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Case Report

Amotivational Syndrome Associated with Selective Serotonin Reuptake Inhibitors in Children and Adolescents

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ABSTRACT

A frontal lobe syndrome has previously been reported in adults treated with selective serotonin reuptake inhibitors (SSRIs), but not in children. Five typical cases of apathy and lack of motivation, one accompanied by disinhibition, are described in a child and four adolescents. Symptoms were dose related and reversible. The subtlety of symptoms, lack of insight in patients, disabling effects, and delayed onset indicate a need for clinicians to inform families of these potential symptoms when SSRIs are prescribed.

INTRODUCTION

A REVERSIBLE, DOSE-RELATED amotivational syndrome has been reported in adults treated with fluoxetine or fluvoxamine (George and Trimble 1992; Hoehn-Saric et al. 1990, 1991). It is characterized by apathy, lack of motivation, lack of appropriate concern, and in some cases disinhibition. The characteristic clinical presentation, single proton emission computed tomography changes, and associated specific changes in neuropsychological tests support the hypothesis that this is a reversible frontal lobe syndrome (Hoehn-Saric et al. 1990) rather than an excessive reduction in anxiety. This side effect is not diagnosis specific, occurring in patients being treated for panic disorder, obsessive-compulsive disorder, and depression. It occurs in the absence of sedation, hypomania, or other side effects and tends to have a delayed onset. It was noted that the same patients had not experienced these amotivational effects when treated with monoamine oxidase inhibitors, tricyclic antidepressants (Hoehn-Saric et al. 1990), or even clomipramine (Hoehn-Saric et al. 1991). Theoretical mechanisms include the effects of selective serotonin reuptake inhibitors (SSRIs) on frontal projections of serotonergic pathways or indirect effects on dopaminergic pathways (George and Trimble 1992) as evidenced by extrapyramidal side effects (Gerber and Lynd 1998) as well as prolactin elevation (Amsterdam 1997). The primary treatment is dose reduction or change of medication class. There is no reported prevalence data for this phenomenon, and it may be underrecognized due to its subtlety and delayed onset. In a specialized child and adolescent mood and anxiety disorders clinic, this syndrome has been observed with all of the SSRIs; however, it has often been unrecognized by both patients and physicians. Therefore, five cases are reported to increase awareness of this infrequent but potentially disabling side effect of SSRIs in young people.

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CASE REPORTS

The following cases were seen in a tertiary care child and adolescent mood and anxiety disorders clinic that provides consultation, pharmacotherapy, and cognitive-behavioral treatment. The characteristics of these representative cases are summarized in Table 1.

Case 1

A 14-year-old male was treated with paroxetine 20 mg for his second episode of major depression. He had a prior history of major depression a year previously that had resolved with a course of St John's Wort and a premorbid history of subclinical social anxiety and overanxious traits. He was an honor roll student who was compliant with parental expectations. The current episode was initially treated by the family physician with imipramine, but at 50 mg his depression had not resolved, and anticholinergic side effects and tachycardia were disabling. With the switch to paroxetine 20 mg, he was in full remission after 6 weeks of treatment. Within the next month, when seen in routine follow-up, he was free of depression but his affect was markedly flat to the point of having the mask-like appearance associated with parkinsonism; there were no associated features of muscular rigidity, tremor, or other extrapyramidal side effects. He seemed unconcerned about his schoolwork and generally apathetic. The parents were quite concerned about this change of personality, as was the clinician, but the patient was quite satisfied with his life and did not recognize a problem. He had experienced a reduction in social anxiety that allowed him to speak with friends at school more comfortably. He did agree to reduce the paroxetine to 10 mg, and there was no recurrence of depression or anxiety and some improvement in his flat affect. However, the family, treating clinician, and the therapists in the adolescent depression group he attended remained concerned about his apathy. He was spending increased time on the computer and seemed less influenced by parental expectations. There was, however, only minimal decline in his schoolwork, and he was not disinhibited. Because of his flat presentation, however, his paroxetine was reduced earlier than planned to 5 mg after 4 months of remission and discontinued after another month. His affect returned to normal but without return of earlier subclinical anxiety symptoms. He has since remained well. Despite his well above average intelligence, he did not at any point comprehend the change that his family and others observed but accepted the recommendations to reduce medication. He was not using any recreational drugs or alcohol.

