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A systematic review into the incidence, severity and duration of antidepressant withdrawal effects: Are guidelines evidence-based?

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HIGHLIGHTS

- More than half (56%) of people who attempt to come off antidepressants experience withdrawal effects.
- Nearly half (46%) of people experiencing withdrawal effects describe them as severe.
- It is not uncommon for the withdrawal effects to last for several weeks or months.
- Current U.K. and U.S.A. Guidelines underestimate the severity and duration of antidepressant withdrawal, with significant clinical implications.

ABSTRACT

Introduction: The U.K.'s current National Institute for Health and Care Excellence and the American Psychiatric Association's depression guidelines state that withdrawal reactions from antidepressants are 'self-limiting' (i.e. typically resolving between 1 and 2 weeks). This systematic review assesses that claim.
Methods: A systematic literature review was undertaken to ascertain the incidence, severity and duration of antidepressant withdrawal reactions. We identified 24 relevant studies, with diverse methodologies and sample sizes.
Results: Withdrawal incidence rates from 14 studies ranged from 27% to 86% with a weighted average of 56%. Four large studies of severity produced a weighted average of 46% of those experiencing antidepressant withdrawal effects endorsing the most extreme severity rating on offer. Seven of the ten very diverse studies providing data on duration contradict the U.K. and U.S.A. withdrawal guidelines in that they found that a significant proportion of people who experience withdrawal do so for more than two weeks, and that it is not uncommon for people to experience withdrawal for several months. The findings of the only four studies calculating mean duration were, for quite heterogeneous populations, 5 days, 10 days, 43 days and 79 weeks.
Conclusions: We recommend that U.K. and U.S.A. guidelines on antidepressant withdrawal be urgently updated as they are clearly at variance with the evidence on the incidence, severity and duration of antidepressant withdrawal, and are probably leading to the widespread misdiagnosing of withdrawal, the consequent lengthening of antidepressant use, much unnecessary antidepressant prescribing and higher rates of antidepressant prescriptions overall. We also recommend that prescribers fully inform patients about the possibility of withdrawal effects.

1. Introduction

Antidepressants are one of the most commonly used drug classes in the U.K. and U.S.A., with prescriptions and duration of use rising each year. In the U.K. usage has risen since 2000 by 170%, with over seven million adults (16% of the English adult population) being prescribed an antidepressant in England alone last year (2016–17) (DHSC, 2018), and with the number of individual annual prescriptions now topping 65 million (NHS Digital, 2017). Additionally, about half of all antidepressant users [approx. 3.5 million people in England (8% of the population)] have been taking antidepressants for longer than two years, (Johnson et al., 2012). In the U.S.A. almost 8% of the population aged over 12 used antidepressants (in a given month) in 1999–2002, a figure rising to almost 13% (37 million adults) by 2011–2014 (CDCP, 2017). Around one-half of antidepressant users in the U.S.A. [approx. 18 million people (7% of the population)] have been taking them for at least 5 years (Mojtabai & Olfson, 2014). An online survey of antidepressant users in the U.K. found that 36% had been on them for at least five years and 26% expected to stay on them for life (Read, Gee, Diggle, & Butler, 2018). Furthermore, the average duration of antidepressant use has more than doubled since the mid-2000s in both the U.K. (NHS Digital, 2017) and the U.S.A. (Mojtabai & Olfson, 2014).

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Previous research on long-term use has estimated that a third of people in the U.K. who take antidepressants for more than two years have no evidence-based clinical indications for continuing to take them (Cruickshank, MacGillivray, & Bruce, 2008). Similar levels of unnecessary long-term prescribing have also been found in other, non-U.K. settings (Ambresin et al., 2015, Eveleigh et al., 2014, Eveleigh, 2015). If we apply the percentages of such non-indicated prescribing to today's long-term use figures, we could estimate that approximately 1.2 million long-term antidepressant users in England, and 6 million users in the U.S.A., could be taking antidepressants without clinical indication and could therefore try withdrawing.

As a previous review indicates, antidepressants have been long known to induce withdrawal reactions in a large proportion of users (Haddad, 1997). While in some people such reactions may be mild, of short duration and manageable with reassurance and explanation (Haddad, 1997) in other people, even with slow withdrawal, these reactions are severe, long-lasting and can make normal functioning impossible (Anon, 1999). 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 (Warner, Bobo, Warner, Reid, & Rachal, 2006, Healy, 2012). Although the aforementioned symptoms are the most common physical symptoms, there is also evidence that antidepressant withdrawal can induce mania and hypomania, (Goldstein et al., 1999; Naryan & Haddad, 2011) emotional blunting and an inability to cry, (Holguin-Lew & Bell, 2013) and long-term or even permanent sexual dysfunction (Csoka & Shipko, 2006). A recent systematic review of studies about a specific group of antidepressants (Serotonin-Norepinephrine Reuptake Inhibitors - SNRIs) concluded that 'Withdrawal symptoms occurred after discontinuation of any type of SNRI. … Symptoms typically ensued within a few days from discontinuation and lasted a few weeks, also with gradual tapering. Late onset and/or a longer persistence of disturbances occurred as well' (Fava et al., 2018, p. 195).

Current U.S.A. clinical guidelines indicate that withdrawal reactions 'typically resolve without specific treatment over 1–2 weeks' (APA, 2010, p. 39), with current U.K guidelines similarly stating, that '[withdrawal] symptoms are usually mild and self-limiting over about 1 week, but can be severe, particularly if the drug is stopped abruptly' (NICE, 2009, 1.9.2.1 in CG90).

The purpose of the current study, therefore, was to evaluate the accuracy and helpfulness of these guidelines by conducting a systematic review of the research literature on the incidence, duration and severity of antidepressant withdrawal.

2. Methods

The inclusion criteria for the review were any research articles published in peer-reviewed journals, in English, providing clear, comparable data about the incidence, duration or severity of withdrawal from antidepressants. No time restriction was employed in relation to when the studies were conducted. Studies were included regardless of diagnosis, as withdrawal effects are not influenced by the problem for which they are prescribed. Individual ($n = 1$) case studies were noted but excluded from numerical summaries or estimates.

