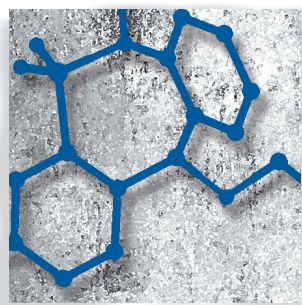


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Pharmacotherapy of emotional and behavioral symptoms associated with autism spectrum disorder in children and adolescents

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Introduction

Autism spectrum disorder (ASD) is a developmental disorder that appears in early childhood and is characterized by persistent deficits in social interaction, as well as restricted, repetitive patterns of behavior, interests, or activities.¹ These core symptoms of ASD are frequently associated with emotional and behavioral disturbances, including anxiety, irritability, labile mood, inattention, hyperactivity, and sleep problems, which may lead to functional impairment and significant emotional and economic burden for caregivers.^{2,3} In 2012, the Center for Disease Control and Prevention reported 1 out of 68 children were affected by ASD.⁴

The treatment for ASD is often multimodal and can include early intensive behavior therapy (applied behavior analysis), speech therapy, occupational and physical therapy, social skills training, special education, and vocational training, among other nonpharmacological interventions. Although there is no cure for ASD, early behavior interventions often improve a child's functioning and outcome.⁵ Currently, there are no medications approved for the management of core symptoms of ASD; however, a psychopharmacological approach may be beneficial in the

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Autism spectrum disorder (ASD) is characterized by impairment in social communication and restricted patterns of behavior. Although there is no pharmacological treatment approved by the US Food and Drug Administration (FDA) for the core symptoms of ASD, there is mounting support in the literature for the management of behavioral symptoms associated with this developmental disorder, in particular, irritability and hyperactivity. Aripiprazole and risperidone are currently approved by the FDA for the treatment of irritability in youth with ASD. Though not FDA-approved, methylphenidate and guanfacine are effective for the management of hyperactivity in children with ASD. Selective serotonin reuptake inhibitors are often used in clinical practice to target anxiety and compulsions; however, there is little evidence to support its use in this population. There is a great need for further research on the safety and efficacy of existing psychotropic medications in youth with ASD, as well as the development of new treatment modalities for the core and associated behavioral symptoms.

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treatment of associated symptoms that can substantially and adversely impact the life of a person with ASD.⁶

Currently, there are only two medications, risperidone and aripiprazole, that are approved by the US Food and Drug Administration (FDA) for the management of symptoms associated with ASD. However, it has been reported that close to half of the insured children with ASD are receiving psychopharmacological interventions with stimulants, α -agonists, antipsychotics, and antidepressants.⁷ It is important to remember that many families seek out natural remedies, supplements, and chelating agents, which all have the potential to cause adverse effects and interact with the prescribed medications.⁸ Therefore, it is essential to inquire about the use of any complementary and alternative therapies utilized by families, provide psychoeducation, and recommend evidence-based approaches for the management of symptoms associated with ASD. In this article, we provide an overview of the current literature on psychopharmacological interventions in treating ASD and comorbid conditions.

Antipsychotics

Risperidone is approved by the FDA for the treatment of irritability associated with autistic disorder in youth aged 5 to 16 years. Youth with ASD receiving risperidone showed an over 50% reduction in the irritability score of the Aberrant Behavior Checklist (ABC-I).⁹⁻¹² The magnitude of the response was greater with moderate-to-severe irritability and lethargy associated with ASD.¹³

The efficacy of risperidone was maintained long term during a 4-month open-label treatment.¹⁴ During the double-blind, placebo-substitution withdrawal part of this study, over 60% of youth relapsed on placebo compared with 12.5% on risperidone. However, symptom improvement with risperidone came at the expense of weight gain, which averaged 5.1 kg. Another open-label extension study demonstrated a decrease in irritability over the course of 21 months.^{10,15} Interestingly, treatment with risperidone was not associated with an improved Clinical Global Impressions-Severity (CGI-S) score, possibly due to it being dichotomized to “improved” or “not improved” and therefore not able to detect subtle changes.

Adequate dosing of risperidone was explored in a double-blind, placebo-controlled study of 96 children, ages 5 to 17 years.¹¹ In this study, higher doses of risperi-

done (1.75 mg/day for >45 kg) contributed to greater change in the ABC-I than lower doses (0.175 mg/day for >45 kg).

Aripiprazole is also approved by the FDA for the treatment of irritability associated with autistic disorder in children and adolescents between the ages of 6 and 17 years. Two large-scale randomized, placebo-controlled studies of children and adolescents taking aripiprazole reported significantly lower scores on the ABC-I and the Clinical Global Impressions – Improvement (CGI-I) scale on active medication than on placebo.^{16,17} Post hoc analysis of the aforementioned studies revealed an association of aripiprazole with improved quality of life in the areas of emotional, social, and cognitive functioning.¹⁸

Aripiprazole did not separate from placebo in a randomized, relapse-prevention trial of 85 children, evaluating long-term treatment effects.¹⁹ In phase 1 of this trial, subjects received flexible doses of aripiprazole (2 to 15 mg/day) for 13 to 26 weeks. Those who achieved more than a 25% decrease in ABC-I and were stable for 12 weeks were randomized to continue active treatment for an additional 16 weeks or were switched to placebo. Although there was no statistically significant difference between the two groups, a post hoc analysis revealed a number needed to treat of 6 to prevent 1 additional relapse. Therefore, aripiprazole may be helpful in long-term management of some patients.

