Prescribing Patterns in a Psychiatrically Referred Sample of Youth With Autism Spectrum Disorder

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ABSTRACT

Objective: The aim of this study was to examine the pattern of psychopharmacologic interventions in a psychiatrically referred sample of youth with autism spectrum disorder (ASD).

Methods: This retrospective chart review aimed at collecting demographic and clinical information, including data on *DSM-IV-TR* criteria–based psychiatric disorders and related current medication treatment and response. Data were collected in December 2011. Clinicians identified the target disorder for each medication and any adverse events. Level of psychopathology and therapeutic response was assessed by the clinician-rated Clinical Global Impressions scale (CGI).

Results: Psychiatrically referred youth with ASD (n = 54) suffered from multiple psychopathologies (mean = 2.3) and had a marked level of morbidity (range of baseline CGI–Severity of Illness mean scores, 4.3–5.6). The most prevalent psychopathology was ADHD (83%), anxiety disorders (67%), bipolar spectrum disorder (43%), and mood disorder not otherwise specified (44%). The majority (80%) of the subjects received combination therapy (mean ± SD number of psychotropic medications = 3 ± 1.5). Forty percent of the participants responded on all treatment target symptoms (CGI-Improvement scale score ≤ 2), and an additional 10% experienced response versus nonresponse on a relatively greater number of target symptoms. Half of the subjects reported an adverse event, most commonly weight gain (28%) and sedation (12%), both from antipsychotic medication use.

Conclusions: Psychiatrically referred youth with ASD suffer from multiple highly impairing psychiatric disorders that require combination pharmacotherapy. These findings highlight the need for further research to guide clinical decision-making and treatment.

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Autism spectrum disorder (ASD) is a highly morbid neurodevelopmental disorder characterized by varying degrees of deficits in social interaction and communication along with restricted, repetitive behaviors or interests that is estimated to affect up to 2% of children and adolescents in the general population.[1,2] Prevalence of ASD is considerably higher in psychiatrically referred populations of youth, ranging from 2% to 14%, and these patients thereby constitute a substantial subgroup of patients referred for psychiatric care.[3–7] Psychiatric referrals of children with ASD are frequently driven by emotional and behavioral symptoms such as irritability/aggression,[8] hyperactivity,[9] anxiety,[10,11] and depression.[12,13] Research indicates a greater burden of comorbidity with psychiatric disorders in referred populations of youth with ASD, including attention-deficit/hyperactivity disorder (ADHD), anxiety disorders, and mood disorders.[4,6,7,14–21]

Despite overwhelming evidence of significant psychopathology associated with ASD, the approved pharmacotherapeutic options are limited to the management of irritability.[22,23] Although there is limited empirical evidence of psychopharmacologic response in ASD patients, clinicians manage psychopathology in ASD youth with medications approved for psychiatric conditions in the general pediatric and adult populations. The scant literature on prescribing patterns is limited to documenting high rates of utilization of pharmacotherapy, with rates of polypharmacy reaching up to 35% in pediatric populations with ASD.[24–30]

The purpose of this study was to assess patterns of pharmacotherapy in a psychiatrically referred sample of youth with ASD. To this end, we conducted a naturalistic study consisting of a retrospective audit of the clinical records of youth with ASD receiving ambulatory psychiatric services at specialized programs for ambulatory psychiatric care affiliated with a major university center. Our aim was (1) to profile the spectrum of psychopharmacologic interventions provided for the management of psychopathology and (2) to document the response to psychopharmacologic interventions in a psychiatrically referred population of youth with ASD. To our knowledge, this is the first naturalistic study in this unique population to assess the response of prescribed pharmacotherapy in a clinic setting.

METHODS

We performed a retrospective, unblinded chart review to assess the psychopharmacologic treatment of a psychiatrically referred sample of youth with ASD. Permission to conduct this research with deidentified data was obtained from the institutional review board. The subjects were children and adolescents under the

Clinical Points

- Psychiatrically referred youth with autism spectrum disorder can suffer from multiple highly impairing psychiatric disorders.
- A majority of psychiatrically referred youth with autism spectrum disorder receive combination pharmacotherapy for the management of associated psychopathology.

care of board-certified child and adolescent psychiatrists (G.J. and J.W.) at specialized programs for ambulatory psychiatric care affiliated with a major university center: (1) a program for autism spectrum disorder and (2) a program for pediatric psychopharmacology for psychiatric disorders. As we previously established, while the 2 referred samples significantly differ by prevalence of ASD subtype, they share substantially similar patterns of psychiatric comorbidity.[7] For each provider, we generated a list of patients with a diagnosis of autistic disorder, Asperger's disorder, or pervasive developmental disorder not otherwise specified (PDD-NOS) using *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision (*DSM-IV-TR*), criteria.[31] The diagnosis of autism and associated psychopathology was established in a clinical setting by a board-certified psychiatrist experienced in evaluating ASD and comorbid psychiatric disorders. The diagnoses of ASD and psychiatric disorders were based on *DSM-IV* criteria. ASD was identified based on *DSM-IV* PDD diagnostic criteria as autistic disorder, Asperger's disorder, or PDD-NOS. The psychiatric diagnostic interview was conducted with the subject and parent/guardian(s), and information was incorporated from multiple sources when available (eg, psychiatric records, schools, social services). Data were collected in December 2011, prior to clinical use of *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition, criteria.[1] We restricted the study to patients who had received care for at least 6 months in the clinic and had been seen at least once in the past 6 months to ensure that clinicians could easily recall the cases and more accurately assign severity and improvement scores. There were no exclusion criteria.

