mhc MENTAL HEALTH CLINICIAN

ORIGINAL RESEARCH Open Access

Antipsychotics in child and adolescent patients with major depressive disorder: A retrospective analysis of prescribing patterns

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How to cite: Dauchot D, Rettey S, Melton BL, Moeller KE. Antipsychotics in child and adolescent patients with major depressive disorder: a retrospective analysis of prescribing patterns. Ment Health Clin [internet]. 2024;14(1):10-6. DOI: 10.9740/mhc.2024.02.010.

Submitted for Publication: July 25, 2023; **Accepted for Publication:** November 16, 2023

Abstract

Introduction: Depression rates in children/adolescents in the United States have increased in the last 10 years. Fluoxetine and escitalopram are the only 2 antidepressants approved for the treatment of major depression disorder (MDD) in children/adolescents. In adults, some antipsychotics are approved for augmented treatment of MDD. However, there is limited research on antipsychotic augmentation in child/adolescent MDD.

Methods: This retrospective chart review evaluated antipsychotic prescribing for MDD in hospitalized patients aged 4 to 17 years to determine the frequency of prescribing antipsychotics for MDD and what factors influence the addition of an antipsychotic. For inclusion, patients were diagnosed with MDD and not on an antidepressant or antipsychotic before admission. Binomial logistic regression was used to analyze variables with prescribed antipsychotics as the dependent variable.

Results: There were 6.8% of patients prescribed an antipsychotic. Binomial logistic regression analysis found that increased age (odds ratio [OR] 1.28; 95% CI = 1.045, 1.568; $P = .017$) and multiple admissions within 1 year (OR 3.277; 95% CI = 2.283, 4.705; $P < .001$) were associated with the use of antipsychotics in patients with MDD. Posttraumatic stress disorder and disruptive mood dysregulation disorder were also associated with the use of antipsychotics.

Discussion: Careful consideration should be taken when using off-label antipsychotics in children due to limited studies on efficacy. Future research is warranted to assess the efficacy and safety of these agents in children and adolescents.

Keywords: psychiatry, children, adolescents, antipsychotic, augmentation, MDD

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Disclosures: The authors have no conflicts of interest to disclose.

Introduction

Depression rates in children/adolescents in the United States have markedly increased over the last decade. In 2020, major depression disorder (MDD) affected 17% of adolescents aged 12 to 17 years, with suicide as the second leading cause of death for ages 10 to 14 years and the third leading cause for ages 15 to 24 years.[1–3] Unfortunately, it is estimated that only 41.6% of adolescents with MDD receive treatment.[4]

Treatment of MDD in children/adolescents is limited with psychotherapy and pharmacotherapy being the main treatment options.[5–7] Only 2 medications are approved by the FDA for

MDD treatment in this population; fluoxetine (≥ 7 years old) and escitalopram (≥ 12 years old).[8,9] While other antidepressants are commonly used off-label for MDD in children/adolescents, some guidelines recommend against specific antidepressants (eg, paroxetine, venlafaxine) because of concerns for increased suicide in young adults.[6,10,11] In 2004, the FDA issued a black box warning for all antidepressants in youths from a meta-analysis, which revealed a 4% risk of new suicidal thinking/behaviors in youths taking an antidepressant compared with 2% in the placebo group.[12] Moreover, studies have found venlafaxine and paroxetine to be associated with an increased risk of suicidal behavior and ideations.[13] This black box warning has complicated treatment for children/adolescents with MDD.

Three guidelines discuss MDD treatment in the child/adolescent population, which recommend psychotherapy and/or pharmacotherapy.[5–7] These guidelines recommend fluoxetine or other selective serotonin reuptake inhibitors, such as sertraline and escitalopram, as first-line pharmacotherapy.[5–7] The American Psychological Association 2019 Clinical Practice Guideline for the Treatment of Depression recommends either cognitive behavioral therapy, interpersonal psychotherapy, or fluoxetine as initial MDD treatment in adolescents.[6] The National Institute for Health and Care Excellence 2019 Guideline for Depression in Children and Young People and the American Academy of Pediatrics Guidelines for Adolescent Depression in Primary Care recommend psychotherapy for mild depression and the addition of pharmacotherapy with selective serotonin reuptake inhibitors for moderate to severe depression similar to the American Psychological Association guidelines.[5,7] Unfortunately, these guidelines have limited recommendations for child/adolescent patients who fail to respond to antidepressants and/or psychotherapy.