In an open-label flexible-dose study of 330 children and adolescents aged 6 to 17 years, where aripiprazole was continued for 52 weeks following two 8-week randomized placebo-controlled trials, the treatment with aripiprazole significantly reduced ABC-I scores in de novo subjects and in those previously receiving placebo.²⁰ Improvement was maintained for those patients who received aripiprazole during the first 8 weeks of treatment. Aripiprazole was generally well tolerated, and common side effects included weight gain, vomiting, insomnia, and dyslipidemia.²¹ The most frequent serious adverse event was aggression. Younger children with higher baseline weight were more likely to gain additional weight when taking aripiprazole.²²

Aripiprazole was directly compared with risperidone in a 2-month double-blind, randomized trial.²³ Both medications decreased the ABC-I scores. Although aripiprazole reduced the symptoms of irritability faster than risperidone, the overall effects on the ABC-I scores were similar in both groups.

Weight gain is often a common concern for patients and families when choosing an antipsychotic medication. Although aripiprazole is usually not associated with significant weight gain in typically developing youths,²⁴ increases in body mass index were similar for aripiprazole and risperidone in children with ASD.²⁵

Several small studies of olanzapine suggest potential benefits in the management of children with ASD. Olanzapine improved symptoms of irritability in a 3-month open-label study of 25 youth aged 6 to 16 years.²⁶ A double-blind, placebo-controlled study of 11 children ages 6 to 14 suggested an overall improvement in global functioning, but at the expense of weight gain.²⁷ The effectiveness of olanzapine was compared with that of haloperidol in an open-label study of 12 children with ASD.²⁸ Both groups improved on the Children's Psychiatric Rating Scale (CPRS Autism Factor) and the CGI-I. Side effects included drowsiness and weight gain for both interventions.

The effectiveness of paliperidone for irritability in children with ASD was evaluated in an 8-week, open-label study of 25 subjects aged 12 to 21 years.²⁹ Significant improvement in irritability was noted in 84% of patients. Side effects included an average weight increase of 2.2 kg and an elevated level of prolactin.

Quetiapine was not effective and was poorly tolerated in the treatment of youth with ASD in two small open-label studies.^{30,31} However, in an open-label trial of 11 adolescents aged 13 to 17 years, quetiapine was well tolerated, and a significant decrease in aggressive behavior and sleep disturbances was noted.³² Ziprasidone is an antipsychotic with a putative reduced propensity for weight gain; improved global functioning attributed to this agent in two studies suggests it may be promising for the management of children with ASD.^{33,34}

Lurasidone did not prove to be beneficial in reducing irritability associated with ASD in a randomized, double-blind, placebo-controlled trial of 150 children and adolescents.³⁵ However, there was an improvement in global functioning on lurasidone 20 mg/day, though not on 60 mg/day. The reasons for the lack of response to the higher dose of lurasidone used in this trial are not yet clear.

There is more evidence to support the use of risperidone and aripiprazole for the treatment of irritability associated with ASD than observed with other second-generation antipsychotics. However, paliperidone and olanzapine may be promising medications in this popu-

lation. Reports of quetiapine are small and show mixed results, whereas lurasidone is not beneficial in the management of irritability in youth with ASD. To our knowledge, there are no published studies of asenapine in the treatment of behavior symptoms associated with ASD.

Anticonvulsants and lithium

Divalproex was beneficial in reducing irritability in a small, randomized, placebo-controlled trial of children with ASD³⁶; however, an earlier double-blind, randomized trial failed to show separation from placebo on the ABC-I.³⁷ An open-label trial of levetiracetam suggested improvements in emotional lability and aggressive behaviors³⁸; however, a randomized, placebo-controlled trial did not find any benefit in the management of repetitive behaviors, impulsivity, and hyperactivity.³⁹

Monotherapy with topiramate has no demonstrated benefit in the treatment of youth with ASD⁴⁰; however, it reduced the ABC-I score when added to risperidone.⁴¹ Lamotrigine was not effective in reducing irritability, a finding based on a double-blind, placebo-controlled study of 27 boys ages 3 to 11 years.⁴²

Although there are no randomized placebo-controlled trials of lithium in children with ASD, a retrospective chart review of 30 children and adolescents with ASD revealed improvements in functioning in subjects with elevated mood and euphoria.⁴³

The current evidence for divalproex in the management of irritability in subjects with ASD is mixed. There is no evidence to support the use of levetiracetam or lamotrigine in the management of ASD. Topiramate may be beneficial as an adjunct to risperidone. Lithium may be helpful in the management of elevated mood symptoms.

