Journal of
Psychopharmacology

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

Journal:	*Journal of Psychopharmacology*
Manuscript ID	JOP-2019-3777
Manuscript Type:	Editorial
Date Submitted by the Author:	12-Feb-2019
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Please list at least 3 keywords which relate to your manuscript::	antidepressive agents, addiction, serotonin uptake inhibitor
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Abstract

Controversy continues in 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 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 the 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, pharmacological considerations, how evidence has accumulated, and gaps that exist in the literature. 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; Tyrer, 1999; Nutt, 2003 Nielsen, Hansen and Gøtzsche, 2012). 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 it is difficult to make a case for antidepressants to be considered "addictive". 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 ten 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). Apart from some monoamine oxidase inhibitors, perhaps only tranylcypromine, it is difficult to see how any antidepressant could fulfil this criterion. 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 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, however, does not seem to have effects on antidepressant withdrawal symptoms (Rosenbaum *et al.*, 1998).

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>=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 (Zajecka *et al.*, 1998; Montgomery *et al.*, 2004), 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 for quantitative analyses, with clear criteria set by journals for inclusion of quantitative data (Cook, Heath and Thompson, 2000; Bethlehem, 2010). 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, Pauli and Montagu, 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 replication, of their review very challenging (Jauhar and Hayes, 2019).

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, Rush and Trivedi, 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 a number of psychiatric and somatic symptoms after successful treatment with paroxetine or sertraline (Michaelson 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 'body as a whole', and 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. 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 (Wiles et al. 2013). 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?

Firstly, in terms of study design, we should rely on the evidence-based hierarchy, as follows;

i) Meta-analysis of randomised double-blind placebo-controlled withdrawal studies (in healthy controls, and in patients)
ii) Placebo-controlled randomised controlled trials (RCTs)
iii) Controlled studies
iv) Case series
v) Questionnaire studies
vi) 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 suggests some people develop withdrawal after prolonged use of SSRIs, as well as longer-term discontinuation. However, data from a limited number of RCTs suggest that duration of treatment beyond 4-6 weeks is not related to risk of withdrawal (Rosenbaum et al. 1998, Baldwin et al, 2007), although this has not been studied in a systematic fashion.

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 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, 2015). 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 24hrs (Tonks, 2002; Nevels, Gontkovsky and Williams, 2016). 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, May and Gunnell, 2006). We identified three randomised placebo-controlled trials, which examined withdrawal effects associated with paroxetine under the somewhat disadvantageous condition of sudden withdrawal. Participants in the paroxetine arm underwent abrupt cessation from daily doses of 20-60mg 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 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 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% CI 17%-29%). Therefore, under unfavourable conditions (abrupt withdrawal), 1 in 4 people experienced some form of withdrawal symptoms. These trials do not cover long-term use of paroxetine, though, as noted above, it remains unclear if increased prior length of antidepressant use elevates risk of withdrawal (Rosenbaum *et al.*, 1998).

Insert Figure 1 about here

Figure 1. Withdrawal symptoms in placebo controlled RCTs of abrupt paroxetine cessation

Withdrawal data for Baldwin et al. 2004 and Lader et al 2004 are included in Baldwin et al. 2007

In addition, GlaxoSmithKline state, in a previously confidential document submitted to the European Medicines Agency, that they have undertaken studies of paroxetine withdrawal in 1,716 healthy volunteers and that "there do not appear to be any difference in withdrawal adverse events reported between patients and healthy volunteers" (https://www.gsk.com/media/1636/question_10.pdf). However, these data are not currently available for further interpretation or reanalysis.

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 concerns regarding the latter patient group.

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.

(Word count 2254 words)

Declaration of conflicting interests

S.J declares no conflicting interests

J.F.H. declares no conflicting interests

G.M.G. holds shares in P1Vital and has served as consultant, advisor or CME speaker for Allergan, Angelini, Compass pathways, MSD, Lundbeck, Otsuka, Takeda, Medscape, Minervra, P1Vital, Pfizer, Servier, Shire and Sun Pharma.