We reviewed subjects' electronic medical records to ascertain their age, sex, psychiatric diagnoses, and current medication regimen. For each medication, treating clinicians identified the target condition, and the presence and severity of any adverse events (AEs). Severity and improvement on target conditions were assessed by treating clinicians on the National Institute of Mental Health Clinical Global Impressions–Severity of Illness scale (CGI-S; 1 = not ill, 7 = extremely ill) and CGI-Improvement scale (CGI-I; 1 = very much improved, 7 = very much worse), respectively.[32,33] The CGI scales have previously been optimized for use with specific disorders.[34] Utility of the CGI scales for assessing severity and improvement in specific disorders has been established by previous retrospective chart reviews of psychiatric treatment.[34–39] Treatment response was operationalized based on the CGI-I score of ≤ 2. A global responder was defined as having improvement in all treatment targets; a substantial responder as having an improvement in a majority, ie, more than half of treatment targets; and a partial responder as having improvement in half of the treatment targets. A treatment nonresponder was defined as a CGI-I score of ≥ 4. A substantial treatment nonresponder was defined as having a lack and/or worsening of response in a majority, ie, more than half of treatment targets, and a global treatment nonresponder was defined as having a lack or worsening of response in all treatment targets. In addition, we determined US Food and Drug Administration (FDA) status for each prescribed medication for its identified target condition. To qualify for FDA on-label use, the subject had to meet FDA criteria for age and target condition for that given medication.

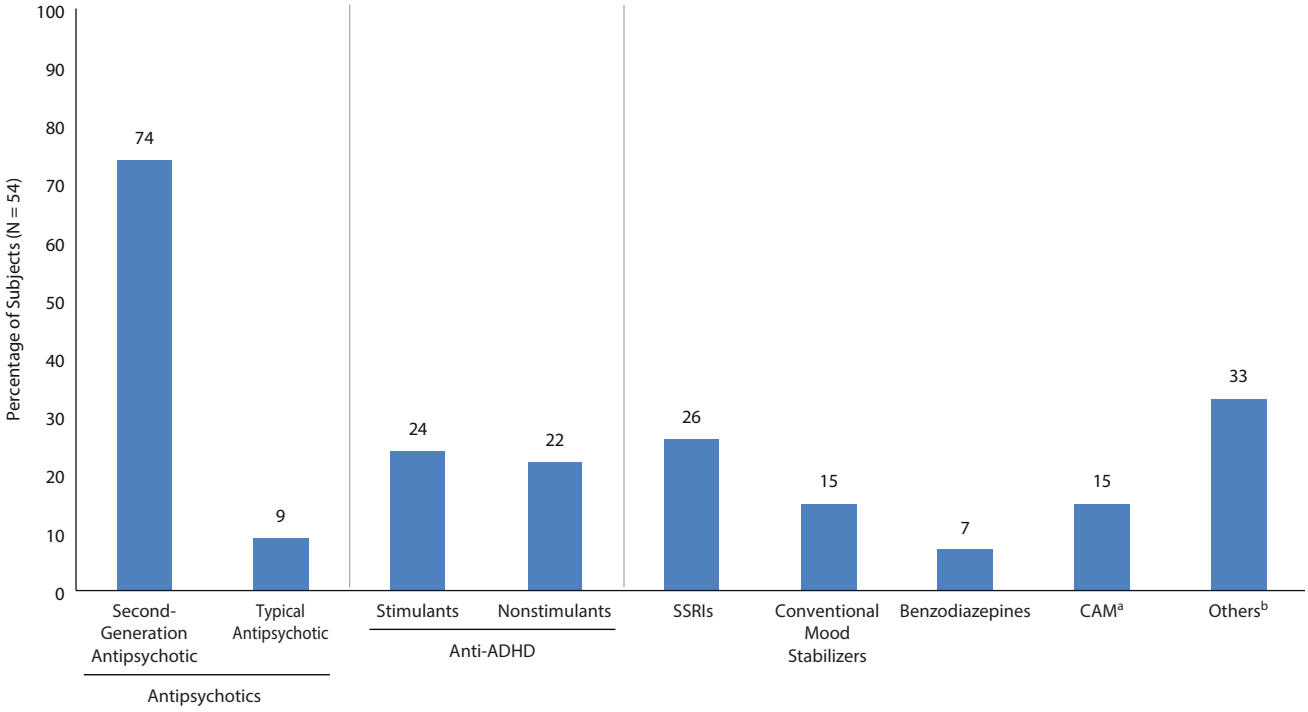
Table 1. Demographic, Clinical, and Treatment Characteristics