A systematic search, informed by PRISMA guidelines (Moher, Liberati, Tetzlaff, & Altman, 2009), was undertaken by one of the two reviewers using MeSH (Medical Subjects Headings) in the MEDLINE/PubMed database. The search terms deployed were: Antidepressants OR Antidepressant Medications (39,626) AND Withdrawal Symptoms (3671) OR Withdrawal Effects (296) OR Withdrawal Syndrome (2583) OR Discontinuation Syndrome (146) OR Discontinuation Symptoms (129) OR Dependence (88,098) OR Addiction (46,785). This produced 312 papers. Reviewing the Abstracts of these 312 revealed that 20 met our inclusion criteria. The other reviewer independently searched PsycINFO, and Google Scholar but found no additional relevant papers. Searching the bibliographies of the 20 papers also produced no further studies. However, a 2015 review identified two additional relevant studies. An additional survey addressing duration and severity (involving one of the reviewers – JD) published in a recent report by the All-Party Parliamentary Group for Prescribed Drug Dependence in the U.K., was included in the review (Davies, Pauli, & Montagu, 2018b). Also included was a paper (Read, Cartwright, & Gibson, 2018), published just after the search, elaborating on the findings of a previous paper (Read, Cartwright, & Gibson, 2014) (involving the other reviewer). These four additions brought the total number of publications to 24, providing 31 sets of findings. A flow diagram for the search process (Fig. 1) shows that 17 of the findings pertained to incidence, four to severity and ten to duration.

3. Results

3.1. Study characteristics

The methodologies of the 24 studies were heterogeneous and the sample sizes ranged from three to 1367. Six of the 24 studies were drug-company funded and a further five involved researchers with conflicts of interest in relation to drug company money (see Tables 1–3). Four of the samples were in the U.K., three each in Canada and the U.S.A., two each in Italy and Japan and one each in Denmark, the Netherlands and New Zealand. The other seven used international samples. Six were published in the 1990s, eight between 2000 and 2009, and ten since 2010, indicating a consistently low research interest in antidepressant withdrawal.

3.2. Incidence

Our search revealed 17 studies providing data on incidence rates, 14 of which were deemed usable when calculating a weighted average (see Table 1). The methodologies were heterogeneous. The most common approaches to assessing withdrawal were the Discontinuation-Emergent Signs and Symptoms (DESS) checklist, covering 43 symptoms (six studies, using from two to four symptoms as the cut off), and self-report based on self-definition of 'withdrawal' symptoms (three studies). Sample sizes ranged from 14 to 1367. Eight provided data that compared antidepressant drugs, which are recorded in Table 1 but not discussed further. Nine of the 17 studies were either drug company funded (six) or involved authors with conflicts of interest from receipt of industry funds (three).

The largest three studies, all independent of drug-company influence, were online surveys. The first, by the Royal College of Psychiatrists (RCPsych) in the U.K. found that of 817 antidepressant users, 512 (63%) experienced varying types and degrees of withdrawal reaction upon antidepressant cessation (RCPsych, 2012). This is similar to the results derived from the largest direct-to-consumer survey of antidepressant users to date. Of the 1367 New Zealand antidepressant users in New Zealand who responded to a question about withdrawal, 55% replied that they had experienced some degree of withdrawal effects (Read et al., 2014). An international survey, utilising almost identical methodology as the New Zealand study, also found that 55% (of 953 antidepressant users) reported withdrawal effects (Read & Williams, 2018). 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 (Cartwright, Gibson, Read, Cowan, & Dehar, 2016).

These three studies had the largest sample sizes to date (and did not restrict the period during which withdrawal reactions were reported), but the samples were neither randomised nor stratified. It is therefore possible that they may have over-represented people who were dissatisfied with antidepressants. However, as the majority of the participants reported that the antidepressants had reduced their depression, in both the New

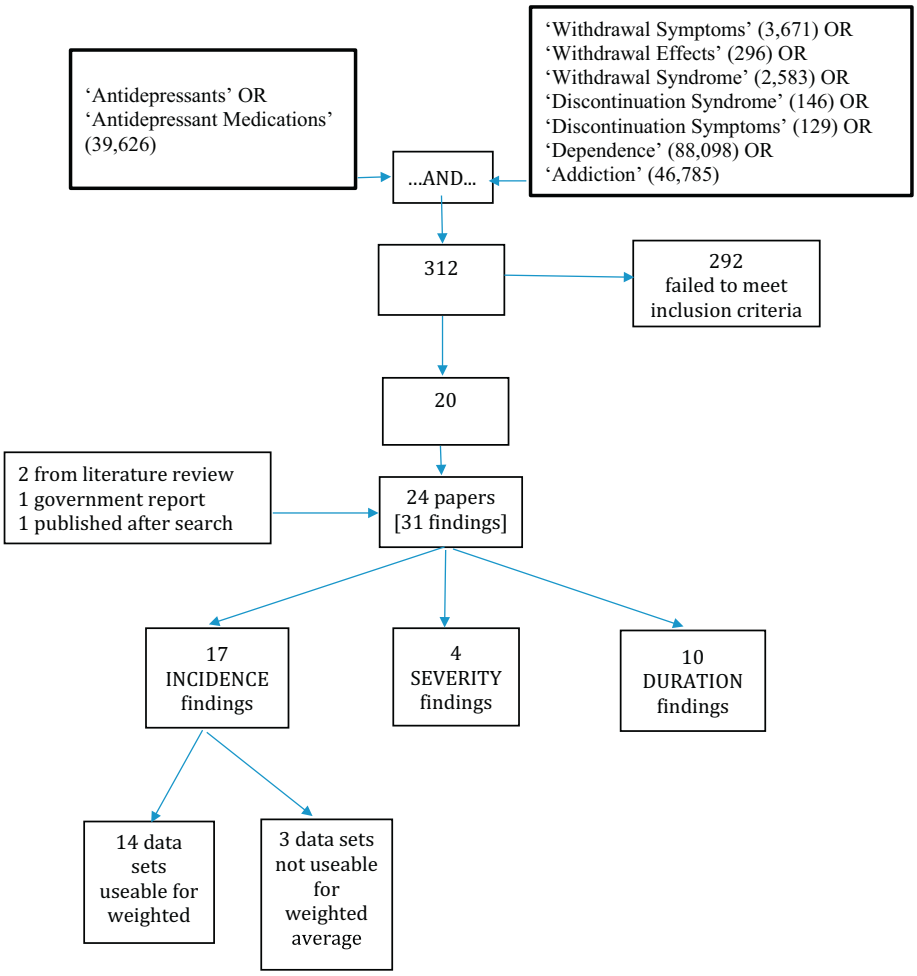

Fig. 1. Flow diagram of search process.