Case 2

A 15-year-old male presented with a mixed anxiety disorder combining specific performance anxiety with a long history of inhibited temperament and difficulty adapting to change. The family had already sought a psychologist's help to reduce test anxiety, but he found that his anxiety consisted of "freezing up" in the situation rather than anticipatory worrying. Cognitive strategies were not helpful, and he was not able to master relaxation strategies. The blanking out in the test situation was adversely affecting his grades. As a skilled player in several high-level team sports, a similar "choking up" under game pressure was affecting his standing and his future hopes. The family was interested in a pharmacotherapy trial as long as it

Table 1. Cases of Amotivational Syndrome with Selective Serotonin Reuptake Inhibitors

Case	*Age (sex)*	*Diagnosis*	*Medication*	*Dose at which symptoms appeared*	*Management*
1	14 (male)	Major depressive disorder	Paroxetine	20 mg	Decrease dose
2	15 (male)	Anxiety disorder NOS	Fluoxetine	10 mg	Decrease dose
3	14 (male)	Obsessive-compulsive disorder	Fluoxetine	40 mg	Decrease dose
4	10 (female)	Obsessive-compulsive disorder	Paroxetine	30 mg	Decrease dose
5	17 (female)	Depressive disorder NOS	Fluoxetine	30 mg	Decrease dose; augment with bupropion

NOS = not otherwise specified.

would not affect his sports performance. Fluoxetine was therefore chosen over alternatives such as propranolol. After 4 weeks of treatment with 10 mg fluoxetine daily, he reported an improvement in test anxiety, with resultant improved grades in several key subjects, and the parents and coach had observed positive results on the sports field. After about 6 weeks of treatment at this same dose, however, there was a gradual change that was not recognized for another month when the parents contacted the clinician because of a developing crisis at school and in competitive sports. At this point, 10 weeks after treatment initiation, the parents were distressed that the patient seemed unconcerned with several major team losses. His coach was dismayed by his "bizarre" blasé attitude about game outcomes during a recent tournament. At the same time, the parents had a call from one of his teachers who knew him well, concerned about the fact that he was no longer doing his homework and even more worried that he seemed entirely nonchalant when confronted about it. She found this "change in personality" alarmingly out of character for him as it seemed more than "just adolescence." It then came to light that a similar lack of initiative and effort to complete work was occurring in other subjects over the previous months. He was also losing items of clothing, neglecting his chores, and generally being criticized for his "irresponsibility" from many adults in his life. When the parents confronted him about these behaviors, he was calm, unconcerned, and did not seem to perceive a problem. They became frustrated and initiated consequences, with little effect. On reflection, however, the mother called the clinician because the parents had been warned about the risks of amotivational syndrome, and she wondered if this could be the cause of the change in her son's behavior. There was no associated sedation, sleep problem, overactivity, or other features suggesting hypomania, and there was no drug use. The psychiatrist recommended discontinuing the medication, as it was already at a low dose. Over the next month, he gradually returned to his usual self. Two months later, however, he himself requested to go back on the fluoxetine at a lower dose because he did not like the subjective experience of his returned anxiety. Cautiously, the clinician reintroduced 2.5 mg of fluoxetine, and over the next month the positive benefits returned without the amotivational features.

Case 3

A 14-year-old male was treated for obsessive-compulsive disorder with 30 mg of fluoxetine, had a good response with more than 50% reduction in symptoms, and was able to manage residual symptoms of moral scrupulosity, religious obsessions, and mental rituals with cognitive-behavioral strategies. After a half year of treatment, due to a breakthrough of disabling symptoms, however, the dose was increased from 30 mg to 40 mg. Over the next 2 months he was transformed from a highly conscientious and successful student who also felt obliged to provide mother with help around the house to a boy who seemed uninterested and apathetic about both of these areas of his life. He was neglecting chores and homework and was less socially and physically active due to general apathy. In a follow-up visit 6 weeks after the dose increase, his affect was flat, and he appeared emotionally disconnected and apathetic. However, he reported that he felt "fine" and was not in any way unhappy or distressed about his situation despite a large drop in his grades. As he was reluctant to decrease the dose because he felt he finally had good relief from obsessive thoughts, close monitoring and more structure were implemented over the next 2 months with some success. Although his grades remained significantly lower due to "not bothering" with homework and other responsibilities, and his motivation during competitive sports was noticeably diminished, he and his mother were reasonably satisfied with the situation as the obsessive-compulsive disorder symptoms were of more concern to them. The clinician, however, strongly encouraged a future trial of dose reduction and increased cognitive-behavioral treatment for any residual obsessive-compulsive symptoms.