Characteristic	Value	
Demographic		
Participants, N	54	
Age, mean ± SD (range), y	13.3 ± 3.1 (7–19)	
Age ≤ 12 y, n (%)	21 (39)	
Male, n (%)	41 (76)	
Clinical		
Prevalence, n (%)		
Autism spectrum disorder		
Autistic disorder	33 (61)	
Asperger's disorder	16 (30)	
PDD-NOS	5 (09)	
Psychopathology		
Mood disorders	51 (94)	
Bipolar spectrum disorder	23 (43)	
Depression NOS	6 (11)	
Mood disorder NOS	24 (44)	
Anxiety disorder (≥ 1)	36 (67)	
ADHD	45 (83)	
ADHD + anxiety disorder + mood disorder	31 (57)	
Severity (CGI-S)	Score, Mean ± SD	Markedly Ill or Worse (score ≥ 5), n (%)
Autism spectrum disorder		
Autistic disorder (n = 32)	4.81 ± 0.78	21 (66)
Asperger's disorder/PDD-NOS (n = 20)	4.30 ± 0.66	8 (40)
Psychopathology		
Mood disorders		
Bipolar spectrum disorder (n = 23)	5.57 ± 0.79	19 (83)
Mood disorder NOS (n = 19)	5.11 ± 0.66	16 (84)
Depression NOS (n = 7)	4.57 ± 0.53	4 (57)
Anxiety disorders		
GAD (n = 3)	4.33 ± 0.58	1 (33)
OCD (n = 4)	5.00 ± 0.82	3 (75)
Anxiety disorder NOS (n = 29)	4.48 ± 0.69	10 (34)
ADHD (n = 43)	4.77 ± 0.61	29 (67)
Treatment		
No. of psychotropic medications, mean ± SD	2.89 ± 1.45	
Psychopharmacologic treatment, n (%)		
None	1 (2)	
Monotherapy	10 (18)	
Combination therapy	43 (80)	
FDA-approved medication(s) only[a]	27 (50)	

[a]Subjects taking only medication(s) meeting FDA criteria for age and target condition.

Abbreviations: ADHD = attention-deficit/hyperactivity disorder, CGI-S = Clinical Global Impressions–Severity of Illness scale, FDA = US Food and Drug Administration, GAD = generalized anxiety disorder, NOS = not otherwise specified, OCD = obsessive-compulsive disorder, PDD = pervasive development disorder.

Figure 1. Treatment Profile of Subjects With Autism Spectrum Disorder



[a]Inositol, melatonin, and omega-3 fatty acids.
[b]Naltrexone (n = 4), buspirone (n = 3), metformin (n = 3), benztropine (n = 2), bupropion (n = 2), duloxetine (n = 2), nortriptyline (n = 1), propranolol (n = 1).
Abbreviations: ADHD = attention-deficit/hyperactivity disorder, CAM = complementary and alternative medicine, SSRI = selective serotonin reuptake inhibitor.

RESULTS

Demographic and Clinical Characteristics

We collected data from 54 charts of children and adolescents with ASD. As shown in Table 1, the mean ± SD age of the sample was 13.3 ± 3.1 years (range, 7–19 years); 21 subjects (39%) were aged 12 years or younger, and 41 subjects (76%) were male. Thirty-three subjects (61%) met criteria for autistic disorder, 16 subjects (30%) met criteria for Asperger's disorder, and 5 subjects (9%) met criteria for PDD-NOS. Almost all subjects had at least 1 comorbid disorder (n = 52, 96%). The most prevalent comorbidities were mood disorders (n = 51, 94%), including bipolar spectrum disorder (which included bipolar I disorder, bipolar II disorder, or bipolar disorder NOS; n = 23, 43%), mood disorder NOS (n = 24, 44%), and depressive disorder NOS (n = 6, 11%); anxiety disorders (n = 36, 67%); and ADHD (n = 45, 83%). Furthermore, the most common presentation of comorbidities was combined mood disorder, anxiety disorder, and ADHD (n = 31, 57%) followed by combined mood disorder and ADHD (n = 13, 24%) and anxiety disorder and ADHD (n = 5, 9%). Less frequent presentations were mood disorder by itself (n = 6, 11%) and combined mood disorder and anxiety disorder (n = 1, 2%). The disorder-specific pretreatment mean CGI-S scores ranged from 4.33 to 5.57, indicating moderate to marked severity of illness. The mean ± SD number of current psychotropic medications per patient was 2.89 ± 1.45. Among the subjects, 1 (2%) was prescribed no psychotropic medication, 10 (18%) were treated with monotherapy, and 43 (80%) received combination therapy.

