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Brief Reports

Multiple Antipsychotic Medication Use in Autism Spectrum Disorder

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Abstract

Objective: The purpose of this study was to explore the use of multiple antipsychotic medications in patients with autism spectrum disorder (ASD) by reviewing the longitudinal medication management of 1100 patients consecutively treated for behavioral symptoms associated with ASD at a tertiary care specialty clinic.

Methods: We identified all patients with ASD treated with daily doses of two or more antipsychotics for at least two visits at our clinic. For each patient meeting inclusion criteria, diagnostic and demographic data were collected. To evaluate clinical need and effectiveness of antipsychotic medications in this sample, we reviewed symptoms targeted with each antipsychotic medication and concomitant medications prescribed. Clinical Global Impressions-Severity (CGI-S) and Clinical Global Impressions-Improvement (CGI-I) scale ratings had been completed at the time of each visit, and the duration of treatment with antipsychotic medications was determined. To evaluate the safety and tolerability of antipsychotic medication use in ASD, we reviewed reported adverse effects and calculated body mass index (BMI) change with treatment.

Results: Seventy patients met the inclusion criteria (6.4% of our sample). The majority of patients were moderately to severely ill Caucasian males, as determined by baseline mean CGI-S of 4.7 (SD = 0.8), and were diagnosed with autistic disorder and comorbid intellectual disability. The mean age was 15.1 years (SD = 10.9), the primary targeted symptoms were agitation/irritability, physical aggression, and self-injury. The majority of patients remained on two or more antipsychotics for >1 year. In this population, patients demonstrated greater symptomatic improvement and generally tolerated treatment without significant adverse effects.

Conclusions: The use of two or more antipsychotic medications may be increasingly common in patients with ASD. This retrospective study demonstrates that this treatment approach may be of some clinical benefit, and is generally well tolerated. Prospective studies focusing on the efficacy and safety of concomitant antipsychotic medication usage in ASD should be considered.

Keywords: autism, autism spectrum disorder, antipsychotics, psychopharmacology, irritability

Introduction

Many patients with autism spectrum disorder (ASD) experience behavioral symptoms such as hyperactivity, impulsivity, mood lability, and irritability (defined as agitation, self-injury, and severe tantrums). Two atypical antipsychotic medications, risperidone and aripiprazole, are approved by the United States Food and Drug administration (FDA) for the treatment of irritability in youth with ASD. Additionally, preliminary evidence supports the use of other antipsychotic drugs for the treatment of ASD-associated irritability (Cohen et al. 1980; Politte and McDougle 2014; Stigler 2014). Emerging evidence has described relatively high rates of concomitant use of at least two antipsychotic medications for treatment of behavioral symptoms in some patients ASD (Schubart et al. 2014). This topic is of special concern, as there remains limited data on the tolerability, safety, and clinical benefit of such treatments, especially longer-term use, despite the frequent clinical occurrence of behavioral symptoms refractory to first-line medications in patients with ASD (Gallego et al. 2012; Adler et al. 2015).

The use of more than one antipsychotic medication in the treatment of child and adolescent psychiatric conditions has increased over the last decade. Recent studies describe rates ranging from 7% to nearly 10% in community samples, and >13% in youth

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requiring psychiatric hospitalization (Constantine et al. 2010; Saldana et al. 2014; Toteja et al. 2014). In these studies, the most frequent diagnoses associated with multiple antipsychotic medication use were attention-deficit/hyperactivity disorder, conduct disorder/oppositional defiant disorder, psychotic disorders, and irritability associated with intellectual disability and developmental disorders. Psychotropic drug usage rates, specifically in youth with ASD, are climbing, with recent studies demonstrating that nearly 65% of these patients receive at least one psychotropic medication, with antipsychotics being the most frequently prescribed drug class (Spencer et al. 2013; Schubart et al. 2014). Multiple antipsychotic medication use rates in youth with ASD ranged from 6.2% in 2000 to 8.7% in 2003 in the recent study by Schubart et al. (2014).