Zealand (83%) and international (65%) studies the 'dissatisfaction bias' concern seems minimal. (Satisfaction data was not provided in the RCPsych study).

Table 1 also summarises eleven other, smaller studies, with diverse methodologies, mostly using assessment periods of just 5–14 days. A multicentre study of 86 people who had been on antidepressants for over 3 months, found that 66 (77%) exhibited withdrawal symptoms within 7 days of having the drug abruptly replaced with placebo (Hindmarch, Kimber, & Cocle, 2000). An 8-week multicentre randomised trial, comparing sertraline and venlafaxine XR patients with major depressive disorder, revealed withdrawal reactions in a combined average of 85% of 129 patients (Sir et al., 2005; Table 4). An RCT study of 95 people who abruptly stopped taking fluoxetine indicated 67% experienced withdrawal reactions, (Zajecka et al., 1998) and a case-report study of 14 people who abruptly withdrew from fluvoxamine found that 86% experienced withdrawal (Black, Wesner, & Gabel, 1993). An additional randomised clinical trial of SSRI withdrawal, covering 185 people, revealed an average withdrawal incidence of 46% (Rosenbaum, Fava, Hoog, Ascroft, & Krebs, 1998). Another study, evaluating 25 outpatients treated with escitalopram, found 14 (56%) experienced withdrawal reactions, with higher dose and lower clearance leading to higher risk of withdrawal (Yasui-Furukori et al., 2016). A further study of 28 users of venlafaxine who were randomised to a three-day or 14-day taper, indicated that 46% experienced withdrawal (Tint, Haddad, & Anderson, 2008). Finally, a small study of 20 outpatients treated with SSRIs before slowly tapering off them found that 45% exhibited withdrawal reactions (Fava, Bernardi, Tomba, & Rafanelli, 2007).

Three studies report somewhat lower rates. One, an open trial of 97 people who discontinued their SSRIs, found 27% experienced withdrawal upon discontinuation (Bogetto, Bellino, Revello, & Patria, 2002). The second, a 12-week randomised, double-blind study of paroxetine patients, showed that of 55 withdrawing from paroxetine 35% developed withdrawal reactions upon abrupt discontinuation (Oehrberg et al., 1995). The third, a randomised, double-blind, placebo-controlled study of escitalopram, found that 27% of 181 people exhibited withdrawal reactions following abrupt replacement with placebo (Montgomery, Nil, Durr-Pal, Loft, & Boulenger, 2005).

These 14 methodologically diverse studies (comprising RCTs, naturalistic studies and surveys) produced incidence rates ranging from 27% to 86%. When grouping the three types of study together, the weighted average for each was: the three surveys, 57.1% (1790/3137); the five naturalistic studies, 52.5% (127/242); and the six RCTs, 50.7% (341/673). The combined median of all studies was 55%, with a weighted average of 55.7% (2258/4052).

Excluded studies

Incidence rates from a further three studies (all outliers, beyond the range of the 14 studies above) were deemed unsuitable for inclusion in the calculation of the weighted average of incidence rates but are noted for completeness. The first was a retrospective study of the medical notes of 385 people who stopped paroxetine. It found that 11% of the patients' notes recorded withdrawal (Himei & Okamura, 2006). As this study excluded any withdrawal commencing 3 days after discontinuation, and only assessed 9 withdrawal symptoms, lower rates may be an artefact of the study design. Furthermore it was a chart-review of medical notes, which relies on practitioners being aware of and

Table 1
Incidence of antidepressant withdrawal reactions.

STUDY and funding*	Antidepressant type	Treatment duration	Abrupt/Tapered	Withdrawal assessment period	Withdrawal incidence
Montgomery et al., 2005 DC	escitalopram	12 weeks	abrupt	2 weeks	**27% (49/181)**[1]
Bogetto et al., 2002 IND	paroxetine fluoxetine	≥ 8 weeks	mixed (67% tapered)	4 weeks	**27% (26/97)**[2] parox 42% (22/52) fluox 9% (4/45)
Oehberg et al 1995 DC	paroxetine	12 weeks	abrupt	2 weeks	**35% (19/55)**[3]
Fava et al., 2007 IND	fluoxetine fluvoxamine paroxetine citalopram sertraline	$\overline{X}$ = 29 months ≥ 6 months	tapered ('slowest possible')	1 year	**45% (9/20)**[1]
Tint et al., 2008 CI	paroxetine fluoxetine venlafaxine citalopram fluvoxamine	≥ 6 weeks	tapered ('brief')	5-7 days	**46% (13/28)**[4] parox 56% (5/8) others 36% (4/11)
Rosenbaum et al., 1998 DC	fluoxetine sertraline paroxetine	$\overline{X}$ = 11 months	abrupt	5-8 days	**46% (86/185)**[1] sertr 60% (38/63) parox 66% (39/59) fluox 14% (9/63)
Read et al., 2014, 2018 IND	paroxetine venlafaxine citalopram. fluoxetine sertraline escitalopram Tricyclics	median (52%) = > 3 years	mixed	indefinite (online survey)	**55% (750/1367)**[5] parox 76% (82/108) venla 70% (19/27) Tricyc 51% (28/55) cital 47% (115/247) fluox 36% (97/273) escit 33% (5/15) sertr 18% (2/11)
Read & Williams, 2018 IND	sertraline fluoxetine citalopram venlafaxine paroxetine escitalopram duloxetine fluvoxamine Tricyclics	median (62%) = > 3 years	mixed	indefinite (online survey)	**55% (528/953)**[5] parox 69% (46/67) Tricyc 63% (37/59) fluox 62% (75/120) venla 60% (48/80) escit 56% (35/63) cital 55% (65/118) sertr 50% (61/121) fluvo 47% (7/15) dulox 31% (5/16)
Yasui-Furukori et al., 2016 CI	escitalopram	> 6 months	tapered	indefinite (every clinic visit)	**56% (14/25)**[6]
R.C.P., 2012 ?	citalopram. fluoxetine venlafaxine sertraline escitalopram mirtazapine paroxetine duloxetine Tricyclics	unknown – real-life	mixed	indefinite (online survey)	**63% (512/817)**[5] venla 82% (89/109) escit 75% (38/51) parox 69% (20/29) dulox 69% (18/26) sertra 62% (55/89) cital 60% (141/235) Tricyc 53% (23/43) fluox 44% (76/173) mirta 21% (8/38)
Zajecka et al., 1998 CI	fluoxetine	12 weeks	abrupt	6 weeks	**67% (64/95)**[7]
Hindmarch et al., 2000 DC	fluoxetine sertraline paroxetine citalopram	≥ 3 months	abrupt	4-7 days	**77% (66/86)**[1] parox 100% (22/22) fluox 77% (17/22) cital 70% (14/20) sertr 59% (13/22)