Medications (not mutually exclusive) included atypical antipsychotics (n = 40, 74%), central nervous system stimulants (n = 13, 24%), mood stabilizers (divalproex sodium, carbamazepine gabapentin, lamotrigine, lithium, topiramate) (n = 8, 15%), nonstimulant ADHD medications (n = 12, 22%), benzodiazepines (n = 4, 7%), selective serotonin reuptake inhibitors (SSRIs) (n = 14, 26%), non-SSRI antidepressants (n = 5, 9%), and complementary and alternative medicines (inositol, omega-3 fatty acids, melatonin) (n = 8, 15%) (Figure 1). Three subjects (6%) were prescribed FDA-approved medication for ASD (aripiprazole) as monotherapy, and 24 subjects (44%) were prescribed FDA-approved medications for ASD in combination with other psychiatric medication. Ninety-three percent of the subjects (n = 50) were prescribed psychotropic medication that is not FDA approved for individuals with ASD. The most commonly prescribed medications were aripiprazole (n = 17, 32%), quetiapine (n = 15, 28%), risperidone (n = 10, 19%), atomoxetine (n = 8, 15%), citalopram (n = 10, 19%), and methylphenidate (n = 10, 19%).

Of the 10 patients (18%) treated with monotherapy, 4 (7% of all patients) were treated with antidepressants: 1 patient with bupropion, 1 with citalopram, 1 with duloxetine, and 1 with sertraline. Of the remaining 6, 3 (6% of all patients) were treated with aripiprazole, 2 (4% of all patients) were

Table 2. Treatment Profile of Subjects With Autism Spectrum Disorder

Medication	Subjects (N = 54), n (%)	Dose, Mean ± SD (range), mg/d
Treatment Profile by Medication Class		
Antipsychotics	40 (74)	
Atypical antipsychotics	40 (74)	
Aripiprazole	17 (31)	13.4 ± 7 (4–22)
Quetiapine	15 (28)	358 ± 225 (25–600)
Risperidone	10 (19)	1.84 ± 1.62 (0.25–6)
Lurasidone	5 (9)	68 ± 18 (40–80)
Others (olanzapine [n = 1], paliperidone [n = 1])	2 (4)	
Typical antipsychotics	5 (9)	
Chlorpromazine	2 (4)	25 ± 0 (25–25)
Perphenazine	3 (6)	8 ± 0 (8–8)
Stimulants	13 (24)	
Methylphenidate salt		
Methylphenidate	10 (19)	22.2 ± 13.4 (10–54)
Dexmethylphenidate	4 (7)	31.25 ± 24 (5–60)
Mixed amphetamine salt		
Amphetamine	3 (6)	26.7 ± 15.3 (10–40)
Lisdexamfetamine	1 (2)	20 ± 0 (20–20)
Nonstimulants	12 (22)	
Atomoxetine	8 (15)	49.2 ± 31.3 (10–80)
Others (amantadine [n = 1], memantine [n = 2])	3 (6)	
α-Agonists	7 (13)	
Clonidine	3 (6)	0.27 ± 0.12 (0.1–0.4)
Guanfacine	4 (7)	1.88 ± 0.85 (1–2)
SSRIs	14 (26)	
Citalopram	10 (19)	19 ± 24 (1–80)
Others (fluoxetine [n = 2], sertraline [n = 2])	4 (7)	
Conventional mood stabilizers	8 (15)	
Anticonvulsants	12 (22)	
Lamotrigine	6 (11)	225 ± 104 (100–350)
Others[a]	7 (13)	
Traditional: lithium	5 (9)	1,110 ± 251 (900–1,500)
Benzodiazepines (clonazepam [n = 2], lorazepam [n = 2])	4 (7)	
CAM	8 (15)	
Melatonin	8 (15)	4.5 ± 1.9 (1–6)
Other (inositol [n = 2], omega-3 fatty acids [n = 1])	3 (6)	
Others[b]	18 (33)	

Medication	Subjects, (N = 54), n (%)
Treatment Profile by Target Symptoms	
Mood dysregulation[c] (n = 40)	
Antipsychotics	39 (98)
Atypical Antipsychotics	38 (95)
Aripiprazole	16 (40)
Quetiapine	15 (38)
Risperidone	10 (25)
Lurasidone	5 (13)
Others[d]	2 (05)
Typical antipsychotic	5 (13)
Perphenazine	3 (08)
Chlorpromazine	2 (05)
Conventional mood stabilizers	11 (28)
Anticonvulsants	8 (20)
Lamotrigine	6 (15)
Others[e]	3 (08)
Traditional: lithium	5 (13)
CAM[f]	3 (08)
Others[g]	3 (08)
Anxiety (n = 20)	
SSRIs[h]	10 (50)
Benzodiazepines[i]	3 (15)
Atomoxetine	3 (15)
Buspirone	3 (15)
Others[j]	5 (25)
ADHD (n = 27)	
Stimulants	18 (67)
Methylphenidate	14 (52)
Mixed amphetamine salts[k]	4 (15)
Nonstimulants	11 (41)
α-Agonists[l]	5 (19)
Atomoxetine	8 (30)
Others[m]	3 (11)
Depression (n = 11)	
SSRIs[n]	8 (67)
Others[o]	4 (33)