Antidepressants

It has been our experience that antidepressants have been commonly prescribed to treat children with ASD with the hope of targeting repetitive behaviors and anxiety symptoms. However, there is insufficient data to support the use of antidepressants in this population. A randomized, placebo-controlled study of citalopram in children and adolescents aged 5 to 17 years failed to find a positive response on the CGI-I scale or the Children's Yale-Brown Obsessive-Compulsive Scale

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(CY-BOCS).⁴⁴ In addition, subjects experienced increased adverse events, such as increased energy levels, impulsiveness, hyperactivity, stereotypy, and insomnia. A study of fluoxetine was conducted in this population; although the study is unpublished, an Autism Speaks press release about the study indicated that fluoxetine was not effective in reducing repetitive behaviors.⁴⁵ An open-label 10-week study of fluvoxamine in 18 children and adolescents suggested a partial response in some individuals, but not in the group as a whole.⁴⁶ A Cochrane review did not find enough evidence to support the use of selective serotonin reuptake inhibitors (SSRIs) in children with ASD.⁴⁷ In addition, there is an increased risk of side effects with SSRI treatment in children with ASD.

Psychostimulants

Methylphenidate has been shown to reduce the symptoms of hyperactivity and inattention in youth with ASD. However, the effect sizes were lower and the rates of adverse events higher than in youth without ASD.⁴⁸⁻⁵⁰ A recently published study, where subjects were randomized to low (10 mg/day) or medium (30 mg/day) doses of an extended-release liquid formulation of methylphenidate, reported significant decreases on ABC subscales of irritability and hyperactivity.⁵¹ Interestingly, the side effects of rebound hyperactivity and aggression at the end of the day decreased in the medium-dose group only. To our knowledge, there are no published trials of methodological rigor regarding the use of amphetamines in children with ASD.

α_2 -Agonists

Guanfacine is effective in reducing hyperactivity in children with ASD.⁵² In a double-blind, placebo-controlled trial of an extended-release formulation of guanfacine, 50% of youth on active treatment improved on the CGI-I scale, compared with 9.4% on placebo.⁵³ Low blood pressure was noted for the first 4 weeks of treatment but returned to baseline at week 8. A gene variant in a multidrug-resistance protein (MDR1) may have an effect on the treatment response to guanfacine in children with ASD.⁵⁴ The studies of clonidine suggest a benefit in reducing hyperactivity symptoms and improving sleep in children with ASD.^{55,56} In general, α -agonists show promise in the management of hyperactivity in children

with ASD; however, larger-scale studies of clonidine are needed to establish its efficacy in this population.

Norepinephrine reuptake inhibitors

Atomoxetine is an alternative to stimulants and α -agonists in treating patients with ASD and associated hyperactivity.^{57,58} In a 10-week randomized, placebo-controlled trial, where the treatment with atomoxetine was compared with parent training, placebo, and a combination of atomoxetine with parent training, response rates were higher in a combination treatment group.⁵⁹ The response was maintained by 60% of subjects in a 24-week extension study.⁶⁰

Oxytocin

Over the past decade, oxytocin has been investigated as a potential agent modulating social responsiveness and communication in subjects with ASD. Although early trials, which involved single-dose administration, were promising, more recent evidence has provided mixed results.⁶¹ A double-blind, placebo-controlled trial of two doses of oxytocin (12 or 24 international units [IU] for 5 days daily, depending on the weight of a child) revealed no separation from placebo in the areas of emotion recognition or social interaction.⁶² Similarly, higher doses of 18 or 24 IU twice daily for 8 weeks did not produce improvement in scores on the Social Responsiveness Scale (SRS) and the CGI-I scale.⁶³ Alternatively, in a study with very young children between the ages of 3 and 8, significant improvements in social behaviors were observed on the parent ratings after administration of oxytocin for 5 weeks.⁶⁴ It is possible that variable efficacy of oxytocin in these trials was due to considerable methodological differences or unequal effect of oxytocin across the person's life cycle. Whereas oxytocin may be a promising agent, larger-scale studies utilizing similar dosing administration of the medication and outcome measures are warranted.

Glutamatergic and γ -aminobutyric acid receptor-modulating agents

Arbaclofen, a selective γ -aminobutyric-acid B receptor (GABA_B) agonist, improved scores from the irritability and lethargy/social withdrawal subscales of ABC, as well as the SRS scores in an 8-week open-label study

of 32 children with ASD.⁶⁵ *N*-acetylcysteine (NAC), a glutamatergic modulator and an antioxidant, has been shown to reduce irritability associated with ASD as an adjunct to risperidone,^{66,67} whereas monotherapy with NAC delivered mixed results.⁶⁸⁻⁷⁰ In addition, NAC did not improve social impairment.⁶⁹ *D*-Cycloserine was considered a promising agent after it showed improvements in social withdrawal.⁷¹ Although these findings were not corroborated in follow-up studies,⁷² cycloserine may still be beneficial in maintaining the effects of social skills training.⁷³

A number of other medications have been beneficial when used in conjunction with risperidone. Memantine, riluzole, and amantadine may help reduce irritability and other behavioral measures when combined with risperidone.⁷⁴⁻⁷⁶ A significant decrease in ABC-I scores was noted in a small randomized, double-blind trial of 44 children aged 4 to 12 years who received pioglitazone in addition to risperidone for 10 weeks.⁷⁷

