All-Party Parliamentary Group for Prescribed Drug Dependence

Antidepressant Dependency and Withdrawal

Antidepressant Submission to the Public Health England Review into Prescribed Drug Dependence and Withdrawal.

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Executive Summary

It is incorrect to view antidepressant withdrawal as largely mild, self-limiting and of short duration.

The available research shows that antidepressant withdrawal reactions are widespread, with incidence rates (i.e. the percentage of antidepressant users experiencing withdrawal) ranging from 27% to 86%, and with nearly half of those experiencing withdrawal describing these reactions as severe. Available research also indicates that withdrawal effects are not 'self-limiting' (i.e. typically resolving between 1-2 weeks). Rather, between approx. 25% of users experience AD withdrawal reactions (such as raised anxiety) for at least 3 months after cessation, with many experiencing AD withdrawal for longer than 6 months.

Antidepressants fulfil key criteria for being dependency-forming medications.

As to whether ADs are considered dependency-forming medications, significantly depends on how dependency is defined. According to DSM and ICD criteria, the WHO's definition of dependency, as well as according to available research, it is more reasonable to class antidepressants as potentially dependency-forming medications than not. As well as causing withdrawal in a large proportion of users, available evidence undermines the claim that ADs do not generate tolerance (tolerance being a key criteria for dependence). Rather, ADs may generate tolerance in a proportion of users (up to 25%). Furthermore, when asked, about a third of users report being addicted to ADs, according to their own definition of that concept.

The escalation of long-term antidepressant use combined with the misdiagnosis of withdrawal reactions warrants serious concern.

The lengthening duration of AD use (which has doubled on average in the last 10 years) has fuelled rising AD prescriptions over the same time period. The evidence suggests that such lengthening duration may be partly rooted in the underestimation of the incidence, severity and duration of AD withdrawal reactions; underestimations which may have led to many withdrawal reactions being misdiagnosed as relapse or as failure to respond to treatment. It warrants serious concern that the misdiagnosis of withdrawal may be contributing to escalating long-term AD use (since drugs are being reinstated rather than withdrawn), given that long-term use is associated with increased severe side-effects, increased risk of weight gain, the impairment of patients' autonomy and resilience (increasing their dependence on medical help), worsening outcomes for some patients, greater relapse rates, and the development of neurodegenerative diseases, such as dementia.

1. Introduction

Over seven million adults were prescribed antidepressants in England alone last year (2016-17), with the number of individual prescriptions topping 67 million. (1) This computes to 13% of the English population (or about 1 in 8 adults) being prescribed an antidepressant in the space of 12 months. Research also indicates that around half of all antidepressant users (up to 3.5 million people in England [6.5% of population]) have been taking antidepressants for longer than two years. (2)

Previous research has shown that a third of people in the UK who take antidepressants long-term (>2 years) have no evidence-based indications to continue them, and could try stopping treatment (3) - findings supported by research denoting unnecessary long-term use in other, non-UK settings. (4) If we apply the percentages of such non-indicated prescribing to today's long-term use figures, we conclude that approximately 1.2 million long-term antidepressant users could be taking ADs unnecessarily and therefore could try withdrawing.

2. Antidepressant Withdrawal

Antidepressants have been long known to induce withdrawal reactions in a large proportion of users. (5) While in many patients such reactions may be mild, short-lasting and manageable with reassurance and explanation (6) in other people, even with slow withdrawal, these reactions are severe, long-lasting and can make normal functioning impossible. (7) Typical antidepressant withdrawal reactions include increased anxiety, flu-like symptoms, insomnia, nausea, imbalance, sensory disturbances, and hyperarousal. Dizziness, electric shock-like sensations, brain zaps, diarrhoea, headaches, muscle spasms and tremors, agitation, hallucinations, confusion, malaise, sweating and irritability are also reported. (8, 9) Although the aforementioned symptoms are the most common physical symptoms, there is also evidence that antidepressant withdrawal can induce mania and hypomania (10, 11) emotional blunting and an inability to cry (12) long-term or even permanent sexual dysfunction (13) and other adverse emotional, psychological and interpersonal effects. (14)

