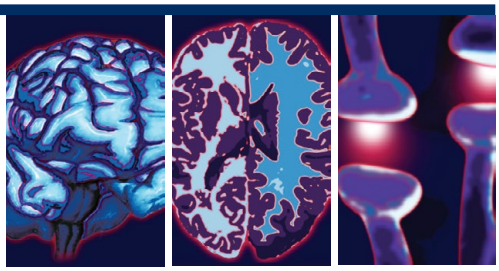
Case Report



Low Doses of Venlafaxine in a Young Man with ASD and Behavioral Disorders: A Case Report

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Abstract

Objective: No specific pharmacological approach to behavioral disorders in patients with severe intellectual disabilities associated with autism spectrum disorder (ASD) exists. Neuroleptics are known to be epileptogenic, and benzodiazepines have an adverse effect on their already limited cognitive capabilities. The possibility of managing behavioral disorders in persons with ASD via antidepressants, namely venlafaxine, could provide a substantial improvement in their overall condition and quality of life and could contribute to the definition of a specific pharmacological indication.

Method: The present case report describes the effect of venlafaxine at low doses (18.75 mg/j) in an 18-year-old patient with ASD, severe intellectual disabilities and behavioral disorders. Based on the records kept by the patient's mother and our clinical observations, we describe the evolution of this young man from birth to 18 years of age.

Results: Since the introduction of venlafaxine, the patient's behavioral troubles improved greatly. There was major progress in attention, and the patient became calm and appeased, able to obey to simple commands and to control his hunger. He became notably less aggressive with himself and others, he became better at managing relationships, and he was more conciliatory and accepting of being touched. Today, this young man continues his apprenticeship of everyday life. He is quieter and has learned simple actions performed in an everyday context. He can smile and lend attention to the environment and to other persons. Some problems remain unresolved, such as movement and double incontinence.

Conclusion: The improvement of our patient is challenging behavior shows encouraging progress in the treatment of ASD's typical behavior disorders. The use of antidepressants represents a substantial improvement in the care of patients with intellectual disabilities, ASD and severe behavioral disorders. These results are evidence of a new pharmaceutical strategy for the improvement of the quality of life of these patients.

Keywords: Autistic spectrum disorder; Behavioral disorders; Pharmacological treatment; Antidepressant; Venlafaxine

Introduction

There are currently no specific pharmacological strategies for the treatment of behavioral disorders in patients with intellectual disabilities, particularly in cases of severe intellectual disabilities associated with autism spectrum disorder (ASD) [1-3].

A major issue when caring for patients with

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ASD is controlling their severe behavioral disorders. Good results have been obtained with neuroleptics and benzodiazepines, but these drugs have side effects that include the worsening of epileptic symptoms [4, 5] and the degradation of cognitive capabilities [6-8].

In patients with intellectual disabilities and ASD, psychotropic treatments are rarely administered via a specific regimen, and in general, these patients are treated analogously. Patients with ASD and behavioral disorders are difficult to study due to their reduced compliance and to the ethical issues associated with the protocols involving this population. Consequently, the scholarly literature on this population tends to be limited [9-14].

Behavioral disorders observed in adults with ASD, such as aggressive attitudes toward themselves, others, or objects, can be very difficult to control, and such disorders are one of the most serious hindrances to social integration, even in specialized institutions. A wide pharmacological range of drugs is used for patients with ASD. The use of neuroleptics with antipsychotic functions is based on sedation. However, we note that patients with autism differ from patients with psychosis, insofar as the presence of delusions and hallucinations is unlikely in patients with ASD and can rarely be objectified due to their minimal language skills [15].

Farmer et al. [16] and Weeden et al. [17] have reported that new research avenues have been developed on cholinergic and glutamatergic treatments and oxytocin. Spooren et al. [18] observed that disorders such as fragile X syndrome, Rett syndrome, and neurofibromatosis are similar to autism and may provide hints for pharmacological studies on glutamatergic receptors. Matson and Hess [19] noted that few studies have captured the relationship between the positive effects of psychotropic treatment on behavioral troubles and the appearance of side effects, and stress the need for studies on the cost–benefit balance of treatment. In a study on children, West et al. [20] underlined the importance of studies on the side effects of psychotropic medications. Memari et al. [21] demonstrated that antipsychotics are widely used in children and adolescents with ASD (57.4%), while the use of antidepressants is very limited (8.7%).