In adults, antipsychotics (aripiprazole, brexpiprazole, cariprazine, olanzapine, and quetiapine) are approved as adjunctive MDD treatment.[6] However, child/adolescent guidelines for MDD treatment have limited recommendations for their use, with only the National Institute for Health and Care Excellence Guidelines recommending augmentation with a second-generation antipsychotic in psychotic depression.[7] Research with antipsychotics for use in depression in children/adolescents is limited to MDD with psychosis or bipolar depression.[14,15] While there is limited research for antipsychotic augmentation in child/adolescent MDD without psychosis, it is practiced clinically.[16,17] The use of antipsychotics can be associated with significant adverse effects in youths, including metabolic abnormalities (diabetes mellitus or weight gain), cardiac arrhythmias, dyslipidemia, hyperprolactinemia, and extrapyramidal symptoms.[18]

The objective of this study was to determine the frequency of prescribing antipsychotics for MDD in child/adolescent patients and what factors influence the utilization of an antipsychotic for children/adolescents diagnosed with MDD without psychosis.

Methods

Study Design and Subjects

This study was a retrospective chart review evaluating antipsychotic prescribing trends for child/adolescent inpatients with MDD. Patients aged 4 to 17 years admitted to a Midwest child/adolescent psychiatric hospital from June 1, 2018, to May 31, 2021, with a diagnosis of MDD were identified through the Healthcare Enterprise Repository for Ontological Narration Dataset, an internal research database.[19,20] Electronic health records of identified patients were then reviewed to identify patients not on an antidepressant or antipsychotic before admission. Patients were excluded if they were taking 1 of these medications before admission or had any of the following diagnoses: MDD with psychotic features, bipolar disorder, schizophrenia, schizoaffective disorder, or autism spectrum disorder. Patients were followed through admissions to inpatient psychiatry for 1 year from diagnosis of MDD. Patients were divided into groups based on initiation (antipsychotic group) or no initiation of antipsychotic medication (non-antipsychotic group) during an inpatient psychiatry admission. A sample size of 600 patients was determined to be sufficient for analyses and review within the research timeline. The University of Kansas Medical Center institutional review board approved this study.

Outcomes

The primary outcome was the frequency of the prescribing of antipsychotics for MDD in child/adolescent patients. Secondary outcomes included factors that influenced the addition of an antipsychotic for child/adolescent patients with MDD without psychosis and which psychotropic medications were prescribed for patients with and without antipsychotics.

Data Collection

The electronic health records were reviewed for demographics, home life (eg, 1- or 2-parent household, divorced parents, foster care, homeless, number of siblings, etc), education, insurance status, psychiatric diagnoses, past medical history, symptoms of depression on admission, length of stay, newly initiated psychotropic medications, and prior to admission medications. Data were collected using REDCap®, a secure data collection platform.

Statistical Analysis

Continuous variables were analyzed for demographic information using mean, median, and interquartile range, and

discrete variables using frequency and percentages. χ^2 and Fisher's exact tests compared groups with discrete variables. Binomial logistic regression was used to analyze variables with the presence or absence of prescribed antipsychotics as the dependent variable. Variables, including patient demographics, length of stay, number of admissions, education, insurance, home life, symptoms of depression, comorbidities, and medications, were evaluated in the regression model. Statistical significance was defined as a P value $< .05$. Analysis was completed using SPSS v.27 (IBM, Armonk, New York).

Results

There were 3535 patients identified via the Healthcare Enterprise Repository for Ontological Narration as age younger than 18 years and admitted to inpatient psychiatry during the study period with a diagnosis of MDD. Of those patients, 1460 were randomly reviewed for 600 included patients. Full inclusion and exclusion criteria can be found in the Figure. There were 41 of 600 patients (6.8%) prescribed an antipsychotic with a diagnosis of MDD. The Table shows patient demographics and baseline characteristics. Patients were 70.2% female, with an average age of 14.2 years. Notable differences between groups include a higher incidence of patients identifying as male, sleep disturbances, posttraumatic stress disorder (PTSD), and disruptive mood dysregulation disorder (DMDD) in the antipsychotic group.