3. Incidence of Antidepressant Withdrawal Reactions

While the form and severity withdrawal takes is various, there is a high incidence of antidepressant withdrawal (i.e. the percentage of AD users experiencing withdrawal). A survey by the Royal College of Psychiatrists found that of the 817 antidepressants users assessed, 512 (63%) experienced varying types and degrees of withdrawal reaction upon antidepressant cessation (15). This is similar to the results derived from the largest direct-to-consumer survey of antidepressant users to date: of the 1,367 New Zealand AD users in New Zealand who responded to a question about withdrawal, 55% replied that they had experienced some degree of withdrawal effects.(16) An international survey, utilising almost identical methodology as the New Zealand study, also found that 55% (of 953 AD users) reported withdrawal effects. (17) In the New Zealand cohort the percentage reporting withdrawal effects rose to 74% among those who had been on the drugs

for more than three years (18). In both the New Zealand and international studies, duration of taking ADS was therefore strongly correlated ($p < .001$) with withdrawal.

A possible limitation of these three studies is that they were not randomised or stratified samples. It is therefore theoretically possible that they may have over-represented people who were dissatisfied with ADs. However, as the majority of the participants reported that the ADs had reduced their depression, in both the New Zealand (83%) and international (65%) studies (this data was not provided in the RCPsych study), the 'dissatisfaction bias' objection may be weak. Additionally, many other studies also broadly confirm the high incidence of withdrawal. A study of 95 people who abruptly stopped taking Fluoxetine, for instance, indicated 67% experienced withdrawal reactions,(19) while a further small study of 14 people who abruptly withdrew from fluvoxamine found that 86% experienced withdrawal.(20) While these studies indicate high withdrawal incidence, some studies exist that indicate lower rates: a study of 80 people who abruptly stopped paroxetine showed 34% experienced withdrawal,(21) while another showed of 95 who discontinued their SSRI's 27% experienced withdrawal, even when treatment may have been of very short duration.(22)

In summary, the seven studies, when taken together, indicate that over half of AD users report experiencing withdrawal effects, with the incidence ranging from 27% to 86%, and with the weighted average being 56% (1919/3421) of AD users. Additionally, in those studies where explicit tapering protocols (of differing kinds) were implemented, incidence of withdrawal is only slightly lower, varying from 46% (23) to 45% (24) to 56% (25), with an average incidence rate of 49% (36/73).(26)

4. Severity

Referring to three studies above, in the New Zealand cohort 25% of all AD users reported 'severe' withdrawal effects, which was very similar to the 24% finding in the international sample. A further recent Dutch study, surveying over 1,750 people, found that of the 692 who had previously tried to come off their ADs, 671 (97%) had experienced some degree of withdrawal effects. Of those 671, a total of 339 (51%) reported the most extreme of six levels of withdrawal; describing the extent of their withdrawal effects as 'very much' (point 7 on a seven point sale of severity). (27) Additionally, of those reporting any level of withdrawal effects the following percentages ticked the most extreme point on the scale provided ('severe' or 'very much') were 46% and 43%, for the New Zealand and International surveys respectively. Therefore the three studies consistently find that that nearly half of people who experience withdrawal report the experience as highly significant.

5. Duration of Antidepressant Withdrawal Reactions.

Given antidepressant withdrawal is ubiquitous, it is critical to assess the length of withdrawal reactions.

The evidence for withdrawal duration is mixed. There are a few small studies that, taken on their own, would suggest withdrawal is of short duration. One study, for example, which covered only 95 patients (treated for approx. 8 weeks), showed withdrawal was experienced for an average 5 days when discontinuing under clinical supervision.(28) Another small study showed that 3/9 people (33%) experienced withdrawal for more than a month, under the 'slowest possible tapering' (29).

