

REVIEW ARTICLE

## A possible explanation for dizziness following SSRI discontinuation

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### Abstract

Dizziness is the most commonly reported symptom of abrupt discontinuation from the selective serotonin reuptake inhibitor (SSRI) category of antidepressants. The reported dizziness is exacerbated by even slight head movement, and therefore is likely to be vestibular in origin. The SSRIs most implicated are those with short half-lives and which are most selective for serotonin (as opposed to noradrenaline), e.g. paroxetine and sertraline. Since the vestibular nucleus complex (VNC) has an abundance of serotonin receptors, the abrupt withdrawal from an SSRI is likely to have a substantial impact on the electrophysiological activity of neurons within it. Here we suggest that the abrupt withdrawal from an SSRI is likely to cause a sudden decrease in serotonin in the VNC, which will disrupt the function of VNC neurons bilaterally, causing dizziness without vertigo.

**Keywords:** *Serotonin, vestibular nucleus, antidepressant*

### Introduction

Dizziness is a common symptom of withdrawal from antidepressants belonging to the selective serotonin reuptake inhibitor (SSRI) category [1–4]. Black et al. [5] analysed 46 case reports of discontinuation from fluoxetine, fluvoxamine, paroxetine or sertraline, and found that of 53 symptoms reported, dizziness was the most common. Van Geffen et al. [6] studied 66 patients who recently discontinued SSRI therapy and found dizziness to be one of the most commonly reported symptoms. In an analysis of the results of nine clinical trials, Perahia et al. [7] found that dizziness was reported significantly more frequently in 12.4% of patients who abruptly discontinued treatment with duloxetine compared to placebo. Given that one in five patients have been reported to abruptly withdraw from SSRI therapy [6], withdrawal symptoms such as dizziness have the potential to be clinically significant.

Dizziness has been identified as one of the discontinuation symptoms that occurs to a greater extent with SSRIs than with other antidepressants such as

tricyclics [8,9]. It appears to be worse for SSRIs with a short half-life, such as paroxetine, sertraline and fluvoxamine [1,4,5,9]. By contrast, there are few reports of dizziness after discontinuation from fluoxetine [2]. Interestingly, paroxetine and sertraline are also among the most selective and potent SSRIs in blocking the reuptake of serotonin, suggesting that the effects on serotonergic systems in the CNS, rather than on noradrenergic systems, are likely to be the main cause of the dizziness [10]. Since dizziness associated with SSRI withdrawal is often exacerbated by slight head movement [8], it is unlikely to be due to cardiovascular changes and more likely to be due to the effects of the drug withdrawal on the vestibular system.

### Possible effects of SSRI discontinuation on the vestibular system

Since the long-term effect of SSRIs is to inhibit the reuptake of serotonin, thereby increasing serotonin concentrations in the synaptic cleft, it is presumed

that the SSRI discontinuation syndrome is due to a decrease in serotonin and its effects on neurons that had become adapted to the increased levels of the neurotransmitter [10]. Although the specific neuronal effects of abrupt SSRI withdrawal are not known and may vary from one area of the brain to another, it is conceivable that post- and/or pre-synaptic serotonin receptors may up-regulate in response to a decrease in serotonin concentrations.

Serotonin has been found in the peripheral vestibular system, in the vestibular labyrinth, although its function there is poorly understood (see Smith and Darlington [11] for a review). Serotonin is also known to be an important neurotransmitter in the brainstem vestibular nucleus, which along with the cerebellar flocculus, is the only area of the brain to receive direct input from the vestibular nerve carrying vestibular sensory information from the inner ear. Serotonin exists in high concentrations in the vestibular nucleus complex (VNC) and an important source of serotonergic projections to the VNC comes from the dorsal raphe nucleus [12,13]. Licata et al. [12] showed that electrical stimulation of the dorsal raphe could alter the electrical activity of single neurons in the lateral, superior and inferior vestibular nuclei. Interestingly, approximately one-eighth of the serotonergic dorsal raphe neurons projecting to the VNC also project into the central amygdaloid nucleus [13], suggesting a surprising connection between the vestibular system and anxiety. VNC neurons express a number of different serotonergic receptor subtypes, including 5-HT<sub>1A</sub>, 5-HT<sub>1F</sub>, 5-HT<sub>2A</sub> and 5-HT<sub>3</sub> receptors [11,14]. Electrophysiological studies have shown that serotonin has effects on the spontaneous firing rate of medial vestibular nucleus neurons via 5-HT<sub>1A</sub> and 5-HT<sub>2</sub> receptors [11]. A 5-HT<sub>1A</sub> receptor agonist has also been shown to modulate the response of lateral vestibular nucleus neurons to roll tilt [15].