Escitalopram was the most prescribed antidepressant in the antipsychotic group (29.3%, 12/41 patients), followed by sertraline (26.8%, 11 patients). In the non-antipsychotic group, fluoxetine was most prescribed (29.7%, 166/559 patients), followed by escitalopram (24.1%, 135 patients) and sertraline (20.4%, 114 patients). There was a lower incidence of patients prescribed fluoxetine in the antipsychotic group compared with the non-antipsychotic group (4.9% vs 29.7%, $P < .001$). There were 2 of 41 patients (4.8%) in the antipsychotic group and 42 of 559 patients (7.6%) in the non-antipsychotic group that received a different antidepressant, including amitriptyline, bupropion, duloxetine, mirtazapine, and venlafaxine. In the antipsychotic group, 32.4% of patients were not prescribed an antidepressant, compared with 18.2% of patients in the non-antipsychotic group ($P = .013$). Of the 41 patients who received a scheduled antipsychotic for MDD, quetiapine was most prescribed (46% of patients), followed by aripiprazole (37%), olanzapine (10%), risperidone (5%), and lurasidone (2%).

Binomial logistic regression analysis was used to compare patients who were initiated on an antipsychotic with those who were not, based on relationship to length of stay, number of admissions, age, sex assigned at birth, gender identity, race, ethnicity, school, home life, insurance status, suicide attempt, Columbia Suicide Severity Rating Scale, symptoms of depression, and comorbidities. When holding all other variables constant, it was found that the odds of antipsychotic initiation increased by 1.28 for every 1-year increase in age (odds ratio [OR] 1.28; 95% CI = 1.045, 1.568; $P = .017$). It was also