The majority of studies we found, however, indicate withdrawal reactions of longer duration. A recent review of 15 randomized controlled studies, 4 open trials, 4 retrospective investigations, and 38 case reports, concluded that withdrawal symptoms 'typically occur within a few days from drug discontinuation and last a few weeks. However, many variations are possible, including late onset and/or longer persistence of disturbances.' (30) For example, the review found two studies documenting the persistence of withdrawal symptoms up to one year following paroxetine discontinuation, and, also found, in relation to the same drug, that 'Only in a few cases did symptoms spontaneously remit in about 2 weeks'.

The recent RCPsych survey of 817 antidepressant users, published by the RCPsych in their document 'Coming Off Antidepressants', found that withdrawal symptoms were experienced by the majority (63%) and 'generally lasted for up to 6 weeks' and that 'A quarter of our group reported anxiety lasting more than 12 weeks' – as to how much longer than 12 weeks was not specified. (31)

A similar British survey found that 79 of 247 people (32%) who had succeeded in withdrawing from antidepressants took at least three months to do so, while 15% took at least six months. (32)

A 2017 British survey, conducted at Roehampton University (in preparation for publication), found the following results among 157 antidepressant users, all of whom self-identified as experiencing moderate or severe withdrawal, when asked 'How long have you experienced withdrawal symptoms?' the vast majority (85.4%) reported experiencing withdrawal reactions for at least two months, with 22.9% experiencing them for one to three years. (33) Additionally, a recent study on a patient population likely to have experienced withdrawal difficulties assessed the content of a sample of online posts (173) on antidepressant withdrawal. It revealed that the mean duration of withdrawal symptoms was 22 months for SSRI users and 11 months for SNRI users, results indicating protracted withdrawal in a proportion of AD users. (34)

Other studies also suggesting longer duration include a study of 58 patients who abruptly withdrew from ADs. The results indicate that 40% (23/58) were still experiencing withdrawal symptoms at 6 weeks after discontinuation, with no further follow up.(35) A further study that reviewed 24 case reports of 'AD discontinuation manic states', 8 for which the duration was known, found a mean duration of 43 days - ranging of 9-198 days (36). Additionally, a review of 3 cases being treated for withdrawal with CBT, reported withdrawal duration for over 3 months for all cases. (37)

In short, the research suggests more than half of AD users experience withdrawal, with around 25% reporting their withdrawal as severe. Furthermore, around 25% of certain withdrawal reactions last for at least 3 months after cessation, with other reports indicating that withdrawal can last for months and sometimes years for certain people. Given that around 7 million individuals were prescribed antidepressants in England alone last year (13% of the population), it is possible that between 1.7 and 2.2 million people in England (around 4% of the population) may experience antidepressant withdrawal for at least 3 months after cessation (assuming current prescribing guidelines are adhered to, and patients adhere to treatment).

6. 'Discontinuation Syndrome' or 'Withdrawal Reaction'.

Given the incidence and duration of antidepressant withdrawal, in this submission we will use (and advocate that others use) the phrases **'**withdrawal reaction' or 'withdrawal symptom' or just 'withdrawal' rather than 'discontinuation syndrome'.

The now established meaning of 'discontinuation syndrome' was first operationally defined at the 'Discontinuation Consensus Panel' funded by Eli Lilly in 1996. (38, 39) The panel comprised psychiatrists, who aimed to distinguish SSRI withdrawal from other contentious withdrawal forms such as those generated by benzodiazepines and sedative hypnotics. (40) It did so by promoting use of the phrase 'discontinuation syndrome', which it defined as a 'self-limiting syndrome' (e.g. comprising mild, transient and/or more distressing symptoms that can lead to impairments in functioning or productivity) and 'typically resolving within 2 to 3 weeks'. (41) In short, along with others, we reject the conclusions of the Eli Lilly panel (and thus the validity of the term 'discontinuation syndrome') for the following reasons:

