



# Fluoxetine Induced Fecal Incontinence in a 9 Year Old Child with Autistic Spectrum Disorder: A Case Report

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**ÖZET:** Otistik spektrum bozukluğu tanılı dokuz yaşında bir olguda fluoksetin kullanımına bağlı fekal inkontinans: Bir olgu sunumu

Yaygın gelişimsel bozukluk (YGB) tanılı çocuk ve ergenlerde selektif serotonin geri alım inhibitör'lerinin (SSGI) kullanımındaki belirgin artışa rağmen, yapılan araştırmaların çoğunluğu YGB hastalarının bu ilaçlara düşük oranda tolerabilite gösterdiğini ortaya koymuştur. SSGI'lerle görülen ters ilaç etkileri arasında gastrointestinal yan etkiler (GIS-YE) siktir ve genellikle hafif ve kendini sınırlayıcı niteliktedir. YGB tanılı çocuklarda gastrointestinal şikayetler sık olarak izlenmektedir. Her ne kadar önceden gösterilmemişse de, YGB'li çocuklar SSGI'lerin ciddi GIS-YE'ne daha yatkın olabilirler. Bu olgu sunumunda, 9 yaşında YGB, başka türlü adlandırılmayan (YGB-BTA) tanılı bir olguda fluoksetin kullanımı ile, ilacın kesimine yol açan, fekal inkontinans gelişiminden bahsedilecektir. Klinisyenler YGB tanılı çocuklarda SSGI kullanırken ciddi GIS-YE açısından dikkatli olmalıdır.

**Anahtar sözcükler:** Fluoksetin, fekal inkontinans, SSGI, YGB, çocuk

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**ABSTRACT:** Fluoxetine induced fecal incontinence in a 9 year old child with autistic spectrum disorder: a case report

Despite the dramatic rise in the use of selective serotonin reuptake inhibitors (SSRIs) in children and adolescents with pervasive developmental disorders (PDD) in recent years, the majority of studies of SSRI use in PDD population demonstrated lower tolerability compared to children without PDD. Among the adverse reactions to SSRI use, gastrointestinal adverse effects (GIS-AE) are common and usually reported to be mild and self limited. Children with PDD are shown to have higher rates of gastrointestinal symptoms including stool inconsistencies than the general childhood population and although not previously shown, they may be more vulnerable to severe GIS-AE of SSRIs. We present a case of a 9 year old girl with PDD not otherwise specified (PDD-NOS) who developed fecal incontinence (FI) in the treatment of fluoxetine which led to the discontinuation of the agent. Clinicians must be aware of severe GIS-AE when using SSRIs in children with PDD.

**Key words:** Fluoxetine, Fecal incontinence, pervasive developmental disorders (SSRI), child

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## INTRODUCTION

Despite the dramatic rise in the use of selective serotonin reuptake inhibitors (SSRIs) in children and adolescents, there are still concerns about the tolerability of these agents in younger ages (1). It is suggested that, in general, children and adolescents may be more vulnerable to some adverse effects of these agents when compared with adults (2,3). The adverse effects of SSRIs may be classified in several subgroups including gastrointestinal adverse effects (GIS-AE), sleep disturbances, physical symptoms, and psychiatric adverse effects (PAE) (1,4). The etiopathology and course of these reactions is not completely identified.

Pervasive developmental disorders (PDD) are characterized by impairments in reciprocal social interaction and communication plus restrictive, repetitive and stereotypic behaviors, activities and interests (5). In the milder forms of PDD, especially in PDD-NOS,

Asperger's Syndrome and high functioning autism (HFA), patients may exhibit depressive and/or anxiety disorder symptoms which are sometimes reactive to difficulties of socialization and academic failure (6-9).

