



# Is Fluvoxamine Effective for Repetitive Behavior in Tic Disorder and Autism?

Xiaoyan Ma\*, Ranli Li, Feng Jia, Ying Wang, Jie Li

Department of Mental Health, Tianjin Anding Hospital, China

## ABSTRACT

Emotional and behavioral abnormalities are prominent in mental disorders, especially in autism, tic disorder and Obsessive-Compulsive Disorder (OCD). Repetitive behavior seems to be characteristic of them. It is difficult to distinguish stereotyped or compulsive-like behavior for diverse clinical symptoms exhibited in these patients. Selective Serotonin Reuptake Inhibitor (SSRIs) was recommended as the first line in treatment for OCD. Fluvoxamine was a good choice for OCD especially in children. Behavior and emotion were improved under therapy with SSRIs including fluvoxamine in autism and tic disorder. Moreover, the disease get remission is also based on improvement in behavior and emotion. Repetitive behavior seems to be common feature of autism, tic disorder and OCD. It also plays a key role in therapy and prognosis of the disease. Behavior improved in our report cases treated with fluvoxamine, so fluvoxamine maybe a good choice for abnormal behavior regardless of the diagnosis of the disease. However, a clinical study in a larger sample is needed to confirm its efficacy in patients with abnormal behavior especially with repetitive behavior and to elucidate the mechanism underlying its effect.

Keywords: Tic disorder; Autism; Fluvoxamine; Repetitive behavior; Obsessive-Compulsive Disorder

## INTRODUCTION

Psychopathological symptoms are complicated in mental disorders. The clinical symptoms are diverse in different patients even though diagnosed as the same mental disorder according to the current classification of diseases. And more and more patients are difficult to diagnose with a certain disease. Comorbidity is very common in mental disorders in recent research [1-3]. However, some similar clinical symptoms are found in different mental disorder. Emotional and behavioral abnormalities are prominent in mental disorders, especially in Obsessive Compulsive Disorder (OCD), Tic Disorder (TD) and Autism. Restrictive, repetitive, and stereotyped patterns of behavior seem like the core symptom but not characteristic symptoms in Autism

patients [4]. Similar symptoms also occur in patients with OCD patients especially in those patients with compulsive behavior [3]. Recurrent stereotyped motor movement also appear in Tic disorder patients, characterize by a sudden rapid, non-rhythmic movement [5]. Repetitive behavior seems to be a common feature of autism, OCD and tic disorder.

Comorbidities are very common in mental disorders. About 50% of tic disorder patients are comorbid with obsessive-compulsive disorder. 17%-37% of young people with Autism also experience OCD symptoms [6,7], although the proportion of youth with OCD who also meet diagnostic criteria for tic disorder is less clear. People with co-morbid conditions have clinically distinct psychopathology and impairment compared to those

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**Corresponding author** Xiaoyan Ma, Department of Mental Health, Tianjin Anding Hospital, China, E-mail: ma\_xiaoyan81@126.com, Jie Li, Department of Mental Health, Tianjin Anding Hospital, China, E-mail: jieli@tjmhc.com

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with autism or OCD only [2,8,9]. Structural abnormalities in key brains including frontal and temporal lobe regions result in similar symptoms with autism or OCD were found by Zhan et al. in autism comorbid with OCD patients which may be attributed to the developmental consequences of changes in neural circuits caused by changes in specific genes (the methyl CpG binding protein 2, MeCP2) [10]. Neural circuit abnormal was found in OCD patients especially in Cortico-Striato-Thalamo-Cortical (CSTC) circuit. And at the same time, abnormal activities occur in CSTC circuit which involved in tic disorder [11]. CSTC circuit is related to the regulation of emotion and behavior. The abnormality of neurotransmitters in some brain areas in CSTC neural loop may be involved in the pathological mechanism of autism, obsessive-compulsive disorder and tic disorder. Studies show that Selective Serotonin Reuptake Inhibitors (SSRIs) drugs are effective in the treatment of these diseases; SSRIs are a class of antidepressants which are sometimes given to help anxiety or obsessive compulsive behaviors [12]. Fluvoxamine was prescribed for treatment in autism patients, repetitive thoughts and behaviors, aggression, social relatedness, and repetitive language improved significantly with minor adverse effects including nausea and sedation [4]. Fluvoxamine is recommended a first-line drug for the treatment of OCD and it take effective in treatment of psychiatric comorbid conditions in Tic disorder. Repetitive or compulsive-like behaviors were the characteristic symptoms in OCD, autism and tic disorder. So is fluvoxamine effective for compulsive-like behavior? Here we report some cases treated by fluvoxamine. The cases have obtained informed consent from themselves or their legal guardians.

