

## SSRI-Induced Apathy Syndrome: A Clinical Review

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The authors review the literature pertaining to selective serotonin reuptake inhibitor (SSRI)-induced apathy syndrome. A literature search of Medline and International Pharmaceutical Abstracts from 1970 to the present was performed for relevant articles. Twelve relevant case reports and one open-label treatment trial were identified. An amotivational, or apathy, syndrome has been reported in a number of patients receiving SSRI treatment over the last decade. This adverse effect has been noted to be dose-dependent and reversible, but is often unrecognized. This phenomenon has caused significant negative consequences for adults as well as social and academic difficulties in adolescents. (*Journal of Psychiatric Practice* 2004;10:196-199)

KEY WORDS: apathy syndrome, amotivational syndrome, selective serotonin reuptake inhibitors

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An amotivational, or apathy, syndrome has been reported in a number of patients receiving selective serotonin reuptake inhibitor (SSRI) treatment over the last decade.<sup>1-4</sup> This adverse effect has been noted to be dose-dependent and reversible,<sup>1-4</sup> but is often unrecognized.<sup>4</sup> This phenomenon has caused significant negative consequences for adults<sup>1</sup> as well as social and academic difficulties in adolescents.<sup>4</sup> We review a proposed definition of and differential diagnosis for apathy, case reports of this adverse effect, possible mechanisms involved in this phenomenon, and treatment strategies that should be considered when this adverse effect occurs.

### Aren't Most Depressed Patients Apathetic?

Although apathy is conventionally defined as indifference, a clinical definition must be more specific, since there are many cases in which a manifest indifference would not be considered the result of apathy (e.g., intoxication, sedation). Marin<sup>5</sup> suggested the following definition of apathy: a syndrome in which there is a primary absence of motivation that is not attributable to cognitive impairment, emotional distress, or diminished level of consciousness. Based on this definition, he suggests that the following conditions comprise the differential diagnosis of apathy: delirium, dementia, abulia, akinesia, despair, demoralization, and, perhaps most important for the purposes of this review, depression,<sup>6</sup> since depressed patients are often characterized

as being apathetic. However, Marin noted that, although externally inactive, these patients may be in great emotional distress internally.

There is subjective evidence that the inactivity or loss of interest experienced in depression is different from the apathy that may be experienced as a late-onset side effect in SSRI treatment. One patient noted that this experience was unlike the lack of motivation she had sometimes experienced during prior episodes of depression.<sup>1</sup> Another noted that her feelings of apathy bore no relationship to depression.<sup>1</sup> Several adolescent patients who experienced such an effect reported being unconcerned or feeling "fine."<sup>4</sup>

Objectively, the data indicate that this effect diminishes with a decrease in SSRI dose, even when the dose has been titrated to a level that remains effective in treating the patients' symptoms.<sup>1</sup> Further, cerebral blood flow changes, evidenced by single proton emission computed tomography, as well as the pattern of changes demonstrated in neuropsychological testing, support the hypothesis that the effect in question is a reversible frontal lobe syndrome<sup>2</sup> rather than a residual component of mental illness. It should be noted,

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however, that this study involved only one subject and his diagnosis was obsessive-compulsive disorder, not depression.

### Case Reports

Case reports of SSRI-induced apathy are summarized in Table 1. Hoehn-Saric et al. reported five patients receiving fluvoxamine or fluoxetine who were observed to develop apathy, indifference, loss of initiative, or disinhibition without concurrent sedation or hypomania.<sup>1</sup> These cases included two patients with panic disorder on fluvoxamine, and three patients with major depression on fluoxetine. The manifestation of apathy appeared to be dose-related; a reduction in dose affected the symptoms temporally in a manner that seemed dependent on each drug's half-life. Thus, appropriate titration of fluoxetine was significantly more difficult than titration of fluvoxamine, due to its longer half-life. In three of the five patients described, the authors noted that it was possible to titrate the SSRI used to a dose that provided symptom relief, but at which apathy symptoms abated.

Hoehn-Saric et al. reported the occurrence of apathy, indifference, inattention, and perseveration in a patient with obsessive-compulsive disorder who was receiving high doses of fluoxetine.<sup>2</sup> They reported that these changes were associated with a decrease in cerebral blood flow in the frontal lobes and changes in neuropsychological tests generally associated with frontal lobe impairment. It was noted that these changes disappeared 4 weeks after the discontinuation of fluoxetine.

Subsequently, George and Trimble reported their experience with a patient who had both obsessive-compulsive disorder and Tourette's syndrome who, after 4 weeks of therapy with fluvoxamine, was noted to be more apathetic and indifferent, but not depressed.<sup>3</sup> It was reported that this patient's indifference was so profound that he could not "will" himself to make a necessary turn while driving home, and instead continued driving straight. Apathy abated when the fluvoxamine dose was reduced.