It's suggested that children and adolescents with developmental disabilities and PDD may be more prone to the adverse effects of SSRIs (10). To date, one placebo controlled and three open label studies have been conducted to examine the use and tolerability of fluoxetine in children with PDD. All four studies yielded encouraging results for its efficacy and more variable results for its tolerability (11-14). The only placebo controlled study, conducted by Hollander et al. (14), interestingly showed that fluoxetine was almost as tolerable as placebo. However, by contrast, three open labels studies offered more equivocal rates of tolerability (11-13).

GIS-AE including nausea, vomiting, diarrhea and upset stomachs are commonly reported when using SSRIs

in children with or without PDD. Fortunately, most of these symptoms are usually mild in nature, short-lived and responsive to lowering the dose. Thus, although GIS-AE are common, they are reported to be easily managed and not significantly impairing (4). To the authors' knowledge, fecal incontinence (FI) as an adverse effect of an SSRI has not been previously reported.

In this article we aim to present the case of a 9 year old girl with PDD-NOS who developed FI in the fluoxetine treatment and this adverse effect led to the discontinuation of the treatment.

## CASE REPORT

### Diagnostic Assessment

B.E., a 9 year old girl, was first admitted to our clinic displaying lack of sociability, poor peer relations and an unwillingness to share pleasures and interests with her parents. She was reported to be sitting alone in the class breaks at school, avoiding play with her classmates. At home, she failed to initiate any conversations with either her mother or her younger brother.

Her developmental history revealed a moderate delay in her expressive language. She completed her toilet training at the age of 4 and her parents did not report any toileting problems after this age.

From early childhood, she displayed no interest in imaginative, pretend-play games and playing with toys. According to her mother, she had made no repetitive movements, nor had she developed ritualistic behaviors or evidenced unusual interests. According to her teacher, she had limited social interaction with other children and usually did not understand when they were joking. Her grades in the current year were slightly below the average of her classmates. At her first visit, she had mildly limited eye contact with us and answered most of our questions in only a few words. Her intellectual testing revealed a total IQ (intelligence quotient) in the borderline range (IQ:82). At the time of admission, she had no medical complaints. Her past medical history had also not revealed any presence of disease, or any chronic medical symptoms. A diagnosis of PDD-NOS in the 1<sup>st</sup> axis and borderline IQ in the 2<sup>nd</sup> axis was made according to DSM IV criteria (5). B.E. commenced special education sessions twice a week and continued to attend her regular school.

### History of Follow-up

At the 3 month follow-up session, her mother reported that B.E. had shown a gradual decline in her academic performance over the last 2 months. She repeatedly said "I am a fool; I can't get a good grade" to her mother. She spent most of her time in her room and rarely responded to her brother when he wanted to play with her. According to her mother, B.E. had the feeling that she was not as clever as her classmates and she was very worried she might fail at school. No significant negative life events at home, or at school, which might predispose her to complaints, were reported by her parents. In the clinic, she did not respond to our questions verbally, she would only nod her head in approval when asked about her sadness and worries about school. In addition to the PDD-NOS diagnosis, a diagnosis of major depression with anxiety symptoms was made according to DSM-IV criteria. A multimodal treatment plan including psychoeducation, supportive psychotherapy, cognitive behavioral approaches and medication treatment was initiated. For the medication treatment, liquid fluoxetine at the dosage of 5 mg/day was started. In order to prevent any wrong dosage, B.E.'s mother was carefully instructed on how to administer the drug in the ordered dosage.

On the 6<sup>th</sup> day of the 5mg/day fluoxetine treatment, her mother came to our clinic and reported that B.E. had been having daily and nocturnal soiling episodes from the beginning of the treatment. It started on the very first day and was persistent over the next 6 days of treatment. Soiling was first identified by the family after noticing the streaks in B.E.'s underwear. B.E. stated that she was unaware of the soiling at first, which she later became aware of, mostly through the smell. During the 6 days, apart from the ones at home, she also had soiling episodes at school. On several occasions, her teacher called B.E.'s mother to take her home after she noticed the smell. Most of the episodes were in the daytime, however, she also had 4 soiling episodes in the night as well which were not reported as specific to any particular time of the night. She did not have fever, stomach aches, diarrhea or constipation. With the suspicion of an adverse effect, fluoxetine was stopped and the case was referred to the pediatrics clinic. In order to investigate a pre-diagnosis of FI, a detailed physical examination was made and several medical tests including a total blood count, liver and renal

