arguments proposed for addiction include the presence of withdrawal symptoms and the evolution of the concept of benzodiazepine dependence (and the similarity of some symptoms of antidepressant and benzodiazepine withdrawal).

Putting aside the fact that antidepressants are a very heterogeneous pharmacological group of compounds (see below), with the possible exception of tranylcypromine and amineptine it is difficult to make a case for antidepressants to be considered 'addictive (Haddad, 1999)'. The *Diagnostic and Statistical Manual of Mental Disorders, 5th Edition* (DSM-5) (American Psychiatric Association, 2013) has taken a broader conceptualisation of addiction, and adapted the DSM-IV concept of substance-related disorders to substance-related and addictive disorders. Antidepressants are not included within the 10 substance classes put forward within DSM-5 criteria (unlike sedatives, hypnotics and anxiolytics). Looking at the features of substance-use disorders, it is difficult to see how these could be applied to antidepressants. DSM-5 is careful to state that occurrence of symptoms such as withdrawal during medical treatment are not to be considered as criteria for substance-misuse disorders, though allowances are made for opioid addiction, where substances are used inappropriately and symptoms of compulsive drug-seeking are seen (American Psychiatric Association, 2013). Compulsion is fundamental here – the disease model of addiction is built on this concept, where 'initially, drug use is a voluntary behavio[u]r, but when that (metaphorical) switch is thrown, the individual moves into the state of addiction, characterized by compulsive drug seeking and use' (parentheses added) (Leshner, 1997; 46). This contrasts with benzodiazepine dependence, where compulsion may be seen in those who abuse them. It is also worth noting that not all those exposed to benzodiazepines at a dose and period sufficient to cause dependence will develop it. Repeated studies have indicated that around 35% of people will develop dependence, and these people appear more likely to have been taking benzodiazepines for longer periods (>5 years) and have dependence-prone personalities (Murphy and Tyrer, 1991). The duration of prior use of

antidepressants, seems to have effects on antidepressant withdrawal symptoms, though this depends on the drug. Specifically, the Committee of Safety of Medicines expert working group report analysis of published and unpublished clinical trial data, found treatment duration to increase incidence of withdrawal from paroxetine, escitalopram, with some evidence for venlafaxine, though not clearly so for mirtazapine, sertraline and fluoxetine (Weller et al., 2005).

How have withdrawal effects been studied?

Using SSRI withdrawal as an example, the first descriptions were case reports, identifying increased reporting of withdrawal symptoms with paroxetine (Price et al., 1996). This was accompanied by randomised controlled trials (RCTs), which included randomised double-blind studies with drug interruption using unstructured and, subsequently, standardised assessment measures such as the Discontinuation-Emergent Signs and Symptoms (DESS) checklist (Oehrberg et al., 1995; Rosenbaum et al., 1998). This was followed by a number of randomised placebo-controlled studies across a range of disorders, an example being a summary of studies reported by Baldwin et al. who found withdrawal incidence (change in DESS$\geqslant$4 in the ranges of 1.9– 12.2% (continuation of placebo), 6.9–27.3% (escitalopram to placebo), 28.4–32.7% (paroxetine to placebo) and a figure of 31.5% for venlafaxine to placebo (Baldwin et al., 2007). It is worth noting the presence of a ‘nocebo’ response to dummy withdrawal, which in some studies was numerically higher than after withdrawal of active drug (Montgomery et al., 2004; Zajecka et al., 1998), a fact omitted from the Davies and Read review (Jauhar and Hayes, 2019).

Much of the evidence provided in Davies and Read’s review comes from online surveys, many of which are their own. Though undoubtedly rich in qualitative data, these convenience sample surveys are not generally accepted as quantitative analyses with clear criteria set by journals for inclusion of quantitative data (Bethlehem, 2010; Cook et al., 2000). This makes it impossible to extrapolate data from such surveys to the general population of people receiving antidepressants. The estimates of withdrawal severity by Davies and Read were only taken from such surveys. Two of the four surveys were from people self-identifying as experiencing withdrawal requiring treatment (people using tapering kits (Groot and Van Os, 2018) and people contacted through withdrawal websites (Davies and Read, 2018)). By the very nature of the sampling method, this population is likely to report severe symptoms. Despite this, the authors did not measure study quality or comment on potential selection bias in these surveys. Their interpretation of any observed effects as being directly attributable to the drug ignores a host of potential ascription and other confounding factors which contribute to the reporting of withdrawal symptoms under non-blinded conditions and are seen in the placebo condition in well-designed discontinuation studies. This, and other troublesome methodological errors (such as no clear inclusion or exclusion criteria), makes not only interpretation but also replication of their review very challenging (Jauhar and Hayes, 2019).