Case 4

A 10-year-old female developed acute obsessive-compulsive disorder characterized by prominent intrusive thoughts about needing to kill herself or family members. There was no associated depression and no prior history except that she was somewhat "sensitive" and inhibited in temperament. Treated by the family physician initially with 10 mg and then 20 mg of paroxetine, her symptoms improved about 50% and went into full remission when the dose was increased after 2 months to 40 mg. When seen in the clinic for assessment, she had subclinical symptoms for which cognitive-behavioral therapy was recommended. How-

ever, her mother reported that she also had a problem of disinhibition, which had emerged after the dose was increased to 30 mg and worsened at 40 mg. She had interpersonal boundary problems, asking people inappropriate personal questions, having poor judgment and thereby insulting and alienating both peers and adults. This was quite out of character for her, as she had previously been quite polite and sensitive to others. She did not seem to have insight into how inappropriate her statements were at the time. When her behavior was pointed out to her, she would appear to be upset about it later primarily because her mother warned her that this could cause her to lose friends. However, when describing her actions to the psychiatrist, she showed no appropriate embarrassment. She appeared unusually unconcerned and flat in affect, but the clinician had no baseline to compare, not having seen her prior to medication. There was no evidence of general behavioral activation or hypomania such as overactivity, pressure of speech, irritable or elevated mood, or hyperarousal in the form of sleep disturbance. The parents were puzzled by this new symptom. When asked, they also noted a decrease in responsibility for schoolwork and her lack of concern about this. The parents were keen to continue the medication dose as the obsessive-compulsive disorder symptoms were more upsetting, but a few weeks later because of persistence and impact of this disinhibited social behavior despite coaching and feedback, they requested to reduce the dose. Disinhibited symptoms improved after 2 weeks at 30 mg but recurred a few weeks later even at that dose. The dose was further reduced to 20 mg with resolution of disinhibition but an increase in obsessive thoughts. Cognitive therapy was recommended to manage these. The parents continued to find her somewhat less conscientious than her usual self, even at the lower dose of paroxetine. At 10 mg of paroxetine, however, mother reported that she had returned to her "usual sparkling personality," and her affect became fully responsive.

Case 5

This 17-year-old female was treated for a diagnosis of depressive disorder characterized by recurrent and chronic symptoms of mild major depression with irritability and affective instability. A prior history of mild attention deficit disorder was suspected based on parental report, but teacher ratings did not support this. She was very active in high-level competitive sports, was employed part time, was an average student, and had experienced longstanding family conflict treated with family therapy. Subjective depression and irritability greatly improved with fluoxetine 20 mg initiated by the family physician in the summer. When seen for assessment at the end of summer, she had also been using marijuana daily over the previous month and recreationally once or twice a week for 3 months prior to that but was reducing to weekend use only as school was about to start and she had begun physical training to prepare for her sports season. At this point her dose was increased to 30 mg daily as her depression was in partial remission. On the next visit a few weeks later, she reported improved mood, her parents saw her as less irritable but her clinical presentation was quite flat compared to her previous lability, and she seemed unmotivated for school and sports. She was at this point not using any marijuana and was judged to be a reliable reporter of her use as it was understood that this information would be kept in confidence by the psychiatrist. With the hypothesis that this represented residual depression, her does was increased to 40 mg of fluoxetine. At this dose, her subjective mood became quite stable, and the parents were pleased with resolution of her irritability. Over the next month, however, she seemed to lose interest in socializing and also in sports. She changed from someone realistically working toward an athletic scholarship for college to someone who no longer cared about going on with her competitive sports. She appeared quite apathetic and flat in affect with facial akinesia but had few complaints except for some mental "tiredness" without physical fatigue and mild hypersomnia (10 hours). At this point, the family was far less concerned about her as she was no longer volatile and there was less conflict about curfews as she was less interested in going out with her friends. However, the treating psychiatrist was very concerned due to the loss of goals and motivation as well as the clinical presentation. Over the next 2 months, the fluoxetine dose was reduced in increments to 20 mg, and bupropion 150 mg was added, which led to normalization of her affect and improvement in motivation and initiative. However, her lack of participation in sports during a crucial part of the season had a lasting impact on her career plans. Several months later, not being involved in a competitive sports team, she briefly returned to daily marijuana use, which resolved again with considerable support. She was able to complete her graduation year without recurrent depressive symptoms and became

involved in less competitive community sports but decided to go to work rather than to postsecondary education.