(continued)

[a]Carbamazepine (n = 1), divalproex sodium (n = 2), gabapentin (n = 2), topiramate (n = 2).
[b]Naltrexone (n = 4), buspirone (n = 3), metformin (n = 3), benzotropine (n = 2), bupropion (n = 2), duloxetine (n = 2), nortriptyline (n = 1), propranolol (n = 1).
[c]Except depression.
[d]Olanzapine (n = 1), paliperidone (n = 1).
[e]Divalproex sodium (n = 2), carbamazepine (n = 1).
[f]Inositol (n = 2), omega-3 fatty acids (n = 1).
[g]Naltrexone (n = 2), lorazepam (n = 1).
[h]Citalopram (n = 7), fluoxetine (n = 1), sertraline (n = 2).
[i]Clonazepam (n = 2), lorazepam (n = 1).
[j]Nortriptyline (n = 1), gabapentin (n = 2), topiramate (n = 1), risperidone (n = 1).
[k]Amphetamine (n = 3), lisdexamfetamine (n = 1).
[l]Clonidine (n = 2), guanfacine (n = 3).
[m]Bupropion (n = 2), amantadine (n = 1), memantine (n = 2).
[n]Citalopram (n = 5), fluoxetine (n = 2), sertraline (n = 1).
[o]Bupropion (n = 2), duloxetine (n = 2).
Abbreviations: ADHD = attention-deficit/hyperactivity disorder, CAM = complementary and alternative medicine, SSRI = selective serotonin reuptake inhibitor.

treated with methylphenidate, and 1 (2% of all patients) was treated with lorazepam.

Medications for Comorbid Conditions

Medications used to target mood, depression, anxiety, and ADHD are shown in Table 2. The mean ± SD number of medications used specifically to treat mood was 1.83 ± 0.93. The mean ± SD number of medications to treat anxiety and ADHD was 1.20 ± 0.41 and 1.26 ± 0.45, respectively. Monotherapy was used to target depression in all subjects (n = 11) receiving treatment for depression.

Thirty-seven percent of patients (n = 20) received medication therapy exclusively for mood, and 9% (n = 5) received medication therapy exclusively for ADHD. The most common combination of medication was treatment for mood, attention, and anxiety (n = 11, 20%) followed by mood

Table 3. Treatment Outcome on the Clinical Global Impressions–Improvement Scale (CGI-I)

Treatment Outcome on CGI-I	n (%)	CGI-S Score, Mean ± SD		*t* Statistic	*P* Value
		Baseline	Current		
Treatment Responders (CGI-I score ≤ 2)					
Target symptom improvement					
Mood dysregulation (n = 37)	22 (59.5)	5.1 ± 1.0	3.6 ± 1.1	$t_{36} = -8.30$	< .001
Anxiety (n = 17)	13 (76.5)	4.9 ± 0.7	3.2 ± 1.2	$t_{16} = -6.37$	< .001
ADHD (n = 23)	12 (52.2)	4.7 ± 0.7	3.3 ± 0.6	$t_{22} = -8.18$	< .001
Depression (n = 11)	5 (45.5)	4.5 ± 0.6	3.2 ± 0.7	$t_{35} = -8.97$	< .001
Composite symptom improvement (n = 50)					
Global responder[a]	20 (40)				
Substantial responder[b]	5 (10)				
Partial responder[c]	8 (16)				
Treatment Nonresponders (CGI-I ≥ 4)					
Global nonresponder[d]	0 (0)				
Substantial nonresponder[e]	15 (30)				

[a]All treatment targets responded.
[b]Majority (> 1/2) of the treatment targets responded.
[c]Equal number of treatment targets responded.
[d]Lack/worsening of response in all treatment targets.
[e]Lack/worsening of response in majority (> 1/2) of the treatment targets.
Abbreviations: ADHD = attention-deficit/hyperactivity disorder, CGI-S = Clinical Global Impressions–Severity of Illness scale.

and attention (n = 9, 17%), mood and anxiety (n = 6, 11%), and attention and anxiety (n = 2, 4%). Fifty-three percent of subjects (n = 19) taking an antidepressant medication were treated concurrently with an atypical antipsychotic. Treatment with conventional mood stabilizers in all subjects (n = 13) was in combination with an atypical antipsychotic medication.

The most common reason for combined therapy was to treat comorbid mood disorder (n = 48, 89%). In addition to treatment of comorbid psychiatric diagnoses (ADHD, anxiety, and mood disorder), 13% of patients were treated for weight gain with medications including metformin (n = 3), naltrexone (n = 2), and topiramate (n = 2); 17% of patients were treated for insomnia with medications including melatonin (n = 8) and clonidine (n = 1); and 4% of patients were treated for extrapyramidal symptoms with benztropine (n = 2).