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Differentiating illness relapse from discontinuation symptoms

Most published literature relates to people with defined mental illness and therefore it must be considered whether new symptoms emerging on antidepressant cessation represent a withdrawal syndrome or a return of illness (Jha et al., 2018). The question of whether withdrawal symptoms constitute a relapse of illness has been addressed in controlled studies examining people with depression who have responded to antidepressant treatment, where responders can develop withdrawal symptoms on discontinuation. One example is self-limiting somnolence and dizziness in a fluoxetine discontinuation RCT (Zajecka et al., 1998), and another example concerns a number of psychiatric and somatic symptoms after successful treatment with paroxetine or sertraline (Michelson et al., 2000). Increased depressive symptoms and adverse effects on social functioning were noted in the paroxetine group in a similarly designed RCT in people with successfully treated depression, receiving either fluoxetine or paroxetine. When DESS symptoms were examined by category, differences were seen in the ‘body as a whole’, and in the digestive and nervous systems, suggesting symptoms secondary to discontinuation (Judge et al., 2002).

However, these trials are not necessarily representative of antidepressant use in clinical practice (Wiles et al., 2013). A large number of patients will be partial responders to antidepressants, with just over one-third achieving full remission with their first prescribed antidepressant (Rush et al., 2006). Therefore, the risk of interpreting illness relapse as withdrawal is particularly high in these populations and may go some way to explain the high rates identified by surveys. Exclusion of relapse symptoms from drug withdrawal can only be properly done in studies of healthy volunteers receiving antidepressants or by identifying DESS symptoms which have no depression or anxiety symptom analogue.

How best to measure withdrawal effects?

Given these considerations, how would one best examine the nature, incidence, severity and duration of antidepressant withdrawal?

In terms of study design, we should rely on the evidencebased hierarchy as follows;

- **(a)** Meta-analysis of randomised double-blind placebo-controlled withdrawal studies (in healthy controls, and in patients)
- **(b)** Placebo-controlled RCTs
- **(c)** Controlled studies
- **(d)** Case series
- **(e)** Questionnaire studies
- **(f)** Self-report

What are the gaps in the literature?

Some of the concerns of critics of previous RCTs of withdrawal symptoms include length of follow-up and length of antidepressant treatment before cessation. Data suggest withdrawal

phenomena can be non-normally distributed (Price et al., 1996) and most treatment trials only last 12 weeks or less. Survey data suggest that some people develop withdrawal after prolonged use of SSRIs, as well as longer-term discontinuation symptoms. However, this has not been studied in a systematic fashion, or in naturalistic settings, as noted above.

There is also a dearth of animal studies examining discontinuation effects and possible brain mechanisms in animal models, and studies that have been conducted are predominantly with fluoxetine within a short time-frame (Renoir, 2013).

The ideal studies would include blinded RCTs in healthy volunteers with a full range of antidepressants, treatment durations and prolonged follow-up, which would be necessary to fully understand withdrawal phenomena: these are unlikely to be feasible. However, other RCTs are underway. An example is the *ANTidepressants to prevent reLapse in dEpRession* (ANTLER) trial (https://ukctg.nihr.ac.uk/trials/trial-details/trial-details?trialNumber=ISRCTN15969819) which will examine cessation effects for up to 52 weeks, in patients who have taken medication for >9 months, thereby overcoming some of the previous RCT limitations.

Pharmacological considerations; the example of paroxetine

The concept of an ‘antidepressant’ medication is an old one, borrowing from the serendipitous way in which these compounds were first discovered. Modern, neuroscience-based nomenclature (NbN) suggests classification according to pharmacological properties (Zohar, 2014). This makes it easier to understand the therapeutic effects and side-effects.

In the case of antidepressant withdrawal, it helps to differentiate compounds such as agomelatine (a melatonin receptor agonist with antagonist effects on $5HT_{2B}$ and $5HT_{2C}$ receptors) which has no reported withdrawal syndrome (Montgomery et al., 2004) from, for example, paroxetine. As well as being the most potent SSRI, paroxetine has the greatest affinity for the muscarinic M1 receptor, is also the most potent inhibitor of cytochrome P450 2D6 (which means it slows its own metabolism) and has a relatively short half-life of less than 24 h (Nevels et al., 2016; Tonks, 2002). For these reasons, paroxetine is one of the antidepressants with a particularly high propensity for withdrawal symptoms. It is therefore worth examining data on paroxetine withdrawal symptoms in more detail.

