

CASE REPORT

Withdrawal Symptoms from Paroxetine

COLIN MILLIKEN¹ and STEPHEN J. COOPER^{2*}¹*Department of Psychiatry, Belfast City Hospital, Belfast, UK*^{2*}*Department of Mental Health, The Queen's University of Belfast, Whitla Medical Building, 97 Lisburn Road, Belfast BT9 7BL, UK*

Cessation of tricyclic antidepressant drugs can result in 'cholinergic type' withdrawal symptoms. There is also evidence for withdrawal symptoms following sudden cessation of SSRI antidepressants. Observations made on three patients are described following abrupt cessation of paroxetine, prescribed for treatment of depression. The withdrawal symptoms described are suggestive of some form of serotonergic effect and the different frequencies with different SSRIs may relate to their different potencies for serotonin re-uptake inhibition as well as to pharmacokinetic differences. © 1998 John Wiley & Sons, Ltd.

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INTRODUCTION

The selective serotonin reuptake inhibitors (SSRIs) have become increasingly used in the treatment of depression. While they do not appear to differ from tricyclic antidepressants (TCAs) in terms of efficacy, they have a different side effect profile and are safer in overdose. A withdrawal syndrome has been reported on sudden cessation of TCAs. There is now evidence for a withdrawal syndrome following sudden cessation of SSRI antidepressants. We report the cases of three patients who developed apparent withdrawal symptoms after abrupt discontinuation of paroxetine ('Seroxat', SmithKline Beecham), a widely prescribed SSRI. The nature of the symptoms is suggestive of a serotonergic mechanism for this syndrome.

CASE REPORTS

Case 1

A 38 year old lady (Mrs A) presented complaining of low mood, tearfulness, anxiety, anorexia and initial insomnia. She had no past psychiatric history. She was commenced on paroxetine 20 mg

mane with improvement in her symptoms, which was evident at regular review. Six months later, while still taking paroxetine 20 mg mane, she suffered a relapse of symptoms, complaining of depressed mood and similar somatic features. The dose of paroxetine was increased to 40 mg mane. This again produced a symptomatic improvement.

She continued under review, but had to be seen as an emergency 6 months later having abruptly discontinued paroxetine 1 week previously. She complained of depressed mood together with a number of somatic symptoms: restlessness, dizziness, headache, nausea, paraesthesiae and 'jerkiness' which had commenced approximately 36–48 h after her last dose of paroxetine. She had not previously described such somatic symptoms, either at initial presentation or during treatment with paroxetine. These symptoms resolved within a few days of resuming paroxetine 20 mg mane.

Case 2

A 26 year old woman (Mrs B) presented with post-partum depression of mood, loss of interest, early waking and poor appetite. She had a previous episode of depression in 1989, also related to pregnancy, and gave a family history of depressive

*Correspondence to: Stephen J. Cooper.

illness. She was commenced on paroxetine 20 mg mane which produced a gradual improvement. This was sustained at regular review until 8 months later when she presented with a relapse of her depressive symptoms. Paroxetine was increased to 40 mg mane with good effect. The dose was reduced to 20 mg mane 4 months later but increased to 30 mg mane after 3 months due to a further depressive relapse.

One month later she presented with mild akathisia, apparently related to the dose increase. Paroxetine was immediately discontinued and lofepramine ('Gamanil', Merck) 70 mg nocte was commenced. Seventy two hours later she noted restlessness, palpitations, irritability and anxiety. These complaints were described by her as subjectively different from the previous akathisia and resolved within 3 h of resumption of paroxetine 20 mg mane.

Case 3

A 45 year old gentleman (Mr C) presented complaining of episodic anxiety, initial insomnia and poor concentration. He had no previous psychiatric history. Treatment was initially with reducing doses of benzodiazepines and anxiety management techniques. However, 1 month later he complained of low mood, anorexia and anhedonia as well as continuing symptoms of anxiety. Sertraline ('Lustral', Pfizer) 50 mg mane was commenced. This had marginal effect and 2 months later was changed to paroxetine 20 mg mane, increased to 40 mg mane 3 months later due to lack of response.