In an 8-week randomized trial of youth aged 4 to 17 years, memantine was directly compared with risperidone.⁷⁸ Both medications significantly reduced irritability, social withdrawal, inappropriate speech, and hyperactivity; however, there was no statistically significant difference between the two groups. More patients in the risperidone group were “very much improved,” a finding based on the Clinical Global Impression, Improvement score (CGI-I). Memantine did not demonstrate improvement on the SRS in a 12-week randomized, placebo-controlled study with a 48-week open-label extension.⁷⁹

Other agents

Secretin has been studied extensively for the treatment of core symptoms of ASD; however, a Cochrane review concluded that there is no evidence for its effectiveness, and it should not be recommended for the management of ASD.⁸⁰ Effectiveness of monotherapy with buspirone has been investigated in a small randomized, placebo-controlled trial of children with ASD aged 2 to 6 years.⁸¹ Although the composite score of the Autism Diagnostic Observation Schedule (ADOS) did not change between groups, there was a significant improvement noted in the restricted and repetitive behavior score of the ADOS with buspirone 2.5 mg twice daily. A combination of buspirone and risperidone was more effective in reducing the ABC-I score than a combination of risperidone and placebo during 8 weeks of treatment.⁸²

Conclusions

Despite the recent advances in the pharmacotherapy of ASD, current evidence-based options for treatment remain limited. There is no evidence that any of the reviewed medications have a significant impact on social withdrawal, which is one of the characteristic symptoms of this developmental disorder. However, there are more options available for the management of associated symptoms. The treatment of irritability has received the most attention. Two second-generation antipsychotics—risperidone and aripiprazole—have the highest level of evidence for the treatment of irritability associated with ASD and are approved by the FDA for this purpose. Olanzapine and paliperidone may be beneficial, but larger trials are needed to establish safety and efficacy. Lurasidone is not effective, and quetiapine showed mixed results; they are therefore not recommended in the treatment of irritability in ASD. Trials involving mood stabilizers and lithium have generally not been sufficiently powered. The evidence for monotherapy with divalproex is mixed. Lithium has been effective in children with ASD exhibiting manic symptoms.

A number of medications may be effective when used in combination with an antipsychotic, such as risperidone. NAC, memantine, riluzole, amantadine, and buspirone reduced irritability in children with ASD when given in conjunction to risperidone.

Attention-deficit/hyperactivity disorder (ADHD) symptoms are also prevalent in youth with ASD and lead to significant functional impairment. Methylphenidate has been reported to be effective in managing hyperactivity; however, the effect size in children with ASD is generally lower and the rates of adverse effects higher than in typically developing youth. Surprisingly, there are little data regarding the use of amphetamines in youths with ASD. Guanfacine extended release has been shown to be effective in the management of comorbid ADHD. The studies evaluating the effect of clonidine are generally small but, overall, show some benefit.

Stereotypy and repetitive behaviors are challenging to address with psychopharmacologic agents. Antidepressants did not show significant benefit in this area. Moreover, children with ASD tend to experience more activating side effects with antidepressants, and their use for treating stereotypy is not recommended.

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As outlined in this review, clinical trials have provided some evidence that a number of pharmacological interventions are not beneficial in the management of ASD and associated symptoms. There could be several factors affecting the results of these studies. In general, these trials may not be sufficiently powered to detect the effect of the medication. In addition, the studies show considerable methodological differences, utilize a variety of rating scales, and have different baseline scores, which could all contribute to the statistical analysis showing lack of effectiveness. The effect of the medications across the life span of a child with ASD is yet to be determined; it may be possible that earlier psychopharmacological interventions would be more beneficial. In addition, behavioral management is an essential factor in managing a child with autism; however, it is not included in most of the clinical trials.

Despite the interest and major advances in the autism field, more research is needed to establish efficacy and safety of the pharmacological and behavioral interventions in the management of ASD and comorbid conditions. Several clinical trials are currently addressing this need. An online search for active studies on

clinicaltrials.gov produced 225 hits, including medication, behavior interventions, and psychotherapeutic treatment options. More studies are needed to evaluate the safety and efficacy of long-term treatment of ASD in youth, as well as comparative trials of existing medications. ASD is a heterogeneous group of developmental conditions, and there may be subgroups that could benefit from more targeted pharmacologic interventions. Further understanding of genetics and pathophysiology of ASD could lead to the development of novel treatment options that could directly address the core symptoms of autism. □

