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Antidepressant Discontinuation Syndromes

Clinical Relevance, Prevention and Management

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Abstract

Discontinuation symptoms are recognised with tricyclic antidepressants, monoamine oxidase inhibitors, selective serotonin reuptake inhibitors (SSRIs) and miscellaneous antidepressants. A wide variety of symptoms have been described, differing somewhat between antidepressant classes, and several symptom clusters or discontinuation syndromes appear to exist. A common feature is onset within a few days of stopping the antidepressant or, less commonly, reducing the dosage. Discontinuation syndromes are clinically relevant as they are common, can cause significant morbidity, can be misdiagnosed leading to inappropriate treatment and can adversely effect future antidepressant compliance.

Preventative strategies include tapering antidepressants prior to stoppage and educating patients and healthcare professionals to ensure that antidepressants are taken consistently and not stopped abruptly. Most reactions are mild and short-

lived and require no treatment other than patient reassurance. Severe cases can be treated symptomatically or the antidepressant can be reinstated before being gradually withdrawn. Reinstatement usually leads to symptom resolution within 24 hours. Some individuals require very conservative tapering schedules to prevent the re-emergence of symptoms. With SSRIs and venlafaxine another strategy to consider is switching to fluoxetine, which may suppress the discontinuation symptoms, but which has little tendency to cause such symptoms itself. Neonatal discontinuation symptoms can follow maternal use of antidepressants during pregnancy and possibly breast feeding. The patient and doctor must take this into consideration when making prescribing decisions.

Discontinuation symptoms have received little systematic study with the result that most of the recommendations made here are based on anecdotal data or expert opinion. Research is needed to provide a firm evidence base for future recommendations.

1. Antidepressant Discontinuation Syndromes

Antidepressant discontinuation symptoms (also referred to as withdrawal symptoms) were first reported with imipramine, the first tricyclic antidepressant (TCA), over 40 years ago.[1,2] Subsequent reports confirmed this finding and discontinuation symptoms were documented as occurring with other TCAs and related compounds[3-14] and the monoamine oxidase inhibitors (MAOIs).[15-21] However, with the exception of work by Dilsaver and colleagues[6,19,22,23] the area attracted little interest. During the late 1980s and early 1990s the selective serotonin (5-hydroxytryptamine; 5-HT) reuptake inhibitors (SSRIs) emerged as an important new antidepressant class. More recently several miscellaneous antidepressants have been launched. These include venlafaxine, a serotonin and noradrenaline reuptake inhibitor, nefazodone, which inhibits serotonin reuptake and blocks post-synaptic 5-HT_{2A} receptors, and mirtazapine, a noradrenergic and specific serotonergic antidepressant. All 5 SSRIs (i.e. citalopram, fluoxetine, fluvoxamine, paroxetine and sertraline) have been reported as causing discontinuation symptoms[24-29] as have venlafaxine,[30-32] nefazodone[33] and mirtazapine.[34] To date at least 21 different antidepressants, covering all the major classes, have been implicated (table I).

In recent years interest in antidepressant discontinuation symptoms has increased. Nevertheless, the area remains under-researched with much data originating from case reports and small case series which contain numerous confounder. Only a few randomised placebo-controlled trials exist. This paper ex-

Table I. Some antidepressants that have been reported as causing discontinuation symptoms. The references provide examples of reports only; they are not a summary of all reports for each agent

Tricyclics and related compounds
Amineptine[3]
Amitriptyline[3,4]
Amoxapine[5,6]
Clomipramine[3,7]
Desipramine[6,8]
Doxepin[9]
Imipramine[1-3,10,11]
Nortripyline[12]
Protriptyline[13]
Trazodone[14]
Monoamine oxidase inhibitors
Isocarboxazid[15]
Phenelzine[16-18]
Tranylcypromine[19-21]
Selective serotonin reuptake inhibitors
Citalopram[24]
Fluoxetine[24-26]
Fluvoxamine[24,27]
Paroxetine[24,25,28]
Sertraline[24,25,29]
Miscellaneous antidepressants
Venlafaxine (SNRI)[30-32]
Nefazodone[33]
Mirtazapine (NaSSA)[34]

NaSSA = noradrenergic and specific serotonergic antidepressant; **SNRI** = serotonin and noradrenaline reuptake inhibitor.

plores the clinical relevance of antidepressant discontinuation syndromes and strategies for their prevention and management. Before considering these issues some background material is presented including a definition of a discontinuation syndrome, a review of the range of syndromes encountered and a summary of the key clinical features.

1.1 Definition

Based on previous work[35,36] a discontinuation syndrome can be defined as having the following elements:

- characteristic symptoms
- onset shortly after stopping a drug or, less commonly, reducing the dosage
- short duration
- rapid reversal on restarting the original drug
- distinct from a re-appearance of the underlying disorder for which the drug was prescribed
- not attributable to other causes.

A diverse range of antidepressant discontinuation symptoms have been described and these vary somewhat between antidepressant classes. A review of 47 case reports of SSRI discontinuation reactions revealed over 50 different symptoms.[37] The severity of discontinuation reactions varies across a spectrum; some patients manifest an isolated symptom, others a cluster of symptoms, and symptoms vary from mild to severely disabling. This raises a 'threshold' issue for defining a discontinuation syndrome.