The use of Selective Serotonin Recapture Inhibitors (SSRI) has been described in cases of aggressiveness in children and adolescents with ASD and behavioral problems. Moreover, sertraline has been shown to be effective in the short and long term in cases of aggressiveness and self-injurious behaviors (SIBs) in adults [22] and in adolescents and young adults [23] with developmental disabilities. Steingard et al. [24] reports that sertraline at a dose of 25–50 mg/day is effective in 2–8 weeks for symptoms such as anxiety, panic attacks, irritability, or agitation in children with ASD aged between 6 and 12 years. Davanzo et al. [25] describes an improvement in SIB in patients with intellectual disabilities treated with paroxetine. A study involving the use of fluoxetine showed some improvement in adults and pediatric patients with SIB [26]. Other SSRIs, such as citalopram [27] and fluvoxamine [28, 29], are reported to improve psychiatric symptoms such as anxiety, agitation, depression, and obsessive–compulsive disorder in individuals with ASD.

Another promising treatment is venlafaxine [30, 31], an antidepressant that causes the inhibition of the reuptake of serotonin, norepinephrine, and, to a lesser extent, dopamine [32, 33]. Hollander et al. [34] described venlafaxine treatment in 10 subjects with ASD according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition [35], starting with a dose of 12.5 mg/day and further adjusted on a clinical basis. Six of the ten subjects reacted positively to the treatment, with a score of 1 (very good response) or 2 (much improved) on the Clinical Global Impressions Improvement (CGI-I) Scale [36]. Low doses (average, 24.37 mg/day; range, 6.25 to 50 mg/day) of venlafaxine were effective and well tolerated. Positive effects included such aspects as repetitive behaviors, restricted interests, social deficits, communication and language, and inattention and hyperactivity.

As suggested by Hollander et al. [34], we utilized venlafaxine in our practice, and we witnessed that low-dose venlafaxine was able to quickly reduce behavioral problems and improve the psychic state in three of our young patients with intellectual disabilities associated with developmental disorders (autism and related disorders) [37]. In the presence of pervasive developmental disorders, venlafaxine has been effective in behavior disorders, irritability, anxiety, and aggressiveness.

We hypothesized that venlafaxine operates via serotonergic mechanisms, as suggested by the studies on SSRIs mentioned previously. Knowledge of the effect of venlafaxine in

patients with ASD facilitates the understanding of the neurobiological mechanisms active in the pathophysiology of the illness and the therapeutic response to venlafaxine.

Antidepressants constitute a clinically well-tolerated alternative psychopharmacological treatment that could promote substantial improvement in the care of ASD patients with behavioral troubles [3, 24].

In a previous study, we reported behavioral improvement in adults with ASD treated with low doses of venlafaxine. In a follow-up double-blind study, we found significant differences between the venlafaxine and placebo groups in multivariate analyses. The relevance of this result is that it provides evidence of the efficacy of this new pharmaceutical strategy to control behavioral disorders in patients with intellectual disabilities and ASD.

It should be noted is that the population under study has a specific fragility with respect to cognitive skill and epilepsy. Neuroleptics are known to be epileptogenic and benzodiazepines have an adverse effect on their already limited cognitive capabilities. The possibility of managing behavioral disorders in persons with ASD via an alternative psychopharmacological strategy, such as antidepressants, could introduce a substantial improvement in their overall condition and quality of life and could contribute to the definition of a specific pharmacological recommendation [21, 24].

Case Report

The present case report describes the effect of low-dose venlafaxine in an 18-year-old patient with ASD, severe intellectual disabilities and behavioral disorders. We describe this young man's clear improvement in behavior and quality of life after the introduction of a low dose venlafaxine (18.75 mg/j).