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REFERENCES

1. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. Washington, DC: American Psychiatric Association; 2013.
2. Simonoff E, Pickles A, Charman T, Chandler S, Loucas T, Baird G. Psychiatric disorders in children with autism spectrum disorders: prevalence, comorbidity, and associated factors in a population-derived sample. *J Am Acad Child Adolesc Psychiatry*. 2008;47(8):921-929.
3. Buescher AV, Cidav Z, Knapp M, Mandell DS. Costs of autism spectrum disorders in the United Kingdom and the United States. *JAMA Pediatr*. 2014;168(8):721-728.
4. Christensen DL, Baio J, Van Naarden Braun K, et al; Centers for Disease Control and Prevention (CDC). Prevalence and characteristics of autism spectrum disorder among children aged 8 years—autism and developmental disabilities monitoring network, 11 Sites, United States, 2012. *MMWR Surveill Summ*. 2016;65(3):1-23.
5. Tonge BJ, Bull K, Brereton A, Wilson R. A review of evidence-based early intervention for behavioural problems in children with autism spectrum disorder: the core components of effective programs, child-focused interventions and comprehensive treatment models. *Curr Opin Psychiatry*. 2014;27(2):158-165.
6. Ji N, Findling RL. An update on pharmacotherapy for autism spectrum disorder in children and adolescents. *Curr Opin Psychiatry*. 2015;28(2):91-101.
7. Madden JM, Lakoma MD, Lynch FL, et al. Psychotropic medication use among insured children with autism spectrum disorder. *J Autism Dev Disord*. 2017;47(1):144-154.
8. Levy SE, Hyman SL. Complementary and alternative medicine treatments for children with autism spectrum disorders. *Child Adolesc Psychiatr Clin N Am*. 2015;24(1):117-143.
9. Shea S, Turgay A, Carroll A, et al. Risperidone in the treatment of disruptive behavioral symptoms in children with autistic and other pervasive developmental disorders. *Pediatrics*. 2004;114(5):e634-e641.
10. McCracken JT, McGough J, Shah B, et al. Risperidone in children with autism and serious behavioral problems. *N Engl J Med*. 2002;347(5):314-321.
11. Kent JM, Kushner S, Ning X, et al. Risperidone dosing in children and adolescents with autistic disorder: a double-blind, placebo-controlled study. *J Autism Dev Disord*. 2013;43(8):1773-1783.
12. Pandina GJ, Bossie CA, Youssef E, Zhu Y, Dunbar F. Risperidone improves behavioral symptoms in children with autism in a randomized, double-blind, placebo-controlled trial. *J Autism Dev Disord*. 2007;37(2):367-373.
13. Levine SZ, Kodesh A, Goldberg Y, et al. Initial severity and efficacy of risperidone in autism: results from the RUPP trial. *Eur Psychiatry*. 2016;32:16-20.
14. Research Units on Pediatric Psychopharmacology Autism Network. Risperidone treatment of autistic disorder: longer-term benefits and blinded discontinuation after 6 months. *Am J Psychiatry*. 2005;162(7):1361-1369.
15. Aman M, Rettiganti M, Nagaraja HN, et al. Tolerability, safety, and benefits of risperidone in children and adolescents with autism: 21-month follow-up after 8-week placebo-controlled trial. *J Child Adolesc Psychopharmacol*. 2015;25(6):482-493.
16. Marcus RN, Owen R, Kamen L, et al. A placebo-controlled, fixed-dose study of aripiprazole in children and adolescents with irritability associated with autistic disorder. *J Am Acad Child Adolesc Psychiatry*. 2009;48(11):1110-1119.
17. Owen R, Sikich L, Marcus RN, et al. Aripiprazole in the treatment of irritability in children and adolescents with autistic disorder. *Pediatrics*. 2009;124(6):1533-1540.