1.2 Range of Syndromes

The situation is made more complex as different symptom clusters, or discontinuation syndromes, can occur. The most common syndrome seen with the SSRIs comprises 6 main symptom groups and includes physical and psychological symptoms (table II). The most common symptoms include dizziness, nausea, lethargy and headache.[37] Provisional operational criteria for this 'general' SSRI discontinuation syndrome have been proposed.[37]

The most common syndrome associated with the TCAs also involves physical and psychological symptoms. This 'general' TCA syndrome comprises 4 symptom groups which are common to the general SSRI syndrome (i.e. general somatic symptoms, sleep disturbance, gastrointestinal symptoms and affective symptoms). The remaining 2 SSRI symptom groups, sensory abnormalities and problems with equilibrium, are rare with TCAs and can be regarded as SSRI specific. Whether the 'general' SSRI and 'general' TCA syndromes would be better regarded as several sub-syndromes is unclear.

Rare discontinuation syndromes associated with TCAs include hypomania[3,8,13,38] and movement disorders including akathisia[39] and parkinsonism.[3,23] Table III summarises some typical cases. Cardiac arrhythmias have followed abrupt termi-

Table II. Key symptom groups of the 'general' selective serotonin reuptake inhibitor discontinuation syndrome. This table only lists the more common symptoms, many others can occur[37]

Dysequilibrium
Light headedness/dizziness
Vertigo
Ataxia
Sensory symptoms
Paraesthesia
Numbness
Electric–shock-like sensations
General somatic symptoms[a]
Lethargy
Headache
Tremor
Sweating
Anorexia
Sleep disturbance[a]
Insomnia
Nightmares
Excessive dreaming
Gastrointestinal symptoms[a]
Nausea
Vomiting
Diarrhoea
Affective symptoms[a]
Irritability
Anxiety/agitation
Low mood

a These symptoms are also common following termination of tricyclic antidepressants.

Table III. Examples of reports of hypomania and movement disorders following termination of tricyclic antidepressants (TCAs)

No. of patients	Drug	Symptoms	Symptom Course	Reference
2	Desipramine	Hypomania	Onset within 36h of stopping desipramine. Remitted within 24h of restarting desipramine	8
7	Amitriptyline (n = 3); protriptyline (1); unknown (3)	Hypomania	Onset within 2 to 7 days of stopping TCA. 3 patients recovered without treatment, 3 recovered following treatment with an antipsychotic, 1 recovered following treatment with an antipsychotic and lithium	13
1	Clomipramine	Hypomania	Onset within 1 day of stopping clomipramine. Several days later clomipramine was restarted and the symptoms resolved	38
3	Imipramine	Akathisia	Onset about 24h after stopping imipramine. Resolution on restarting imipramine	39
1	Desipramine	Parkinsonism (i.e. bradykinesia, shuffling gait and cogwheel rigidity)	Symptoms appeared the morning after the night-time dose of desipramine was withheld. Remitted once desipramine was reintroduced	23
1	Amineptine	Resting tremor of the jaw, tongue, upper extremities and rigidity	Symptoms resolved spontaneously within 4 days	3

nation of amitriptyline,[3] imipramine[40] and clomipramine.[41] Panic attacks have been noted following termination of amitriptyline[42] and delirium after abrupt stoppage of doxepin.[9]

Hypomanic and extrapyramidal symptoms may follow SSRI stoppage but are rare. Reports of extrapyramidal symptoms are limited to a single report of a dystonic reaction for paroxetine[43] and fluoxetine.[44] Hypomanic symptoms are confined to one case with fluvoxamine[45] and three with paroxetine.[46,47] None of these patients had a past history of hypomania. In 3 cases[45,46] the hypomanic symptoms formed the first stage of a biphasic discontinuation syndrome, the second stage consisting of aggressive feelings and impulsive behaviour. Kasantikul[48] reported a patient who developed delirium on 2 consecutive occasions that he attempted to stop fluoxetine; both episodes resolved rapidly after fluoxetine was restarted. Cardiac arrhythmias have not been reported following SSRI stoppage.

The discontinuation syndrome seen with venlafaxine[31] appears similar to the 'general' SSRI discontinuation syndrome.[37] Occasionally auditory[30,49] and visual[50] hallucinations complicate the picture. Akathisia, abating within hours of restarting venlafaxine, has been reported.[51] Irregularities in blood pressure have been noted as discontinuation effects with venlafaxine[50] and sertraline.[52]

Discontinuation syndromes with MAOIs, particularly tranylcypromine, are usually more severe than with other antidepressants. An acute confusional state with disorientation, paranoid delusions and hallucinations may occur.[16] A worsening of depressive symptoms, exceeding the severity of the state that originally led to treatment, is also recognised[19] as is hypomania.[15] Generalised seizures have been described following stoppage of tranylcypromine.[21]

1.3 Key Clinical Features

Despite their variety, antidepressant discontinuation syndromes share several common features. These include:

- Antecedent. Symptoms usually commence after antidepressant stoppage. Onset following dosage reduction is less common[53] and may only occur after a substantial reduction from the original dose has been made.[30]
- Onset. Symptoms generally appear within a few days of stopping, or reducing the dosage of, the antidepressant. Onset more than 1 week later is unusual. For example, in an analysis of 160 spontaneous adverse drug reaction (ADR) reports of paroxetine discontinuation reactions, made by UK doctors to the Medicines Control

Agency (MCA), the median interval between stopping paroxetine and symptom onset was 2.1 days.[54] Symptoms occurred within 4 days in 86% and within 1 week in 93%.

