Why does milnacipran produce so few discontinuation syndromes following abrupt withdrawal?

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Several selective serotonin reuptake inhibitors (SSRI), especially paroxetine, have been reported to produce a number of post-treatment emergent adverse events following abrupt withdrawal (Coupland et al 1996; Haddad 1997). More recently a SSRI-induced neonatal withdrawal syndrome has been described (Sanz et al 2005) in infants born of mothers treated with SSRI during pregnancy. In both of these situations, paroxetine has been associated with the greatest incidence (Warner et al 2006; Sanz et al 2005). Other SSRIs and the selective serotonin and noradrenaline reuptake inhibitor (SNRI) venlafaxine can, however also cause a withdrawal syndrome in patients (Trenque et al 2002). In contrast, milnacipran, another SNRI, has been reported to present a lower risk of withdrawal-induced adverse events (Vandel et al 2004). Furthermore the spectrum of the symptoms was different from that produced by paroxetine.

In our clinic, a discontinuation syndrome is sometimes seen when SSRIs or SNRIs are discontinued suddenly, or when doses are missed or forgotten. In a total cohort of 2675 depressed patients, we identified 124 cases of antidepressant withdrawal syndrome. Sixty-three of the cases resulted from withdrawal from fluvoxamine (from a total of 1306 treated patients), 55 were withdrawn from paroxetine (from a total of 453 treated patients), while 6 were withdrawn from milnacipran (from a total of 916 treated patients). With paroxetine and fluvoxamine, respectively, the incidence of discontinuation syndrome was 18.4 times greater and 7.3 times greater than that found with milnacipran (Table1). These differences were highly significant as determined by the χ^2 test. These results are qualitatively similar to those obtained in a double-blind comparative study of milnacipran and paroxetine by Vandel et al (2004), who found an incidence of discontinuation syndrome of 13% with milnacipran and 32% with paroxetine following withdrawal after 6 weeks of treatment.

Paroxetine has systematically been found to have the highest incidence of discontinuation syndrome (Warner et al 2006) while fluvoxamine has an incidence 10-fold lower and fluoxetine 100-fold lower (Westenberg and Sandner 2006). Paroxetine is the most potent inhibitor of the serotonin transporter (Sanchez and Hyttel 1999) and this potency may be a significant factor in the frequency of discontinuation syndromes for paroxetine in comparison with fluvoxamine (Westenberg and Sandner 2006) and milnacipran (Moret et al 1985). Furthermore, paroxetine is unique among the SSRI because its relatively high affinity for muscarinic receptors is similar to that of imipramine (Schatzberg et al 1997; Sanchez and Hyttel 1999). A cholinergic rebound, as observed on withdrawal of tricyclic antidepressants (Dilsaver et al 1987), could also partly explain the discontinuation syndrome paroxetine. Neither fluvoxamine nor milnacipran have any significant affinity for the muscarinic receptor (Moret et al 1985; Sanchez and Hyttel 1999).

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Table 1 Number and ratios of discontinuation syndrome with SSRIs and SNRI in our clinic

Drug	Total number of patients	Discontinuation syndrome	% of patients
Paroxetine	453	55	12.1
Fluvoxamine	1306	63	4.8
Milnacipran	916	6	0.7

Note: Significances between subgroups:
• Paroxetine vs fluvoxamine, $p < 0.001$ ($\chi^2 = 28.78$, df = 1).
• Paroxetine vs milnacipran, $p < 0.001$ ($\chi^2 = 93.93$, df = 1).

Pharmacokinetics are thought to play an important role in the incidence of withdrawal effect, with compounds with shorter half-lives having the greatest incidence of withdrawal effects. The apparent correlation between the occurrence of SSRI discontinuation syndrome and shorter drug half-lives has been highlighted (Schatzberg et al 1997). The half-life of paroxetine (21 h) may explain the relatively high incidence of discontinuation syndromes compared with fluoxetine which has a long half-life (parent compound 1–6 days, active metabolite 7–9 days). Pharmacokinetic factors, however, do not explain the low incidence of withdrawal effects with milnacipran, since the half-life of the SNRI (8 h) is shorter than that of paroxetine (Puozzo et al 1998).

It is possible that low incidence of withdrawal effects with milnacipran may be related to its dual action on the reuptake of noradrenaline and serotonin compared with the selective effect of SSRI such as paroxetine on the reuptake of serotonin. It seems unlikely, however, that a simple action on the noradrenaline transporter is sufficient to explain the situation. Firstly, paroxetine is the SSRI with the highest affinity for the noradrenaline transporter (Sanchez and Hyttel 1999) and, secondly, the SNRI venlafaxine has an incidence almost as high as paroxetine (Trenque et al 2002). Although venlafaxine is considered to be a SNRI, it is, in fact, a preferential serotonin reuptake inhibitor and produces clinically relevant inhibition of noradrenaline reuptake only at high doses where serotonin reuptake is very extensively inhibited (Harvey et al 2000).

A unique property of milnacipran which may be relevant is the fact that it inhibits both noradrenaline and serotonin reuptake with similar potency (Moret and Briley 1997). A recent study of changes in long-term potentiation following repeated treatment with milnacipran (Tachibana et al 2006) has shown that interactions between noradrenergic and serotonergic mechanisms play an important role in the modulation of synaptic plasticity. It is thus possible that the balance between serotonergic and noradrenergic neurotransmission may be essential in determining the nature and extent of withdrawal-related symptoms. Further preclinical and clinical studies are required to test this hypothesis.

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