

Persistent adverse neurological effects following SSRI discontinuation (PANES).

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These **prolonged** reactions were first described here in Spring 2000. No other reports are known of, although this condition may well be more widespread than is presently recognised. Selective serotonin reuptake inhibitor (SSRI) discontinuation syndrome has been described in the literature as a cluster of symptoms and signs that occur after SSRIs such as paroxetine, sertraline and fluoxetine have been discontinued. Abrupt withdrawal of antidepressant therapy for 5-8 days is associated with symptoms such as dizziness, ataxia, paraesthesiae, gastrointestinal and flu-like symptoms, and other sensory and sleep disturbances. Psychiatric symptoms include anxiety, agitation, lability of mood, hypersexuality, crying spells, behaviour change and irritability.

The SSRI discontinuation syndrome appears to be most marked with paroxetine and to a lesser degree sertraline, with few symptoms seen with fluoxetine (Rosenbaum et al, 1998). The frequency and severity of these symptoms appear to vary according to the half-life of the SSRI (Schatzberg et al, 1997). Schatzberg et al comment that most discontinuation symptoms are 'short-lived', but that some effects may be longer lasting. Traditional explanations of the pharmacology of SSRIs discuss the effects on the postsynaptic serotonin receptor, but the SSRIs work at a variety of locations and their effects reverberate through the nervous and endocrine systems, so that in animal models there may be altered neuroendocrine function for weeks after ceasing fluoxetine. Even 60 days after discontinuation of fluoxetine, the oxytocin response in animals was still significantly reduced by 26% compared with controls.

Transient dystonias and dyskinesias of the jaw have previously been described with SSRIs (Fitzgerald & Healy, 1995). This report considers four patients on SSRIs who all suffered

prolonged neurological symptoms for months after discontinuing their medication

Mrs A. a 29 year old married lady with a moderate depressive disorder was switched to paroxetine by her general practitioner after an initial prescription of dothiepin. She had found the tricyclic dothiepin too sedating and after a week or so of this medication requested a change. After two weeks on paroxetine 20 mg daily she was reviewed by a consultant psychiatrist who increased the dose to 40 mg daily. The patient suffered a dystonic reaction to the paroxetine that required physician review and admission, but apparently responded well to procyclidine. The paroxetine was discontinued. Unfortunately the dystonic reaction persisted off all medication and required further medical admission and the re-prescription of procyclidine. The depression continued unabated and a tricyclic was started with some improvement in mood. Seven months after the paroxetine had been stopped the tardive dystonia was noted to be present and to vary with anxiety levels, body posture, alertness, and emotional state.

A 35-year-old man (Mr B) was prescribed paroxetine 30 mg daily for depression. The depression resolved and the paroxetine was continued at the same dose for two years. The medication was discontinued in a staged way, with reductions to 20, then 10 mg, managed over six weeks or so. Symptoms of withdrawal occurred throughout this period and comprised vivid nightmares, lability of mood, irritability, hypersexuality, episodic lightheadedness, episodic electric-shock like sensations, glove paraesthesiae, and ataxia. These symptoms ended two weeks after the withdrawal regime was finished.

Nevertheless the patient continued to describe problems of an episodic nature well after the paroxetine had been discontinued. These episodes lasting hours to days at a time and comprised paraesthesiae, dizziness, mild ataxia, and slurred speech. These episodes have occurred intermittently throughout twelve months of follow-up during which time the patient has been drug-free. There are no focal neurological signs or any features suggestive of progressive neurological disease, nor was there a family history of neurological disease.

Mrs C., a 29-year-old mother of one, became ill with depression when her son was aged eight months. She was suicidal and required hospital admission where she was started on fluoxetine 20 mg daily. The antidepressant worked well and her mood was restored within four weeks of admission. She was discharged home, but commented that her sleep was occasionally disturbed by bad dreams and she was aware of twitching in the bed. She was kept on the fluoxetine for a further twelve months and at outpatient reviews mentioned that her sleep was still occasionally disturbed by nocturnal twitching. She said that her husband had started to sleep separately, because he was 'tired of being kicked' in the middle of the night. The fluoxetine was discontinued eighteen months after the admission. Mrs C described no worsening of her mood and was euthymic and outpatient review. However, she was distressed to report that her nocturnal twitching, which took the form of sudden myoclonic jerks of her limbs, had actually worsened off fluoxetine. During the day these abnormal involuntary movements were less marked and more easily disguised, but nonetheless problematic for the patient. At follow-up eight months after discontinuation the untoward myoclonic jerks were continuing. There are no focal neurological signs or any features suggestive of progressive neurological disease, nor was there a family history of neurological disease.

Mrs D., a 49 year old health professional was prescribed 20 mg paroxetine daily in April 2000 for a depressive disorder. This relieved the depression, but after three months the patient started to develop paresthesiae in the right hand, and some weeks later experienced her fingers being 'fumbly'. She visited her GP and complained that although her mood was satisfactory there were unpleasant side effects. He asked her to reduce the dose to 10 mg daily. Mrs D began to experience painful, restless legs at night and vivid dreams. The tingling in her hand spread into her body and head. After a week of the 10 mg dose the patient discontinued the paroxetine altogether in the belief that the paroxetine would be out of her system in a few days and her symptoms would subside. The symptoms however persisted. She took a week off work, but the following symptoms persisted for the next three months:

- *paraesthesiae in hands and feet spreading up arms and legs intermittently*
- *stiffness in calf muscles*
- *unsteadiness on her feet with wide gait*
- *clumsy fingers*
- *loose bowels*
- *disinhibited mood*

These symptoms appeared worst at the end of the day, following heavy physical work, and with even small amounts of alcohol. By December, four months after discontinuing the paroxetine most of the symptoms had reduced in severity to near normal.

Mrs E., a 48 year old woman was prescribed citalopram by her GP for eleven months. The indication for the prescription was chronic anxiety. For fifteen months following the discontinuation of this therapy she suffered headaches and dizziness. She also complained of a fluttering sensation across her scalp. To date there has been little improvement.

Discussion

These five patients all demonstrated neurological side effects or withdrawal effects that occurred either during SSRI therapy or in the discontinuation phase associated with an SSRI. However, these neurological effects **persisted** for months after discontinuation and in most cases persist up until the time of writing. Whether the association with treatment or discontinuation is causal could be debated, but the chronological association seems good and three of the five patients (Mr B, Mrs C and Mrs D) were psychotropic drug-naïve at the start of the SSRI therapy and wholly drug free following this.

The three SSRIs prescribed and mentioned above (fluoxetine, paroxetine and citalopram) differ in terms of structural and pharmacokinetic properties, but share a relatively selective ability to affect serotonin re-uptake. Paroxetine and citalopram have a relatively short half-life and it may be that they are more prone to association with the discontinuation effects and PANES. It may be that this common ability of the SSRIs (to affect serotonin re-uptake), or an indirect consequence of this ability is responsible for these persistent adverse neurological effects. These effects appear to have been first described in this report. There is something of a similarity to the effects seen after benzodiazepine discontinuation (Ashton, 1987). In benzodiazepine

withdrawal the symptoms occur 1-2 weeks after withdrawal and may persist to some degree. The mechanism is thought to be related to GABA-ergic systems.

Further case reports and surveillance data are needed to establish the significance or otherwise of what we propose to be persistent adverse neurological effects of SSRIs (PANES).

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See also [Venlafaxine - long-term adverse effects \(2002\)](#)