- Treatment length. Discontinuation symptoms rarely occur with treatment of less than 5 weeks duration.[37]
- Duration. Left untreated, most antidepressant discontinuation reactions are shortlived, resolving between 1 day and 3 weeks. For example in 71 untreated paroxetine discontinuation reactions reported as ADRs[54] the median duration was 8 days (range 1 to 52 days).
- Suppression. Symptoms rapidly resolve upon re-starting the original antidepressant.

2. Clinical Relevance

Discontinuation symptoms are clinically relevant as they are common, can cause significant morbidity, may be misdiagnosed leading to inappropriate treatment and can adversely effect future antidepressant compliance.

2.1 Incidence

Defining the incidence of discontinuation symptoms is problematic; incidence varies between antidepressants, confounders exist (e.g. treatment duration, rate of taper) and methodological issues include how one defines a discontinuation symptom or syndrome, how one detects symptoms (spontaneous report or symptom check list) and how one controls for adverse events unrelated to stopping active medication including placebo discontinuation effects. These issues have best been explored for the SSRIs.

An analysis of UK spontaneous ADR reports[54] showed that the rate of reports of discontinuation reactions per 1000 prescriptions was 100 times higher with paroxetine than with fluoxetine (fig. 1). This analysis was based on reports received by the MCA up to March 1993. This predates any major publication regarding the propensity of paroxetine to cause discontinuation symptoms and so a publicity bias can be discounted. ADR analyses from other countries have confirmed that paroxetine is more frequently reported to cause discontinuation symptoms than other SSRIs.[55,56] Since most ADRs are not reported to monitoring agencies, ADR data can only estimate the relative incidence of an adverse event. Estimates of true incidence require clinical studies.

Figure 2 shows the incidence of discontinuation symptoms in a retrospective case note review of patients who stopped an antidepressant under supervision.[53] The highest incidence occurred with the TCA clomipramine (30.8%; n = 4/13). The next highest incidence was with paroxetine (20.0%; n = 10/50). Weaknesses of this study include the retrospective design, the absence of a placebo group and lack of standardisation in terms of antidepressant dosage, treatment duration, rate of taper and time between antidepressant stoppage and assessment. Several recent studies have attempted to overcome these weaknesses.

Oehrber et al.[28] investigated the incidence of paroxetine discontinuation symptoms in an extension to a 12-week double-blind placebo-controlled efficacy study in patients with panic disorder. At the end of the study paroxetine was abruptly switched to placebo. Adverse events were detected by obser-

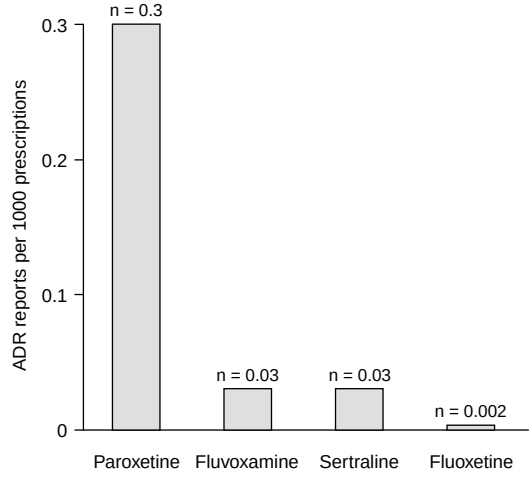

Fig. 1. Data from an analysis of UK spontaneous adverse reaction (ADR) reports of selective serotonin reuptake inhibitors showing the number of discontinuation reactions per 1000 prescriptions.[54]

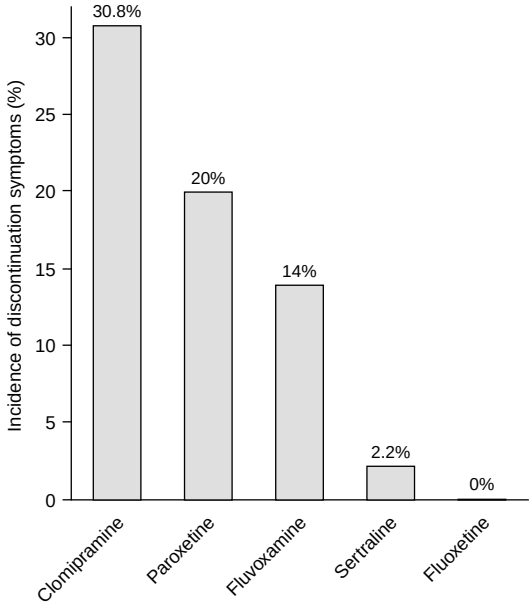

Fig. 2. Incidence of discontinuation symptoms from a retrospective case note review of patients who stopped treated with an antidepressant under supervision.[53]

vation, spontaneous reports or in response to an open question.

The incidence of new adverse events during the 2 weeks following paroxetine termination was 34.5% (n = 19/55) compared with 13.5% (n = 7/52) for those stopping placebo. The most common symptom was dizziness.