At 18 years of age, the Intellectual Quotient (IQ) of the patient was not testable with the Wechsler Adult Intelligence Scale [38]. The Vineland Adaptive Behavior Scales [39] yielded a mental age inferior to one year and the Childhood Autism Rating Scale [40] was rated at 37.

The patient is the eldest of two siblings, his brother being two years younger. The antenatal history of the patient was characterized by the presence of premature contractions at 6 months. Vaginal delivery with the application of forceps occurred at 38 weeks with cervical bleeding after delivery. The Apgar index was 9 after 1 minute and 10 at 5 minutes. Birth weight was 3060 g, length was 48 cm and cranial circumference was 36 cm.

At 1 month, the baby presented with a sterno-mastoid hematoma and congenital torticollis, which resolved with physiotherapy treatment. Evan was a smiling baby, looking at his parents with no apparent concern.

At 8-9 months, there was a suspicion of epileptic twisting episodes, with shaking of the right lower limb without loss of consciousness, sometimes followed by collapse and hypotonia. The EEGs were normal, but the toddler presented visible psychomotor retardation. At 10 months, he began trying to sit up, without managing, showing thumb adductus and poor handling. He started to screech (different from typical infant yelling and crying).

At 12-13 months, he managed to stand up, but his thumbs were always turned inward. Evan exhibited copious drooling and placed everything in his mouth. At approximately 12 months of age, he began psychomotricity therapy.

Seizures and agitation continued, and at 2 years of age, episodes of clonic movements of the right lower limb began, resulting in falls with no cyanosis or loss of contact. Valproate treatment was started (25 mg/kg/day), but it was stopped after 6 months because the patient presented red skin patches and biting marks inside the cheeks. He exhibited hypotonic phases alternated with aggressive outbursts and biting of others. His sleep became instable.

Metabolic and genetic assessment as well as karyotype and fragile X tests were negative. Cardiopulmonary assessment and neurological evaluation were average (sharp and symmetrical deep tendon reflex, rudimentary thumb adductor 3-finger clip). The eye fundus was found to be within the norm. Magnetic resonance imaging (MRI) showed no pathological signs. Allergy testing was negative.

From a developmental point of view, there was absence of speech and verbal comprehension. The child presented stereotypical irritability with cries and restricted interests. Clinical observation revealed the presence of the autistic triad together with severe autism disorders.

At 2 years old, the child was able to stand, cried frequently, and presented drooling and severe

agitation. Psychomotor assessment determined that the ability to walk had not developed. The child could not follow a simple order, or name or designate an image. His thumbs were always turned inward, and he was not able to manipulate cubes. The child was able to sit on the floor in a W shape.

At 2 and half years old, he could walk autonomously, but only on tiptoes. The child could not pronounce words, but he could babble. His playing activities were focused on turning the wheels of his toys. He ripped books apart. He could not tolerate anyone touching his head, and he frequently pulled his hair. He had trouble falling asleep and sleeping. Hearing and vision tests were normal. A specific genetic test failed to detect any sign of fragile X syndrome. The child was hypotonic in the lower limbs and hypertonic in the whole body.

There was a suspicion of epilepsy. A blood test revealed a slight increase of glutamine citrulline. Treatment with carbamazepine was introduced (10 mg/Kg/day). The child began psychomotor therapy, which continued when he entered a specialized school in Geneva.

Between 4 and 5 years old, the child continued to be very agitated, but he could remain quiet for hours "scratching" a radiator in search of vibrations or turning the wheels and watching toys from all angles. He was abrupt but precise in his movements (like throwing a small car right in his parents' face). He was active throughout the day and required continuous supervision, as he had no awareness of danger. He constantly presented challenging behaviors, such as yelling and sputum (drooling).

At 6 years old, the concomitant presence of carbamazepine's side effects (biting the inside of his cheeks) and a relative amelioration of the epileptic condition (a partial disappearance of the left frontal epilepsy) were observed. This, together with obsessive-compulsive disorders associated with carbamazepine, led to the decision to progressively cease this treatment.