18. Varni JW, Handen BL, Corey-Lisle PK, et al. Effect of aripiprazole 2 to 15 mg/d on health-related quality of life in the treatment of irritability associated with autistic disorder in children: a post hoc analysis of two controlled trials. *Clin Ther*. 2012;34(4):980-992.
19. Findling RL, Mankoski R, Timko K, et al. A randomized controlled trial investigating the safety and efficacy of aripiprazole in the long-term maintenance treatment of pediatric patients with irritability associated with autistic disorder. *J Clin Psychiatry*. 2014;75(1):22-30.
20. Marcus RN, Owen R, Manos G, et al. Aripiprazole in the treatment of irritability in pediatric patients (aged 6-17 years) with autistic disorder: results from a 52-week, open-label study. *J Child Adolesc Psychopharmacol*. 2011;21(3):229-236.
21. Marcus RN, Owen R, Manos G, et al. Safety and tolerability of aripiprazole for irritability in pediatric patients with autistic disorder: a 52-week, open-label, multicenter study. *J Clin Psychiatry*. 2011;72(9):1270-1276.
22. Mankoski R, Stockton G, Manos G, et al. Aripiprazole treatment of irritability associated with autistic disorder and the relationship between prior antipsychotic exposure, adverse events, and weight change. *J Child Adolesc Psychopharmacol*. 2013;23(8):572-576.
23. Ghanizadeh A, Sahraeizadeh A, Berk M. A head-to-head comparison of aripiprazole and risperidone for safety and treating autistic disorders, a randomized double blind clinical trial. *Child Psychiatry Hum Dev*. 2014;45(2):185-192.
24. De Hert M, Dobbelaere M, Sheridan EM, Cohen D, Correll CU. Metabolic and endocrine adverse effects of second-generation antipsychotics in children and adolescents: a systematic review of randomized, placebo controlled trials and guidelines for clinical practice. *Eur Psychiatry*. 2011;26(3):144-158.
25. Wink LK, Early M, Schaefer T, et al. Body mass index change in autism spectrum disorders: comparison of treatment with risperidone and aripiprazole. *J Child Adolesc Psychopharmacol*. 2014;24(2):78-82.
26. Kemner C, Willemsen-Swinkels SH, de Jonge M, Tuynman-Qua H, van Engeland H. Open-label study of olanzapine in children with pervasive developmental disorder. *J Clin Psychopharmacol*. 2002;22(5):455-460.
27. Hollander E, Wasserman S, Swanson EN, et al. A double-blind placebo-controlled pilot study of olanzapine in childhood/adolescent pervasive developmental disorder. *J Child Adolesc Psychopharmacol*. 2006;16(5):541-548.
28. Malone RP, Cater J, Sheikh RM, Choudhury MS, Delaney MA. Olanzapine versus haloperidol in children with autistic disorder: an open pilot study. *J Am Acad Child Adolesc Psychiatry*. 2001;40(8):887-894.
29. Stigler KA, Mullett JE, Erickson CA, Posey DJ, McDougle CJ. Paliperidone for irritability in adolescents and young adults with autistic disorder. *Psychopharmacology (Berl)*. 2012;223(2):237-245.
30. Martin A, Koenig K, Scahill L, Bregman J. Open-label quetiapine in the treatment of children and adolescents with autistic disorder. *J Child Adolesc Psychopharmacol*. 1999;9(2):99-107.
31. Findling RL, McNamara NK, Gracious BL, et al. Quetiapine in nine youths with autistic disorder. *J Child Adolesc Psychopharmacol*. 2004;14(2):287-294.
32. Golubchik P, Sever J, Weizman A. Low-dose quetiapine for adolescents with autistic spectrum disorder and aggressive behavior: open-label trial. *Clin Neuropharmacol*. 2011;34(6):216-219.
33. Dominick K, Wink LK, McDougle CJ, Erickson CA. A Retrospective naturalistic study of ziprasidone for irritability in youth with autism spectrum disorder. *J Child Adolesc Psychopharmacol*. 2015;25(5):397-401.
34. Malone RP, Delaney MA, Hyman SB, Cater JR. Ziprasidone in adolescents with autism: an open-label pilot study. *J Child Adolesc Psychopharmacol*. 2007;17(6):779-790.
35. Loebel A, Brams M, Goldman RS, et al. Lurasidone for the treatment of irritability associated with autistic disorder. *J Autism Dev Disord*. 2016;46(4):1153-1163.
36. Hollander E, Chaplin W, Soorya L, et al. Divalproex sodium vs placebo for the treatment of irritability in children and adolescents with autism spectrum disorders. *Neuropsychopharmacology*. 2010;35(4):990-998.
37. Hellings JA, Weckbaugh M, Nickel EJ, et al. A double-blind, placebo-controlled study of valproate for aggression in youth with pervasive developmental disorders. *J Child Adolesc Psychopharmacol*. 2005;15(4):682-692.
38. Rugino TA, Samscock TC. Levetiracetam in autistic children: an open-label study. *J Dev Behav Pediatr*. 2002;23(4):225-230.
39. Wasserman S, Iyengar R, Chaplin WF, et al. Levetiracetam versus placebo in childhood and adolescent autism: a double-blind placebo-controlled study. *Int Clin Psychopharmacol*. 2006;21(6):363-367.
40. Mazzone L, Ruta L. Topiramate in children with autistic spectrum disorders. *Brain Dev*. 2006;28(10):668.
41. Rezaei V, Mohammadi MR, Ghanizadeh A, et al. Double-blind, placebo-controlled trial of risperidone plus topiramate in children with autistic disorder. *Prog Neuropsychopharmacol Biol Psychiatry*. 2010;34(7):1269-1272.
42. Belsito KM, Law PA, Kirk KS, Landa RJ, Zimmerman AW. Lamotrigine therapy for autistic disorder: a randomized, double-blind, placebo-controlled trial. *J Autism Dev Disord*. 2001;31(2):175-181.
43. Siegel M, Beresford CA, Bunker M, et al. Preliminary investigation of lithium for mood disorder symptoms in children and adolescents with autism spectrum disorder. *J Child Adolesc Psychopharmacol*. 2014;24(7):399-402.
44. King BH, Hollander E, Sikich L, et al. Lack of efficacy of citalopram in children with autism spectrum disorders and high levels of repetitive behavior: citalopram ineffective in children with autism. *Arch Gen Psychiatry*. 2009;66(6):583-590.
45. Autism Speaks announces results reported for the study of fluoxetine in autism (SOFIA) [Autism Speaks press release]. <http://www.autismspeaks.org/about-us/press-releases/autism-speaks-announces-results-reported-study-fluoxetine-autism-sofia>. Published Feb 18, 2009. Accessed October 2017.
46. Martin A, Koenig K, Anderson GM, Scahill L. Low-dose fluvoxamine treatment of children and adolescents with pervasive developmental disorders: a prospective, open-label study. *J Autism Dev Disord*. 2003;33(1):77-85.
47. Williams K, Brignell A, Randall M, Silove N, Hazell P. Selective serotonin reuptake inhibitors (SSRIs) for autism spectrum disorders (ASD). *Cochrane Database Syst Rev*. 2013(8):CD004677.
48. Pearson DA, Santos CW, Aman MG, et al. Effects of extended release methylphenidate treatment on ratings of attention-deficit/hyperactivity disorder (ADHD) and associated behavior in children with autism spectrum disorders and ADHD symptoms. *J Child Adolesc Psychopharmacol*. 2013;23(5):337-351.
49. Jahromi LB, Kasari CL, McCracken JT, et al. Positive effects of methylphenidate on social communication and self-regulation in children with pervasive developmental disorders and hyperactivity. *J Autism Dev Disord*. 2009;39(3):395-404.
50. Research Units on Pediatric Psychopharmacology Autism Network. Randomized, controlled, crossover trial of methylphenidate in pervasive developmental disorders with hyperactivity. *Arch Gen Psychiatry*. 2005;62(11):1266-1274.
51. Kim SJ, Shonka S, French WP, Strickland J, Miller L, Stein MA. Dose-response effects of long-acting liquid methylphenidate in children with attention deficit/hyperactivity disorder (ADHD) and autism spectrum disorder (ASD): a pilot study. *J Autism Dev Disord*. 2017;47(8):2307-2313.
52. Handen BL, Sahl R, Hardan AY. Guanfacine in children with autism and/or intellectual disabilities. *J Dev Behav Pediatr*. 2008;29(4):303-308.
53. Scahill L, McCracken JT, King BH, et al. Extended-release guanfacine for hyperactivity in children with autism spectrum disorder. *Am J Psychiatry*. 2015;172(12):1197-1206.
54. McCracken JT, Aman MG, McDougle CJ, et al. Possible influence of variant of the P-glycoprotein gene (*MDR1/ABCB1*) on clinical response to guanfacine in children with pervasive developmental disorders and hyperactivity. *J Child Adolesc Psychopharmacol*. 2010;20(1):1-5.
55. Jaselskis CA, Cook EH, Fletcher KE, Leventhal BL. Clonidine treatment of hyperactive and impulsive children with autistic disorder. *J Clin Psychopharmacol*. 1992;12(5):322-327.
56. Ming X, Gordon E, Kang N, Wagner GC. Use of clonidine in children with autism spectrum disorders. *Brain Dev*. 2008;30(7):454-460.
57. Harfterkamp M, Buitelaar JK, Minderaa RB, van de Loo-Neus G, van der Gaag RJ, Hoekstra PJ. Long-term treatment with atomoxetine for attention-deficit/hyperactivity disorder symptoms in children and adolescents with autism spectrum disorder: an open-label extension study. *J Child Adolesc Psychopharmacol*. 2013;23(3):194-199.