The incidence of venlafaxine discontinuation symptoms was investigated under double blind conditions by Fava et al.,[31] though the sample was small. After a 6 to 10 week treatment period, placebo and venlafaxine (extended release formulation) were stopped and the rate of adverse events assessed by open questioning. During the next 3 days, 7 (78%) of 9 venlafaxine-treated individuals and 2 (22%) of 9 placebo-treated patients reported the emergence of adverse events, a statistically significant difference. This was despite the protocol incorporating a taper of up to 2 weeks for the venlafaxine subjects.

Two studies have compared the incidence of SSRI discontinuation symptoms (paroxetine, sertraline, fluoxetine) under double blind conditions using an interruption design.[25,57] In the Rosenbaum et al. study[25] 242 patients, successfully treated for a depressive illness for 4 months or more, had their treatment interrupted in a randomised double-blind fashion so that they received placebo substitution for 5 to 8 days. Depressive symptoms were assessed using the Montgomery-Asberg Depression Rating Scale (MADRS) and 28-item Hamilton Depression Rating Scale ($HDRS_{28}$). Adverse events were assessed by spontaneous patient report and the Discontinuation Emergent Signs and Symptoms (DESS) checklist. Patients were assessed prior to interruption, immediately after the interruption period and 1 week after restabilisation on their SSRI.

Prior to interruption, mean scores for depressive symptomatology (MADRS and $HDRS_{28}$) and the mean number of adverse events (DESS checklist and spontaneous reports) did not differ significantly between the 3 SSRI groups. Following placebo interruption, fluoxetine-treated patients experienced fewer adverse events than either sertraline-treated or paroxetine-treated patients as assessed by the DESS checklist ($p < 0.001$) and spontaneous reports ($p \leq 0.001$). Fluoxetine-treated patients also experienced less re-emergence of depressive symptoms (MADRS and $HDRS_{28}$) than either sertraline-treated or paroxetine-treated patients ($p < 0.001$). Comparisons within drug treatment groups confirmed this pattern (fig. 3). At the end of the 1 week restabilisation period, scores on all measures were similar to baseline with little difference between the 3 SSRI groups, that is symptom changes were transient.

Analysis was repeated using categorical variables. Patients were classified as experiencing a 'discontinuation syndrome' if the number of DESS checklist events increased by four or more during the interruptions period. The incidence of an SSRI discontinuation syndrome in the fluoxetine-treated patients was significantly lower than the pooled incidence for the sertraline-treated and paroxetine-

treated patients (14, 60, 66% respectively; $p < 0.001$). A 'depressive relapse' was defined as an increase of 8 points or more in the $HDRS_{28}$ score and a total score of 16 or higher. The proportion of patients experiencing a relapse was significantly lower in fluoxetine-treated patients than in the pooled group of patients treated with sertraline or paroxetine (2, 14, 27% respectively; $p < 0.001$).

Michelson et al.[57] conducted a similar study but with improved methodology. In particular, all patients underwent identical 5 day periods of treatment interruption and continued active treatment under double-blind, order-randomised conditions. Analyses compared the blinded periods within each medication group thus minimising expectation about treatment group influencing the results. Assessments included a 17-item adverse events scale administered on a daily basis. The results were similar to Rosenbaum et al.[25] Mean severity worsened (to a statistically significant degree) by the end of the fourth day of placebo substitution for 13 out of the 17 items on the adverse events scale for paroxetine-treated patients, for 3 out of 17 among sertraline-treated patients and for no items among fluoxetine-treated patients. For both paroxetine and sertraline-treated patients dizziness was the item with the greatest number of patients reporting an increase in severity (percentage of paroxetine recipients worsening: active-treatment 5.7%, placebo 57.1%, $p < 0.001$; percentage of sertraline recipients worsening: active treatment 6.1%, placebo 42.4%, $p = 0.002$). Spontaneous reports of dizziness also increased in patients treated with paroxetine (placebo substitution 33.3%; active treatment 0.0%; $p < 0.001$) and sertraline (placebo substitution 35.3%. active treatment 5.9%, $p = 0.007$). The fluoxetine-treated group showed no statistically significant increase in spontaneous reports of any symptom during placebo substitution.

It is unlikely that the observed increase in symptoms in these studies reflects depressive relapse rather than a drug discontinuation effect. Consistent findings across the reviewed studies are a predominance of physical symptoms, including nausea and dizziness, which commence within days of antidepressant stoppage; neither feature is typical of depressive relapse. Another potential criticism is that the long half-life of fluoxetine, and its active metabolite norfluoxetine, may delay the onset of discontinuation symptoms relative to other SSRIs. This could impair their recognition in clinical practice and minimise the incidence in studies with a short interruption period. Work by Zajecka et al.[58] indicates that this is unlikely to be a major confounder.

