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A retrospective analysis of vortioxetine utilization in children and adolescents with major depressive disorder in clinical practice

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Abstract

Background Treating depression in children and adolescents has always been a challenge in clinical pharmacotherapy. Vortioxetine, as a new type of antidepressant, is considered to have the potential for use in the treatment of depression in children and adolescents. This study aimed to evaluate the usage of vortioxetine and its efficacy and tolerability in children and adolescents with major depressive disorder in a real-world study.

Methods A retrospective survey of vortioxetine treatment was conducted at a Class A tertiary mental health hospital. Data regarding the demographic and clinical characteristics were collected among children and adolescents with major depressive disorder from electronic medical record system.

Results The study included a total of 253 depressive patients, comprising 96 males and 157 females, who were prescribed vortioxetine at any time during the research period. One hundred and twenty-three patients (43.62%) received vortioxetine treatment at the initial visit. Of the total patients, 27 (10.67%) reported side effect, such as nausea, vomiting, dizziness, palpitations, diarrhea, drowsiness, and itching. Additionally, 20 (7.91%) discontinued medical treatment due to adverse effect. No significant difference was found between males and females in drug-related adverse events ($X^2 = 0.56$, $P = 0.454$). Furthermore, 96 (37.94%) reported relief from their symptoms in all patients, with a significant difference observed between males and females in reporting symptom relief ($X^2 = 3.934$, $P = 0.047$). But this difference disappeared in patients who took vortioxetine alone and those who took it for more than three months.

Conclusion There exists a certain proportion of children and adolescents suffering from depression who are prescribed vortioxetine in an off-label manner in psychiatric clinics. Vortioxetine demonstrates well tolerability in clinical practice. However, the proportion of self-report symptom alleviation is comparatively unsatisfactory. Furthermore, gender appears influence on self-report symptom relief.

Keywords Vortioxetine, Major depressive disorder, Children, Adolescents, Retrospective analysis

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Background

Recently, children and adolescents depression have raised a great concern from public [1]. Approximately 25% of severe depression manifest before the age of 19. A meta-analysis indicates that the prevalence of depression is 2.8% (95% CI 1.8–3.8) in children and 5.7% (95% CI 5.1–6.3) in adolescents [2]. The incidence of adolescent depression and associated challenges in treatment services is on the rise [3]. The World Health Organization's Burden of Disease study indicated that depression within the 10 to 24 age range caused greater physical disability among young people than any other disease [4]. A previous study showed that an earlier onset of depression in adult depressive patients was associated with greater difficulties in social interactions, career, quality of life, and mental health [5]. Approximately 60% of young men who commit suicide were diagnosed as depression, and 40 – 80% of teenage suicides were linked to depression [6]. Patients suffering from depression during adolescence had an elevated risk of relapse [7]. As a result, intervention in children and adolescents depression is a priority despite the limited availability of its treatment.

Vortioxetine, a novel antidepressant with multimodal activities, was approved by FDA (U.S. Food and Drug Administration) for the treatment of severe depression in adults in 2013. Its unique mechanism of action and distinctive clinical characteristics make it a potential candidate for replacing first-line drugs or serving as an effective option for subsequent treatment [8]. However, there are limited data on its use in children and adolescents depressive patients. In China, vortioxetine is increasingly being prescribed as off-label treatment for children and adolescents depression in clinical practice due to its minimal impact on cognitive function. This study aims at exploring the efficacy and tolerability of vortioxetine through a real-world study and provide valuable insights in its use in clinical practice.

Methods

Participants

This cross-sectional study was conducted at a Class A mental health hospital in Chendu, China from May 2018 to May 2023, involving participants under the age of 18. Class A hospitals are the highest-level medical institutions in China, as classified by the National Health Commission. The hospital specializes in the treatment of psychiatric and psychological disorders, including depression and mental health issues in children and adolescents. Additionally, the hospital has dedicated outpatient clinics and inpatient wards for children and adolescent. All participants were diagnosed as major depressive disorder according to the ICD-10 (International Classification of Diseases 10th edition, ICD-10) and were prescribed vortioxetine. Data were collected based on case records and prescription records from electronic medical record system.