- The panel's characterisation of withdrawal as 'self-limiting' (resolving within 2-3 weeks) was not supported by the evidence the panel cited to substantiate the 'self-limiting' claim. (42) Additionally, the 'self-limiting' claim is contradicted by subsequent evidence (see section on 'duration' above).
- The commercial interests and influence of the panel's sponsor, Eli Lilly, potentially biased the consensus reached (e.g. the panel promoted use of the sponsor's drug [Prozac] as minimising the effects of 'discontinuation syndrome'; a term that also distances ADs from the more commercially inconvenient term of 'withdrawal' which is more closely associated with 'dependency').
- The term 'syndrome' threatens to subtly medicalise withdrawal by associating it with a disease or disorder endogenous to the person; when in fact withdrawal is a non-dysfunctional reaction to the cessation of a drug. (43)
- Defining 'withdrawal syndromes' as those pertaining to benzodiazepines and antipsychotic drugs, while 'discontinuation syndromes' as pertaining to SSRIs does not reflect the evidence in the literature (44) and has thus erroneously separated AD withdrawal from other CNS drug withdrawals. (45)

- The use of the term ‘discontinuation syndrome’ has minimized the vulnerabilities induced by SSRIs. (46)
- The term discontinuation syndrome is misleading since withdrawal may occur without discontinuation, for example, in between two doses of rapid-onset and short-acting drugs and with a decrease in medication. (47)

For these reasons we agree with researchers such as Fava et al. (48) that the term ‘discontinuation syndrome’ should be replaced with a term betting fitting the evidence, such as ‘withdrawal reaction’.

7. Do Antidepressants Produce Tolerance?

Loss of response to antidepressant treatment over time has attracted different names. The popular term in the user community is AD ‘poop out’ - an experience referred to in the medical literature as ‘tachyphylaxis’. (49) Another more generic term (deployed by both users and medical professionals) is AD ‘tolerance’ - a term implying physiological acclimatisation to either the concentration or actions of the drug over time.

There is controversy about whether loss of antidepressant response indicates ‘tolerance’ or other factors such as worsening depression, the effects of a new medicine being instated or a new medical condition arising. (50) In short, the true incidence of AD tolerance in contrast to other explanations for loss of AD response is not known. (51) Therefore questions as to what causes loss of AD response still remain. One immediate implication is that all statements declaring that ‘ADs do not produce tolerance’ are *not evidence-based*, and therefore should not be issued. What follows is an overview of evidence not only indicating that denying AD tolerance goes counter to what the evidence allows us to say, but that AD tolerance is a viable explanation for much loss of AD response.

Firstly, it is clear that loss of AD response is widespread. It was first recognised in people receiving monoamine oxidase inhibitors (MAOIs) where people who lost their initial response to an MAOI responded poorly to subsequent treatment and revealed greater depressive severity after relapse than before the new treatment was initiated. (52, 53) More recently, Frank et al. reported that 18% of people initially responding to imipramine in a three-year treatment maintenance study relapsed during that time period. (54)

Loss of AD response was also later recognised in people receiving SSRIs, after these drugs were introduced in the United States in the late 1980s. (55, 56, 57) From a meta-analysis of studies published prior to 1993, Byrne and Rothschild calculated the rate of AD ‘tachyphylaxis’ or ‘tolerance’ to be between 9% and 33% of people treated for depression (58). More recently, a 20-year follow up study of 103 MDD patients (i.e. National Institute of Mental Health Collaborative Depressive Study) reported that the rate of ADT tachyphylaxis/tolerance was 25%. (59) While these rates are high, other studies put them higher, such as a 2011 survey indicating that

during treatment of dysthymia in the SSRI group, tolerance/tachyphylaxis was observed in 41.9% of cases. (60)

In short, the rate of ADT tolerance is estimated to be approximately 25% of people treated for depression (rising to 41.9% in SSRI treatment of dysthymia). However, as causes other than tolerance may help account for diminishing AD effects, (61) we must ask if it is possible to disentangle AD tolerance from other explanations for loss of AD response.

There is some evidence that this is possible. Firstly, Fava and Offidani state that the phenomena associated with loss of AD effect in mood disorder bear strong resemblances with progressive loss of response observed with both antidepressant and antianxiety drugs in anxiety disorders. (62) Furthermore, a recent meta-analysis of maintenance treatment studies which showed that people taking antidepressant medications run the risk of relapse progressively increasing from 23% within 1 year to 34% in 2 years and 45% in 3 years (63) may be another strong indicator of tolerance.