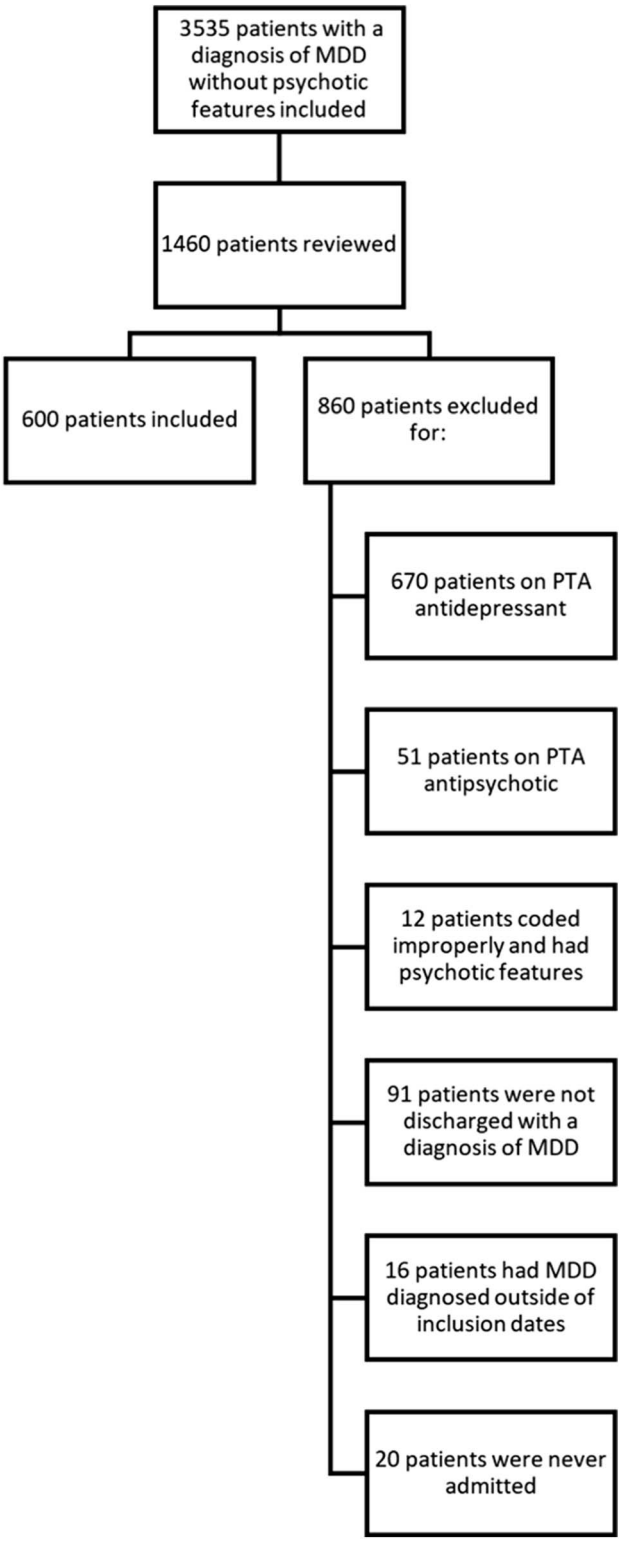

FIGURE: Inclusion and exclusion criteria; PTA = prior to admission

TABLE: Patient demographics and baseline characteristics

Characteristics	Antipsychotic Group, N = 41	Non-Antipsychotic Group, N = 559	*P* Value
Age, median (IQR)	15 (14-16)	14 (13-16)	.071
Length of stay in days, median (IQR)	4 (3-5.5)	4 (3-4)	.011
Number of admissions in 1 yr, median (IQR)	2 (1-3)	1 (1-1)	<.001
Sex assigned at birth—female, n (%)	23 (56.1)	398 (71.3)	.041
Gender identity, n (%)			
Male	22 (53.7)	178 (32)	.006
Female	17 (41.5)	370 (66.3)	.001
Nonbinary	2 (4.9)	9 (1.6)	.17
Other	0	2 (0.4)	>.99
Race, n (%)			
White	31 (75.6)	380 (68.1)	.31
Black	5 (12.2)	60 (10.8)	.793
Asian	1 (2.4)	8 (1.4)	.474
Other	4 (9.8)	111 (19.9)	.113
Insurance, n (%)			
Government (Medicaid or Medicare)	21 (51.2)	232 (41.6)	.224
Commercial	18 (43.9)	268 (47.9)	.617
Self-pay	2 (4.9)	59 (10.6)	.418
School, n (%)			
Public	35 (85.4)	483 (86.6)	.862
Home school	3 (7.3)	41 (7.3)	>.99
Private	3 (7.3)	35 (6.3)	.738
Depressive symptoms, n (%)			
Sleep	31 (75.6)	335 (59.9)	.047
Appetite	27 (65.9)	354 (63.3)	.746
Energy	20 (48.7)	334 (59.9)	.168
Interest	19 (46.3)	322 (57.7)	.16
Concentration	19 (46.3)	285 (51.1)	.566
Psychomotor agitation/retardation	13 (31.7)	154 (27.6)	.566
Suicide attempt, n (%)	13 (31.7)	147 (26.3)	.450
Psychiatric Comorbidities			
Posttraumatic stress disorder	20 (48.8)	159 (28.5)	.006
Generalized anxiety disorder	18 (43.9)	165 (29.5)	.054
Attention-deficient/hyperactivity disorder	5 (12.2)	82 (14.7)	.664
Disruptive mood dysregulation disorder	5 (12.2)	5 (0.9)	.0002
Social anxiety disorder	4 (9.8)	82 (14.7)	.386
Cannabis use disorder	4 (9.8)	40 (7.2)	.53
Oppositional defiant disorder	3 (7.3)	28 (5)	.462
Personality disorder/traits	3 (7.3)	12 (2.2)	.076
Conduct disorder	2 (4.9)	7 (1.3)	.121
Other SUD	1 (2.4)	16 (2.7)	>.99
Panic disorder	0	6 (1.1)	>.99
Obsessive compulsive disorder	0	2 (0.4)	>.99

IQR = interquartile range; SUD = substance use disorder.

found that the odds of antipsychotic initiation increased by 3.28 for every admission after the initial admission within 1 year (OR 3.277; 95% CI = 2.283, 4.705; $P < .001$).

Discussion

This study, to our knowledge, is the first to assess the frequency of prescribing and factors associated with antipsychotic augmentation for child/adolescent MDD. This study found that an increased number of admissions within a year and increasing age increased the likelihood of being prescribed an antipsychotic for child/adolescent inpatients with MDD. Previous studies have found that a high number of previous admissions and poor prognosis increase psychiatric hospital readmission rates.[21] Multiple admissions are probable markers of disease progression, highlighting the need for alternative or additional treatments. Other studies have found that older

adolescent age is associated with the use of more psychotropic medications compared with younger children/adolescents.[22] It is plausible that clinicians are more comfortable prescribing agents approved in adults as an adolescent's age approaches adulthood.

In this study, child/adolescent patients with MDD who had comorbid PTSD or DMDD were more commonly prescribed antipsychotics. A study in adults also found that patients with MDD and comorbid PTSD were more likely to receive antipsychotic augmentation.[23] There is some evidence in adults for the use of adjunctive antipsychotics in treating PTSD in patients with hyperarousal or re-experiencing symptoms.[24] One study found that patients with childhood trauma are less likely to remit from symptoms of PTSD and have a longer time to remission.[25] This could explain augmentation with antipsychotics in younger patients with PTSD. DMDD, a childhood-specific psychiatric disorder, has been associated with increased use of antipsychotics outside of comorbid MDD.[18] Other adult studies looking at factors associated with antipsychotic use for MDD found depression severity, medical comorbidities, alcohol use disorder, and obsessive-compulsive disorder were associated with antipsychotic use, which was not found in our child/adolescents study.[23,26] Depression severity, as shown by depressive symptoms in this study, was not different between groups, though it relied heavily on chart documentation. This study had a low incidence of obsessive-compulsive disorder and substance use disorders, making it difficult to find differences in these patient groups.