Remission criteria

In this study, remission was defined based on both self-reported symptom relief by patients and clinical evaluations conducted by physicians. Patients were asked to report their subjective experiences of symptom improvement during follow-up consultations. Additionally, physicians conducted clinical interviews to assess the overall mental state and functioning of the patients. The combination of these self-reported outcomes and the clinical judgment of physicians formed the basis for determining remission. No specific standardized scales were utilized; rather, the assessment relied on qualitative clinical inquiries and the patients' subjective feedback regarding their depressive symptoms.

Procedure

Clinical psychiatrists conducted retrospective medical record surveys on both inpatients and outpatients who got treatments in the hospital during the study period, collected demographic and clinical data including age, gender, diagnosis, the disease course, previous antidepressant use, vortioxetine dosage, duration of vortioxetine use, reported symptom relief, adverse drug reactions after using vortioxetine, and the combinations of vortioxetine with other drugs.

Statistical analysis

All statistical tests were two-tailed, and p values < 0.05 were considered significant. Statistical analyses were conducted using IBM SPSS statistics software version 26. The demographic and clinical characteristics of all patients were described, and the remission and adverse drug reactions reported by gender differences were compared using the Pearson Chi-square test.

Results

A total of 253 children and adolescent depressive patients, comprising 96 males and 157 females, with an average age of 15.72 ± 1.33 years were included in the study. One hundred twenty-three (43.62%) patients were receiving antidepressant treatment for the first time and 185 (73.12%) had taken medication for less than 3 months. Additionally, 18 (7.11%) of the patients adhered to the treatment for over 6 months, and 26 (10.28%) had taken for over a year. The most common dosage of medication was 10 mg per day (66.40%), followed by 5 mg per day (25.69%). Furthermore, 54 (21.34%) patients received vortioxetine as a single treatment. Considering combination prescriptions, Aripiprazole (21.74%) was the most commonly prescribed, followed by Lorazepam (21.34%) (Table 1).

Table 1 Demographic and clinical characteristics in all patients

Gender	Male	Female	Total
	***N*=69**	***N*=184**	***N*=253**
Age	15.74 ± 1.52	15.71 ± 1.26	15.72 ± 1.33
Course, year	1.37 ± 1.02	1.74 ± 1.61	1.64 ± 1.48
Comorbidities, n (%)			
No	59	159	218 (86.17)
Yes	10	25	35 (13.83)
Anxiety disorder	4	16	20 (7.90)
Obsessive compulsive disorder	3	5	8 (3.16)
PTSD	1	4	5 (1.98)
ADHD	1	0	1 (0.39)
With psychotic symptoms, n (%)			
No	59	152	211 (83.40)
Yes	4	23	27 (10.67)
Unknown	6	9	15 (5.93)
Outpatient, n(%)			
No	67	178	245(96.83)
Yes	2	6	8(3.17)
Dosage(mg/d)			
2.5	1	1	2 (0.79)
5	20	45	65 (25.69)
10	43	125	168 (66.40)
15	3	6	9 (3.56)
20	2	6	8 (3.16)
Number of previous drug trials, n (%)			
0	32	91	123 (48.62)
1	21	66	87 (34.39)
2	8	15	23 (9.09)
3	4	4	8 (3.16)
4	0	1	1 (0.39)
Unknown	4	7	11 (4.35)
Duration of medication, month, n (%)			
Less than 3 months	52	133	185 (73.12)
More than 3 months, less than 6 months	7	17	24 (9.49)
More than 6 months, less than 9 months	4	14	18 (7.11)
More than 9 months	6	20	26 (10.28)
Drug combination, n (%)			
No	16	38	54 (21.34)
Yes	53	146	199 (78.66)
Quetiapine	5	23	28 (11.07)
Tandospirone	8	30	38 (15.02)
Aripiprazole	8	47	55 (21.74)
Oxazepam	8	14	22 (8.70)
Lorazepam	13	41	54 (21.34)
Lithium	3	13	16 (6.32)
Valproate	4	15	19 (7.51)
Lamotrigine	9	23	32 (12.65)
Olanzapine	3	7	10 (3.95)
Alprazolam	0	10	10 (3.95)
Buspirone Hydrochloride	1	10	11 (4.35)
Trazodone	1	4	5 (1.98)