Table 4. Adverse Events

Medication	Adverse Event	n (%)
Overall (ie, any AE [n = 50])		25 (50)
Most common	Weight gain[a]	14 (28)
	Sedation[b]	6 (12)
Stimulants (n = 13)	Any AE	2 (15)
Amphetamine (n = 3)	Any AE	2 (67)
	Weight gain	1 (33)
	Appetite decrease	1 (33)
Nonstimulant: clonidine (n = 3)	Sedation	1 (33)
Antipsychotics (n = 40)	Any AE	22 (55)
Atypical Antipsychotics (n = 40)	Any AE	21 (53)
Aripiprazole (n = 17)	Any AE	11 (65)
	Insulin, tics	1 (6)
	Sedation	3 (18)
	Tremor	1 (6)
	Weight gain	6 (35)
Lurasidone (n = 5)	Weight gain	2 (40)
Olanzapine (n = 1)	Any AE	1 (100)
	Weight gain	1 (100)
	Akathisia	1 (100)
Paliperidone (n = 1)	Weight gain	1 (100)
Quetiapine (n = 15)	Any AE	7 (47)
	Weight gain	7 (47)
	Akathisia	1 (7)
	Sedation	1 (7)
Risperidone (n = 10)	Any AE	3 (30)
	EPS	1 (10)
	Weight gain	2 (20)
Typical Antipsychotics (n = 5)	Any AE	2 (40)
Chlorpromazine (n = 2)	Sedation	1 (50)
Perphenazine (n = 3)	Sedation	1 (33)
Conventional Mood Stabilizers (n = 8)	Any AE	4 (50)
Anticonvulsants		
Divalproex sodium (n = 2)	Weight gain	1 (50)
Lamotrigine (n = 6)	Headache	1 (17)
Traditional: lithium (n = 5)	Any AE	2 (40)
	Cognitive dulling	1 (20)
	Tremor	1 (20)

[a]Adverse event due to atypical antipsychotic for all 14 subjects.
[b]Adverse event due to antipsychotic for all 6 subjects.
Abbreviations: AE = adverse event, EPS = extrapyramidal side effects.

Response to Pharmacotherapy

Mean current CGI-S ratings for target symptoms ranged from 3.2 to 3.6. There was meaningful improvement (CGI-I score ≤ 2; much or very much improved) of anxiety in 77%, mood in 60%, ADHD in 52%, and depression in 46% of subjects (Table 3). Forty percent of subjects (20/50) showed a global response with meaningful improvement in all treatment targets, and 10% of subjects (5/50) showed a substantial response with meaningful improvement in more than half of treatment targets. Sixteen percent of subjects (8/50) had a partial response.

Adverse Events

Fifty percent of patients (n = 25) reported an AE (Table 4). In this sample, the most common AEs were weight gain (n = 14, 28%) and sedation (n = 6, 12%), both from antipsychotic medication use. Notably, all 14 subjects reporting weight gain were prescribed an atypical antipsychotic, most commonly aripiprazole (n = 6) and quetiapine (n = 7). All 6 subjects reporting sedation were prescribed either a typical or an atypical antipsychotic, most commonly aripiprazole (n = 3).

DISCUSSION

This study examined patterns of pharmacotherapy in psychiatrically referred youth with ASD. In our sample, the majority of patients at referral were suffering from moderate to marked severity of psychopathology. Patients were on average prescribed 3 medications, with over three-quarters of the sample receiving combination pharmacotherapy. Among the classes of medications prescribed, atypical antipsychotics were most common, used by almost three-quarters of subjects, followed by stimulants and mood

stabilizers. A substantial majority of the patients receiving pharmacotherapy had a meaningful response in at least 1 disorder.

The heavy burden of psychopathological comorbidity in this sample is consistent with the high prevalence of ADHD, anxiety disorders, and mood disorders in referred youth with ASD.[4,6,7,14–21] Furthermore, consistent with prevailing literature, this psychiatrically referred sample of youth with ASD was suffering from multiple psychiatric disorders that necessitated combination pharmacotherapy. In national and international surveys,[21,28,40] up to 70% of children with ASD had at least 1 comorbid disorder, while over 40% had 2 or more. In contrast, 95% of youth with ASD in a psychiatrically referred sample had a lifetime history of 3 or more comorbid disorders, and almost three-quarters had 5 or more psychiatric disorders—a burden of psychopathology which was significantly higher than that observed in the referred population of youth without ASD.[6] The level of psychopathology associated with ASD when assessed on a measure of emotional dysregulation, a construct operationalized as elevated scores in the anxiety/depression, aggression, and attention subscales of the Child Behavior Checklist, documented significantly higher rates and severity of emotional dysregulation in psychiatrically referred youth in the presence of ASD (ASD = 84% vs ADHD = 53%; $P < .001$).[41] Consistent with this finding, the most common reason for combined pharmacotherapy in our sample was for the management of coexisting ADHD, mood disorders, and anxiety disorders.

