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Selective Serotonin Reuptake Inhibitor-Induced Apathy: A Pediatric Case Series

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ABSTRACT

Objectives: **Selective serotonin reuptake inhibitor (SSRI)-induced apathy is characterized by a lack of motivation that is not a result of sedation or symptoms of depression. This report describes two pediatric cases of SSRI-induced apathy, one of which is the first reported case in a child with a non-OCD (obsessive compulsive disorder) anxiety disorder.**

Methods: **The sample included 43 participants from the Johns Hopkins University site of the Research Units on Pediatric Psychopharmacology (RUPP) study of fluvoxamine in pediatric anxiety disorders. Data were reviewed for adverse events of at least moderate severity or that required a slowing of drug titration during the protocol; fluvoxamine blood levels were examined.**

Results: **Two (2) cases of apathy were identified (5%), 1 in a 9-year-old child and the other in a 16-year-old adolescent; neither had depressive illness. Similarities to existing reports included: Lack of insight, delayed onset, dose dependency, and reversibility with SSRI dose reduction or discontinuation. Plasma fluvoxamine levels were 459 ng/mL and 87 ng/mL, representing, respectively, the 90th percentile and 50th percentile, of the blood level sample groups at the time of apathy presentation (weeks 8 and 24). The 16-year-old also exhibited co-occurring disinhibition symptoms.**

Conclusions: **Educating patients and families, and close monitoring by clinicians for symptoms of SSRI-induced apathy, are important to limit the impact of this reversible adverse event on compliance and quality of life.**

INTRODUCTION

Selective serotonin reuptake inhibitor (SSRI)-induced apathy is generally marked by lack of motivation that is not a result of sedation, change in level of consciousness, or symptoms of a mood disorder (Barnhart et al. 2004; Hoehn-Saric et al. 1990; Marin 1991). The term apathy is usually defined as a lack of self-initiated responsiveness to stimuli or lack of motivation (Marin 1991; van Reekum et al. 2005). Apathy, or amotivational syndrome, has mainly been reported in adults taking SSRIs (Barnhart et al., 2004; Hoehn-Saric et al., 1990), although a few adolescents—and even fewer children—have been described (Garland and Baerg 2001). Several names have been used to describe this phenomenon, including SSRI-induced apathy, amotivation, emotional blunting, and drug-induced indifference (Balon 2002; Garland and Baerg 2001; Hoehn-Saric et al. 1990; Riddle et al. 1991).

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This SSRI adverse effect (AE) is easily missed or ascribed to underlying psychopathology and misinterpreted as medication failure, particularly in depressed patients (Garland and Baerg 2001). This clinical error can sometimes prompt medication dose increases, with consequent exacerbation of the apathy. The anhedonia and reduced activity seen in depressive illness is usually accompanied by affective symptoms and a subjective sense of indifference, which differentiates patients with SSRI-induced apathy who are often unconcerned with their amotivation (Barnhart et al. 2004). Other medications can also contribute to apathy symptoms; SSRI-induced apathy differs from antipsychotic-induced emotional blunting in that the patient's motivation and behavior are affected without any concomitant extrapyramidal symptoms or cognitive effects. SSRI-induced amotivational syndrome can sometimes present with disinhibition (Garland and Baerg 2001; Riddle et al. 1991), which may cause impaired functioning in adults (Hoehn-Saric et al. 1990), as well as children and adolescents.

Although the etiology of this AE is still unclear, single photon emission computed tomography (SPECT) scan studies and neuropsychological tests of a patient with SSRI-induced apathy suggested an underlying reversible frontal lobe syndrome (Hoehn-Saric et al. 1991). The unknown effects of SSRIs on serotonergic frontal pathways or feedback on dopaminergic neurons represent possible theoretical mechanisms through which SSRIs might induce apathy (George and Trimble 1992).

To our knowledge, there is only one other report in the literature of SSRI-induced pediatric apathy (Garland and Baerg 2001), which described 5 patients, 4 of whom were adolescents. Their diagnoses included: Major depressive disorder, depressive disorder not otherwise specified (NOS), obsessive-compulsive disorder (OCD) (2 patients, including the 1 child), and anxiety disorder NOS. In contrast, this paper includes the first reported case to date of SSRI-induced apathy in a child with a non-OCD anxiety disorder. This is also the first report of apathy from a research sample with a defined participant population; these subjects participated in a clinical research study at the Johns Hopkins University (Baltimore, Maryland) from 1997 to 2000. In addition, fluvoxamine blood levels are examined in this report.