Furthermore, as Targum notes, (64) several reports and reviews have suggested that ADT tachyphylaxis/tolerance may result from increasing drug sensitization that causes a pharmacokinetic and/or pharmacodynamic tolerance of the concentration or actions of the drug (65, 66). 'In this regard', states Targum, 'prolonged antidepressant treatment may induce sensitization changes not unlike the tolerance/dependence issues induced by chronic benzodiazepine exposure'. (67, 68)

Given the aforementioned studies, it is probable that ADs generate tolerance in a proportion of users and therefore satisfy one central criterion for being dependency-forming medications.

8. Are Antidepressants Dependency-Forming?

There is debate in the clinical and academic community as to whether antidepressants are dependency forming. This debate revolves around how dependency should be defined. Contrary to earlier assessments of antidepressant dependency,[69] which overlooked key diagnostic criteria, if we assume the validity of the following criteria for substance dependence, antidepressants meet many recognised criteria for a dependency forming substance:

DSM-III's Definition

According to DSM-III's definition of dependence, antidepressants can be classed as dependency-forming as the DSM-III criteria for substance dependence 'requires only evidence of tolerance *or* withdrawal.'(70)

DSM-IV's Definition

With respect to DSM-IV, the definition of dependence becomes more restrictive, specifying that a person must experience 3 or more of the following 7 symptoms to meet criteria for dependence: (71)

1. Tolerance, as defined by either of the following: (a) a need for markedly increased amounts of the substance to achieve intoxication or desired effect, or (b) markedly diminished effect with continued use of the same amount of the substance
2. Withdrawal, as manifested by either of the following: (a) the characteristic withdrawal syndrome for the substance, or (b) the same (or closely related) substance is taken to relieve or avoid withdrawal symptoms.
3. The substance is often taken in larger amounts or over a longer period than intended.
4. There is a persistent desire or unsuccessful efforts to cut down or control substance use.
5. A great deal of time is spent in activities necessary to obtain the substance, use the substance, or recover from its effects
6. Important social, occupational, or recreational activities are given up or reduced because of substance use
7. The substance use is continued despite knowledge of having a persistent physical or psychological problem that is likely to have been caused or exacerbated by the substance (e.g., current cocaine use despite recognition of cocaine-induced depression, continued drinking despite recognition that an ulcer was made worse by alcohol consumption). (72)

As many antidepressant users clearly meet criteria 2 (they generate withdrawal), 6 (i.e. they cause sexual dysfunction in a large proportion of users), arguably 1 (up to 25% of users experience diminish effects) and arguably 4 (as criterion 4 does not exempt psychological compulsion), antidepressants are dependency forming according to DSM-IV criteria.

DSM-5's Definition

The same can be said for the most recent criteria for substance dependence, in DSM-5. Two criteria out of the following 10 must be met to warrant the specification of mild dependency:

1. Taking the substance in larger amounts and for longer than intended
2. Wanting to cut down or quit but not being able to do it
3. Spending a lot of time obtaining the substance
4. Craving or a strong desire to use the substance
5. Repeatedly unable to carry out major obligations at work, school, or home due to substance use
6. Continued use despite persistent or recurring social or interpersonal problems caused or made worse by substance use
7. Stopping or reducing important social, occupational, or recreational activities due to substance use
8. Recurrent use of the substance in physically hazardous situations
9. Consistent use of the substance despite acknowledgment of persistent or recurrent physical or psychological difficulties from using the substance
10. Tolerance as defined by either a need for markedly increased amounts to achieve intoxication or desired effect or markedly diminished effect with continued use of the same amount.
11. Withdrawal manifesting as either characteristic syndrome or the substance is used to avoid withdrawal.