(*continued on next page*)

Table 1 (*continued*)

STUDY and funding*	Antidepressant type	Treatment duration	Abrupt/Tapered	Withdrawal assessment period	Withdrawal incidence
Sir et al., 2005 DC	sertraline venlafaxine	8 weeks	tapered	2 weeks	**85% (110/129)**[8] sertr 58% (39/67) venla 71% (44 /62)
Black et al., 1993 DC	fluvoxamine	8 months	abrupt	2 weeks	**86% (12/14)**[9]
			WEIGHTED	**AVERAGE**	**55.7% (2258/4052)**

* DC = study funded by drug company; CI = conflict of interest, i.e. author(s) in receipt of drug company funding, or drug company employee; IND = independent; ? = unknown - no conflict of interest statement

[1] ≥ 4 of the 43 symptoms in Discontinuation-Emergent Signs and Symptoms (DESS) checklist

[2] ≥ 2 DESS symptoms

[3] observation or spontaneous self report of any adverse event (i.e. not specifically asked about withdrawal symptoms or administered DESS)

[4] ≥ 3 DESS symptoms

[5] self defined

[6] ≥ 3 of a reduced DESS symptom list (25/43)

[7] ≥ 1 'new or worsened adverse event'

[8] AntiDepressant Discontinuation Scale (ADDS)

[9] any new symptom

recording withdrawal reactions. An earlier chart-review, of 171 outpatients who tapered off their antidepressants, found a similar overall incidence of 12%, and suffered from similar methodological limitations (Coupland, Bell, & Potokar, 1996). A large study of people taking part in a withdrawal programme using tapering strips found that 97% had experienced withdrawal during previous attempts to stop antidepressants, but such a high rate is to be expected in this group, who are not representative of all antidepressant users (Groot & Van Os, 2018). If these three studies had been included, the weighted average would have been slightly increased (to 56.5% – 2992/5300).

In addition, two of the large surveys asked participants whether they had experienced addiction to the antidepressants. In the New Zealand survey (Read et al., 2014; Read, Cartwright et al., 2018) 27% reported addiction (with 80% describing their addiction as 'moderate' or severe'). In the international survey 37% reported addiction (with 62% 'moderate' or 'severe' (Read & Williams, 2018). These findings, while important in their own right, were not included in the calculation of the weighted average as addiction and withdrawal are inter-related but different phenomena.

Five other studies, all funded by drug companies, compared the average numbers of 'discontinuation symptoms' resulting from the funder's product and the competitors' products, typically following artificially short treatment periods of eight to 12 weeks, and always using assessment periods of only five to 14 days (Baldwin, Cooper, Huusom, & Hindmarch, 2006; Judge, Parry, Quail, & Jacobson, 2002; Michelson et al., 2000; Montgomery, Huusom, & Bothmer, 2004; Montgomery, Kennedy, Burrows, Lejoyeux, & Hindmarch, 2004). Because they also failed to report incidence rates in terms of percentages, these studies could not be included in Table 1. Nevertheless some of these studies produce further evidence that withdrawal reactions are common. For example one found that after just 8 weeks on venlafaxine people experienced an average of five withdrawal symptoms when they stopped taking the drug (Montgomery et al., 2004).

3.3. Severity

Our review discovered five studies reporting the severity of withdrawal effects. Four large, independently funded, studies found that nearly a half of people who have experienced withdrawal effects choose the most extreme option in the scale offered to them to describe the severity of those effects (see Table 2).

All four studies involved surveys of antidepressant use in the real world and therefore covered broad ranges of types of antidepressant and duration of treatment. For example, the large New Zealand study covered a range of antidepressants (see Table 1) and 52% had taken antidepressants for more than three years. This survey found that 46% of the 750 antidepressant users who reported withdrawal effects ticked 'severe' and a further 32% ticked 'moderate', on a mild–moderate–severe scale. (Read et al., 2014). This was similar to the 43% (severe) and 25% (moderate) findings for the 528 withdrawers in the large international sample, using the same scale (Read & Williams, 2018). A recent Dutch study of people involved in a tapering programme found that of the 671 who had experienced withdrawal effects 339 (51%) reported the most extreme level of withdrawal; 'very much' (point 7 on a seven point sale of severity) (Groot & Van Os, 2018). In a recent international survey, 580 people who had attempted withdrawal from antidepressants responded to the question 'how severely do you feel withdrawal has impacted upon your life' On a scale of 0–10). The mean response was 8.35 (SD = 2.05) denoting that the majority experienced severe reactions (median = 9, mode = 10), with 249 (43%) indicating the highest level of severity on the scale (10) (Davies et al., 2018b).