The trend toward increasing use of more than one antipsychotic in the treatment of ASD-associated behavioral symptoms is concerning, considering the risks of adverse effects associated with these medications. Weight gain and associated metabolic risks have been reported consistently with antipsychotic treatment in ASD. In the large placebo-controlled trials of risperidone and aripiprazole that led to FDA-approval, rapid weight gain occurred with treatment (Research Units on Pediatric Psychopharmacology Autism Network 2002; Marcus et al. 2009). Our group recently reported a significant increase in body mass index (BMI) *Z*-score with both risperidone and aripiprazole in naturalistic treatment of youth with ASD (Wink et al. 2014). Furthermore, antipsychotics are associated with other adverse effects, including parkinsonism, dystonia, akathisia, tardive dyskinesia, neuroleptic malignant syndrome, hyperprolactinemia, orthostasis, cardiac QTc prolongation, sedation, constipation, hypersalivation, leukopenia, decreased seizure threshold, and liver impairment. Although safety data specific to patients with ASD receiving more than one antipsychotic medication are not available, a review of safety and tolerability of this treatment approach by Gallego et al. (2012) demonstrated a global increase in side effect rates when combining antipsychotics (Gallego et al. 2012).

In this retrospective chart review we present an initial investigation into the effectiveness and safety of the use of multiple antipsychotic medications in ASD via a review of our longitudinal medication management database. Based on our clinical experience, we hypothesized that the patients treated at our clinic with more than one antipsychotic medication would be severely ill at baseline (as demonstrated by a Clinical Global Impressions-Severity [CGI-S] score of ≥5) and would generally tolerate and respond well to treatment with this pharmacotherapeutic approach.

Methods

As part of a larger ongoing comprehensive assessment of medication management in ASD, we analyzed data drawn from 1100 patients evaluated and treated at the Christian Sarkine Autism Treatment Center (Indianapolis, IN) from July 2004 through April 2012. This work was approved by our local Institutional Review Board. From our RedCap medication management database, we identified patients prescribed daily doses of two or more antipsychotic medications concurrently for at least two clinic visits. Patients treated with multiple antipsychotic medications used only ''as needed'' were excluded. For each subject, age, race, sex, ASD diagnostic subtype, presence of intellectual disability, and presence of comorbid genetic syndrome at baseline were determined. ASD diagnosis (autistic disorder, pervasive developmental disorder not otherwise specified [PDD-NOS] or Asperger's disorder) was made by clinicians with expertise in ASD (C.J.M., C.A.E.) using the Diagnostic and Statistical Manual of Mental Disorders, 4th ed., Text Revision (DSM IV-TR) (American Psychiatric Association 2000). Intellectual disability diagnosis was based upon review of neuropsychological testing and school reports (when available) combined with elements of the clinical interview focused on adaptive functioning and cognition.

To evaluate clinical indication for antipsychotic medication use, we recorded the CGI-S scale reported at first clinic visit when two or more antipsychotics were prescribed (referred to as the baseline visit). The CGI-S is a clinician-rated global assessment of symptom severity scale ranging from 1 to 7 (1 = normal, not at all ill; 2 = borderline ill; 3 = mildly ill; 4 = moderately ill; 5 = markedly ill; 6 = severely ill; 7 = among the most extremely ill patients). We identified the symptoms targeted for treatment with each antipsychotic. We also reviewed all concomitant medications prescribed (including ''as needed'' antipsychotics and medications outside of the antipsychotic class). As a qualitative measure of treatment response, we recorded CGI-S and Clinical Global Impressions-Improvement (CGI-I) scale scores at the last recorded clinic visit when two or more antipsychotics were prescribed (referred to as the final visit). The CGI-I is a clinician-rated global assessment of symptom change rated on a scale from 1 to 7 (1 = very much improved; 2 = much improved; 3 = minimally improved; 4 = no change; 5 = minimally worse; 6 = much worse; 7 = very much worse). To evaluate safety, we collected all reported adverse effects and compared BMI at baseline and final visit. Finally, we calculated duration of antipsychotic treatment and combinations of antipsychotics prescribed. Means and standard deviations for all results were calculated, and comparisons from baseline to final visits were made using the nonparametric Wilcoxon signed rank test to control for outliers.

Results

Seventy patients met inclusion criteria (6.4% of patients in our medication management database). One patient was excluded from further analysis because of having no listed ASD diagnosis, and eight were excluded because of a lack of consecutive clinic visits during which they were receiving treatment with two or more antipsychotics. As a result, 61 patients were included in our analysis. Because of incomplete clinical documentation, CGI-S, CGI-I, and BMI data were only available for a subset of included participants. The majority of included patients were treated with a maximum of two concurrent antipsychotics; however, eight patients received three concurrent antipsychotics at some point in their treatment during the analyzed time frame.