PTSD: Post-Traumatic Stress Disorder, ADHD: Attention Deficit Hyperactivity Disorder

Table 2 Treatment-related adverse events (TRAEs), reported symptom remission and gender differences in all patients

Gender	Male	Female	Total	χ^2	*P* value
	N = 69	*N* = 184	*N* = 253		
Patients with TRAEs, n (%)				0.56	0.454
0	59	160	219 (86.56)		
≥ 1	10	18	28 (11.07)		
Nausea	7	11	18 (7.11)		
Vomiting	1	4	5 (1.98)		
Dizziness	0	1	1 (0.39)		
Diarrhea	1	0	1 (0.39)		
Cardiopalmus	1	0	1 (0.39)		
Drowsiness	0	1	1 (0.39)		
Itchiness	0	1	1 (0.39)		
Patients with TRAEs leading to discontinuation, n (%)	4	16	20 (7.91)		
Report remission of symptoms, n (%)				3.93	0.047
No	36	121	157 (62.06)		
Yes	33	63	96 (37.94)		

Table 3 TRAEs, reported symptom remission and gender differences in patients with taking vortioxetine alone

Gender	Male	Female	Total	χ^2	*P* value
	N = 16	*N* = 38	*N* = 54		
Patients with TRAEs, n (%)				0.245	0.621
0	15	34	49 (90.74)		
≥ 1	1	4	5 (9.26)		
Nausea	0	3	3 (5.56)		
Vomiting	1	1	2 (1.98)		
Report remission of symptoms, n (%)				0.439	0.507
No	9	25	34 (62.96)		
Yes	7	13	20 (37.04)		

TRAEs: Treatment-Related Adverse Events

Among all the patients, 28 (11.07%) reported adverse drug reactions such as nausea, vomiting, dizziness, diarrhea, cardiopalmus, drowsiness, and itching. Out of these, 20 (7.91%) patients discontinued therapeutic drugs due to intolerable adverse drug reactions. It was found that there was no significant difference between male and female patients in experiencing adverse reactions during vortioxetine treatment ($\chi^2 = 0.56$, $P = 0.454$). Ninety-six (37.94%) patients reported symptom relief after taking vortioxetine. Interestingly, a significant difference between males and females in reporting symptom relief ($\chi^2 = 3.934$, $P = 0.047$) (Table 2).

In patients treated with vortioxetine alone, 5 (9.26%) reported adverse drug reactions, 20 (37.04%) patients reported symptom relief after taking vortioxetine. However, there was no significant difference between males and females in reporting adverse reactions ($\chi^2 = 0.245$, $P = 0.621$) or symptom relief ($\chi^2 = 0.439$, $P = 0.507$) among patients taking vortioxetine alone (Table 3). In patients taking vortioxetine for more than 3 months, 8 (11.76%) reported adverse drug reactions, 52 (76.47%) patients reported symptom relief after taking vortioxetine. No significant differences were found between males and females in reporting adverse reactions ($\chi^2 = 0.000$, $P = 1.000$) or symptom relief ($\chi^2 = 1.744$, $P = 0.322$) (Table 4).

Discussion

This study indicates that nearly half of children and adolescent patients are prescribed vortioxetine as an initial treatment for depression. The first step in the efficient development of a pediatric prescription plan involves studying the effects of the medication on adults through thorough comparison and comprehensive research [9]. It is imperative not to apply clinical practices without reliable research data.

In this study, symptom relief was reported in 37.94% of all patients and 37.04% of patients taking vortioxetine alone, which was consistent with the findings of a recent randomized double-blind control study on vortioxetine use in adolescents with depression [10]. The study compared the effects of different doses of vortioxetine with fluoxetine and placebo. The results showed that the placebo response rate was 36%, with relief rates of 50% for fluoxetine, 42% for vortioxetine 10 mg, and 43% for vortioxetine 20 mg [10]. Patients in all groups had improved symptoms reduction by the end of the study, with no difference between combined doses of vortioxetine and

Table 4.1 TRAEs and gender differences in patients with taking the drug for more than 3 months