As many antidepressants users would meet criteria 11 (the generate withdrawal), 7 (they cause sexual dysfunction in a large proportion of users), arguably 10 (up to 25% of users experience diminish effects), and arguably 4 (as criterion 4 does not exempt psychological compulsion) antidepressants could again be classed as dependency forming.

ICD-10's Definition

ICD-10 claims that a 'definite diagnosis of dependence should usually be made only if three or more of the following have been present together at some time during the previous year'. (73)

1. A strong desire or sense of compulsion to take the substance;
2. Difficulties in controlling substance-taking behaviour in terms of its onset, termination, or levels of use;
3. A physiological withdrawal state when substance use has ceased or have been reduced, as evidenced by: the characteristic withdrawal syndrome for the substance; or use of the same (or closely related) substance with the intention of relieving or avoiding withdrawal symptoms;
4. Evidence of tolerance, such that increased doses of the psychoactive substance are required in order to achieve effects originally produced by lower doses (clear examples of this are found in alcohol- and opiate-dependent individuals who may take daily doses sufficient to incapacitate or kill non-tolerant users);
5. Progressive neglect of alternative pleasures or interests because of psychoactive substance use, increased amount of time necessary to obtain or take the substance or to recover from its effects;
6. Persisting with substance use despite clear evidence of overtly harmful consequences, such as harm to the liver through excessive drinking, depressive mood states consequent to periods of heavy substance use, or drug-related impairment of cognitive functioning; efforts should be made to determine that the user was actually, or could be expected to be, aware of the nature and extent of the harm.

As many antidepressants users would meet criteria 3 (withdrawal), 5 (i.e. they cause sexual dysfunction in a large proportion of users) arguably 4 (up to 25% of users experience diminish effects) and arguably 1 (as criterion 1 does not exempt psychological compulsion), antidepressants should be classed as dependency forming.

In addition to fulfilling diagnostic criteria for dependency, there is growing evidence that high percentages of AD users, when asked directly, report 'that they experience the drugs to be "addictive"'. For instance, a 2014 review of studies of 'Patient-centred perspectives on antidepressant use' found that 'the most frequently mentioned reason for a negative opinion of antidepressants is that they may be addictive'. (74) For example, of 192 people in the Netherlands who had been taking ADs for six months, 30% reported that antidepressants are 'addictive', with 30% also stating that 'a person who starts taking antidepressants can never stop using them'.(75) Of 493 antidepressant users in Denmark, 57% agreed with 'When you have taken antidepressants over a long period of time it is difficult to stop taking

them' and 56% agreed with 'Your body can become addicted to antidepressants'.(76) Among 87 users in Scotland, 74% reported that 'antidepressants are addictive'. (77)

The largest direct-to-consumer survey of antidepressant users to date found that of 1,521 users in New Zealand who answered a question about addiction 27% reported that they did experience addiction, 23% of whom described the addiction as 'severe'. (78) In the international survey 37% reported being addicted and 36% of those described the addiction as 'severe'. (79) In both the New Zealand and international studies self-reported addiction was strongly correlated with length of time talking the ADs.

Furthermore, when the Nordic Cochrane Centre reviewed 45 papers on benzodiazepine addiction and 31 papers on SSRI so-called 'discontinuation syndrome' its concluded: 'Withdrawal reactions to SSRIs appear to be similar to those for benzodiazepines; referring to these reactions as part of a dependence syndrome in the case of benzodiazepines, but not selective serotonin re-uptake inhibitors, does not seem rational'. (80) The Nordic Cochrane Centre thus concluded that SSRI antidepressants should be considered drugs of dependence like benzodiazepines, given the similarity of the withdrawal reactions. This conclusion is consistent with the World Health Organisation's view of dependence: "When the person needs to take repeated doses of the drug to avoid bad feelings caused by withdrawal reactions, the person is dependent on the drug". (81)

Furthermore, withdrawal charities in the UK are now encountering widespread antidepressant withdrawal in clients. For instance, the Bristol and District Tranquiliser Project reports that more people are now requesting support for antidepressant than for benzodiazepine withdrawal. Ian Singleton of BDTP says: ''Antidepressants seem to cause just as many problems as benzodiazepines... many of the symptoms are the same as benzodiazepine withdrawal... in many cases we have found that the symptoms of antidepressant withdrawal go on for even longer than benzodiazepine withdrawal." (82)