## CASE REPORT

### Case 1

A 13-year-old boy was diagnosed as tic disorder for more than 2 years. He felt sad by his left shoulder, head and mouth tic but without sound. Thiopril was prescribed for one year with 100 mg, but the clinic effect is poor, the tic movement still existed. Aripiprazole 5 mg QD was prescribed as combination therapy for 3 months, the frequency and amplitude of tic movement was reduced. His parents found tic movement was obvious when the boy was nervous. And poor sleep and unstable sleep was existed. So fluvoxamine 25 mg QN was added for release the anxiety. 2 weeks later, sleep and anxiety improved obviously, and meanwhile tic movement was reduced significantly than before. Tic movement was seldom observed by others.

### Case 2

A 15-year-old boy with a 13-year history of autism, who can't speak, but can make voice simply. He doesn't look at people when communicating. He doesn't sleep well, with difficulty in falling asleep and waking up early. He was scratching the skin repeatedly. He likes to dismantle things and destroy them. The boy's parents complained that the boy was abnormal when he was 2-year-old. He could not speak and play alone always. He was not close to his parents. He was diagnosed with autism in pediatrics of psychiatric hospital and was treated intermittently. The specific treatment process was not remembered by his parents. Risperidone, olanzapine, haloperidol, aripiprazole and other antipsychotics was for treatment, but extrapyramidal re-

actions such as hanging from the corners of his eyes, hydrostomia etc., and result in failure of standardized therapy. Due to poor sleep and irritability, children were given benzodiazepines such as eszolam and alprazolam to improve sleep, and the effect was not very satisfactory. His parents complained that he was very nervous when he was outside. And along with scratching behavior repeatedly increased and insomnia worsened when retuning home. 50 mg fluvoxamine combinations with 2 mg clonazepam were treated for two weeks. Repeated scratching behavior was significantly reduced and sleep improved at the same time.

### Case 3

A 45-year-old male has repeatedly checked for more than 3 years. He has to repeatedly confirm whether the door is locked when he goes out. The similar behavior seems prominent in home. He prone to confirm where the wallet and keys repeatedly. He had to repeatedly think about some unimportant things and some trivial things in life. Although he knew it's unnecessary and still could not control it. His mood is slightly low, the attention is not concentrated, and even when communicating with other people, and he often lost his mind. He suffered from insomnia, waked up early. He felt troublesome and realize some wrong happened to him before seeing a doctor. He was diagnosed as OCD and treated with 50 mg fluvoxamine combination with 5 mg zolpidem tartrate tablets. Sleep improved first after taking medicine for one week. The dosage of fluvoxamine was increased to 100 mg. The behavior of repeated examination and repeated thinking were less than before after treatment for 1 week. After about 4 weeks of treatment, the patients' symptoms of compulsion and obsession was reduced significantly, this had little impact on his life.

## DISCUSSION

Autism is a developmental disorder which characterized by problems with social interaction and communication, as well as repetitive behaviors and limited activities and interests. Restrictive, Repetitive, and Stereotyped patterns of Behavior (RRBS) is the core symptom in autism, it is difficult to distinguish between compulsive and stereotyped behavior based on repetitive behaviors. Compulsive or compulsive-like behaviors maybe the most important diagnostic marker of autism in children. Adults who had autism exhibited more compulsive behaviors such as touching, tapping, rubbing, hoarding, and self-damaging than adults who had OCD [13]. The patient showed more compulsive behaviors with self-damaging in our report case. So is it comorbidity of autism and OCD or subtype of autism? It is estimated that 17%–37% of young people with ASD also experience OCD symptoms [6,7]. The results of animal studies show the comorbidity of autism and obsessive-compulsive disorder and the similarity of symptoms. The behaviors in autism patient are variety. Patients comorbid with OCD and autism show clinically distinct psychopathology and impairment compared to those with autism or OCD only [2,8,9]. And elevated blood serotonin levels in individuals who had autism were found by researchers [14]. They also found that serotonin system dysfunction showed impact on critical areas of the brain, including the cerebellum, thalamus, and frontal cortex [14]. These areas are the critical areas of the brain in the CSTC loop. CSTC loop is also involved

in pathological mechanism of OCD in regulation for mood and compulsive behaviors. So it seems to be plausible in similarities between RRBIs in ASD and the repetitive and obsessive behaviors observed in OCD. Similarities between RRBIs in autism and the repetitive and obsessive behaviors observed in OCD, where pharmacologic treatments with SSRIs are considered a first-line treatment, led to research on the effects of SSRI interventions in autism [15]. Significant improvements in repetitive thoughts and behaviors, aggression, social relatedness, and repetitive language in autism were confirmed by McDougle and colleagues' study [16]. SSRIs are effective in autism, which was observed in our report case treated by fluvoxamine. SSRIs are effective in treatment for anxiety or obsessive-compulsive behaviors. In addition to its primary effects on the serotonin transporter, fluvoxamine also involved in dopamine regulation [17]. Serotonin system and other neurotransmitter systems including dopamine play an important role in regulation of human behavior and mood such as aggression, anxiety, repetitive behaviors, mood, impulsivity, sleep, ingestion, reward systems, etc., which was observed in autism.