D.S.B. has attracted research funding (between 1994-2018) from the following pharmaceutical and biotechnology companies: AstraZeneca, Bristol-Myers Squibb, Cephalon, Eli Lilly Ltd, Glaxo-SmithKline, H. Lundbeck A/S, Pharmacia, Pierre Fabre, Pfizer Ltd, Servier, Vernalis Ltd, and Wyeth Ltd. He has attended advisory boards organised by Grunenthal, Liva Nova, Mundipharma, Roche, and Sumitomo; and has received personal honoraria for lecture engagements organised by

AstraZeneca, Bristol-Myers Squibb, Eli Lilly Ltd, Glaxo-SmithKline, Janssen, H. Lundbeck A/S, Pharmacia, Pierre Fabre, Pfizer Ltd, Servier, and Wyeth Ltd.

P.C has no conflicting interests during the last three years

- D.J.N. Advisor - British National Formulary, MRC,
- Past President - British Neuroscience Association - European Brain Council
- Past President - European College of Neuropsychopharmacology
- Chair – DrugScience [UK]
- Member International Centre for Science in Drug Policy
- Editor of the Journal of Psychopharmacology
- Advisory Boards - Nalpharm, Mundipharma, Ranvier, Indivior, Opiant
- Speaking honoraria (in addition to above) Lundbeck BMS/Otsuka, Janssen, Martindale
- Member of the Lundbeck International Neuroscience Foundation, Chair Campus editorial board
- Grants or clinical trial payments: Wellcome Trust, MRC
- Share options – P1vital, Alcarelle Director Equasy Enterprises
- Expert witness in a number of legal cases relating to psychotropic drugs
- Edited/written >32 books - some purchased by pharma companies

Funding

SJ is supported by a JMAS Sim Fellowship form the Royal College of Physicians (Edinburgh) and National Institute for Health Research (NIHR) Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care.'

JFH is supported by a Wellcome Trust Clinical Research Career Development Fellowship and the UCLH NIHR Biomedical Research Centre.

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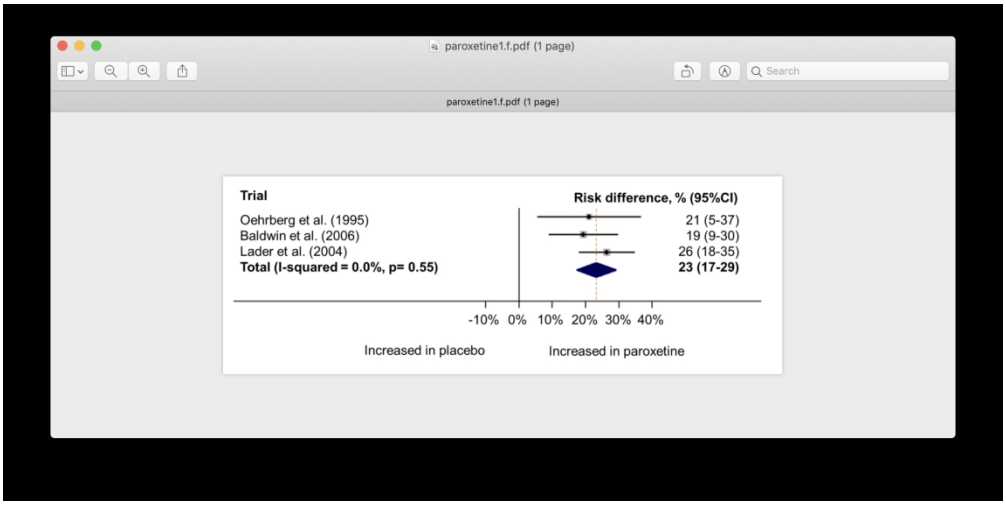

Figure 1. Withdrawal symptoms in placebo controlled RCTs of abrupt paroxetine cessation

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

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