Gender	Male	Female	Total	χ2	*P* value
	N = 17	*N* = 51	*N* = 68		
Patients with TRAEs, n (%)				0.000[a]	1.000
0	15	46	60(88.24)		
≥ 1	2	5	8(11.76)		
Nausea	2	2	4(5.88)		
Vomiting	0	2	2(2.94)		
Itchiness	0	1	1(1.47)		

TRAEs: Treatment-Related Adverse Events; a: Fisher's exact test

Table 4.2 Self-report remission of symptoms and gender differences in patients with taking the drug for more than 3 months

Gender	Male	Female	Total	χ2	*P* value
	N = 17	*N* = 51	*N* = 68		
Report remission of symptoms, n(%)				1.744[a]	0.322
No	2	14	16(23.53)		
Yes	15	37	52(76.47)		

placebo [10]. Our result showed that the number of patients who took vortioxetine for more than 3 months reported a significant increase in symptom relief (76.47%) which warrants careful interpretation. This finding may reflect a combination of clinical and psychosocial factors. Patients who experienced poor symptom relief or intolerable side effects may have discontinued vortioxetine within the first three months. Consequently, those who continued treatment beyond this period likely represent a subset with better initial responses or higher tolerance to the medication, leading to an overestimation of the observed symptom relief rate. Prolonged adherence to vortioxetine treatment may be an indicator of patients' greater commitment to the prescribed regimen. Adherence often correlates with better clinical outcomes, as sustained exposure to the medication allows its therapeutic effects to manifest more fully. Patients who maintained vortioxetine treatment for an extended duration may have benefited from stronger social or family support systems. These external factors can positively influence mental health outcomes by reinforcing adherence and providing emotional stability. However, the delay in the onset time of the drug that may affect the improvement of symptoms also needs to be taken into account. Studies have shown that the onset of action for many antidepressants typically occurs within 2 to 4 weeks, while some patients may require a longer duration to achieve significant therapeutic effects [11]. Nevertheless, this reminds us that vortioxetine has more potential to improve the effect of depression in children and adolescents.

Additionally, significant gender differences were observed in reporting symptom relief in all patients in our study. But the difference disappeared in patients who took vortioxetine alone and those who took it for more than three months. Whether there are gender differences in antidepressant efficacy is a controversial topic. Research showed that gender-based variations in the efficacy of antidepressants were potentially influenced by factors such as changes in body fat and weight distribution, hormone levels, drug transport, and clearance rates [12]. It is noteworthy that females may exhibit a better response to selective serotonin reuptake inhibitors than males [13, 14], whereas for tricyclic antidepressants like imipramine, males' treatment response is significantly higher than that of females [15, 16]. However, other studies have failed in detecting such differences with several types of antidepressants [17, 18]. Also, the exploratory subgroup analyses by gender did not find differences in randomized controlled trials of the efficacy of vortioxetine use in adolescents [10]. Further investigation is warranted to assess the impact of gender on the therapeutic efficacy of vortioxetine among children and adolescents, especially considering existing research has not consistently demonstrated differing antidepressant efficacy between males and females [19–21].

Regarding the tolerability, our data show that the most frequently reported adverse drug reaction is nausea (7.11%) which is consistent with previous research. Studies indicate that over 5% of adolescents taking vortioxetine experience adverse drug reactions, encompassing nausea, headache, vomiting, nasopharyngeal inflammation, diarrhea, and dizziness [10, 22]. In a randomized double-blind controlled study, the highest discontinuation rate due to adverse drug reactions was only 5.6% (vortioxetine 20 mg) [10]. However, in our study, regardless of the medication dosage, 7.91% of patients reported discontinuation due to adverse drug reactions overall. This difference may be attributable to the lack of timely professional interpretation and assistance for patients experiencing medication-related discomfort. Patients involved in clinical studies may exhibit higher medication

adherence and greater tolerability to adverse drug reactions under the supervision of the medical team. In addition, some patients' adverse reactions may be exacerbated by the combination of multiple drugs. Although we have made efforts to mitigate this by reviewing medical records, we explicitly recorded adverse reactions occurring after taking vortioxetine, and only noted patients who discontinued vortioxetine while continuing with other medications as discontinuing the medication due to adverse drug reactions. Importantly, no serious adverse drug reactions following the use of vortioxetine, such as severe allergic reactions, effects on liver and kidney function, or increased suicidal ideation were identified. Overall, vortioxetine is well tolerated in clinical practice, with the majority of patients in our study taking doses between 5 mg and 10 mg. Notably, the 10 mg dose was the most commonly prescribed, suggesting that this dosage demonstrates good tolerability.