This study also found that males were more frequently prescribed antipsychotics, which is consistent with previous studies showing higher rates of antipsychotic use in males aged 11 to 17 years.[27] This increased use in males could be related to behavioral problems or conduct disorder. However, because of the retrospective nature of our study, we could not establish causality for males being prescribed antipsychotics.

Quetiapine and aripiprazole, both FDA approved for adult MDD adjunctive treatment, were the most prescribed antipsychotics in this study. Quetiapine is FDA approved for schizophrenia in patients 13 years and older and for bipolar–mania in those 10 years and older.[28] Additionally, aripiprazole has FDA approvals in children/adolescents for schizophrenia, Tourette's syndrome, irritability in autism, and bipolar I disorder.[29,30] Previous studies evaluating off-label prescribing trends of antipsychotics in children/adolescents have found rates of antipsychotic prescribing increased in children/adolescents after new FDA approvals in both adults and children, which may explain their use in our study.[31] Moreover, quetiapine is often prescribed off-label for sleep, which may account for its use in this study, as sleep disturbances were more commonly observed in the antipsychotic group.[32]

Escitalopram and sertraline were both commonly prescribed antidepressants in both groups; however, there was a noticeable difference in fluoxetine prescribing. Fluoxetine was most commonly prescribed to patients in the non-antipsychotic group (29.7%), while it was only used in 4.9% of patients with antipsychotic augmentation. With fluoxetine being 1 of 2 FDA-approved antidepressants in children/adolescents, it is plausible that some patients who had antipsychotic augmentation had previously failed a trial of fluoxetine before switching to another antidepressant and the later initiation of an antipsychotic. An unexpected finding was the number of patients without antidepressant treatment in both groups. In the antipsychotic group, 32.4% of patients were not prescribed an antidepressant, compared with 18.2% in the non-antipsychotic group. This is concerning as antidepressants are the most studied pharmacologic treatment for child/adolescent MDD. It is possible that the patients who were not prescribed an antidepressant were receiving psychotherapy, had an intolerance to antidepressants, or their guardians did not consent to the medications recommended. Another explanation for the absence of antidepressants in the antipsychotic group may be that the physicians were attempting to rule out other psychiatric conditions, such as bipolar disorder, where antipsychotic monotherapy would be appropriate.

Investigators note several limitations of this study. This single-site study analyzed prescribing patterns for patients admitted to 1 facility in the Midwest. The retrospective nature of the study required reliance on documentation, which was not standardized and varied based on the provider for Columbia Suicide Severity Rating Scale scoring and symptoms of depression due to lack of utilization of a standardized rating scale, making it difficult to appropriately assess these endpoints. Provider preferences were not accounted for during analysis and may be considered a confounder. Guardian consent and nonpharmacologic-only recommendations were not accounted for when looking at those who received no medications. The dosing of pharmacologic agents and time from diagnosis to medication initiation were not collected and, therefore, could not be assessed. Specific indications for each medication and assessment of metabolic syndrome were not included in prescriber documentation, though it could have affected pharmacologic decision-making. Finally, we included patients diagnosed with DMDD in our study, which may have affected the results. Although there are no approved medications for the treatment of DMDD, antipsychotics, stimulants, or serotonergic antidepressants are commonly used for this diagnosis.[33]

Conclusion

Despite limited evidence for antipsychotic efficacy for MDD in children/adolescents, antipsychotics were initiated

in 6.8% of patients in this study. These results highlight the need for further research focused on evaluating the efficacy and safety of alternative treatments for MDD in children/adolescents, especially in patients who are refractory to guideline-recommended treatment with psychotherapy and/or antidepressants. Clinicians should consider the potential risks antipsychotics pose, including metabolic effects and extrapyramidal symptoms. Careful consideration and thoughtful treatment planning must occur before prescribing antipsychotics for children/adolescents with MDD because of the lack of sufficient evidence for efficacy, appropriate dosing, and long-term adverse effects.

Acknowledgments

The authors acknowledge their student researchers Melinda Landry and Haley Jones.

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