In the Zajecka et al.[58] study patients successfully treated for major depression with fluoxetine for 12 to 14 weeks underwent a double-blind randomisation to continued fluoxetine or abrupt substitution with placebo. Spontaneously reported adverse events were assessed at 1, 2, 4 and 6 weeks after randomisation. There was no significant difference between the 2 groups in the number of patients reporting one or more new or worsened symp-

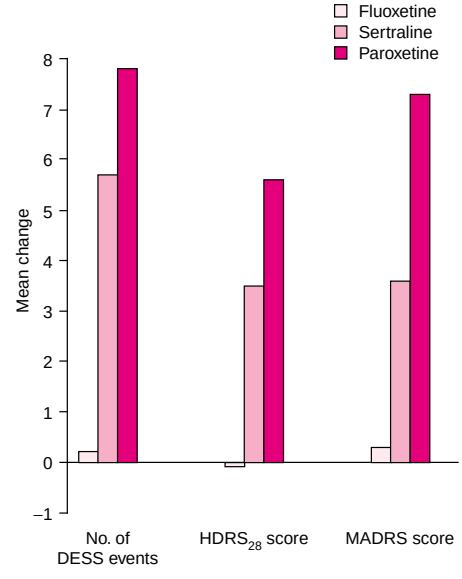

Fig. 3. Mean change in outcome measures following serotonin reuptake inhibitor interruption.[25] Mean change in number of Discontinuation Emergent Signs and Symptoms (DESS) events, 28-item Hamilton Depression Rating Scale ($HDRS_{28}$) scores and Montgomery-Asberg Depression Rating Scale (MADRS) scores were significant for patients treated with sertraline ($p < 0.001$) and paroxetine ($p < 0.001$) but not for fluoxetine-treated patients ($p = 0.578$ to 0.943).

tom at any time point or over the whole 6 week period. However, at week 4 and week 6 there were significantly more reports of dizziness in patients who had discontinued fluoxetine, though the rates were low. For example at week 4 dizziness was reported by 7% (n = 5/75) of patients stopping fluoxetine versus 1% (n = 4/279) of those continuing fluoxetine (p = 0.023) The dizziness, which was usually mild, may represent a delayed discontinuation symptom. Nevertheless the overall data refutes the idea that a clinically significant discontinuation syndrome has been missed in studies or in clinical practice because of delayed onset.

In summary, with several 'newer' antidepressants, including sertraline,[57] paroxetine[28,57] and venlafaxine,[31] abrupt discontinuation after a moderate length of treatment leads to at least 1 out of 3 patients spontaneously reporting one or more discontinuation symptoms. Higher rates are reported when information on symptoms is solicited[25] and in one study approximately 2 out of 3 paroxetine and sertraline recipients fulfilled criteria for a discontinuation syndrome.[25] The incidence of discontinuation symptoms seen with these drugs is comparable with, or lower than, that reported with several older antidepressants including imipramine (100.0%),[10] amitriptyline (80.0%)[4] clomipramine (33.33%)[7] and phenelzine (32.2%).[18]

2.2 Morbidity

Most discontinuation reactions are mild and transient, but a minority are severe, of longer duration and cause considerable morbidity. Symptoms may last up to 13 weeks.[59] With SSRIs, ataxia can cause enforced immobility,[29] falls[26] and absence from work[60] while electric shock-like sensations can cause difficulty walking and driving.[59] Patients may present for urgent medical help[61,62] and occasionally require inpatient admission.[16,17,20,50]

In one study 5 of 14 patients who stopped fluvoxamine developed discontinuation symptoms that resulted in them taking at least one day off work and 3 sought medical attention.[27] In a survey of 194 UK doctors, who reported consecutive paroxetine discontinuation reactions to the MCA over a 1 year period, 79% of respondents rated the reactions that they had reported as moderate or severe, 58% had restarted their patients on paroxetine as a result and 23% had commenced their patients on other pharmacological treatment.[54] In the Michelson et al. [57] study patients treated with paroxetine or sertraline reported a statistically significant deterioration in functioning following placebo substitution for 5 days. However, the measure of occupational and social functioning employed appears to have been nonstandardised.

2.3 Misdiagnosis

Discontinuation symptoms may be misdiagnosed. For example, a patient who has recovered from a depressive illness and who is advised to stop antidepressant treatment may then develop a discontinuation reaction with anxiety, sleep disturbance, and lethargy which may be misdiagnosed as a recurrence of depression (i.e. a further depressive episode) leading to unnecessary and long term reinstatement of the antidepressant. The same discontinuation symptoms occurring because of noncompliance during acute antidepressant treatment could lead to the erroneous conclusion that treatment is ineffective. Consequently the antidepressant may be increased in dosage, augmented or switched to an alternative. These scenarios waste money (cost of unnecessary drug treatment and psychiatric follow-up), put patients at unnecessary risk of drug adverse effects and lead to an incorrect and more negative prognosis that may have social implications.

When antidepressants are switched, because of adverse effects or lack of efficacy, discontinuation effects from the first antidepressant may be misinterpreted as adverse effects of the new antidepressant[63] leading to unnecessary treatment changes. Most discontinuation symptoms are physical, not psychological (table II). Failure to recognise the syndrome may lead to unnecessary referrals and investigations in an attempt to elucidate a 'physical' problem.[26,29,62] How often these scenarios occur is unknown. However, the likelihood of misdiagnosis is increased as many health professionals are unaware of discontinuation phenomena.[64-66]