Thus, the percentages selecting the most extreme level of severity on offer in these four studies ranged from 43% to 51%, with a weighted average of 45.7% (1157/2529).

Excluded study

The fifth study was a drug company funded study comparing sertraline versus venlafaxine. After a 2 week taper, the withdrawal reactions of 110 patients were rated as 'severe' by two and as 'very severe' by one (Sir et al., 2005). These low severity rates would have been minimised by the treatment period being artificially short (8 weeks), compared to the four surveys of the real life experiences of people on antidepressants for months or years. Furthermore, in the drug company study severity was clinician-rated rather than the self-report used in the other four studies. Including this outlier in the weighted average would have reduced it slightly, to 43.9% (1158/2639).

3.4. Duration

Regarding the duration of withdrawal reactions, we identified ten relevant studies (see Table 3). Three involved conflicts of interest but none were drug-company funded.

One open trial study of 26 patients (treated for 8 weeks or more) who experienced withdrawal effects when discontinuing under clinical supervision found that the effects lasted for an average of 5 days (Bogetto et al., 2002). Another small open trial showed that three out of nine people (33%) experienced withdrawal for longer than a month,

Table 2
Severity of withdrawal effects.

STUDY and funding[a]	Treatment duration	Type of scale	Percentage choosing most extreme level of severity
Groot & Van Os, 2018 IND	Unknown	0–7	**51% (339/671)**
Read et al., 2014 IND	Mode (52%) ≥ 3 years	None/mild/ Moderate/severe	**46% (342/750)**
Read & Williams, 2018 IND	Mode (62%) ≥ 3 years	None/mild/ Moderate/severe	**43% (227/528)**
Davies et al., 2018b IND	Unknown	0–10	**43% (249/580)**
	WEIGHTED	**AVERAGE**	**45.7% (1157/2529)**

[a] IND = independent.

under the 'slowest possible tapering' (Fava et al., 2007). A study of spontaneous reports by U.K. doctors to a national data base found that 71 reported on duration of withdrawal effects. The effects lasted for between one and 52 days, with an average of 10.5 days. (Price, Waller, Wood, & MacKay, 1996). However, 34% of the 430 people who had had a withdrawal reaction when stopping paroxetine had reactions that were so severe and/or long-lasting that they had to be treated with a reintroduction of the drug, so the actual duration of untreated withdrawal reactions was minimised.

The RCPsych survey of antidepressant users found that for the 512 who experienced withdrawal the symptoms 'generally lasted for up to 6 weeks' and that 'A quarter of our group reported anxiety lasting more than 12 weeks' (how much longer than 12 weeks was not reported) (RCPsych, 2012). A recent international survey found that of the 580 people who had experienced antidepressant withdrawal and who answered the question 'How long have you experienced withdrawal symptoms?' 86.7% responded at least 2 months, 58.6% at least one year, and 16.2% more than three years (Davies et al., 2018b).

Additionally, a recent content analysis of a population likely to have experienced withdrawal difficulties assessed the content of 137 online posts about antidepressant withdrawal in the real world. The mean duration of withdrawal symptoms was 90.5 weeks for the 97 SSRI users and 50.8 weeks for the 40 SNRI users (Stockmann, Odegbaro, Timimi, & Moncrieff, 2018).

A randomised control trial of discontinuation from fluoxetine found that 40% of 58 people who abruptly withdrew were still experiencing withdrawal symptoms at 6 weeks after discontinuation, with no further follow up (Zajecka et al., 1998). In a study reviewing cases of 'antidepressant discontinuation manic states', the eight for which duration of withdrawal reactions was known, produced a mean duration of

Table 3
Duration of withdrawal effects.

STUDY and funding	Antidepressant type	Treatment duration	Abrupt/Tapered	Withdrawal assessment period	N	Duration
Bogetto et al., 2002[a] IND	Paroxetine Fluoxetine	≥8 weeks	mixed	4 weeks	26	$\overline{X}$ = 5 days (range 1–10 days)
Price et al., 1996[b] IND	Paroxetine	Unknown – real-life	unknown – real-life	indefinite	71	$\overline{X}$ = 10 days 46% ≤ 1 week 41% 8–14 days 13% > 2 weeks
Black et al., 2000[c] ?	Paroxetine Fluoxetine Fluvoxamine Sertraline	> 1 month	mixed	indefinite	26	42% < 1 week 58% 1–13 weeks
Fava et al., 2007[d] IND	SSRIs	$\overline{X}$ = 29 days months ≥6 months	'slowest possible tapering'	1 year	9	67% ≤ 1 month 33% > 1 month
R.C.P., 2012[e] ?	Multiple (see Table 1)	Unknown – real-life	mixed	indefinite	512	'generally up to 6 weeks' 25% > 12 weeks
Zajecka et al., 1998[f] CI	Fluoxetine	12 weeks	abrupt	6 weeks	75, 58	35% (26/75) in week 4 40% (23/58) in week 6
Narayan & Haddad, 2010[c] CI	TCAs, SSRIs, MAOIs, SNRIs	≥4 weeks median = 3 months	mixed	indefinite	8	$\overline{X}$ = 43 days (range 9–198 days)
Belaise et al., 2014[c] CI	Paroxetine	> 4 years	various	indefinite	3	100% > 3 months
Davies et al., 2018b[e] IND	TCAs, SSRIs, MAOIs, SNRIs	Unknown – real-life	unknown – real-life	indefinite	605	87% ≥ 2 months 59% ≥ 1 year 16% > 3 years
Stockmann et al., 2018[e] IND	SSRIs SNRIs	$\overline{X}$ = 5 days years	tapered	indefinite	137	$\overline{X}$ = 79 weeks SSRIs $\overline{X}$ = 90 weeks SNRIs $\overline{X}$ = 51 weeks

[a] ≥ 2 of the 43 symptoms in Discontinuation-Emergent Signs and Symptoms (DESS) checklist
[b] spontaneous reports to national data base
[c] case studies
[d] ≥ 4 DESS symptoms
[e] self-report
[f] = ≥ 1 'new or worsened adverse event'.