Patients were treated with various combinations and doses of 14 different antipsychotic medications (risperidone, aripiprazole, quetiapine, paliperidone, ziprasidone, olanzapine, loxapine, thioridazine, asenapine, clozapine, haloperidol, pimozide, trifluoperazine, chlorpromazine). Patients' mean age at baseline was 15.1 years (SD = 10.9). The majority of patients were male, Caucasian, diagnosed with autistic disorder, and had a comorbid diagnosis of intellectual disability. Five had fragile X syndrome-associated ASD (8.2%). Additional demographic details are provided in Table 1.

Patients treated with more than one antipsychotic medication were moderately to severely ill, with mean CGI-S at baseline of 4.7 (SD = 0.8, $n = 52$). Symptoms targeted by antipsychotic medications at both the baseline visit and final visit were primarily agitation/irritability (88.5%/90.2%), physical aggression (82.0%/82.0%), and self-injury (23.0%/24.6%). Other targeted symptoms included insomnia, anxiety, compulsive/repetitive behavior,

Table 1. Characteristics of Study Sample *(N=61)*

Measurement	
Mean Age, years ± SD	15.1 ± 10.9
Sex (M/F)	53/8
Race (% Black)	7/54 (13.0%)
DSM-IV-TR diagnoses *n* (% of sample)	
Autistic Disorder	44 (72.1%)
PDD NOS	14 (23.0%)
Asperger's disorder	3 (4.9%)
Intellectual disability	41 (67.2%)
Fragile X syndrome-associated ASD	5 (8.2%)

DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders* 4th ed., Text Revision; PDD NOS, pervasive developmental disorder not otherwise specified; ASD, autism spectrum disorder.

Table 2. Concomitant Psychotropic Medications

Medication	*No. Patients*	*% Patients*
Trazodone	19.0	31.1
Clonidine	15.0	24.6
Sertraline	11.0	18.0
Lorazepam	10.0	16.4
Valproic acid	10.0	16.4
Benztropine	9.0	14.8
Guanfacine	8.0	13.1
Melatonin	8.0	13.1
Lamotrigine	6.0	9.8
Atomoxetine	5.0	8.2
Mirtazapine	5.0	8.2
Propranolol	5.0	8.2
Supplements	4.0	6.6
Lithium	4.0	6.6
Diphenhydramine	3.0	4.9
Metformin	3.0	4.9
Riluzole	3.0	4.9
Carbamazepine	3.0	4.9
Quetiapine	2.0	3.3
Chlorpromazine	2.0	3.3
Clomipramine	2.0	3.3
Fluvoxamine	2.0	3.3
Methylphenidate	2.0	3.3
Adderall XR	2.0	3.3
Dexedrine	2.0	3.3
Clonazepam	2.0	3.3
Temazepam	2.0	3.3
Oxcarbazepine	2.0	3.3
Paliperidone	1.0	1.6
Olanzapine	1.0	1.6
Duloxetine	1.0	1.6
Escitalopram	1.0	1.6
Fluoxetine	1.0	1.6
Venlafaxine	1.0	1.6
Methylphenidate ER	1.0	1.6
Amphetamine salts	1.0	1.6
Baclofen	1.0	1.6
Buspirone	1.0	1.6
Acamprosate	1.0	1.6
Amitriptyline	1.0	1.6
Fish oil	1.0	1.6
Naltrexone	1.0	1.6
Imipramine	1.0	1.6
Diazepam	1.0	1.6
Hydroxyzine	1.0	1.6
Alprazolam	1.0	1.6
Other	16.0	26.2

hyperactivity, verbal aggression, psychosis, communication impairment, obsessions, tics, depression, impulsivity, mania, motor stereotypies, inattention, and sexually inappropriate behavior. The most common concomitant medications prescribed other than antipsychotics were trazodone ($n=19$), clonidine ($n=15$), sertraline ($n=11$), valproic acid ($n=10$), lorazepam ($n=10$), and benztropine ($n=9$) (Table 2). The mean CGI-S at final visit was 4.6 (SD = 0.8, $n=58$), with no significant change in global severity of illness from baseline (mean change –0.12, SD = 1.0, $n=51$, $p=0.45$). The mean CGI-I at final visit was 3.1 (SD = 1.3, $n=57$), demonstrating minimally improved symptoms from baseline.

