

## Case Report

# Vortioxetine Add-On to Methylphenidate for the Treatment of Symptoms of Sickness Behavior in Attention-Deficit Hyperactivity Disorder: Report of Two Cases

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**Abstract:** Youth with Attention-Deficit Hyperactivity Disorder (ADHD) may suffer from comorbid difficulties, such as anxiety–depressive symptoms, social withdrawal, and somatic complaints. Although stimulants remain the ADHD cornerstone treatment, mental fatigue, school problems and low self-esteem may persist, often being the most unacceptable symptoms for these patients. We present two cases of adolescents (14 and 15 years old) with methylphenidate-treated ADHD, where cognitive fatigability, depressive thoughts, anxiety, irritability, and poor social relationships remained. Based on clinical observation and the completion of parent and child rating scales, the aforementioned manifestations appeared to progressively reduce by the time of the subsequent control visits planned 1, 3, and 5 months after, following the use of vortioxetine (up to 10 mg/day) as add-on therapy to methylphenidate. No significant side effects were reported in both cases in a follow-up period of 3 months, also supporting the stability of the observed clinical improvement. Vortioxetine monotherapy has already been tested for the treatment of anxiety–depressive symptoms in youth, as well as ADHD in adulthood. The cases presented here suggest that vortioxetine could also be an effective option for ADHD treatment in childhood and adolescence, warranting further investigation of its potential benefits as both a monotherapy and adjunctive therapy to stimulants.



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## 1. Introduction

According to the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5), Attention-Deficit Hyperactivity Disorder (ADHD) is a childhood-onset neurodevelopmental condition, characterized by attentional fluctuations, increased motor activity and impulsive behavior, interfering with the subject's daily activities in social and school/job contexts. It is considered to affect executive functions, including planning skills, working memory, and behavioral inhibition. ADHD can often be associated with psychiatric comorbidities, such as Conduct Disorder and Oppositional Defiant Disorder during childhood, as well as mood and anxiety symptoms in both children and adults. Anxiety may be reported over an ADHD patient's lifetime, from inhibiting impulsivity during childhood to aggravating working memory impairments during adolescence and exacerbating sleep difficulties during adulthood [1]. Irritability and Disruptive Mood Dysregulation Disorder (DMDD) have also been associated with ADHD, increasing the risk of depression in adulthood [2].

Pharmacotherapy with stimulants such as methylphenidate (MPH) and amphetamines is still the cornerstone treatment for ADHD. Evidence also suggests there are beneficial

effects of behavioral approaches, mainly on ADHD-related cognitive symptomatology, supporting their use in combination with medications [3]. However, even when multi-modal treatments are offered, ADHD patients may still present with cognitive difficulties and fatigue, distractibility, reduced motivation and interest, poor social interaction, and anhedonia. In such cases, further titration of stimulants may not be indicated, in order not to expose the patient to potential adverse effects, such as inappetence, cardiovascular events, or sleep disturbances. Conversely, therapy does not appear so ineffective as to justify switching to non-stimulant drugs such as atomoxetine.

Here, we report the cases of two ADHD adolescents undergoing treatment with methylphenidate. Despite initial compensation in terms of attention span and school performance, residual mental fatigue, social problems, anxiety, and depression-like symptoms led to the choice of an add-on treatment with vortioxetine (VTX).

## 2. Case Reports

The persistence of easy cognitive fatigability and potentially stimulant-related anxiety were not such as to justify MPH suspension in favor of alternative treatments, nor its titration because of the increasing risk of adverse effects. Before starting VTX, suicidal risk and/or excessive aggressiveness were ruled out and the willingness to undertake a second pharmacological treatment was assessed. After fully explaining the VTX add-on, parents' written informed consent was retained and patients' assent was also obtained *viva voce*. Clinical progress was evaluated through both a physician's observation, by using the Clinical Global Impression (CGI) scale to assess (i) the severity of illness, (ii) global improvement, and (iii) treatment efficacy [4] (Table 1), and self-reported measures, by using the Conners Rating Scale–Revised (CRS–R) [5] (Table 2). Evaluations occurred before VTX use and at 1-, 3- and 5-month follow-up. Medication dosage ranged from 5 to 10 mg once daily.

**Table 1.** Progress of the clinical picture, as rated by clinicians using the Clinical Global Impression (CGI), to assess (i) severity of illness, (ii) global improvement, and (iii) treatment efficacy, before starting vortioxetine and then after 1, 3 and 5 months.