More recently, Garland and Baerg reported five cases of apathy and lack of motivation, one accompanied by disinhibition, in one child and four adolescents.<sup>4</sup> Symptoms were reported to be dose-related and reversible. In four of the five cases, management consisted of dose reduction of the SSRI. In the fifth case, the dose was reduced and bupropion was added. The authors stress that the subtlety of symptoms, lack of

insight in patients, and delayed onset may result in a lack of recognition of this phenomenon by both families and clinicians. Consequently, this adverse effect may not be addressed appropriately; instead, the dose of the SSRI may be increased to treat what is interpreted as symptoms of the illness or potential nonresponse to treatment. The authors suggest more careful monitoring for this syndrome and better patient and family education regarding apathy as a potential side effect of SSRI treatment.

### Further Evidence

In a recent study of patients whose depressive symptoms had responded to treatment but who had SSRI-induced sexual dysfunction, Opbroek et al. noted that up to 80% of patients in the study reported "treatment-emergent emotional blunting."<sup>7</sup> Patients reported a decreased ability to cry and also diminished creativity. However, this study had a number of limitations. The study only had a small number of participants, used a scale, the Laukes Emotional Intensity Scale, that lacked validity, included only patients with sexual dysfunction, did not have a control group that included patients who were receiving an SSRI but without reports of sexual dysfunction, and did not gather baseline data for the patients in the study.<sup>8</sup> Despite these limitations, emotional blunting may be more common than previously thought and further evaluation is needed.<sup>7</sup>

### Mechanism

Currently there is not a clear explanation for this observed syndrome. In a response to the case report by George and Trimble, Hoehn-Saric et al. suggested two possibilities.<sup>3</sup> The SSRIs may modulate frontal lobe activity via serotonergic systems. Alternatively, the SSRIs may influence serotonergic systems, which in turn modulate midbrain dopaminergic systems (projecting to the prefrontal cortex), triggering the symptoms described above. There have been limited reports of improvements in SSRI-induced apathy with sulpiride,<sup>3</sup> bupropion,<sup>4</sup> and olanzapine.<sup>9</sup> These include case reports<sup>3,4</sup> and one open-label study.<sup>9</sup> However, these three medications have different mechanisms of action; thus any inference regarding the mechanism underlying this apathy and subsequent pharmacologic attenuation is inconclusive. In addition, the fact that not all patients develop this syndrome may imply that a neurophysiologic or pharmacokinetic vulnerability is

**Table 1. Summary of case reports of SSRI-induced apathy\***

Reference	Case	Age	Sex	Diagnosis	Medication (mg/day)	Dose	Intervention	Effect on Apathy
Hoehn-Saric et al. <sup>1</sup>	1	55	M	Panic	Fluvoxamine	300	Dose reduction	Resolved
	2	35	F	Panic	Fluvoxamine	400	Dose reduction	Resolved
	3	39	F	MDD	Fluoxetine	20	Switch to MAOI	Resolved
	4	37	F	MDD	Fluoxetine	20	Switch to TCA	Resolved
	5	50	F	MDD	Fluoxetine	20	Dose reduction	Improved
Hoehn-Saric et al. <sup>2</sup>	6	23	M	OCD	Fluoxetine	100	Discontinued	Resolved <sup>†</sup>
George and Trimble <sup>3</sup>	7	42	M	OCD	Fluvoxamine	150	Dose reduction	Resolved
Garland and Baerg <sup>4</sup>	8	14	M	MDD	Paroxetine	20	Dose reduction	Resolved
	9	15	M	ANX	Fluoxetine	10	Dose reduction	Resolved
	10	14	M	OCD	Fluoxetine	40	Dose reduction	Improved
	11	10	F	OCD	Paroxetine	30	Dose reduction	Resolved
	12	17	F	DEP	Fluoxetine	30	Dose reduction/ bupropion augmentation	Resolved

*KEY: OCD = obsessive-compulsive disorder; MAOI = monoamine oxidase inhibitor; Panic = panic disorder; TCA = tricyclic antidepressant; MDD = major depressive disorder; ANX = anxiety disorder not otherwise specified; DEP = depressive disorder not otherwise specified*

*\*Form adapted from Garland and Baerg<sup>4</sup>*

*†OCD symptoms relapsed upon discontinuation of medication but apathy resolved*

also involved as a cofactor,<sup>4</sup> making it all the more difficult to identify the mechanism or mechanisms that may be involved.