Between 6 and 7 years old, the child's only relationship with other children consisted in pulling their hair and clothes, spitting, and screaming. He could not tolerate his parents wearing anything on their head, and he pulled glasses off other people.

The child made some progress, his contact improved and he started imitating gestures. He still presented restricted activities. He could not point but began to include simple instructions in context, and he was able to say 10 words and imitate animal noises. His attention span remained short. The physical examination was normal apart from lesions on the hands due to mild self-injurious behavior. The sores were slow to heal as he did not tolerate bandages and kept scratching his wounds.

He could not tolerate change, throwing everything within reach. He looked at himself in a mirror at length and seemed to enjoy vibrations (large balls, guitar chords).

Sleep disturbance persisted (delayed falling asleep and frequent awakenings during the night).

Occupational and speech therapy were added to accompany the psychomotor treatment.

At 9 and half years old, while there was no improvement in the behaviors described above, risperidone (Risperdal) was introduced (0.5 mg/day) to reduce agitation and crying. Because of the persistence of sleep disorders, he began to take melatonin 3 mg at 20 h to facilitate sleep.

Carbon insoles were introduced to mitigate mild problems in walking, but did not show improvement after one year.

Between 9 and 10 years old, the child was mesmerized watching cartoons, and he was able to look at them without "moving" or jumping up and down. It was possible to leave him unattended for a long time.

At 10 years old, moderate problems in posture were noticed, as well as internal rotation of both hips. The child could walk and run without difficulty, but maintained the tendency to walk on tiptoes.

Between 9 and 10 years of age, there was little change; agitation and the typical behavior persisted. The child was growing and gaining strength. He could walk but sometimes refused to move. He continued to sit in a W posture and traveled in strollers.

At 11 years old, retraction of the Achilles tendons was observed. Developmentally, language evolved slightly, allowing the child to express anger and indicate the parts of the body. He still could not perform symbolic play, limiting himself to repetitive play (turning wheels). He learned to bike with side wheels. Social contact was restricted but good, without gaze avoidance; he was able to point with his fingers. He had no autonomy in normal daily

activities. Due to his double incontinence, he always wore diapers, night and day. Routine physical and neurological examinations did not show problems. Orthopedic radiological examinations of his hips showed that they were correctly positioned. Some side effects appeared with risperidone, such as compulsive appetite, impatience and body tension.

At 12 years old, the child entered a specialized residence. Walking difficulties worsened with progressive bilateral equinovarus (clubfoot), causing falls. Repeated episodes of tonic hyperextension or flexion of the upper and lower limbs was observed, together with backward arching triggered or untriggered by emotions. Risperdal 0.5 mg was still administered in the evening. Sleep quality was good, but difficulties in falling asleep persisted. Clinical and neurological examination revealed decreased tone of the upper limbs, normal and symmetrical osteo-tendinous reflex, increased lower limb tone, slight tendon retraction, shortened Achilles tendon and hollow legs. No ataxia or developmental regression was detected, but language progress was slow or absent. Presence of stereotypies or mannerisms was noted. Psychomotor therapy, speech therapy and occupational therapy were introduced.

Between 12 and 13 years of age, the child showed a constantly high level of agitation, but he could stay quiet for long time periods in front of cartoons. No improvement was registered in the behaviors described above. His integration in the residence proceeded with many conflicts with other guests. He was attracted to bicycles, tractors, and motorcycles, and he did not show an awareness of danger and would run away frequently. He presented behavior disorders, such as tightening, stiffening and bending over from head to toe.

Transitions from school to home were difficult; he reacted by striking, shouting and spitting. During this period, constipation problems appeared, associated with a bulimic tendency. He was always hungry.

EEG tracing failed to detect any epileptic focus. No spasms were detected during the exam. Some artifacts were detected. Traces had no worrying anomalies, but a slight asymmetry of background activity to the detriment of the right side.