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58. Harfterkamp M, van de Loo-Neus G, Minderaa RB, et al. A randomized double-blind study of atomoxetine versus placebo for attention-deficit/hyperactivity disorder symptoms in children with autism spectrum disorder. *J Am Acad Child Adolesc Psychiatry*. 2012;51(7):733-741.
59. Handen BL, Aman MG, Arnold LE, et al. Atomoxetine, parent training, and their combination in children with autism spectrum disorder and attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry*. 2015;54(11):905-915.
60. Smith T, Aman MG, Arnold LE, et al. Atomoxetine and parent training for children with autism and attention-deficit/hyperactivity disorder: a 24-week extension study. *J Am Acad Child Adolesc Psychiatry*. 2016;55(10):868-876.e2.
61. Alvares GA, Quintana DS, Whitehouse AJ. Beyond the hype and hope: Critical considerations for intranasal oxytocin research in autism spectrum disorder. *Autism Res*. 2017;10(1):25-41.
62. Dadds MR, MacDonald E, Cauchi A, Williams K, Levy F, Brennan J. Nasal oxytocin for social deficits in childhood autism: a randomized controlled trial. *J Autism Dev Disord*. 2014;44(3):521-531.
63. Guastella AJ, Gray KM, Rinehart NJ, et al. The effects of a course of intranasal oxytocin on social behaviors in youth diagnosed with autism spectrum disorders: a randomized controlled trial. *J Child Psychol Psychiatry*. 2015;56(4):444-452.
64. Yatawara CJ, Einfeld SL, Hickie IB, Davenport TA, Guastella AJ. The effect of oxytocin nasal spray on social interaction deficits observed in young children with autism: a randomized clinical crossover trial. *Mol Psychiatry*. 2016;21(9):1225-1231.
65. Erickson CA, Veenstra-Vanderweele JM, Melmed RD, et al. STX209 (arbaclofen) for autism spectrum disorders: an 8-week open-label study. *J Autism Dev Disord*. 2014;44(4):958-964.
66. Nikoo M, Radnia H, Farokhnia M, Mohammadi MR, Akhondzadeh S. N-acetylcysteine as an adjunctive therapy to risperidone for treatment of irritability in autism: a randomized, double-blind, placebo-controlled clinical trial of efficacy and safety. *Clin Neuropharmacol*. 2015;38(1):11-17.
67. Ghanizadeh A, Moghimi-Sarani E. A randomized double blind placebo controlled clinical trial of N-acetylcysteine added to risperidone for treating autistic disorders. *BMC Psychiatry*. 2013;13:196.
68. Hardan AY, Fung LK, Libove RA, et al. A randomized controlled pilot trial of oral N-acetylcysteine in children with autism. *Biol Psychiatry*. 2012;71(11):956-961.
69. Wink LK, Adams R, Wang Z, et al. A randomized placebo-controlled pilot study of N-acetylcysteine in youth with autism spectrum disorder. *Mol Autism*. 2016;7:26.
70. Dean OM, Gray KM, Villagonzalo KA, et al. A randomised, double blind, placebo-controlled trial of a fixed dose of N-acetyl cysteine in children with autistic disorder. *Aust N Z J Psychiatry*. 2017;51(3):241-249.
71. Posey DJ, Kem DL, Swiezy NB, Sweeten TL, Wiegand RE, McDougle CJ. A pilot study of D-cycloserine in subjects with autistic disorder. *Am J Psychiatry*. 2004;161(11):2115-2117.
72. Minshawi NF, Wink LK, Shaffer R, et al. A randomized, placebo-controlled trial of D-cycloserine for the enhancement of social skills training in autism spectrum disorders. *Mol Autism*. 2016;7:2.
73. Wink LK, Minshawi NF, Shaffer RC, et al. D-Cycloserine enhances durability of social skills training in autism spectrum disorder. *Mol Autism*. 2017;8:2.
74. Ghaleiha A, Asadabadi M, Mohammadi MR, et al. Memantine as adjunctive treatment to risperidone in children with autistic disorder: a randomized, double-blind, placebo-controlled trial. *Int J Neuropsychopharmacol*. 2013;16(4):783-789.
75. Mohammadi MR, Yadegari N, Hassanzadeh E, et al. Double-blind, placebo-controlled trial of risperidone plus amantadine in children with autism: a 10-week randomized study. *Clin Neuropharmacol*. 2013;36(6):179-184.
76. Ghaleiha A, Mohammadi E, Mohammadi MR, et al. Riluzole as an adjunctive therapy to risperidone for the treatment of irritability in children with autistic disorder: a double-blind, placebo-controlled, randomized trial. *Paediatr Drugs*. 2013;15(6):505-514.
77. Ghaleiha A, Rasa SM, Nikoo M, Farokhnia M, Mohammadi MR, Akhondzadeh S. A pilot double-blind placebo-controlled trial of pioglitazone as adjunctive treatment to risperidone: effects on aberrant behavior in children with autism. *Psychiatry Res*. 2015;229(1-2):181-187.
78. Nikvarz N, Alaghband-Rad J, Tehrani-Doost M, Alimadadi A, Ghaeli P. Comparing efficacy and side effects of memantine vs. risperidone in the treatment of autistic disorder. *Pharmacopsychiatry*. 2017;50(1):19-25.
79. Aman MG, Findling RL, Hardan AY, et al. Safety and efficacy of memantine in children with autism: randomized, placebo-controlled study and open-label extension. *J Child Adolesc Psychopharmacol*. 2017;27(5):403-412.
80. Williams K, Wray JA, Wheeler DM. Intravenous secretin for autism spectrum disorders (ASD). *Cochrane Database Syst Rev*. 2012(4):CD003495.
81. Chugani DC, Chugani HT, Wiznitzer M, et al. Efficacy of low-dose buspirone for restricted and repetitive behavior in young children with autism spectrum disorder: a randomized trial. *J Pediatr*. 2016;170:45-53.e41-e44.
82. Ghanizadeh A, Ayoobzadehshirazi A. A randomized double-blind placebo-controlled clinical trial of adjunctive buspirone for irritability in autism. *Pediatr Neurol*. 2015;52(1):77-81.