METHODS

Subjects were participants in the Johns Hopkins site of the Research Units on Pediatric Psychopharmacology (RUPP) double blind, placebo-controlled fluvoxamine study for pediatric anxiety disorders (RUPP Anxiety Study). Details regarding the study design and participants have been previously published RUPP Anxiety Study Group 2001). Briefly, the RUPP Anxiety Study enrolled 128 participants, ages 6–17 years, with one or more of the following anxiety disorders: Separation anxiety disorder, social anxiety disorder, and generalized anxiety disorder. Participants were randomized to fluvoxamine or placebo for 8 weeks of treatment. Dosage was determined by flexible, forced titration. A child and adolescent psychiatrist evaluated adverse events. At the week 8 visit, blood was obtained for fluvoxamine levels, approximately 12 hours after the last dose. Following this 8-week study, participants were eligible to begin a 6-month open-label follow-up phase, which included monthly visits for medication monitoring. Placebo nonresponders were subsequently given open-label fluvoxamine treatment for 8 weeks, followed by 24 weeks of long-term follow-up. At the week 24 visit of the follow-up phase (week 32 of drug treatment), fluvoxamine levels were again obtained approximately 12 hours after the last dose.

The database from the Johns Hopkins RUPP site was reviewed, consisting of 43 subjects who received fluvoxamine during the various phases of the study. The database was reviewed for any adverse events that were of at least moderate severity or that required a slowing of drug titration during the protocol. Upon review of the data, 2 participants were found to have apathy, 1 participant had brief, unsustained fatigue for one visit, and 2 participants had fatigue for at least 2 consecutive study weeks. The 2 participants with apathy are described below.

Case 1

A 16-year-old girl with prominent anxiety symptoms developed apathy in the course of her participation in the RUPP Anxiety Study. She lived with her parents and siblings and had a paternal family history that was significant for specific phobias and depression. Her past medical history was significant for a febrile seizure at age 2 and chronic ear infections. All developmental milestones were within normal limits. She was also described as shy and anxious "all of her life." At study intake, she had observable symptoms of social and generalized anxiety symptoms. She was particularly anxious when faced with new social stimuli, such as when making class presentations, as well as upon eating or writing in public. The result was procrastination that impaired her ability to complete her homework. The participant also presented symptoms of worrying, muscle tension, restlessness, irritability, headaches, and difficulty concentrating; she needed parental involvement in her daily routine and to complete tasks. Moreover, she had a fear of bridges and insects that affected her daily routine. She had previously received supportive psychotherapy for her anxiety symptoms but not pharmacotherapy. On mental status exam at study entry, the participant was shy and reserved, but easy to engage, and brightened as the interview progressed. The remainder of the examination was unremarkable. In summary, this 16-year-old girl was diagnosed with social phobia and generalized anxiety disorder, with marked impairment in academic function, social interaction, and family function.

The participant and her mother assented and consented to participate in the study. Fluvoxamine dosage was titrated, according to study protocol, to 125 mg/day by week 4 and continued at that dose, with weekly follow-up visits with a child psychiatrist. The participant's anxiety symptoms improved substantially over the 8-week study. After the 8-week blinded trial, the participant continued fluvoxamine, 125 mg/day, in the 6-month, open-treatment continuation phase of the study, without any recurrent anxiety symptoms. At the 20th week of long-term treatment, she and her mother reported "disinhibition," and friends worried that her personality had changed. Her friends noted that she seemed "different" and had become overly confident with strangers. The participant was noted to have engaged in more risk-taking behaviors and seemed socially disinhibited, although she did not exhibit any other manic symptoms; nor did she have any depressive symptoms. She was paradoxically simultaneously amotivated to do her usual daily activities; her fluvoxamine dose was lowered to 100 mg daily. At the 24th week of follow-up, the participant was no longer disinhibited, but was noted to be increasingly unmotivated and lacked drive to accomplish tasks after taking 100 mg fluvoxemine over the previous 4 weeks. Whereas her anxiety symptoms had completely remitted, she lacked motivation to "do things" and had difficulty doing schoolwork in particular. At week 24, her fluvoxamine blood level was 87 ng/mL (the 50th percentile for blood-level samples at week 24). Fluvoxamine dosage was lowered to 75 mg/day, which alleviated this adverse event. On follow-up telephone interview 4 weeks later, she reported remission of apathy symptoms. The participant was referred back to her outpatient child psychiatrist for ongoing care.

Case 2

A 9-year-old boy was evaluated for longstanding anxiety symptoms. His family history included paternal and maternal anxiety. The remainder of the past psychiatric, medical, and developmental history was not contributory. The child presented with a longstanding history of feeling anxious, including fears of being separated from family members. He also worried about "everything," but specifically bad things happening to him, his health, homework, and his academic performance. There was no evidence of rituals or stereotypies. Mental status examination was essentially unremarkable, except for anxious, restricted affect. The participant received a diagnosis of generalized anxiety disorder, with features of separation anxiety disorder.