The 3 most commonly prescribed medications were atypical antipsychotics (74%), followed by atomoxetine (15%), citalopram (19%), and methylphenidate (19%). The high rates of ADHD comorbidity and the relatively lower use of methylphenidate treatment is consistent with evidence demonstrating a lower magnitude of response and higher frequency of adverse events than typically expected in the treatment of hyperactivity associated with ASD.[9] This result is in contrast to the pattern of psychotropic medication use in youth without ASD who have bipolar disorder, among whom almost two-thirds of the bipolar disorder patients with ADHD were treated with stimulants.[35] Additionally, over three-quarters of the ASD patients with mood disorder and ADHD were treated with the atypical antipsychotic class of mood stabilizing agents that also have anti-ADHD effect.[42]

The rate of combination pharmacotherapy in the present clinical sample is higher than the rates of up to 35% in population-based samples.[24–28] By the nature of the specialty clinic, patients with ASD seek referral to a specialized ambulatory care program for the management of severely impairing psychopathologies, as is well illustrated by the moderate to marked severity of illness observed in the majority of the sample. Increased use of psychotropic medications and combined pharmacotherapy are more likely in children and adolescents with co-occurring medical (seizures, gastrointestinal symptoms) and psychiatric (ADHD, anxiety disorders, depression, and bipolar disorder) illness as well as in youth referred for psychiatric services.[26,27]

Combination pharmacotherapy was most frequently used for the treatment of comorbid mood, attention, and anxiety in one-fifth of this sample, with treatment of comorbid mood and attention in almost one-fifth of subjects. Our findings are in line with previous studies on this topic documenting that antipsychotic medications and stimulants are some of the most frequently prescribed treatments in youth with ASD, with common combinations being antipsychotics and antidepressants, antipsychotics and ADHD medications (including stimulants and α agonists), and antidepressants and ADHD medications.[25,26,28,42,43]

A clinically significant minority of youth with ASD suffer from bipolar disorder, the combination of which confers a high degree of functional impairment.[44,45] A series of identically designed, short-term, open-label trials[44,46–49] of atypical antipsychotics in youth with bipolar disorder indicated that atypical antipsychotic treatment was equally efficacious and well-tolerated irrespective of the comorbidity with ASD. Accordingly, more than half of the subjects taking antidepressant medication in this study were prescribed in combination an atypical antipsychotic for mood stabilization in the context of a bipolar depression. Poor antidepressant response of youth with bipolar disorder to atypical antipsychotic treatment is consistent with our earlier report on open-label quetiapine monotherapy in preschool and school-aged children with bipolar spectrum disorder that suggested weaker antidepressant effect than documented in adult populations with bipolar disorder.[43]

Despite high rates of combination pharmacotherapy, there were no medication-related adverse events reported in half of the subjects. Consistent with the high rate of antipsychotic use in this sample, weight gain and sedation were the most commonly reported adverse events. Weight gain was exclusively caused by atypical antipsychotic use, and sedation was associated with typical and atypical antipsychotic treatment. Previously, we reported on the prescribing practices for treatment of BPD in youth attending the same pediatric psychopharmacology specialty clinic.[35] A similar percentage of these subjects experienced adverse events with use of atypical antipsychotic medications and mood stabilizers (54% and 60%, respectively). In this referred population of youth with BPD, the pattern of treatment and response paralleled that of this ASD sample. There was a comparatively high rate of combination pharmacotherapy, as patients on average were also prescribed 3 medications, with more than two-thirds of the BPD youth receiving treatment for a comorbid disorder. Thus, our findings in this ASD population mirror the prescribing pattern of combination therapy observed in a psychiatrically referred population of youth with BPD.

In the United States, FDA-approved treatments for ASD populations are limited to the use of risperidone and aripiprazole for the management of irritability.[22,23] In a recent meta-analysis of 39 studies, 1 in 6 youth with ASD received antipsychotics, with risperidone most frequently prescribed (44.4%) followed by aripiprazole (26.4%).[50] A systemic review of 33 randomized control trials in ASD

further confirms that these medications, in addition to haloperidol, have "established evidence" for treatment of irritability and hyperactivity (risperidone and aripiprazole), negative behavioral symptoms (haloperidol), and stereotypy (aripiprazole).[51] While second-generation antipsychotics were most frequently prescribed in this sample, it is notable that 50% of subjects were prescribed off-label medication. This finding highlights the gulf between the limited number of FDA-approved psychotropic medications for patients with ASD and the utilization of different psychotropic agents in clinical practice that have a limited evidence base in this population.