Multiple antipsychotic medication use was generally well tolerated in this patient population with only 11 of 61 patients (18.0%) reporting an adverse event at final visit whose severity required change in management (i.e., dose adjustment, adding medication to treat adverse effects, stopping medication). Reported adverse effects at final visit included weight gain ($n=4$), sedation/tiredness ($n=2$), tics ($n=1$), drooling ($n=1$), self-injury ($n=1$), speech problems ($n=1$), repetitive tongue/mouth movements ($n=1$), and withdrawal dyskinesia ($n=1$). It is important to note that nine patients were treated with benztropine, suggesting the need for medication treatment of antipsychotic-related extrapyramidal symptoms in 14.8% of included patients. The majority of patients were overweight, with mean BMI at baseline of 25.8 (SD = 8.7, $n=39$), and mean BMI at final visit of 25.0 (SD = 7.7, $n=42$). BMI increased slightly in those with BMI recorded at baseline and final visit ($n=30$), although this change was not significant (BMI change = 0.4, SD = 3.8, $p=0.08$).

The mean duration of treatment with two or more antipsychotics was 509 days (SD = 533 days, minimum 35 days, and maximum 2659 days). The most commonly prescribed initial antipsychotic combination was risperidone plus quetiapine ($n=10$, 16.4%), followed by risperidone plus aripiprazole ($n=9$, 14.8%), and aripiprazole plus quetiapine ($n=7$, 11.5%). At the final visit, risperidone plus quetiapine was the most common combination ($n=10$, 16.4%), followed by aripiprazole plus quetiapine ($n=8$, 13.1%), and risperidone plus aripiprazole ($n=5$, 8.2%).

Discussion

To our knowledge, this is the first report describing the use of multiple antipsychotic medications for treatment of behavioral symptoms in ASD. In this review, 6.4% of patients included in our longitudinal medication management database received multiple antipsychotic medication treatment. These patients were primarily moderately to severely ill, irritable, adolescent males with ASD and intellectual disability. This group of patients that had not improved in a clinically significant way with one antipsychotic medication demonstrated global clinical improvement with combination treatment. Overall, the use of more than one antipsychotic medication was well tolerated in this group, with few recorded adverse effects. The majority of patients were overweight at baseline and BMI increased slightly during treatment, although the change was statistically nonsignificant.

Limitations

This report must be viewed in the context of its limitations. Primarily, this is a retrospective review of medical records and the

data are incomplete. Only a portion of included patients had reported CGI-S, CGI-I, and BMI data, limiting the inferences that could be made regarding these results. Additionally, we do not have safety data such as electrocardiogram (ECG) reports or metabolic laboratory measurements; therefore, we cannot comment on whether multiple antipsychotic medication use in this sample resulted in ECG changes or worsening metabolic profiles. Furthermore, standardized measures (beyond clinical examination notes) assessing abnormal motor movement side effects associated with antipsychotics were not available, limiting our ability to adequately assess this potential area of concern. We additionally had no method for assessing the impact of any potential drug–drug interaction and the resulting influence this may have had on treatment response or the presence of side effects. Finally, we do not have information on concomitant psychiatric and medical diagnoses that may have impacted the results.

Conclusions

Multiple antipsychotic medication use may be increasingly common in patients with ASD. This initial review demonstrates that the subgroup of patients with ASD treated with multiple antipsychotics is significantly ill, and demonstrates global clinical improvement with this treatment approach. Additionally, this group tolerated treatment with combination antipsychotics without significant adverse events. This review has significant limitations, particularly in the areas of incomplete data and safety monitoring, which must be considered when interpreting these results. This study may inform the design of future prospective studies focusing on efficacy and safety of concomitant antipsychotic usage for treatment of symptoms refractory to monotherapy antipsychotic medication treatment in ASD.

Disclosures

Dr. Wink has served as a past consultant for Otsuka. Dr. Erickson is a consultant to and holds equity in Confluence Pharmaceuticals and is a consultant to Alcobra Pharmaceuticals. Dr. Erickson is a past consultant to Novartis and the Roche Group. Dr. Erickson holds unrelated IP held by Cincinnati Children's Hospital Medical Center (CCHMC) and Indiana University. Dr. Erickson receives research grant support from Autism Speaks, CCHMC, the John Merck Fund, the National Fragile X Foundation, Neuren Pharmaceuticals, Riovant Sciences Ltd., the Roche Group, and Synapdx. Dr. Pedapati receives research support from the Cincinnati Children's Hospital Research Foundation. Dr. Horn and Dr. McDougle have no disclosures to report.

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