Cases	Time Point	CGI-S	CGI-I	CGI-E Treatment Efficacy	CGI-E Side Effects
Case 1	T0	5	-	-	-
	T1	3	2	Marked	None
	T2 *	4	5	Moderate	None
	T3	3	3	Moderate	None
Case 2	T0	4	-	-	-
	T1	3	3	Moderate	Do not significantly interfere with patient's functioning
	T2	2	2	Marked	None
	T3	2	2	Marked	None

\* Ratings after enuresis episode; T0, before vortioxetine initiation; T1, 1-month follow-up; T2, 3-month follow-up; T3, 5-month follow-up; CGI-S, CGI-Severity of illness; CGI-I, CGI-Global Improvement; CGI-E, CGI-Efficacy Index.

**Table 2.** Progress of the clinical picture, as rated by both the adolescent and the parents, before starting vortioxetine and then after 1, 3 and 5 months.

Case	Time Point	Form Type	Conners' Scale T Score																										
			Family Problems	Emotional Problems	Conduct Problems	Cognitive Problems-Inattention	Anger Control Problems	Hyperactivity	ADHD Index	DSM-IV Inattentive	DSM-IV Hyperactivity/Impulsivity	DSM-IV Total	Oppositional	Cognitive Problem-Inattention	Hyperactivity	Anxious-Shy	Perfectionism	Social Problems	Psychosomatic	ADHD Index	Restless/Impulsivity	Emotional Lability	Global Index	DSM-IV Inattentive	DSM-IV Hyperactivity	DSM-IV Total			
Case 1	T0	Self (CASS:L)	42	66	53	51	66	74	45	54	60	58																	
	T1	Self (CASS:L)	35	43	42	38	53	51	40	46	50	48																	
	T2 *	Self (CASS:L)	35	57	42	39	61	70	43	43	52	47																	
	T3	Self (CASS:L)	37	66	49	46	66	58	56	50	56	53																	
	T0	Parent (CPRS:R)	62	60	64	94	88	88	63	60	61	53	60	58	67	63													
	T1	Parent (CPRS:R)	54	52	56	60	62	58	47	51	53	59	55	48	57	53													
	T2 *	Parent (CPRS:R)	56	55	60	79	69	95	70	55	53	71	58	51	61	57													
	T3	Parent (CPRS:R)	50	55	58	73	69	88	60	54	53	65	56	50	61	56													
	Case 2	T0	Self (CASS:L)	42	57	44	64	59	60	60	66	63	67																
		T1	Self (CASS:L)	46	64	44	58	53	67	63	60	62	62																
		T2	Self (CASS:L)	41	47	46	56	44	41	48	51	46	48																
		T3	Self (CASS:L)	41	47	46	56	44	41	49	51	46	48																
		T0	Parent (CPRS:R)	60	65	60	61	63	90	68	64	64	59	64	59	78	68												
		T1	Parent (CPRS:R)	52	64	56	55	48	74	48	59	57	59	59	62	64	64												
		T2	Parent (CPRS:R)	52	64	52	55	48	74	48	57	49	59	59	62	64	64												
		T3	Parent (CPRS:R)	54	54	48	55	43	74	58	46	45	43	44	47	53	53												

\* Ratings after enuresis episode; T0, before vortioxetine initiation; T1, 1-month follow-up; T2, 3-month follow-up; T3, 5-month follow-up; CASS: L, Conners-Wells Adolescent Self Report Scale-Long form; CPRS: R, Conners' Parent Rating Scale-Revised; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, 4th edition.

### 2.1. Subject 1

Subject 1 is a 14-year-old male, diagnosed with ADHD, associated with a Specific Learning Disorder (SLD) Mixed-type, when he was 9 years old. As the third born of a normal pregnancy, his neuromotor development was described as normal. A lack of concentration and persistent motor restlessness were observed since early childhood in both home and school environments. The clinical diagnosis was supported by CRS-R interview administration to confirm the diagnosis. Additionally, his elder sister suffers from ADHD, associated with anxiety and tics, treated with MPH and the selective serotonin reuptake inhibitor (SSRI) fluoxetine.

After being offered educational counselling and psychotherapy, the latter being still in place, in 2017, the persistence of attentional difficulties led to MPH initiation at a dosage of 10 mg/day, then titrated up to 30 mg/day. Later, poor appetite early in the day, motor and vocal tics, mild phobic and obsessive compulsive symptoms, and somatic anxiety associated with intense headache, abdominal pain, and sporadic enuresis, were observed. By the end of 2020, mild depression as well as performance anxiety, self-devaluation, and absences from school were reported. To alleviate anxiety and support cognition, VTX was initiated at the dosage of 5 mg/day. At the 1-month follow-up, an overall clinical improvement was reported, with the boy resuming school attendance with good results. No adverse effects were reported. Routine blood test and electrocardiogram results were normal. To sustain improvement, VTX was titrated to 10 mg/day. At the 3-month follow-up, due to an unpleasant single episode of enuresis at school, the boy refused to attend school again for fear of judgement. Distance learning was then offered. Despite a good cognitive response, anxiety and irritability fluctuations were reported. A further titration of VTX to 15 mg once daily was considered, but not implemented by the parents as, following a transient and partial relapse, at the 5-month follow-up, the patient was reported to recover and maintain progress, also returning to school.