This study reveals a therapeutic dilemma for children and adolescent depression which inappropriately applies research findings for clinical practice which is not in line with FDA principles [23]. Adolescence represents a unique developmental phase characterized by significant changes in the brain, social maturity, and cognition. When it comes to the treatment of depression in children and adolescents, extrapolating efficacy from adult studies, while superficially appealing, is not reasonable [24]. In line with recent clinical research, this study did not observe a higher rate of symptom relief in all children and adolescent patients after taking vortioxetine. Regardless well tolerability of vortioxetine, the risk of discontinuation due to adverse drug reactions may be higher in clinical practice. This serves as a reminder that caution should be exercised when choosing antidepressants for children and adolescent patients suffering depression. As revealed in a comprehensive meta-analysis, when evaluating the cost-effectiveness of antidepressants for severe depression, these medications do not appear to offer significant advantages for children and adolescents [25].

Our study represents the first exploration of vortioxetine use among children and adolescents in real-world settings. While our retrospective analysis and cross-sectional surveys inevitably introduce various confounding factors into the research results, we have carefully extracted and analyzed the data to reflect patients' reported experiences as accurately as possible, particularly concerning symptom relief and the drug's side effects. However, retrospective analysis of real-world clinical data has always faced the problem of a lack of consistent scale evaluation tools. Although the case descriptions accurately capture the actual changes in the patient's condition, the significant differences in how each doctor assesses and selects evaluation tools represent a major limitation of our research.

Conclusion

There exists a specific proportion of children and adolescents suffering from depression who are prescribed vortioxetine. The proportion of receiving antidepressant treatment for the first time revealed that off-label drug use is common among doctors treating children and adolescent depression in China. The most frequently prescribed dosage is 10 mg per day, often used in conjunction with other medications like aripiprazole and lorazepam. Overall, vortioxetine is well-tolerated; however, the reported symptom relief proportion is not satisfied, and gender differences may impact self-report symptom alleviated. One major limitation of this retrospective case-note study is the lack of consistent documentation in patient records. This inconsistency may introduce variability in the interpretation of clinical outcomes, potentially impacting the reliability and generalizability of our findings. Future studies should adopt more structured data collection methodologies, such as standardized assessment tools and consistent follow-up protocols, to ensure uniformity and reduce bias. Also, further randomized controlled trials are necessary to validate the efficacy of vortioxetine in treating children and adolescent depression. Additionally, gathering real-world data on the use of vortioxetine in treating children and adolescent depression is crucial to bolster its tolerability and effectiveness.

Abbreviations

ADHD	Attention Deficit Hyperactivity Disorder
FDA	U.S. Food and Drug Administration
ICD-10	The International Classification of Diseases and Related Health Problems,10th edition
PTSD	Post-Traumatic Stress Disorder
TRAEs	Treatment-Related Adverse Events

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Author contributions

XL, YZ, MD, and KP contributed to conception and design of the study. XL, SY, LC and FL contributed to retrieval and collection of research data. XL, YZ, MD and HZ performed the data analysis and wrote the draft of paper. All authors contributed to data interpretation, manuscript revision, read, and approved the submitted version.

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Data availability

The data that support the findings of this study are available from the authors but restrictions apply to the availability of these data, which were used under license from the Chengdu Fourth People's Hospital for the current study, and so are not publicly available. Data are, however, available from Xianmei Luo (email: 360972923@qq.com) upon reasonable request and with permission from the Chengdu Fourth People's Hospital.

Declarations

Ethics approval and consent to participate
This study was conducted in accordance with the principles outlined in the Declaration of Helsinki. The study protocol was reviewed and approved by by the Ethics Committee of the Fourth People's Hospital of Chengdu. As the research involved minors but posed minimal risk and did not affect participants' rights or welfare, the Institutional Review Board granted a waiver of informed consent(Approval No: 2023-13). All necessary precautions were taken to ensure the privacy and confidentiality of the participants.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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Not applicable.

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