Finally, on the 24th Oct 2016 the BMA published its call for national dedicated services to support people affected by prescribed drug dependence. This call resulted from an extensive evidence gathering process and stakeholder consultation during which the BMA had considered whether antidepressants should be included in this work. The conclusion was that they should; a conclusion supported at that time by the following stakeholders who contributed to the BMA review: RCPsych, RCGP, NICE, Academy of Medical Royal Colleges, Medical Schools Council, GMC and the British Psychological Society among others. (83)

9. Misdiagnosis of Withdrawal Effects (withdrawal vs. relapse)

There is considerable concern in the withdrawal community that many doctors are not recognising withdrawal, but rather misreading it as relapse. So how possible it is

to distinguish withdrawal reactions accurately from true relapse of depression or anxiety?

One prevailing view is that such distinctions are possible on the grounds that withdrawal usually commences within a few days after cessation and resolves quickly if the drug is reinstated, whereas relapse is uncommon in the first weeks after stopping treatment. (84) However, many withdrawal variations are possible, including late onset of withdrawal and/or longer persistence of disturbances, meaning withdrawal symptoms may be easily misidentified as signs of impending relapse. (85) For example, for drugs like fluoxetine, with a longer half-life, it is possible that withdrawal may commence many days or even weeks after cessation, confounding beliefs about withdrawal's close proximity to cessation.[86] Furthermore differing metabolic rates can also confound accurate predictions about the onset of withdrawal. Additionally, and perhaps most problematically, re-emergent symptoms of depression and anxiety are a regular feature of withdrawal itself. (87) For example, the RCPsych's own survey found that the withdrawal reaction rated severe by most people was increased anxiety, with approximately 25% of users experiencing anxiety for longer than 3 months after stopping their antidepressant. (88) As around 40% of all antidepressant users are now prescribed antidepressants for some kind of anxiety-related problem, and as increased anxiety is a common withdrawal reaction, ignorance of withdrawal reactions could have led, in the past, to an overestimation of relapse rates when antidepressants were withdrawn (89) and could still be leading, in the present, to genuine withdrawal being misread as relapse with drugs being reinstated as a consequence and a more negative prognosis be issued.

While we have solely focused above on how withdrawal can be mistaken for relapse, Haddad et al. list a number of other ways in which AD withdrawal can be commonly confused, misdiagnosed and thus overlooked. It is useful to paraphrase them below:

1. *Misdiagnosis as failure to respond to an AD*. Withdrawal reactions due to covert non-adherence to acute AD treatment may be mistaken as worsening of the underlying 'illness' leading the doctor to conclude incorrectly that treatment is ineffective. As a result, the AD dose may be increased, and an augmentation strategy adopted or an unnecessary switch made to another AD.
2. *Misdiagnosis of withdrawal reactions (e.g. 'mania' and 'hypomania')*. Withdrawal reactions such as 'manic' and 'hypomanic' symptoms, if not properly recognised as withdrawal reactions, may lead to the person being wrongly diagnosed with 'bipolar I' or 'bipolar II' and inappropriately started on long-term treatment with a mood stabiliser.
3. *Misdiagnosis as a result of switching medications*. Withdrawal reactions that follow switching a person's antidepressant may be incorrectly diagnosed as side effects of the new antidepressant, which may be stopped on the assumption that the patient cannot tolerate the new drug.
4. *Misdiagnosis as physical disorder*. Many withdrawal reactions are physical. Failure to diagnose them may lead to unnecessary referrals and investigations in an attempt to identify a 'physical' problem.(90)

Misreading and misdiagnosing AD withdrawal as either relapse or a failure to respond to treatment would be a predictor for rising long-term antidepressant use, as many patients, having their withdrawal experiences misread, would have their drugs reinstated (and/or their dosage increased). Such rising long-term use is precisely what we find.