### 2.2. Subject 2

Subject 2 is a 15-year-old male, diagnosed with ADHD, associated with Specific Reading and Writing Disorder, in 2017. He is a first born, and his neuromotor development was reported to be normal. Family history included anxious–depressive syndrome in his mother as well as ADHD in his younger brother, successfully treated with MPH. Hyperkinetic behavior, reduced attentional span and planning skills, and low self-esteem and confidence were observed. The clinical diagnosis was supported by CRS-R interview administration to confirm the diagnosis. MPH treatment was initiated at 20 mg/day, with good response. According to body weight, medication dosage was then adjusted up to 40 mg/day in 2019. In December 2020, persisting school difficulties were reported, both at the social and performance level, associated with emotional lability. VTX add-on was initiated at 5 mg/day, with good effect on mood and irritability. Transient and occasional headache was observed in the first few days of treatment. Routine blood test and electrocardiogram results were normal. The VTX dosage was increased to 10 mg/day. At the 5-month follow-up, symptoms remained improved, including distractibility and anxiety, with the latter being still reported but to a lower extent.

## 3. Discussion

Vortioxetine (VTX) is an antidepressant with a multimodal mechanism of action: it acts as serotonin reuptake inhibitor, 5-HT<sub>7</sub>, 5-HT<sub>3</sub> and 5-HT<sub>1D</sub> receptor antagonist, 5-HT<sub>1B</sub> receptor partial agonist, and 5-HT<sub>1A</sub> receptor agonist. It is thought to modulate several neurotransmitters, including histamine, norepinephrine, acetylcholine, glutamate, and  $\gamma$ -aminobutyric acid (GABA) [6,7]. This broad range of activity possibly accounts for the antidepressant and anxiolytic-like effects as well as for improvement in cognitive performance, learning, and executive functions.

Symptoms including, but not limited to, malaise, fatigue, depressed mood, impaired concentration, and reduced social drive and emotional range, have been gathered under

the term symptoms of sickness behavior [8]. A very recent review of the evidence suggests that key sickness behavior symptoms represent a transdiagnostic feature, being reported across different diagnostic categories, and possibly share neurobiological underpinnings. It is thus imperative to provide adequate treatment for such common phenomena [9]. Its wide spectrum pharmacological action deems VTX potentially eligible for the treatment of such symptoms and limited evidence supports its clinical utility in ADHD. Consistently, a randomized, double-blind, placebo-controlled, proof-of-concept study performed in a group of ADHD patients aged 18–55 years old showed an overall reduction in the interference of ADHD symptoms with psychosocial functioning, alongside a reduced rate of adverse effects [10]. Although off-label, the efficacy and tolerability of VTX in children and adolescents with a depressive or anxiety disorder have been confirmed through a prospective open-label multinational multisite multidose trial, and its benefits as an add-on therapy to MPH have already been investigated in a 15-year-old ADHD girl [11,12]. Interestingly, another antidepressant, the selective norepinephrine reuptake inhibitor (NRI) viloxazine, has been recently approved in the USA for the treatment of ADHD in pediatric patients aged 6–17 years [13].

The case reports presented here provide further evidence that VTX may be a promising agent for the treatment of ADHD in children and adolescents, especially in the presence of established comorbid learning difficulties in major academic domains, as well as wider symptoms of sickness behavior. In fact, VTX seemed to express most of its therapeutical potential in enhancing cognition and social drive, possibly resulting in an overall better adaptive behavior. Instead, despite evident, the effects of VTX in reducing the somatic and emotional components of anxiety appeared to be more nuanced. Further studies, conducted in larger samples and in the context of rigorous clinical trials, will weigh the potential of VTX in the treatment of the multifaceted symptoms of ADHD, when not adequately controlled, as well as the role that VTX may play in patients displaying symptoms at an older age or with a heterotypic continuity [14].