There was an improvement in his symptoms but 2 months later he discontinued paroxetine abruptly. He subsequently complained of increased anxiety, restlessness, muscle twitching and paraesthesiae, symptoms which began approximately 36–48 h after his last dose of paroxetine. These symptoms resolved gradually over a period of 10–14 days, without additional treatment.

DISCUSSION

Our patients complained of symptoms similar to those described in a number of recent reports, suggesting the existence of a withdrawal syndrome following cessation of SSRI antidepressants. These reports have involved patients discontinuing fluvoxamine (Black *et al.*, 1993; Mallya *et al.*, 1993), fluoxetine (Cooper, 1988; Stoukides and Stoukides, 1991), paroxetine (Committee on Safety of

Medicines, 1993; Choo, 1993) and sertraline (Louie *et al.*, 1994). The symptoms reported here and elsewhere can best be divided into four groups: general somatic and gastrointestinal (anxiety, sweating, dry mouth, nausea, diarrhoea); sleep disturbance (insomnia, abnormal dreaming); psychological (fatigue, irritability, restlessness); neurological/sensory (dizziness, headache, paraesthesiae, visual disturbance, muscle twitch).

In our patients the symptoms were reported between 1 and 3 days after abrupt discontinuation of paroxetine, in two cases from a dose of 40 mg daily, in the other from 30 mg daily. In two cases the symptoms resolved rapidly following reintroduction of paroxetine. In the other, further medication was refused and the symptoms resolved over 10–14 days. This is fairly typical of the time course found by Price *et al.* (1996) using the MCA database: most cases began within 2–4 days of cessation, and 93% within 7 days, untreated 87% resolved within 14 days and reintroduction of the SSRI seems to be the best way to achieve rapid resolution of symptoms. Interestingly, in Case 2, use of a non-SSRI antidepressant (lofepramine) did not prevent the emergence of withdrawal symptoms.

Withdrawal phenomena from TCAs are well recognized and include symptoms of gastrointestinal upset, general somatic distress, sleep disturbance and movement disorder. These are explained by the cholinergic overdrive hypothesis (Dilsaver *et al.*, 1987). While some of the symptoms reported on SSRI withdrawal are similar to those following abrupt withdrawal of TCAs the 'neurological/sensory' group of symptoms, which account for 30–40% of the symptoms reported with SSRIs (Price *et al.*, 1996), are rarely reported for TCAs. This particular group of symptoms is similar to those often reported as part of the 'serotonin syndrome' (Sternbach, 1991), suggesting that this withdrawal syndrome may be due to serotonergic effects rather than cholinergic effects. If we consider pharmacodynamic factors, using K_i values for potency of inhibition of serotonin (5-HT) re-uptake, paroxetine appears to be the most potent of these drugs *in vitro* and *in vivo* (Johnson, 1991). The SSRI withdrawal syndrome has been least often reported with fluoxetine, which is the least potent of those SSRIs available in the UK up to 1995. In 1993, the Committee on Safety of Medicines reported that the frequency of reporting of the withdrawal syndrome per 1000 prescriptions was 0.3 for paroxetine as compared with 0.03 for sertraline and fluvoxamine and 0.002 for fluoxetine.

While pharmacodynamic differences between the SSRIs may account for the difference in frequency of reports of the withdrawal syndrome, it is more often suggested that pharmacokinetic differences are important. The short elimination half life of paroxetine (20 h), relative to some other SSRIs, may contribute to its propensity to induce a withdrawal syndrome. However, the elimination half lives of sertraline (25 h) and fluvoxamine (15 h) are not dissimilar. The effects of active metabolites with long elimination half-lives might contribute to preventing emergence of a withdrawal syndrome. However, only the metabolite of fluoxetine has significant pharmacological activity. The metabolites of paroxetine, sertraline and fluvoxamine are weak inhibitors of 5-HT reuptake.

Thus, we would suggest that pharmacodynamic as well as pharmacokinetic factors may play a part in the different frequency of withdrawal symptoms between paroxetine and other SSRIs. Finally, although most SSRI antidepressants have insignificant activity at muscarinic receptors, paroxetine has an *in vitro* potency similar to that of desipramine. Thus, part of the excess of reports of withdrawal symptoms with paroxetine may relate to cholinergic-type symptoms.

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