functions, blood electrolytes, fecal examination and culture, urine analysis and a one hour routine EEG consisting of both wakefulness and sleep were performed. All of the test results were within the normal range with no pathologic findings or any medical condition which might explain the FI. Two days after the discontinuation of fluoxetine, B.E.'s mother reported that the FI had ceased; moreover B.E. had no further soiling episodes in the 30 day follow-up after the discontinuation of the SSRI treatment.

In the 2 months follow-up, B.E. attended weakly supportive psychotherapy and cognitive behavioral therapy sessions in our clinic. B.E.'s negative thoughts about herself were focused and alternated with more positive ones. A system of positive reinforcement and rewarding saw a gradual increase in her social activities and her academic motivation increased. Her regular psychiatric sessions also included the teaching of problem specific solutions and coping skills. Both B.E.'s parents and her school teacher were informed about her strengths and handicaps and were advised to hold more realistic expectations of her. After 2 months, although not completely resolved, B.E.'s depressive symptoms significantly decreased and her academic performance improved.

## DISCUSSION

In this case, the development of soiling with the start of fluoxetine use and the rapid disappearance of this symptom with the discontinuation of the drug strongly suggests that the soiling was an adverse effect of fluoxetine. The adverse reaction, the soiling in this case, may be referred to as "encopresis" with a behavioral perspective, or the term "FI" may be used, categorizing it as a gastrointestinal symptom. For the diagnosis of encopresis, along with the other criteria, DSM-IV seeks the absence of a general medical condition or a substance use as a causative factor (5). Since the symptom emerged secondarily to a drug use in this case, it does not fit DSM-IV encopresis criteria. FI, is defined as the involuntary passage of fecal material through the anal canal (15). Passive FI is fecal leakage without awareness of the patient (16) and this appears as the best definition for the symptom in the present case.

Regarding the course of FI, B.E.'s mother stated that FI diminished approximately 36 hours after the last dose of the drug. This correlates with the relatively long half

life of fluoxetine which is estimated to be between 2-7 days with a mean of 2.2 days (17).

As above mentioned, GIS-AE are frequently reported with SSRI use. In their retrospective chart review of adverse events in the general population of children and adolescents treated with SSRIs, Wilens et al. (1) found that GIS-AE, with a ratio of 29%, were the second most common adverse reactions after sleep disturbance. In this study, under the domain of GI disturbances, varying numbers of patients underwent appetite and weight changes, nausea, diarrhea and constipation but there were no children who developed FI. Other studies also reported high rates of GIS-AE, especially diarrhea and constipation with fluoxetine use in children (18-21).

For the children with PDD, GIS-AE of SSRIs may require special attention. In the chart review of Henry et al. (22) GIS-AE were common and 12 children of 89 (13%) had any gastrointestinal adverse events with SSRIs none of whom were reported to have FI. In a Japanese study, 6 of the 28 children with PDD experienced GIS-AE with fluvoxamine use and the drug was discontinued in one patient owing to diarrhea in addition to other adverse effects (23).

Other than the ones related to the medications, gastrointestinal symptoms and abnormalities in stool consistency were frequently reported by parents of children with PDD. Molloy and Manning-Cortney (24), in their sample of 137 children with PDD, found that 24% had a history of at least one chronic GIS symptom with diarrhea being the most common, occurring in 17%. In a more recent study, Levy et al. (25) found a higher prevalence of GIS abnormalities (54%), including abnormal stool consistency in children with PDD despite the lack of medical causes.