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## References

1. D'Agati, E.; Curatolo, P.; Mazzone, L. Comorbidity between ADHD and anxiety disorders across the lifespan. *Int. J. Psychiatry Clin. Pr.* **2019**, *23*, 238–244. [[CrossRef](#)] [[PubMed](#)]
2. Eyre, O.; Langley, K.; Stringaris, A.; Leibenluft, E.; Collishaw, S.; Thapar, A. Irritability in ADHD: Associations with depression liability. *J. Affect. Disord.* **2017**, *215*, 281–287. [[CrossRef](#)] [[PubMed](#)]
3. Lambez, B.; Harwood-Gross, A.; Golumbic, E.Z.; Rassovsky, Y. Non-pharmacological interventions for cognitive difficulties in ADHD: A systematic review and meta-analysis. *J. Psychiatr. Res.* **2020**, *120*, 40–55. [[CrossRef](#)] [[PubMed](#)]

4. Guy, W. *ECDEU Assessment Manual for Psychopharmacology*; Department of Health, Education, and Welfare Public Health Service Alcohol, Drug Abuse, and Mental Health Administration: Rockville, MD, USA, 1976.
5. Conners, C.K.; Sitarenios, G.; Parker, J.D.A.; Epstein, J.N. The Revised Conners' Parent Rating Scale (CPRS-R): Factor Structure, Reliability, and Criterion Validity. *J. Abnorm. Child Psychol.* **1998**, *26*, 257–268. [[CrossRef](#)] [[PubMed](#)]
6. Bang-Andersen, B.; Ruhland, T.; Jørgensen, M.; Smith, G.; Frederiksen, K.; Jensen, K.G.; Zhong, H.; Nielsen, S.M.; Hogg, S.; Mørk, A.; et al. Discovery of 1-[2-(2, 4-Dimethylphenylsulfanyl) phenyl] piperazine (Lu AA21004): A Novel Multimodal Compound for the Treatment of Major Depressive Disorder. *J. Med. Chem.* **2011**, *54*, 3206–3221. [[CrossRef](#)] [[PubMed](#)]
7. Mørk, A.; Pehrson, A.; Brennum, L.T.; Nielsen, S.M.; Zhong, H.; Lassen, A.B.; Miller, S.; Westrich, L.; Boyle, N.J.; Sánchez, C.; et al. Pharmacological Effects of Lu AA21004: A Novel Multimodal Compound for the Treatment of Major Depressive Disorder. *J. Pharmacol. Exp. Ther.* **2011**, *340*, 666–675. [[CrossRef](#)] [[PubMed](#)]
8. Safadi, J.M.; Quinton, A.M.G.; Lennox, B.R.; Burnet, P.W.J.; Minichino, A. Gut dysbiosis in severe mental illness and chronic fatigue: A novel trans-diagnostic construct? A systematic review and meta-analysis. *Mol. Psychiatry* **2021**, 1–13. [[CrossRef](#)]
9. Guessoum, S.B.; Le Strat, Y.; Dubertret, C.; Mallet, J. A transnosographic approach of negative symptoms pathophysiology in schizophrenia and depressive disorders. *Prog. Neuro-Psychopharmacol. Biol. Psychiatry* **2020**, *99*, 109862. [[CrossRef](#)] [[PubMed](#)]
10. Biederman, J.; Lindsten, A.; Sluth, L.B.; Petersen, M.L.; Ettrup, A.; Eriksen, H.-L.F.; Fava, M. Vortioxetine for attention deficit hyperactivity disorder in adults: A randomized, double-blind, placebo-controlled, proof-of-concept study. *J. Psychopharmacol.* **2019**, *33*, 511–521. [[CrossRef](#)] [[PubMed](#)]
11. Findling, R.L.; Robb, A.S.; DelBello, M.P.; Huss, M.; McNamara, N.K.; Sarkis, E.H.; Scheffer, R.E.; Poulsen, L.H.; Chen, G.; Lemming, O.M.; et al. A 6-Month Open-Label Extension Study of Vortioxetine in Pediatric Patients with Depressive or Anxiety Disorders. *J. Child Adolesc. Psychopharmacol.* **2018**, *28*, 47–54. [[CrossRef](#)] [[PubMed](#)]
12. Naguy, A.; Alamiri, B. Successful Add-on Vortioxetine for an Adolescent With Attention-Deficit/Hyperactivity Disorder. *J. Clin. Psychopharmacol.* **2018**, *38*, 407–409. [[CrossRef](#)] [[PubMed](#)]
13. Lamb, Y.N. Viloxazine: Pediatric First Approval. *Pediatr. Drugs* **2021**, *23*, 403–409. [[CrossRef](#)] [[PubMed](#)]
14. Epstein, J.N.; Loren, R.E.A. Changes in the definition of ADHD in DSM-5: Subtle but important. *Neuropsychiatry* **2013**, *3*, 455–458. [[CrossRef](#)] [[PubMed](#)]