10. Long-Term Antidepressant Use

Antidepressant prescriptions have doubled in the last 10 years (to over 67m prescriptions in England alone in 2016), with over 7 million adults in England being prescribed an antidepressant last year. As prescriptions per patient have also doubled over the same period, (91, 92) the average length of antidepressant usage has steadily increased, with now half of all antidepressant users taking them for >2 years. (93) Increases in long-term antidepressant treatment are therefore a contributing factor to the on-going rise in antidepressant prescriptions. (94)

Questions as to why more people are taking antidepressants for longer are particularly important because research indicates that a large proportion of long-term users may have overcome their difficulties and should be actively withdrawing, (95), and that recommendations on maintenance treatment with antidepressants in primary care are not evidence-based, as no RCTs were performed in primary care to address the efficacy of maintenance treatment with antidepressants as compared to placebo. (96) While current NICE guidance advocates maintenance treatment in some cases, it is useful to acknowledge that not all guidelines agree on what this precisely means. A 2010 international review of 13 sets of prescribing guidelines revealed that recommendations for duration of continuation treatment varied from 4 to 12 months and maintenance treatment from 1 year to lifelong or indefinite. (97) Research on the subjective nature of guideline formation may help explain such divergences. (98)

In short, there is clear evidence that antidepressants are being taken for longer. We believe this to be partly driven by people finding it difficult to stop and the misreading of withdrawal as relapse, leading to the drugs being reinstated.

11. Permanent or Long-Term Neurological Damage

While shorter AD usage is associated with more successful antidepressant discontinuation, (99) rising long-term AD use, fuelled in part by the misdiagnosis of withdrawal, is a matter for serious concern. In addition to the obvious economic costs, the human costs of long-term use are well documented, as such use is linked with the following serious adverse effects: increased severe side-effects, (100) the impairment of patients' autonomy and resilience (increasing their dependence on medical help) (101), increased weight gain, (102) worsening outcomes for some patients, (103) poorer long-term outcomes for major depressive disorder (104) greater relapse rates (105) and an increased risk of developing neurodegenerative disease, such as dementia. (106)

12. Conclusions

The available research shows that antidepressant withdrawal reactions are widespread, with incidence rates (i.e. the percentage of antidepressant users experiencing withdrawal) ranging from 27% to 86%, and with nearly half of those experiencing withdrawal describing these reactions as severe. Available research also indicates that withdrawal effects are not 'self-limiting' (i.e. typically resolving between 1-2 weeks). Rather, between approx. 25% of users experience AD withdrawal reactions (such as raised anxiety) for at least 3 months after cessation, with many experiencing AD withdrawal for longer than 6 months.

Additionally, evidence refutes the claim that ADs do not generate tolerance. Rather, the available evidence suggests that ADs may generate tolerance in a proportion of users (up to 25%) and therefore satisfy a central criterion for their being dependency-forming medications. Furthermore, as to whether ADs are considered dependency-forming medications, significantly depends on how dependency his defined. Even so, according to the DSM and ICD criteria, available research and the WHO's definition of dependency, it is more reasonable to class antidepressants as potentially dependency-forming medications than not. Furthermore, when asked, about a third of users report being addicted, according to their own definition of that concept.

Finally, the lengthening duration of AD use (which has doubled on average in the last 10 years) has fuelled rising AD prescriptions over the same time period. The evidence suggests that such lengthening duration may be partly rooted in the underestimation of the incidence, severity and duration of AD withdrawal reactions; underestimations which may have led to many withdrawal reactions being misdiagnosed as relapse or as failure to respond to treatment. It warrants serious concern that the misdiagnosis of withdrawal may be contributing to escalating long-term AD use (since drugs are being reinstated rather than withdrawn), given that long-term use is associated with increased severe side-effects, increased risk of weight gain, the impairment of patients' autonomy and resilience (increasing their dependence on medical help), worsening outcomes for some patients, greater relapse rates, and the development of neurodegenerative diseases, such as dementia.

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