His parents and he, respectively, consented and assented to treatment in the study. He began

fluvoxamine 50 mg/day for 1 week, then 75 mg daily for the 2nd week. At the week-2 visit, the participant presented with markedly increased motor activity, after taking fluvoxamine for 1 week. Fluvoxamine dose was then reduced to 50 mg, and the hyperactivity resolved over the next week. Medication was titrated as tolerated by the child over 8 weeks, according to study protocol, to 125 mg daily. He showed a good response, with marked diminution of anxiety symptoms, and elected to continue treatment in the open-label phase of the study for medication management. Although the anxiety symptoms had improved at week 8, it was noted that he "didn't care about anything"; he was also found to be somewhat disinhibited and had greatly increased motor activity, without exhibiting any other mania symptoms. He did not demonstrate any depressive symptoms. His plasma fluvoxamine level at week 8 was 459 ng/mL on 125 mg/day. Of note, at week 8, the mean fluvoxamine blood level at the Johns Hopkins site (n = 16) was 222 ± 192 SD ng/mL. The dose was lowered to 100 mg/day, and, after 10 days at that dose, the patient remained disinhibited, hyperactive, and fidgety, with some difficulty falling asleep. Fluvoxamine was lowered to 50 mg/day. He continued this dosage with minimal anxiety and mild activation symptoms for the next 6 weeks until week 14, when he again developed anxiety, including scanning the environment for potential dangers; fluvoxamine was increased back to 75 mg. At week 16, the participant's mother noted only very mild hyperactivity; fluvoxamine dose was increased to 87.5 mg/day for anxiety symptoms. Owing to persistent anxiety, the fluvoxamine dose was increased to 100 mg/day during the week 22 phone visit. At the week 24 visit (end of the study) anxiety symptoms included worries about daily activities and asking multiple questions owing to his fears about unreasonable fears. The fluvoxamine level was 255 ng/mL; no apathy was noted. Three (3) months later, the patient remained at the same dose and described no symptoms of anxiety and no hyperactivity. However, he presented with extreme amotivation and apathy, not caring about anything; he did not want to go to school and didn't care about typical interests. The parents decided to discontinue fluvoxamine; within 14 days, the patient's motivation had returned to baseline levels.

DISCUSSION

There is a paucity of empirical data regarding the prevalence of SSRI-induced apathy, which may be underappreciated and underrepresented (Garland and Baerg 2001; Opbroek et al. 2002). In this paper, 2 cases were observed from 43 study participants receiving fluvoxamine, or a 5% frequency, which suggests a relatively common phenomenon.

Possible risk factors for developing SSRI-induced apathy include: Individual biological vulnerability, specific psychiatric disorder, rate of drug-dosage titration, absolute drug dose, and drug blood level. There is some evidence that the patient's biological diathesis to developing apathy may be linked to the SSRI-mediated effects on the frontal lobe through serotonergic pathways (George and Trimble 1992; Hoehn-Saric et al. 1991). This amotivational syndrome may be the result of a reversible frontal lobe syndrome; however, the actual role of the frontal lobe in behavioral activation, amotivational, and disinhibition syndromes is unknown (Garland and Baerg 2001; Hoehn-Saric et al. 1991).

It is unclear whether specific diagnoses predispose patients to develop SSRI-induced apathy. SSRI-induced apathy also does not seem to occur more frequently with any one particular SSRI; it has been described with many SSRIs, including fluvoxamine, fluoxetine, and paroxetine (Garland and Baerg 2001). The 2 participants in our report were taking fluvoxamine. Of previously reported patients on fluvoxamine, a patient with OCD and Tourette's Disorder became amotivated; however, this reversed upon reducing his dose (George and Trimble 1992), and 2 reversible cases in adults on fluvoxamine were also reported (Hoehn-Saric et al. 1990).

The rate and/or dose of titration may also play a role in SSRI-induced apathy, as is reflected in the 2 cases presented in this paper, who both had relatively fast medication titration. The relatively "forced" titration schedule

employed in clinical trials, such as the RUPP study, attains target doses more quickly and lessens the duration of the participants' exposure to placebo. There are no prior data linking SSRI blood levels to SSRI-induced apathy. The small number of cases in this report limits our ability to draw conclusions from the respective fluvoxamine blood levels; one blood level occurred in the upper 90th percentile and the other in the lower 50th percentile of the sample for their respective time periods. Further studies should examine the role of drug blood levels and possible biological influences related to this adverse event.

The similarities of these cases to the few reports of SSRI-induced apathy/amotivational syndrome are noteworthy. These include: (1) The phenomenology of the syndrome, which is distinctly different from depression, (2) the intensity of the experience—patients experience an overwhelming change in motivation and zest for life, (3) the considerable delay of apathy onset with respect to SSRI initiation—in this report, apathy was identified at 8 and 11 months after SSRI initiation, (4) the presentation of apathy with less prominent disinhibition symptoms, and (5) resolution with decreased or discontinued SSRI dose (Barnhart et al. 2004; Garland and Baerg 2001; Riddle et al. 1991).