2.4 Effect on Compliance

It is not uncommon for patients to miss consecutive antidepressant doses for several days. For example, Demyttenaere et al.[67] showed that over a 9 week period 30% of patients had at least one 3-day 'antidepressant holiday' as assessed using an electronic medication event monitoring system. This is sufficient to precipitate discontinuation symptoms; in the Michelson et al.[57] SSRI interruption study the increase in solicited symptoms for paroxetine-treated patients became statistically significant by the time of the second dose of placebo. Anecdotal reports suggest that venlafaxine discontinuation symptoms can have a particularly rapid onset.[32, 49] The author has seen several patients who developed discontinuation symptoms when they were 4 to 8 hours late in taking their next scheduled dose of venlafaxine despite maintaining daily compliance. This may reflect the drug's unusually short half-life (11 hours)[68] in combination with individual patient susceptibility. Onset of discontinuation symptoms within a few hours of a missed dose has occasionally been noted with imipramine.[69,70]

If a patient recognises the link between noncompliance and discontinuation symptoms but the relationship is not explained, future antidepressant compliance may be jeopardised, particularly if the patient interprets the symptoms as indicating addiction. This is not unlikely given the common lay belief that antidepressants are addictive.[71] Thus discontinuation symptoms can result from, and cause, poor compliance.

In the International Classification of Diseases (ICD)-10[72] and the Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV,[73] substance dependence is a syndrome and diagnosis requires several criteria (table IV). In both classification systems withdrawal or discontinuation symptoms are neither sufficient nor mandatory for diagnosis and behavioural features account for most criteria, for example, excessive time being spent using the drug. In terms of these definitions most antidepressants have no clinically significant potential to cause dependence.[74,75] Two exceptions are amineptine and tranylcypromine, rarely prescribed antidepressants with unusual pharmacodynamic profiles.[75] Antidepressants apart, many drugs can cause discontinuation symptoms but are not associated with addiction or dependence, for example, anticonvulsants, β-blockers, nitrates, diuretics, centrally acting antihypertensives, sympathomimetics, heparin,[76] tamoxifen,[77] dopaminergic agents,[78] antipsychotics[79,80] and lithium.[81] The term antidepressant 'discontinuation' syndrome seems preferable to 'withdrawal' syndrome as it does not have the connotation of dependence or addiction.

3. Prevention

3.1 Tapering at the End of Treatment

Several case reports describe discontinuation symptoms being suppressed by re-introduction of the antidepressant, with subsequent tapering preventing their re-emergence.[82,83] Tapering, as opposed to abrupt stoppage, has been recommended as part of routine practice by several authorities.[84-86] However, as yet there is no controlled data to recommend its effectiveness, the length of time over which it should occur or the minimum dose that one should taper to. The British National Formulary (BNF) recommends that antidepressants administered for 8 weeks or more should, wherever possible, be reduced over a 4 week period.[84] Other au-

Table IV. Diagnostic and Statistical Manual of Mental Disorders-IV[73] criteria for substance dependence (simplified)

A maladaptive pattern of substance use, leading to clinically significant impairment or distress as manifested by three or more of the following, occurring at any time in the same 12-month period:
1. Tolerance
2. Occurrence of withdrawal syndrome
3. Substance taken in larger amounts or over longer periods than intended
4. Persistent desire or unsuccessful attempts to cut down or control use
5. Excessive time spent obtaining, using or recovering from effects of substance
6. Substance use takes priority over social, occupational or recreational activities
7. Substance use continues despite persistent or recurrent harm

thorities recommend more cautious tapers, for example reducing the treatment dosage by one-quarter every 4 to 6 weeks after maintenance treatment.[85] With SSRIs, which are usually initiated at a therapeutic dosage, tablets may need to be halved and alternate day administration used to achieve the required dosage reduction.

In practice, several factors will influence the rate of taper. These include:

- the antidepressant
- the duration of treatment
- previous history of discontinuation symptoms and
- the degree of urgency associated with stoppage (see section 3.2).

Among the newer antidepressants, paroxetine[54,53,25] (figs 1, 2 and 3) and venlafaxine[31] are associated with a high risk of discontinuation symptoms. This may reflect their short half-lives.[87] Fluoxetine, which has a long half-life, rarely causes discontinuation symptoms[25,53,54] and it has been suggested that tapering is not routinely needed.[86] MAOI discontinuation symptoms can be particularly severe[15,16,19,21] and a cautious taper is advisable.

Whether discontinuation symptoms are more common following higher antidepressant dosages is unclear. However, symptoms are more likely with longer periods of treatment. Coupland et al.[53] assessed 93 patients withdrawn from fluvoxamine or paroxetine in a retrospective case note study. The 21 patients who developed discontinuation symptoms had been treated for significantly longer (median 28 weeks) than noncases (median 16 weeks). In an open study of imipramine, Kramer et al.[11] found that 22 of 26 patients treated for 2 months or longer reported discontinuation symptoms compared with only 3 of 19 patients treated for less than 2 months, a statistically significant difference. Virtually all reports of SSRI discontinuation reactions involve more than 5 weeks treatment.[37] Routine tapering appears unnecessary when antidepressants have been prescribed for short periods.