Increased rates of GIS symptoms and the reported significantly low tolerability and risk of GIS-AE with the use of SSRIs in the PDD population must be taken into account when explaining the emergence of FI in this case. FI may be interpreted as a severe and frustrating GIS-AE when compared with the mild GIS symptoms frequently reported in the general children population with SSRIs. In the light of these findings, the development of FI with fluoxetine may reflect the vulnerability of some children with PDD especially to severe GIS-AE of SSRIs.

It is widely known that in a subgroup of children with PDD there are abnormalities in the serotonin system (5-

hydroxytryptamine, 5-HT) and/or its receptors (26,27). A number of studies found increased platelet (28) and whole blood serotonin levels in autistic individuals (26,29). However, the complete etiology and clinical implications of increased serotonin levels in the PDD population have not yet been resolved.

Serotonin, as a neurotransmitter and/or modulator, is abundantly present in the gut, mostly stored in enterochromaffin cell (EC) granules. Released 5-HT stimulates the local enteric nervous reflexes to initiate secretion and propulsive motility and also acts on vagal afferents resulting in altered motility (30). Reuptake of 5-HT limits its diffusion and actions in the GIS tract. In several GIS disorders including chemotherapy-induced nausea and vomiting, carcinoid syndrome, inflammatory bowel disease and irritable bowel syndrome with diarrhea, abnormally increased 5-HT was shown (30). It's also known that the main source of blood 5-HT is gut EC (31).

In patients with PDD, there may be a relation between the well known increased whole blood and/or platelet serotonin levels and serotonin levels in GIS cells. Janusonis (31) suggested that one or more unidentified factors that interfere with brain development in autism may also participate in the regulation of 5-HT release from gut EC and possibly result in hyperserotonemia. In a subgroup of PDD patients, whether the source of increased blood serotonin levels is GIS, brain or unidentified system/factors, there is a considerable possibility of dysregulated or increased serotonin levels in GIS cells. If this is true, we speculate that the formerly high or dysregulated levels of serotonin in a patient with PDD may be overincreased with the use of an SSRI through the blockage of reuptake. Thus, the directly or indirectly overincreased levels of serotonin in GIS cells and its diffusion into the GIS tract may result in altered functioning and motility in GIS. This may lead to abnormal bowel functioning, GI symptoms and possibly

FI. However, it can be argued that we might have expected our patient to have diarrhea to prove this hypothesis since increased GIS motility frequently manifests itself in the form of diarrhea. We believe that, the trueness and/or causative role of these scenarios in this case is uncertain and the exact mechanisms to explain the etiopathology of this adverse reaction is unclear.

Regarding the dose of fluoxetine, Posey et al. (10), in their review of the literature, pointed out that children with PDD somehow respond well to very low doses of SSRIs but experience adverse effects with small dose increments. Since we discontinued fluoxetine on the 6<sup>th</sup> day, there is no evidence for the efficacy of the drug. However, the dose of 5 mg/day was a fairly low dose for treating depression in a 9 year old and this dose resulted in FI. Whether this adverse reaction is dose dependant or idiosyncratic could not be completely identified. However, the emergence of FI with the dose of 5 mg/day, a beginning a dose, strongly indicates that this reaction was idiosyncratic.

It is notable that the prior medical history of our patient did not reveal any chronic GIS symptoms, frequent diarrhea or constipation. It seems likely that the presence or past history of GIS symptoms may increase the risk of GIS-AE with SSRIs. However, one intriguing possibility for patients with PDD is that the patients who don't report clinical GIS symptoms still may have GIS abnormalities and may be vulnerable to GIS-AE of drugs. It is demonstrated that the patients with PDD have multiple pathologic, histopathologic and functional GIS abnormalities when compared with the normal population (32).

Gastrointestinal symptoms must be carefully examined when using SSRIs in children with PDD. It is not known whether the adverse effect of FI is unique to fluoxetine, or if other SSRIs may cause this reaction. Further research is needed to clarify the exact pathophysiologic mechanism of this adverse reaction.

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