Paroxetine is an effective antidepressant that also has established efficacy in a range of anxiety disorders. However, the story of paroxetine has been marred with controversy; it has been the focus of negative documentaries, and trial data have needed to be reanalysed because of the potential downplaying of adverse events (Le Noury et al., 2015). Many clinicians report not prescribing paroxetine because of potential side effects and withdrawal problems (Martin et al., 2006). We identified three randomised placebo-controlled trials which examined withdrawal effects associated with paroxetine under the somewhat disadvantageous condition of sudden withdrawal (Figure 1). Participants in the paroxetine arm underwent abrupt cessation from daily doses of 20–60 mg after 12 weeks treatment for panic disorder (Oehrberg et al., 1995), 20 mg after 12 weeks for generalised anxiety disorder (Baldwin et al., 2006) and 20 mg after 24 weeks for social anxiety disorder

(Lader et al., 2004) The withdrawal data for Baldwin et al., 2006 and Lader et al., 2004 are reported in Baldwin et al., 2007.) The first trial defined withdrawal as 'any withdrawal symptoms' (i.e. a low threshold definition for withdrawal) and the latter two trials defined withdrawal as an increase in DESS>3. In addition, these two trials were industry-sponsored and possibly designed to favour the comparator drug, escitalopram. Withdrawal symptoms were observed in both placebo and paroxetine arms. The difference in risk of withdrawal symptoms (i.e. the risk attributable to the active drug versus placebo) was consistent across trials at 23% (95% confidence interval (CI) 17–29%). Therefore, under unfavourable conditions (abrupt withdrawal), one in four people experienced some form of withdrawal symptoms. These trials do not cover long-term use of paroxetine, though, as noted above, longer use of paroxetine is associated with increased risk of withdrawal (Weller et al., 2005).

Data from published and unpublished clinical trials, employing mandatory taper of 10mg weekly, with at least one week at 20mg, published by the Committee of Safety of Medicines in 2005, gave adverse event rates of 29.9% for people taking paroxetine (n=2794) and 20.1% for those taking placebo (n=18920 on withdrawal from treatment. Approximately 85% of events in the paroxetine group were mild to moderate in intensity (Weller et al., 2005).

Conclusions and future directions

There is minimal evidence, using established classification systems and concepts, that antidepressants should be classified as addictive substances. Whilst withdrawal effects do exist, the available literature suggests modest, albeit heterogeneous, effects of antidepressant drug discontinuation from randomised placebo-controlled trials, which can be contrasted with the survey reports of severe symptoms related to open-label discontinuation. What the survey data do indicate is that there are a number of people who have been taking antidepressants with longer-term symptoms of withdrawal which affect their functioning. The existing evidence is unable to address this population and though current trials (such as ANTLER) may address this to a degree, it is difficult to know if studies will be adequately powered to adequately address these concerns.

What would seem most appropriate for those concerned with policy is to consider balanced scientific evidence, and potential intervention, for those people who may experience longer-term withdrawal problems, rather than accepting uncritically a partisan narrative.

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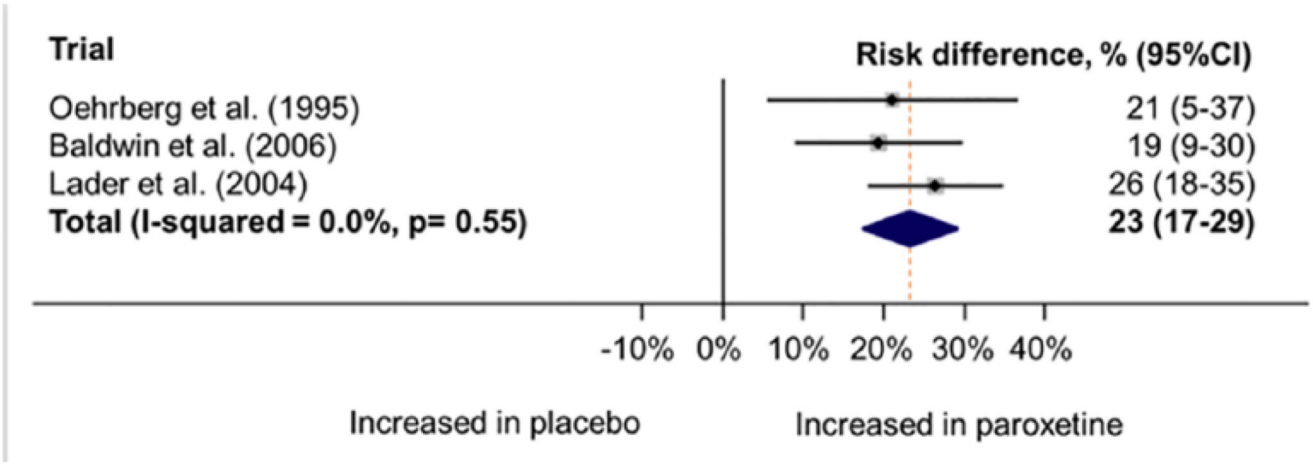

Figure 1. Withdrawal symptoms in placebo-controlled randomised controlled trials (RCTs) of abrupt paroxetine cessation.

CI: confidence interval. Withdrawal data for Baldwin et al., 2006 and Lader et al., 2004 are included in Baldwin et al., 2007.