DISCUSSION

These cases present strikingly similar symptoms of amotivational syndrome to the small number of adult cases described by others (Hoehn-Saric et al. 1990). Similarities include dose dependence; usually apathetic but occasionally disinhibited presentations; occurrence after weeks or months of treatment; and lack of recognition of the problem by the patient until occupational, interpersonal, or academic problems developed. This syndrome occurred when SSRIs were prescribed for a variety of diagnoses. Although it has been suggested that it may be more common with obsessive-compulsive disorder, this may be due to the higher doses used to treat this condition. There was no evidence of accompanying sedation, hypomania, physical behavioral activation, or extrapyramidal side effects. These cases also illustrate the marked detrimental impact on schoolwork, social relationships, and sports involvement at this developmental stage. Nevertheless, symptoms often go unrecognized as they are delayed in onset and subtle. The patients feel "fine," and parents may attribute problems to other causes such as adolescence, suspected drug use, or a "bad attitude." It was difficult for parents to recognize, even when prewarned as they were in case 2, because the delayed onset prevented association with medication. In four of these cases, symptoms were identified by the clinician on a follow-up visit. Even then, as in case 5, the flat affect and lack of motivation can be difficult to distinguish from residual depressive symptoms and might lead to dose increase rather than decrease. In cases 1 and 5, the dramatically flat affect and facial akinesia led to a suspicion of parkinsonian symptoms, but there were no other extrapyramidal motor symptoms. As in the adult cases reported, these young patients could acknowledge the changes in behavior when they were pointed out, but still they were unconcerned; as one adult commented "this is what a frontal lobotomy must feel like" (Hoehn-Saric et al. 1990). It was notable that even when the symptoms of a frontal lobe syndrome were identified, parents were reluctant to decrease medication dose due to worry about return of symptoms. It appeared that parents were more reactive to the volatile symptoms of acute anxiety and depressive irritability than the more "mellow" (several parents used this word) presentation of these children.

In case 5, recent use of marijuana could theoretically have contributed to the presentation, although her use had been relatively short term and was terminating when the amotivational features appeared. Marijuana withdrawal is typically characterized by irritability, anxiety, and somatic symptoms rather than apathy (Haney et al. 1999). However, low motivation has been described with chronic marijuana smoking, and systematic research on acute and long-term effects of cannabis has documented deficits of short-term memory, working memory, and selective attention (Hall and Solowij 1998). Therefore, marijuana use is an important diagnostic consideration when evaluating an amotivational syndrome in adolescents.

It was clear that this amotivational state was not simply a reduction in anxiety, as these patients appeared distinctly apathetic and inappropriately unconcerned rather than merely "not anxious." However, parents, and the adults in previous reports, have tended to initially explain away symptoms in this way, assuming that anxiety was previously inhibiting inappropriate behaviors and maintaining compliance with expectations. Socially anxious children may have transient difficulties when successfully treated with SSRIs, as they have not developed age-appropriate social skills due to their avoidance history. However, the quality and content of disinhibition in case 4 was highly inappropriate for a child of her age. The disinhibition associated with the amotivational syndrome also appears to be different in quality from the typical behavioral activation seen when SSRIs are initiated in children (Riddle et al. 1991). Patients with this more common, early-onset and often transient symptom are not apathetic or unconcerned, and they often have insomnia and overactivity. However, the boundaries between frontal lobe amotivational or disinhibition syndromes, behavioral activation, and extrapyramidal effects such as parkinsonism associated with SSRI treatment need to be better defined.

Of the antidepressants, SSRIs have been uniquely implicated in this amotivational syndrome. In theory it could occur later with fluoxetine due to the longer half-life, but it appeared to develop with any SSRI after 6–8 weeks of treatment or later with a dose increase. The dose at which symptoms first appeared ranged

widely, from as low as 10 mg to as high as 40 mg of fluoxetine. As with extrapyramidal side effects of SSRIs, there is marked interindividual variation, which may represent either neurophysiological or pharmacokinetic vulnerabilities; for example, a choreiform syndrome with fluoxetine has been linked to genetic deficiency in CYP2D6 enzyme (Marchioni et al. 1996). Consistent with previous reports, an amotivational syndrome has not been observed in this clinic with imipramine, desipramine, or venlafaxine, suggesting the role of serotonergic mechanisms; however, it has not been observed with clomipramine. Symptoms improved in each case with dose reduction, but in case 4 they recurred at a lower dose. Dose reduction, medication change to another class, and augmentation with bupropion are commonly used in this clinic to manage amotivational syndrome. In one case not reported here, however, bupropion added to 30 mg of paroxetine converted an apathetic teen into a disinhibited, impulsive one, without evidence of hypomania. This may be similar to a reported case in which stimulating situations produced disinhibition in an apathetic adult treated with fluvoxamine (Hoehn-Saric et al. 1990).

CONCLUSION

An amotivational syndrome in children and adolescents treated with SSRIs may be more common than implied by the lack of published reports. Although it responds to dose reduction, its delayed onset and subtle features may not be recognized or may lead to increase in SSRI dose as the presentation overlaps with symptoms of residual depression and avoidance. Clinicians need to be alert to the potential for this syndrome and educate families to detect it. It is also recommended that children on SSRIs be reviewed at least monthly in the 6 months after symptom remission to detect late onset of symptoms. Further research is required to establish the criteria, prevalence, and physiological basis for this described amotivational syndrome.

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