A previous history of a discontinuation reaction is important as individuals may vary markedly in their susceptibility to develop symptoms. If discontinuation symptoms appear during, or at the end of the taper, it may be necessary to increase the dose and commence a slower taper. Some patients require very gradual tapers.[30,52,88] Liquid antidepressant formulations, if available, can help achieve this. With SSRIs and venlafaxine another strategy to consider is switching to fluoxetine. Anecdotal data indicates that fluoxetine can suppress discontinuation symptoms associated with other SSRIs[60,89] and venlafaxine[32,62] although this is not always the case.[90] If the switch is successful, fluoxetine can usually be stopped without symptoms reappearing. Presumably this reflects the long half-life of fluoxetine (84 hours) and its active metabolite norfluoxetine (4 to 16 days).[68]

3.2 Tapering in Other Situations

Employing a long taper after successful treatment of an affective disorder is straightforward. The situation is more complex when switching antidepressants because of lack of efficacy; the risks of discontinuation symptoms secondary to rapid stoppage need to be balanced against the benefits of starting a new antidepressant quickly. If the patient and clinician are aware that discontinuation symptoms may occur, a rapid taper, or even an abrupt switch, is often acceptable; many of the problems associated with discontinuation symptoms arise when the symptoms are unexpected or misdiagnosed. The potential for drug interactions and the need for a wash-out period also need to be considered when switching antidepressants. Discontinuation symptoms seem less likely when switching between antidepressants with similar pharmacodynamic profiles[32,60,89] but can still occur. For example, Phillips[91] reported a discontinuation reaction when switching from paroxetine to sertraline. Abrupt antidepressant stoppage is justified if patients develop serious adverse effects, there is a medical emergency warranting stoppage or the antidepressant induces mania.

3.3 Education

In a survey of general practitioners in the UK,[66] 30% of respondents rated themselves as poorly

aware of antidepressant discontinuation symptoms and, from other questions, it was apparent that many of the remainder had over-rated their knowledge. A substantial proportion of psychiatrists[64] and pharmacists[65] also appear unfamiliar with this area. Increased professional awareness is necessary if strategies for prevention and treatment are to be implemented.

Patients need to be educated that antidepressants are nonaddictive and that treatment should not be stopped or interrupted abruptly as this can lead to discontinuation symptoms. When antidepressants are tapered prior to stoppage, patients need to informed that this is standard practice and aims to prevent or minimise such symptoms. Drug holidays have been advocated as a way of reducing sexual adverse effects associated with SSRIs,[92] but risk precipitating discontinuation symptoms. Both clinician and patient must consider the relative risks and benefits before adopting this technique.

3.4 Choice of Antidepressant

In a patient with a history of a severe discontinuation reaction, or poor compliance with medication, the clinician may wish to consider prescribing an antidepressant with a low propensity to cause discontinuation symptoms. However, many other factors need to be considered when selecting an antidepressant including past efficacy, tolerability, contraindications and the potential for drug interactions.

4. Management

4.1 Diagnosis

Clinicians should consider the diagnosis of a discontinuation reaction when faced with unexpected physical or psychological symptoms in patients who have recently stopped taking an antidepressant or are currently prescribed an antidepressant; only a few days medication needs to be missed to precipitate a reaction and antidepressant noncompliance is common[67] and often covert unless inquired about. Diagnosis is usually straightforward once one obtains an accurate history of recent antidepressant use versus the onset of the suspected discontinuation symptoms. The characteristics given in section 1.3 will aid diagnosis. When somatic symptoms predominate, clinical judgement will determine whether a physical examination and investigations are needed to exclude physical disorders.

4.2 Differentiation from Recurrence of Depression

A discontinuation reaction that occurs when an antidepressant is stopped following recovery from a depressive illness must be distinguished from a recurrence, i.e. a new episode of depression. Some discontinuation symptoms are identical to those of a depressive illness (e.g. low mood, anxiety, insomnia, fatigue) but many are distinct. These include dizziness and nausea, two of the most common SSRI discontinuation symptoms.[37] Discontinuation symptoms usually commence abruptly within 72 hours of antidepressant termination.[53,54,56] Recurrence is virtually unrecognised at this time, and even a relapse would be rare, should antidepressant treatment have been stopped prior to completion of the continuation phase of treatment. Discontinuation reactions are usually short lived, tending to gradually resolve over 1 day to 3 weeks[53,54,56] while symptoms of a recurrence are of longer duration. This only aids retrospective diagnosis. However, since most discontinuation symptoms are mild, it means that if there are doubts over diagnosis, then the clinician and patient can monitor the course of the symptoms and reserve definitive diagnosis to a later date.

4.3 Treatment

Treatment depends on: (i) whether or not further antidepressant treatment is warranted; and (ii) the severity of the discontinuation reaction. If antidepressant treatment is needed (i.e. the patient is still depressed or at high risk of relapse/recurrence) it is simply a matter of restarting the antidepressant; this scenario usually follows patient noncompliance with medication. If antidepressant treatment is not clinically indicated, then treatment will depend on

symptom severity. Mild reactions, which comprise the majority of cases, only require that the patient be reassured about their benign nature. In moderate cases, symptoms can be treated symptomatically, for example a short course of a benzodiazepine can be prescribed for insomnia. If symptoms are severe, or not amenable to symptomatic treatment, the antidepressant can be reinstated (full resolution usually occurs within 24 hours) and then withdrawn more cautiously. Treatment should always include an appropriate explanation of the symptoms to the patient and psychological support. Experience with benzodiazepine withdrawal suggests that cognitive behavioural therapy techniques, including coping strategy enhancement, may be helpful for some patients.[93]

These treatment principals apply to rarer discontinuation syndromes as well as the 'general' TCA and SSRI discontinuation syndromes. For example hypomanic symptoms caused by stoppage of TCAs[13] and SSRIs[46] have been reported as resolving within a short period without treatment. Hypomanic symptoms have resolved following re-introduction of clomipramine[38] and desipramine;[8] if restarting an antidepressant the clinician must be sure of the aetiology as antidepressants can induce mania. Severe mania may require antipsychotic treatment.[13]

Confusion and psychotic symptoms caused by discontinuation of a MAOI are often severe and require in-patient admission.[16,17,20] Treatment options include restarting the MAOI or treating symptomatically with an antipsychotic.