In terms of understanding the potential functional significance of serotonergic modulation of the VNC, it is important to note that serotonin has been demonstrated to negatively modulate the effects of glutamate on the majority (86%) of VNC neurons [16]. Since glutamate is the major excitatory neurotransmitter in the VNC and the neurotransmitter mediating input from the vestibular nerve [11], this suggests that the impact of changes in serotonin levels on VNC neurons could be dramatic. Consistent with this evidence, 5-HT<sub>1F</sub> receptors have recently been reported to be co-localized with glutamate in the VNC [14]. Ahn et al. [14] suggested that the 5-HT<sub>1F</sub> receptor may modulate the release of glutamate from VNC neurons, which could potentially have a powerful effect on the transmission of information about balance and orientation to the rest of the brain.

There are relatively few functional studies demonstrating that manipulation of the serotonergic systems in the brain can affect vestibular reflexes. However, micro-iontophoretic application of serotonin to the lateral vestibular nucleus of the cat has been demonstrated to alter electromyographic activity in the proximal extensor and flexor muscles, indicating that serotonin can modulate the vestibulo-spinal reflexes (see Smith and Darlington [11] for a review). There is a curious link between balance and anxiety, and SSRIs have been reported to alleviate both dizziness and anxiety in cases where they present together (see Staab et al. [17] for a review). In terms of the potential effects of vestibular activation on serotonin, Ma et al. [18] have reported that caloric vestibular stimulation can substantially alter serotonin levels in the guinea pig VNC. Changes in blood serotonin levels have also been found in patients with vestibular disorders [19].

#### **Possible explanation for dizziness following SSRI discontinuation**

Abrupt discontinuation of an SSRI is likely to result in a decrease in serotonin levels in the VNC, as in many other areas of the brain [10]. If 5-HT<sub>1F</sub> receptors and glutamate are co-localized on VNC neurons and activation of 5-HT<sub>1F</sub> receptors reduces glutamate release [14], then the decrease in serotonin may result in the reduced activation of the 5-HT<sub>1F</sub> receptors, thereby increasing glutamate release by VNC neurons. If this happened bilaterally, as would be expected with a systemically administered drug, then both the left and right VNCs would send increased vestibular signals to the rest of the brain. This hypothesis would be consistent with the evidence that patients discontinuing SSRIs do not experience vertigo (which would require unilateral increased activation of the VNC) but only dizziness, and that the dizziness is exacerbated by head movement [8]. It would also be consistent with the evidence that dizziness is a more common side effect for SSRIs with a much higher selectivity for serotonin than for nor-adrenaline [10].

It is of course possible that dizziness following discontinuation of SSRIs is related to the effects of reduced serotonin in other areas of the brain that are involved in vestibular sensory processing. Vestibular information is transmitted from the VNC to many areas of the limbic system and neocortex via multiple polysynaptic pathways and conceivably any of them could be implicated in the generation of dizziness. However, the high concentration of serotonin receptors in the VNC and the co-localization of the 5-HT<sub>1F</sub> receptor with glutamate suggest a simpler

explanation. Why some patients are affected and others are not, even though they discontinued the same SSRI, is more difficult to explain given our current understanding.

### Possible implications of dizziness following SSRI discontinuation

If a sudden change in serotonin levels in the VNC is the cause of dizziness following SSRI withdrawal, then there are several important implications for vestibular function. First, it suggests that in cases where the natural levels of serotonin in the brain are altered, such as in depression, the change in serotonin levels in the VNC may affect vestibular function. It would therefore be of interest to test vestibular function in depressed patients. In fact, Soza Ried and Aviles [20] reported that patients with major depression who were not medicated exhibited a significant decrease in the slow phase velocity of the vestibulo-ocular reflex for rotation to the right side, suggesting hypoactivity of the right VNC. Synchronized changes in serotonin levels in the VNC and limbic system during affective disorders may also partly explain the common comorbidity of vestibular dysfunction and anxiety and depression [17].

A second implication is that drugs that modulate serotonin and its many receptors, such as tricyclics, monoamine oxidase inhibitors and SSRIs for depression; buspirone for anxiety disorders; ergotamine, the triptans (e.g. sumatriptan), methysergide and pizotifen for migraine; 5-HT<sub>3</sub> receptor antagonists (e.g. ondansetron) for nausea and vomiting; and psilocybin, mescaline, lysergic acid diethylamide (LSD) and methylenedioxymethamphetamine (MDMA, i.e. Ecstasy) as recreational drugs, may also affect vestibular function, in some cases predisposing users to blurred vision and falls. It would therefore be of interest to test vestibular function following administration of such drugs.

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