Genetic testing with array comparative genomic hybridization (array-CGH) showed normal results for males, with no detected anomaly. Additionally, brain MRI showed no detectable abnormalities. Blood and urine laboratory tests were normal.

Between 14 and 15 years of age, disorders related to adolescence started to appear. He challenged his parents' looks, provoking them. He became violent towards others and himself, refusing to eat or drink, hitting the walls and tearing his clothes. Having reached sexual maturity, he presented many masturbation episodes. He isolated himself for compulsive masturbation.

Risperidone was stopped and 3 mg melatonin was administered at night and increased to the maximum dosage. It was then stopped because there was little improvement.

A trial with clonidine (37.5 mcg/day) started at the age of 14, but it provoked paradoxical effects (agitations, insomnia, clastic crisis and seizures) and was stopped after two weeks.

At 16 years old, there was no progress in challenging behavior. He continued to scream and spit continuously, walking agitatedly for several hours. He exhibited crises of violence at night, breaking everything in his room. He was hospitalized for three weeks in a psychiatric unit. Laboratory tests and pupillary light reflex showed no anomalies. He tested negative for intolerance to gluten, lactose and casein.

Quetiapine (6.25 mg) was introduced at night, and then increased to 6.25 mg in the morning, afternoon, and 12.5 mg in the evenings. Mild improvements in the behavioral disorder were observed, with less severe agitation and aggressiveness.

Melatonin was reintroduced at 3 mg at bedtime, this time with satisfactory effects.

A new orthopedic examination revealed that he was still walking on tiptoe with important antetorsion of the hips; with plantigrade feet, he could only make small steps. The examination also revealed bilateral 5° dorsiflexion with extended knees, good mobility of the hips and a properly aligned spine.

To alleviate the alternating episodes of constipation, false diarrhea and real diarrhea, an osmotic laxative and granulate argyle were introduced following normal clinical practice and with positive effects.

Low-dose venlafaxine (18.75 mg/ day) was introduced when he was 17 years old. Screaming and spitting began to disappear and his transitions from school to home were better

handled. He gave kisses, let himself be handled more easily and gained autonomy in everyday activities. He became calmer, more composed and attentive. While he still ripped his clothes and put the threads to his mouth, but he was able to remain very quiet.

At 18 years old, major progress in attention was observed. He could stay calm and appeased. He was able to obey to simple commands and could control his hunger. He became notably less aggressive with himself and others. The episodes of compulsive masturbation disappeared. Screaming and spitting disappeared almost completely. He could better manage his relationships with others, being more conciliatory and more accepting of being touched. He became cunning and playful. He could be "cuddly," giving his parents kisses on the cheek. Transitions in places and situations were better experienced. He was sleeping well, and even though nocturnal awakenings were still present, he could go back to sleep by himself.

Today, this young man continues his apprenticeship of everyday life. He is quieter and has learned simple actions performed in an everyday context. He can smile and be playful and lend attention to the environment and to other persons. His language is composed of about ten words. It progresses slowly but continuously. He sleeps well and eats well. He progresses in his acquisition of small segments of autonomy, but always with the support of the adults. The cries have almost disappeared; sputum is present only in cases of major stress or frustration.

Some problems remain unresolved, such as issues with movement and double incontinence.

Overall, he is peaceful yet interested and present in relationships. He is less parasitized by his "moods," and his character remains unchanged: in the words of his mother, "a strand of opposition and a touch of malice."

Conclusion

The improvements in the challenging behavior of this young man throughout his entire lifetime provides hope for the treatment of ASD's typical behavioral disorders. In this case report, we assess behavioral improvements in a young adult with ASD treated with low doses of venlafaxine. The use of antidepressants could be considered a clinically well-tolerated alternative and could represent a substantial improvement in the care of patients with intellectual disabilities, especially if severe, along with autism spectrum disorder (ASD) and other severe behavioral disorders.

The importance of this result is that it provides confirmation of a new pharmaceutical strategy to improve the quality of life of these patients and contributes to the definition of a specific pharmacological recommendation [21, 24].

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