### Monitoring and Identification

Given the insidious nature of SSRI-induced apathy syndrome, clinicians need to be proactive in monitoring for this adverse effect. When initiating treatment with an SSRI, educating the patient (and his or her family, if possible) to be vigilant for such symptoms as apathy, indifference, loss of initiative, or disinhibition will allow you to recruit them as valuable allies as you periodically evaluate the patient for these symptoms. Differentiating on examination between apathy accompanied by fatigue and apathy without fatigue may also be helpful, since the latter seems to be more indicative of SSRI-induced apathy. Patients should be seen for follow-up visits each month for several months after an effective dose is reached; these visits are crucial times to ask about and examine for apathy. If apathy symptoms are present, it is important to remember that they can be the result of a host of other causes, including hyperthyroidism,<sup>10</sup> dementia,<sup>11</sup> frontal lobe lesions,<sup>12</sup>

and cannabis use.<sup>13</sup> Screening for apathy may help the clinician detect these other conditions if present.

### Management

If SSRI-induced apathy is detected, there are three possible management strategies that can be tailored to the individual patient: 1) titration of SSRI dose, 2) augmentation, and 3) switching to a different class of antidepressant. In several of the cases discussed here, clinicians identified an SSRI dose that relieved some or all of the patient's symptoms but was below the threshold that caused an apathy syndrome. Since this was most readily achieved in patients who were prescribed an SSRI with a shorter versus longer half-life,<sup>3</sup> a change to an SSRI with a relatively shorter half-life may be warranted when titration of patient's current SSRI to an optimum level proves difficult. When titration of the SSRI is not successful, augmentation with bupropion has, in at least one documented instance, been helpful.<sup>4</sup> Finally, if neither of these strategies works, switching classes may be warranted. It has been noted that patients who experienced apathy while taking an SSRI have not experienced such a result when

treated with monoamine oxidase inhibitors or tricyclic antidepressants,<sup>1</sup> or even clomipramine,<sup>2</sup> despite the fact that clomipramine is a strong serotonin reuptake inhibitor. Garland and Baerg, the authors of the child and adolescent study reviewed here, noted that they had not observed medication-induced apathy as a result of venlafaxine treatment.<sup>4</sup>

### Conclusion

Apathy syndrome as a result of SSRI treatment may go undetected and unreported, despite its significant clinical impact. Patient education, regular follow-up, and active assessment are necessary to minimize poor outcomes. The mechanism that underlies this presentation is as yet unclear, but it is most likely a frontal lobe syndrome. Screening for this syndrome is imperative and practical, since SSRI-induced apathy syndrome is both clinically significant and eminently treatable.

### References

1. Hoehn-Saric R, Lipsey JR, McLeod DR. Apathy and indifference in patients on fluvoxamine and fluoxetine. *J Clin Psychopharmacol* 1990;10:343-5.
2. Hoehn-Saric R, Harris GJ, Pearson GD, et al. A fluoxetine-induced frontal lobe syndrome in an obsessive-compulsive patient. *J Clin Psychiatry* 1991;52:131-3.
3. George MS, Trimble MR. A fluvoxamine-induced frontal lobe syndrome in a patient with comorbid Gilles de la Tourette's syndrome and obsessive-compulsive disorder. Response by Hoehn-Saric R. *J Clin Psychiatry* 1992;53:379-80.
4. Garland EJ, Baerg EA. Amotivational syndrome associated with selective serotonin reuptake inhibitors in children and adolescents. *J Child Adolesc Psychopharmacol* 2001;11:181-6.
5. Marin RS. Apathy: A neuropsychiatric syndrome. *J Neuropsychiatry Clin Neurosci* 1991;3:243-54.
6. Marin RS. Differential diagnosis of apathy. *Am J Psychiatry* 1990;147:22-30.
7. Opbroek A, Delgado PL, Laukes C, et al. Emotional blunting associated with SSRI-induced sexual dysfunction. Do SSRIs inhibit emotional responses? *Int J Neuropsychopharmacol* 2002;5:147-51.
8. Balon R. Emotional blunting, sexual dysfunction and SSRIs. *Int J Neuropsychopharmacol* 2002;5:415-6.
9. Marangell LB, Johnson CR, Kertz B, et al. Olanzapine in the treatment of apathy in previously depressed participants maintained with selective serotonin reuptake inhibitors: An open-label, flexible-dose study. *J Clin Psychiatry* 2002;63:391-5.
10. Brenner I. Apathetic hyperthyroidism. *J Clin Psychiatry* 1978;39:479-80.
11. Wells CE. Dementia: Definition and description. In: Plum F, McDowell FH, eds. *Contemporary neurology series*, 2nd Ed. Philadelphia, PA: F.A. Davis; 1977:1-14.
12. Hacaen H, Albert ML. Personality changes with frontal and temporal lobe lesions. In: Benson DF, Blumer D, eds. *Psychiatric aspects of neurologic disease*. New York: Grune and Stratton; 1975:137-50.
13. Dornbush RL, Freedman AM, Fink M. Chronic cannabis use: Introduction. *Ann NY Acad Sci* 1976;282:vii-viii.