43 days – ranging from nine to 198 days (Naryan & Haddad, 2011). A review of three cases being treated for withdrawal with CBT, reported withdrawal duration of over 3 months for all cases (Belaise, Gatti, Chouinard, & Chouinard, 2014). A further case-report study assessed 46 cases of SSRI discontinuation, with 26 containing information on duration symptoms. In 11 of these 26 cases (42.3%), symptoms resolved in less than 1 week, while in the rest of the cases (57.7%) duration ranged from one to 13 weeks (Black, Shea, Dursun, & Kutcher, 2000). In this study the withdrawal symptoms of an additional 17 people only ended after the reintroduction of an antidepressant, meaning that only 26% (11/43) experienced spontaneous remission of their withdrawal symptoms within 1 week.

The ten studies do not permit a weighted average, because of the variety of methodologies and ways duration was reported. Seven out of the ten studies contradict the U.K. and U.S.A. withdrawal guidelines in that they found that a significant proportion of people experiencing withdrawal do so for more than 2 weeks (Belaise et al., 2014; Davies et al., 2018b; Fava et al., 2007; Narayan & Haddad, 2010; Stockmann et al., 2018; RCPsych, 2012; Zajecka et al., 1998).

For example, one study found withdrawal lasting at least 6 weeks in 40% of people (Zajecka et al., 1998) and another found it lasting at least 12 weeks in 25% (RCPsych, 2012). Many examples of longer durations, beyond a year, are reported by two recent, real life samples of people experiencing difficulties with withdrawal (Davies, Pauli, & Montagu, 2018a; Stockmann et al., 2018).

4. Discussion

Our review of the quantitative studies concludes that more than half (56%) of antidepressant users experience withdrawal, with the majority of these describing their withdrawal as moderate or severe, and nearly half (46%) as severe. Seven of the ten very diverse studies providing data on duration contradict the U.K. and U.S.A. withdrawal guidelines in that they found a significant proportion of people who experience withdrawal do so for more than 2 weeks, and that it is not uncommon for people to experience withdrawal for several months and beyond.

Furthermore, two of the studies reviewed indicate that for 40% of people who withdraw the effects last at least 6 weeks (Zajecka et al., 1998) and for 25% they last 12 weeks or more (RCPsych, 2012). Given that around 7 million individuals were prescribed antidepressants in England last year and around 37 million in the U.S.A., it is possible that around 2.8 million people in England and 14.8 million in the U.S.A. (about 5% of the U.S.A. and English populations) may experience antidepressant withdrawal for at least six weeks after cessation, and 1.8 million and 9 million respectively may experience withdrawal for at least 12 weeks. Additionally, and taking England alone, at least 4 million people may experience withdrawal symptoms, and over 1.8 million may experience these as severe.

These findings differ significantly from those implied in both the U.K. (NICE, 2009) and U.S.A. guidelines (APA, 2010) on antidepressant withdrawal. Furthermore, these findings are not alone in contradicting current guidelines. For instance, a 2015 review of quantitative studies and 38 case reports, noted that in only 4 out of 18 case reports (22%) did withdrawal symptoms spontaneously remit within 2 weeks, and in two cases paroxetine withdrawal was present up to 1 year after discontinuation. It concluded that while withdrawal reactions 'typically occur within a few days from drug discontinuation and last a few weeks…. many variations are possible, including late onset and/or longer persistence of disturbances' (Fava, Gatti, Belaise, Guidi, & Offidani, 2015).

4.1. 'Discontinuation syndrome' vs.'withdrawal'

Given that antidepressant withdrawal is of higher incidence, severity and longer duration than current guidelines acknowledge, a number of key implications follow. Firstly, using the term 'discontinuation syndrome' to characterise antidepressant withdrawal runs contrary to the evidence. While 'discontinuation syndrome' has been used sporadically in the literature since the 1960s, its established meaning with respect to antidepressants was first operationally defined at the 'Discontinuation Consensus Panel' funded by Eli Lilly in 1996 (Schatzberg, 1997; Schatzberg et al., 1997), where it was delineated as a 'self-limiting syndrome' (e.g. comprising mild, transient and/or more distressing symptoms that can lead to impairments in functioning or productivity), 'typically resolving within 2 to 3 weeks' (Rivas-Vazquez, Johnson, Blais, & Rey, 1999) and to be distinguished from other contentious withdrawal forms such as those generated by benzodiazepines and sedative hypnotics (Fava et al., 2015).

The panel's characterisation of withdrawal as 'self-limiting' and resolving within 2–3 weeks (a position still broadly reflected in current guidelines), however, appears unsupported not only by the evidence the panel cited to substantiate the 'self-limiting' claim, (ADH, 1996) but by subsequent evidence on duration (such as that covered by this review). Furthermore, defining 'withdrawal syndromes' as those pertaining to benzodiazepines and antipsychotics, and 'discontinuation syndromes' to SSRIs, not only erroneously separates antidepressant withdrawal from other CNS drug withdrawals but also minimises the vulnerabilities induced by SSRIs (Nielsen, Hansen, & Gotzsche, 2012). The term 'discontinuation syndrome' may further mislead as antidepressant withdrawal can occur without discontinuation (e.g. between two doses of rapid-onset and short-acting drugs and with a decrease in medication) (Fava et al., 2015), while the term 'syndrome' subtly medicalises withdrawal by associating it with a disorder endogenous to the person than with a non-dysfunctional reaction to the cessation of a drug. For these reasons, this review supports Fava et al. (2015) in stating that 'discontinuation syndrome' should be replaced with a term more consistent with the evidence, such as 'withdrawal' or 'withdrawal reaction'.