To our knowledge, this study is the first evaluating the level of improvement on the prescribed pharmacotherapy in youth with ASD. More than half (65%) of the ASD participants in this sample demonstrated improvement in target symptoms with treatment. Global response (ie, improvement in all the target symptoms) was achieved by more than a third (40%) of the ASD participants, whereas half of the ASD youth demonstrated global or substantial response to treatment, ie, improvement in more than half of the target symptoms. The most frequent improvement was in the treatment of anxiety, followed by mood and ADHD. Individuals with ASD are significantly burdened by high rates of psychiatric comorbidity.[6] While there are no FDA-approved medications for treating the core social deficits of ASD, by recognizing and treating associated comorbidities, we can significantly improve functioning and quality of life.

The results of our study should be interpreted in light of several limitations. As we examined youth referred to a university-affiliated hospital-based specialized program for ASD, these findings may not generalize to the community. However, our results should generalize to other psychiatrically referred youth. Because data were collected in 2011, there remains a possibility that there are current differences in prescribing patterns, although a recent meta-analysis[29,30] suggests remarkable stability in global prescribing patterns of psychotropic medications in the ASD population. This was a relatively small sample, and only those who remained in treatment were included. The study may therefore underreport on prior failed psychotropic treatments in subjects or may have excluded participants who discontinued psychopharmacologic care due to poor response. Similarly, medication-related adverse events may have been underestimated, as the assessment occurred during the course of clinical care by patient report and clinician query and did not include subjects who may have dropped out of treatment due to adverse events. Likewise, data on duration of treatment were not gathered, as this study provided a cross-sectional perspective on prescribing practices in youth with ASD rather than a longitudinal view. Additionally, we do not have data on concurrent psychosocial treatment of ASD or the level of cognitive impairment in our subjects, both factors that may affect treatment outcomes. Lastly, assessments of baseline severity on the CGI-S were subject to recall bias, as they were made retrospectively by treating clinicians. Interrater reliability of the CGI scales as used in retrospective chart review has been found in 1 study to moderate intraclass correlation coefficients, which may be due to single-item measures and lack of clearly defined item descriptors.[52]

Despite these limitations, our results highlight the importance of combined pharmacotherapy in the management of ASD and its comorbidities as well as the need for further empirical evidence to guide treatment decisions in this unique population.

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Potential conflicts of interest: Since January 2015, **Dr Wozniak** received no outside research support. She is author of the book, *Is Your Child Bipolar?* published May 2008 by Bantam Books. In 2015–2017, her spouse, Dr John Winkelman, received an honorarium from Otsuka; royalties from Cambridge University Press and UpToDate; consultation fees from Advance Medical, Flex Pharma, and Merck; and research support from UCB Pharma, NeuroMetrix, and Luitpold. **Dr Biederman** is currently receiving research support from the following sources: American Academy of Child and Adolescent Psychiatry, US Department of Defense, US Food and Drug Administration, Headspace, Lundbeck, Neurocentria, National Institute on Drug Abuse, Pamlab, Pfizer, Shire, Sunovion, and National Institutes of Health (NIH); he has a financial interest in Avekshan, a company that develops treatments for attention-deficit/hyperactivity disorder (ADHD); his interests were reviewed and are managed by Massachusetts General Hospital (MGH) and Partners HealthCare in accordance with their conflict of interest policies; and his program has received departmental royalties from a copyrighted rating scale used for ADHD diagnoses, paid by Ingenix, Prophase, Shire, Bracket Global, Sunovion, and Theravance; these royalties were paid to the Department of Psychiatry at MGH. In 2017, Dr Biederman was a consultant for Akili, Guidepoint, and Medgenics; was on the scientific advisory board for Alcobra and Shire; received honoraria from the MGH Psychiatry Academy for tuition-funded continuing medical education (CME) courses; and had a US Patent Application pending (Provisional Number #61/233,686) through MGH corporate licensing on a method to prevent stimulant abuse. In 2016, Dr Biederman received honoraria from the MGH Psychiatry Academy for tuition-funded CME courses and from Alcobra and the American Professional Society of ADHD and Related Disorders; was on the scientific advisory board for Arbor Pharmaceuticals; was a consultant for Akili and Medgenics; and received research support from Merck and SPRITES. In 2015, Dr Biederman received honoraria from the MGH Psychiatry Academy for tuition-funded CME courses and from Avekshan and received research support from Ironshore, Magceutics, and Vaya Pharma/Enzymotec. **Dr Joshi** is supported by the National Institute of Mental Health of the NIH under award number K23MH100450; receives research support from Pfizer and the Simons Center for the Social Brain as a principal investigator (PI) for investigator-initiated studies; has received research support from Duke University and Sunovion as a site PI for multisite trials; is a co-investigator for a clinical trial sponsored by the US Department of Defense; and received an honorarium from the Governor's Council for Medical Research and Treatment of Autism in New Jersey for grant review activities and speaker's honoraria from the American Academy of Child and Adolescent Psychiatry, Massachusetts General Hospital Psychiatry Academy, and the Medical Society of Delaware. **Drs Shekunov** and **Pinsky** and **Mss Conroy**, **Fitzgerald**, **de Leon**, and **Belser** report no financial disclosures.

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