Dilsaver et al.[22,23] have reported that antimuscarinic agents, including atropine and benztropine, can help treat TCA discontinuation symptoms. Presumably the discontinuation symptoms reflect cholinergic rebound following a period of blockade by the TCA, the antimuscarinic agent re-establishes this and can then be withdrawn gradually.

5. Neonatal Discontinuation Symptoms

Neonates sometimes show adverse events, including irritability, respiratory difficulty, and poor feeding, that are attributed to maternal use of TCAs[94-97] or SSRIs[98-101] during pregnancy. In assessing this data it is important to differentiate between:

- Symptoms that are unrelated to antidepressant medication. Symptoms may reflect the affective disorder or associated factors such as maternal diet or alcohol and cigarette consumption.
- Symptoms that reflect antidepressant toxicity, that is, the neonate's reaction to a relatively high plasma antidepressant concentration. For example gastrointestinal stasis and urinary retention may occur in newborn infants following maternal TCA use[94] and are toxic effects reflecting the anticholinergic action of TCAs.
- Symptoms that represent a discontinuation effect, that is, the neonate responding to a rapidly falling plasma antidepressant concentration.

Differentiation is often difficult. However a few case reports are strongly suggestive of neonatal discontinuation reactions. These include 2 infants, born to mothers prescribed clomipramine, who developed seizures after birth,[96] and one case report for paroxetine[99] and fluoxetine[100] in which symptoms, including increased muscle tone, tremor, jitteriness and tachypnea, appeared soon after birth. ADR reports have noted suspected neonatal discontinuation reactions in mothers prescribed sertraline and fluoxetine in pregnancy.[98]

Tapering or stopping antidepressants prior to delivery has been suggested[102,103] as a strategy to reduce the risk of adverse drug effects in the neonate. However, it carries the risk of precipitating a relapse of depression in a woman approaching labour. Depressive illness during pregnancy and in the post-natal period can carry high costs for both the mother and the child. Another problem is that one cannot accurately predict delivery. Given the complexity of this area, the decision to initiate antidepressant treatment in pregnancy, and the subsequent pharmacological management, is best undertaken by a specialist. Treatment should be on an individual basis with the patient being involved in the decision making process. It seems prudent that infants, born to mothers who have received antidepressant treatment up to birth, be monitored for discontinu-

ation symptoms during the first week following delivery.

Kent and Laidlaw[104] described a possible discontinuation syndrome associated with breast milk transfer. The mother took sertraline during pregnancy and after delivery. She breast fed and the neonate developed well until 3 weeks after birth when the mother abruptly stopped sertraline. The next day the neonate developed symptoms including restlessness, agitation, poor feeding, constant crying, insomnia and an enhanced startle reaction. The symptoms were intense for 2 days and then subsided over several days. The mother remained well throughout. A small number of ADR reports have suggested that breast milk transfer of SSRIs can cause toxic effects in the neonate.[98] All antidepressants that have been studied,[105] including sertraline,[106] have been detected in breast milk providing a theoretical basis for the occurrence of both toxic and discontinuation effects.

Many authorities recommend that women prescribed antidepressants do not breast feed because of possible toxic effects on the infant. Kent and Laidlaw's case report[104] suggests a further risk, that is, the occurrence of discontinuation symptoms in the infant if breast feeding, or maternal antidepressant use, stops suddenly. On the other hand, breast feeding has advantages for the mother and infant and there are very few reports of adverse effects in nursing infants exposed to antidepressants in breast milk.[105-108] Once again it seems advisable that prescribing decisions are made on an individual patient basis.

6. Conclusions

Discontinuation syndromes occur with antidepressants from all the major classes and can have significant clinical repercussions. Preventative strategies include tapering antidepressants, where possible, and ensuring that patients take antidepressants consistently. When reactions do occur, prompt diagnosis and appropriate treatment is required. All these strategies rely on patients and clinicians being familiar with discontinuation symptoms. Most symptoms are mild and only require reassurance. More severe symptoms can be treated symptomatically or the antidepressant restarted in which case symptoms usually resolve within 24 hours.

Because discontinuation syndromes have attracted little systematic research, the recommendations in this paper largely reflect anecdotal reports and the opinion of experts in the field. Methodologically sound studies are required to provide a more robust evidence base for future recommendations. Key areas for research include further characterisation of discontinuation syndromes, assessment of their clinical relevance and the effectiveness of tapering schedules in prevention.

There is a strong case for arguing that the potential of all new antidepressants, and indeed all new psychotropic drugs, to cause discontinuation symptoms be assessed in double-blind, placebo-controlled studies prior to licensing. Some guidelines on antidepressant use restrict themselves to the dose and duration of treatment with no reference to discontinuation symptoms or the process of stopping treatment. Guidelines should incorporate information on both. If patients and clinicians adopt the strategies outlined in this paper then many of the adverse effects of discontinuation symptoms can be prevented.

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