4.2. Misdiagnosis of withdrawal

Another implication of antidepressant withdrawal being of higher incidence and longer duration than current guidelines acknowledge, is that added credence is given to concerns that many doctors are misdiagnosing withdrawal – e.g. as relapse or treatment failure. One prevailing view deployed to counter this concern, is that misdiagnosis can be avoided, as it is possible to distinguish withdrawal reactions from relapse 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 (Anon, 1999). This view is problematic, however, as 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 (Fava et al., 2015). 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 (Renoir, 2013). Furthermore, differing metabolic rates can also confound accurate predictions about the onset of withdrawal. Additionally, and crucially, re-emergent symptoms of depression and anxiety are a regular feature of antidepressant withdrawal itself (Rosenbaum et al., 1998) – 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 at least 3 months after stopping their antidepressant (RCPsych, 2012). As antidepressants are now widely prescribed for anxiety-related problems, and as increased anxiety is a common withdrawal reaction, ignorance of withdrawal reactions could have led, in the past, to relapse being overestimated when antidepressants were withdrawn (Anon, 1999) and could still be leading, in the present, to genuine withdrawal being misread as relapse with drugs being reinstated and a more negative prognosis being issued.

Withdrawal can also be misdiagnosed in other ways: as failure to

respond to treatment (e.g. where covert non-adherence is mistaken as the condition worsening, leading to dose increase or drug switching); or as bipolar I or II (e.g. where 'manic' of 'hypomanic' withdrawal reactions are misdiagnosed as the early onset of bipolar); or as the result of switching medications (e.g. where withdrawal reactions are misdiagnosed as side-effects of the new antidepressant) (Haddad & Anderson, 2007).

Misdiagnosing antidepressant withdrawal in the aforementioned ways would predict rising long-term antidepressant use, as many users, having their withdrawal experiences misread, would have their drugs reinstated and/or switched (and/or their dosage increased). Such rising long-term use is precisely what we find in the clinical population, with the average duration of antidepressant use more than doubling since the mid-2000s in both the U.K. (NHS Digital, 2017) and the U.S.A. (Mojtabai & Olfson, 2014).

4.3. Consistency with qualitative studies on withdrawal

Qualitative studies, where antidepressant users are either asked open questions in surveys or interviews, or have their spontaneous internet postings published, are also consistent with the findings of the current review. These studies also serve to bring those findings to life. Illustrative examples of personal testimony regarding the severity of withdrawal effects follow:

> I am currently trying to wean myself off of Venlafaxine, which honestly is the most awful thing I have ever done. I have horrible dizzy spells and nausea whenever I lower my dose. (Pestello & Davis-Berman, 2008).

> I forgot to take my Citalopram for two days and woke up one morning with severe dizziness. It was so extreme that I fell over when I tried to get out of bed and I threw up. (Read, Cartwright et al., 2018).

> The withdrawal effects if I forget to take my pill are severe shakes, suicidal thoughts, a feeling of too much caffeine in my brain, electric shocks, hallucinations, insane mood swings. ….. kinda stuck on them now coz I'm too scared to come off it. (Gibson, Cartwright, & Read, 2016).

> While there is no doubt I am better on this medication, the adverse effects have been devastating – when I have tried to withdraw - with "head zaps", agitation, insomnia and mood changes. This means that I do not have the option of managing the depression any other way because I have a problem coming off this medication. (Cartwright et al., 2016).

Testimonies relevant to the duration of the effects include:

> It took me 2 months of hell to come off the antidepressants. Was massively harder than I expected. (Read, Cartwright et al., 2018).

> It took me almost two years to get off Paroxetine and the side effects were horrendous. I even had to quit my job because I felt sick all the time. Even now that I am off of it, I still feel electric shocks in my brain (Pestello & Davis-Berman, 2008).

> The difficulty of getting off has been a tough road and taken me years of trying and is something that doctors could be more knowledgeable of and supportive with. (Cartwright et al., 2016).

4.4. Clinical guidelines on antidepressant withdrawal

A final implication of the incidence, severity and duration of antidepressant withdrawal being higher than guidelines acknowledge, is that current guidelines are misleading doctors on the nature and management of withdrawal. As current U.K. (NICE, 2009) and U.S.A. (APA, 2010) depression guidelines are at variance with the conclusions of this research, a Freedom of Information Request was issued to NICE to ascertain the evidence base for its current statement on withdrawal – namely, that "[withdrawal] symptoms are usually mild and self-limiting over about 1 week" (NICE, 2009, 1.9.2.1 in CG90). NICE responded that its current statement on antidepressant withdrawal was inherited from an earlier statement issued in the previous 2004 guidelines, which stated that:

> There are no systematic randomised studies in this area…. If symptoms are mild, reassure the patient that these symptoms are not uncommon after discontinuing an antidepressant and that they will *pass in a few days*. (NICE, 2004, 4.5.2.48 in CG23 italics added).

NICE confirmed that evidence for both the above claims 'has not been updated' since 2004. Furthermore, this evidence was derived, at the time, from only two pieces of research (e.g. Haddad, 2001; Lejoyeux & Adès, 1997), neither of which, upon analysis, cites a single source that supports NICE's later (2009) one-week claim.

NICE's current position on antidepressant withdrawal was not only originally advanced on weak evidence, but is 14 years out of date and countered by subsequent evidence, as can be seen in this review. This raises concerns for the substantial number of antidepressant users who will experience withdrawal for a longer duration than guidelines recognise. Assuming doctors honour such guidelines, many of these people will likely have their antidepressant withdrawal misdiagnosed – e.g., as relapse or as a failure to respond to treatment – with antidepressants either being reinstated, switched or doses increased as a consequence. These practices, if routinely enacted, would help partly explain lengthening antidepressant use, which has increased the number of antidepressant prescriptions.

That doctors are being misled by guidelines also legitimates concerns raised by affected people that their withdrawal was not properly acknowledged, understood and managed by doctors, something widely reported in survey data (Davies et al., 2018b, Cartwright et al., 2016). This is also confirmed by the two largest surveys to date, which revealed that fewer than 2% of antidepressant users recall being told anything by the prescriber about withdrawal effects, dependence or potential difficulties coming off the drugs (Read, Cartwright et al., 2018; Read & Williams, 2018). Illustrative personal testimonies include:

> I was never fully informed of all side effects, short or long-term. …. If I had been more fully informed I would not have taken the medication for a long time or at all.