SSRI-induced apathy may be a challenge to identify. In particular, SSRI-induced apathy can be difficult to distinguish from depressive illness (Barnhart et al. 2004). SSRI-induced apathy is not simply the resolution of the patient's anxiety symptoms, but a separate and distinct syndrome that can go undetected, as it may mimic symptoms of underlying pathology, such as depression. Neither of the subjects in this report was clinically depressed, based on clinical evaluation and scores on the Children's Depression Rating Scale—Revised (CDRS-R; Poznanski and Mokros 1996). A misdiagnosis of affective illness exacerbation can lead the physician to increase the SSRI dose with the consequential worsening of the patient's apathy. In such a case, the accompanying presence of mood symptoms and lack of pleasure are important to identify affective illness rather than SSRI-induced apathy. Although apathy can also exist in depressive illness, these patients often are concerned with their lack of motivation and have co-occurring mood symptoms; this contrasts with the symptoms of SSRI-induced apathy. The patients reported in this paper did not have depressive illnesses and instead presented only with anxiety symptoms.

Although the intensity suggests SSRI-induced apathy should be a relatively easily identified problem, even adults have been noted to lack insight into this problem (Barnhart et al. 2004). Moreover, children may also under-report amotivational symptoms, owing to their developmental level and difficulty in recognizing the problem. This highlights the need to examine each patient and question parents and other sources of collateral information.

The insidious onset and delayed recognition of SSRI-induced apathy is problematic, because the physician and the patient or their family often won't make the connection between the medication and the onset of amotivation. This delayed onset also presents a challenge in terms of research, as most studies do not continue long enough to cover the period of risk. Close monitoring over at least a year is probably required to identify SSRI-induced apathy, owing to the later presentation and inherent diagnostic challenges. The co-occurrence of SSRI-induced apathy in patients with disinhibition can sometimes lead to the apathy part of the "combination" symptoms being overlooked (Riddle et al. 1991).

The clinician should remain aware of possible apathy symptoms and screen accordingly for them in the patient's follow-up visits. The co-occurrence of other SSRI adverse events is also possible; one study found 80% of patients with SSRI-induced sexual dysfunction described blunting of emotions, highlighting the importance of screening for SSRI-induced apathy (Opbroek et al. 2002)

Once the amotivation problem is identified, it is important to discuss treatment options with the patient and their family. Possible options include dose tapering or switching to a different medication altogether. Apathy may be related to dose, and there is evidence that decreasing the dosage will help alleviate this adverse event, even when it remains sufficient to treat the patient's symptoms (Hoehn-Saric et al. 1990). SSRI-induced apathy typically responds quickly to lowering or discontinuation of medication dose,

although it has been noted that withdrawal of fluoxetine can take longer to resolve owing to its longer half-life (Garland and Baerg 2001; Hoehn-Saric et al. 1990; Riddle et al. 1991). Some parents may find SSRI-induced apathy to be a "scary" syndrome and may wish to rush to stop the medication.

Finding a balance between a sufficient dose to treat psychiatric symptoms, but low enough to avoid apathy, represents a challenging treatment goal. The optimal management other than dose reduction has not been adequately studied owing to the inherent difficulties in doing so. One case report suggested bupropion augmentation might be useful (Garland and Baerg 2001). Also, olanzapine (mean dose, 5.4 mg) was shown to be effective in treating SSRI-induced apathy (n = 21 adults) in an open-label, flexible-dose study (Marangell et al. 2002).

CONCLUSIONS

There are several important clinical implications, including education, monitoring, and responding to SSRI-induced apathy. Prior to starting an SSRI, it is important to discuss potential symptoms of SSRI-induced apathy with the patient and his or her family so that they can help bring the problem to attention. The physician also plays a role in regular, direct monitoring for this adverse event and should regularly screen for SSRI-induced apathy, particularly when the patient appears to be doing well, and has been taking SSRIs chronically. Responses to SSRI-induced apathy will vary according to the patient, the severity of the underlying illness, and the degree of functional impairment.

SSRI-induced amotivational syndrome is a more important and frequent clinical issue than suggested by the paucity of published reports. It may go undetected in its milder forms owing to the delayed onset and variable severity of presentation. Nonetheless, clinicians should remain vigilant for this important AE, as it can affect patients' level of functioning, quality of life, and compliance at every developmental level. More studies are required to describe the phenomenology and treatment of this SSRI-related adverse event that may be related to frontal lobe dysfunction.

DISCLOSURES

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