Tic disorders are complex neuropsychiatric disorders, according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) [18], tics are sudden, rapid, recurrent, non-rhythmic motor movements or vocalizations. Tics may be simple or complex tics that involve the head, neck, trunk and/or extremities (upper or lower) [19]. Motor tics can involve eye blinking, lip smacking, shoulder shrugging, grimacing, head tossing, simultaneous head turning and shoulder shrugging or other movements. Tics usually appear in childhood. Tic disorder is found in 4%-20% of pediatric persons. Motor tics sometimes seemed rigid. Tics are movements especially habit spasms that are sudden, brief, purposeless and involuntary [18,19]. The term, stereotypies, refers to movements that more prolonged than tics; they are purposeless, rhythmic, and repetitive. Stereotypies are impulsive, specific to each patient, and usually begin under age 3 years [20]. In addition to frequent tics, people with tic disorder are at risk for sleep and comorbid including anxiety, depression and OCD et al. psychiatric disorder [21]. 30% to 60% tic disorder comorbid with OCD. The behavior of tic is repetitive and uncontrollable, which is very similar to compulsive behavior. It is sometimes difficult to distinguish between tics with compulsive behavior or tics with stereotype. A subtype of OCD with tics has been classified as an OCD subtype by researchers [22]. The DSM-5 taxonomy removed the term, stereotype, from definition of a tic and also added a new specifier, tic-related, to its Obsessive-Compulsive Disorder (OCD) [18]. The tics can be worsened under the influence of stress or anxiety and they can be voluntarily suppressed for periods of time ranging from minutes to hours. In our report case, the tics are worsened when the boy feels anxious, but the tics significantly reduced under fluvoxamine treatment accompany by the improvement of anxiety.

Involuntary, repetitive and chronic behaviors are exhibited in patients with autism, tic disorder and OCD. And they are core symptoms in these patients. The improvement of these core symptoms is closely related to the overall prognosis of the disease. Although the treatment guidelines have different treatment methods for three diseases, scientific research and clinical practice have confirmed that SSRIs drugs are very effective for

these three diseases. Fluvoxamine was recommended as the first line for OCD especially in child. And it seems like fluvoxamine is also effective in autism and tic disorder. In our case report, abnormal behaviors were shown in these patients maybe more typical, and the patients feel anxiety accompanied by abnormal behavior in these cases. Repetitive, chronic and uncontrollable behaviors seem to be prominent in three cases. Fluvoxamine was added to improve symptoms; overall improvement was seen with reduction of repetitive behaviors and relief of anxiety in our report. The effect was confirmed by other studies [23-25]. Although the regulation of dopamine by SSRI drugs has caused some side effects in the treatment of some mental diseases, fluvoxamine plays an important role in regulation serotonin and dopamine which was involved in abnormal behaviors such as repetitive behaviors, regression and anxiety [4,26]. So maybe fluvoxamine is effective to improve repetitive behaviors and compulsive-like behaviors.

There are some limitations in our report. First, our cases are isolated case could not confirm the efficacy of fluvoxamine in autism, tic disorder and OCD. Large-scale studies are needed in the future to confirm the efficacy in autism, tic disorder. Second, high functional autism, only simple motor tic and compulsive behaviors in our report cases, which similar behaviors were happened in these patients. And exception for compulsive-like behaviors, anxiety was also prominent in these patients. Accumulation of more cases is needed to clarify both the pathological and etiological mechanisms of fluvoxamine in autism and tic disorder. Third, in our report it is difficult to distinguish where compulsive or compulsive-like behaviors are. And we could not differentiate whether these repetitive behaviors are the core symptoms of these disorders or compulsive behaviors caused by comorbid with OCD.

## CONCLUSION

Fluvoxamine was recommended as the first line for treatment OCD. It is effective for reduction of compulsive behaviors. RRBS is the core symptom in autism that it is difficult to identify whether the repetitive behavior is compulsive behavior or stereotyped behavior. Dysfunction in serotonin system in autism implicated that SSRIs may be effective for autism. Fluvoxamine was a good choice for treatment in autism. Motor tic exhibited some compulsive-like behavior, which is related to abnormal structure or function of brain in CSTC loop. CSTC loop is involved in the pathological mechanism of autism, tic disorder and OCD. SSRIs was added for treatment in tic disorder especially comorbid with OCD. Repetitive behaviors in tic were considered to be a subtype for tic-related OCD. Fluvoxamine was effective in improving the repetitive behaviors whether the compulsive behaviors or compulsive-like behaviors showed by patients in our case report. Therefore, regardless of the diagnosis of the disease, fluvoxamine maybe a good choice for abnormal behavior. However, a clinical study in a larger sample is needed to confirm its efficacy in patients with abnormal behavior especially with repetitive behaviors and to elucidate the mechanism underlying its effect.

## CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be

construed as a potential conflict of interest.

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## AUTHOR'S CONTRIBUTION

Xiaoyan ma and Ranli Li contributed equally to this work. Both authors contributed to the conception and design of this manuscript. Both authors wrote the first draft of the manuscript. Feng Jia and Ying Wang are responsible for research literature and check. Jie Li is responsible for revision. All authors contributed to the manuscript revision and approved the submitted version.

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