> I was never informed by doctors of long-term side effects or addiction/development of tolerance and went through extremely severe withdrawal symptoms attempting to get off. (Cartwright et al., 2016).

An additional legitimate concern regarding prescribers being uninformed about withdrawal effects is that they may fail to engage with their patients on this issue *after* the initial prescription. An online survey of 752 CE users in the U.K. found that 48% did not have their drugs reviewed at least every 3 months, and 65% had never had a discussion with the prescriber about whether, or how, to come off (Read, Gee et al., 2018).

5. Limitations

The calculation of our estimates has not factored in differences between antidepressant types, (e.g. differing half-lives affect timing of withdrawal onset) although Table 1 shows that a broad range of SSRI's are represented in the reviewed studies. Limitations have also been imported from the confines of the studies included, which regularly cover treatment of only short duration – 6 weeks (Tint et al., 2008) 8 weeks (Bogetto et al., 2002, Sir et al., 2005) 12 weeks (Zajecka et al., 1998), to a median of 12 weeks (Naryan & Haddad, 2011) – while undertaking

limited follow up: at 3 days (Himei & Okamura, 2006), at 14 days (Black et al., 1993) at 4 weeks (Bogetto et al., 2002) at six weeks (Zajecka et al., 1998) and at 12 weeks (RCPsych, 2012). As short-term treatment will limit the occurrence of withdrawal upon discontinuation (Eveleigh et al., 2017), and as restricted follow-up will inevitably exclude post-follow-up withdrawal reactions, such delimitations will have probably led to the underestimation of both the incidence and duration of withdrawal in the studies reviewed, thus rendering our overall estimates conservative.

Other limitations concern the online surveys reviewed. Insofar as people who experience withdrawal may be more likely to respond to surveys our overall rates of duration and severity may have been affected. Furthermore, none of the studies reviewed determined the role of 'nocebo' effects – i.e. the expectation of feeling worse upon discontinuation, which can lead to negative effects that may be misread as withdrawal effects. Although we were unable to assess what role, if any, nocebo effects played, it is probably minimal due to the nature of the withdrawal symptoms reported.

Future research must determine the extent to which the misdiagnosis of withdrawal (leading to antidepressants being either reinstated or switched) has driven lengthening antidepressant use since the mid-2000s. While shorter antidepressant usage is associated with more successful antidepressant discontinuation, (Eveleigh et al., 2017) rising long-term antidepressant use is of serious concern. In addition to the obvious economic costs incurred, the human costs of long-term use are well documented, being linked with serious adverse effects such as increased severe side-effects, (Ferguson, 2001) the impairment of patients' autonomy and resilience (increasing their dependence on medical help) (Kendrick, 2015), increased weight gain, (Gafoor, Booth, & Gulliford, 2018) worsening outcomes for some patients, (Hengartner, Angst, & Rössler, 2018; Shea, 1992) poorer long-term outcomes for major depressive disorder, (Vittengl, 2017) greater relapse rates, (Viguera, 1998) increased mortality (Maslej et al., 2017) and an increased risk of developing neurodegenerative disease, such as dementia (Richardson et al., 2018). It will also be important, therefore, to determine what people are told about withdrawal pre-treatment, to establish how regularly and accurately they are being forewarned of likely withdrawal reactions; warnings that will impact decision-making around accepting antidepressant treatment.

Finally, given that the evidence reported here on antidepressant withdrawal severity, incidence and duration differs from what guidelines state, future research must readdress the dependency-forming nature of antidepressants. This is particularly important as recent surveys reveal many antidepressant users report being 'addicted' to antidepressants; for example. 37% from a sample of 943 (Read & Williams, 2018) and 27% from a sample of 1521 (Read et al., 2014). Among 493 antidepressant users 57% agreed with the statement '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' (Kessing, Hansen, Demyttenaere, et al., 2005). As withdrawal is a central criterion for dependency, underestimates of withdrawal may well have impacted on past assessments of the extent to which antidepressants are dependency-forming.

6. Conclusion

The available research indicates that antidepressant withdrawal reactions are widespread, with incidence rates ranging from 27% to 86% (weighted average of 56%), and with nearly half (46%) of those experiencing withdrawal describing these reactions as severe. Available research also indicates that current clinical guidelines in the U.K. and U.S are in urgent need of correction, in order to be evidence-based, as withdrawal effects are neither mostly 'mild' nor 'self-limiting' (i.e. typically resolving over 1–2 weeks), but are regularly experienced far beyond what current guidelines acknowledge.

We therefore recommend that both sets of guidelines be urgently updated to reflect the evidence base on antidepressant withdrawal.

As a secondary recommendation we suggest that consideration be given to independent reviews of the processes by which the two bodies concerned construct clinical guidance around mental health interventions (e.g. how are panel members selected, by what criteria, and how is the quality of literature reviews assured). We also suggest that panel members are independent from the pharmaceutical industry, and that panels include experts-by-experience (i.e. antidepressant users) and non-medical mental health professionals.

As the lengthening duration of antidepressant use has fuelled rising antidepressant prescriptions over the same time period, we must understand the drivers of such lengthening use. The evidence set out suggests that lengthening use may be partly rooted in the underestimation of the incidence, severity and duration of antidepressant withdrawal reactions, leading to many withdrawal reactions being misdiagnosed, for example, as relapse (with drugs being reinstated as a consequence) or as failure to respond to treatment (with either new drugs being tried and/or dosages increased). This issue is pressing as long-term antidepressant 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, increased mortality and the development of neurodegenerative diseases, such as dementia.

It is of serious concern that prescribed antidepressant medications are causing withdrawal effects that are often long-lasting and severe, and that this is not being recognised by current clinical guidelines and, by extension, prescribers. It is of additional concern that such poor recognition of antidepressant withdrawal might be increasing the duration of antidepressant use and, therefore, overall rates of antidepressant prescriptions.

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Conflict of interest

Prof John Read and Dr. James Davies have no conflict of interests to declare.

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