Farmacoterapia de los síntomas emocionales y conductuales asociados con el trastorno del espectro autista en niños y adolescentes

El trastorno del espectro autista (TEA) se caracteriza por un deterioro en la comunicación social y una restricción en los patrones conductuales. Aunque la Administración de Alimentos y Fármacos de EE.UU. (FDA) no ha aprobado un tratamiento farmacológico para los síntomas centrales del TEA, en la literatura existe un soporte creciente para el manejo de los síntomas conductuales asociados con este trastorno del desarrollo, en particular la irritabilidad y la hiperactividad. Actualmente el aripiprazol y la risperidona están aprobados por la FDA para el tratamiento de la irritabilidad en jóvenes con TEA. El metilfenidato y la guanfecina son efectivos para el manejo de la hiperactividad en niños con TEA, pero no han sido aprobados por la FDA. Los inhibidores selectivos de la recaptura de serotonina se emplean con frecuencia en la práctica clínica contra la ansiedad y las compulsiones; sin embargo, existe poca evidencia que avale su empleo en esta población. En jóvenes con TEA existe una gran necesidad de futuras investigaciones acerca de la seguridad y eficacia de los fármacos psicotrópicos, como también del desarrollo de nuevas modalidades terapéuticas para los síntomas centrales y las conductas asociadas.

Pharmacothérapie des symptômes émotionnels et comportementaux associés au trouble du spectre de l'autisme chez les enfants et les adolescents

Le trouble du spectre de l'autisme (TSA) se caractérise par des déficits de la communication sociale et des modes comportementaux restreints. Il n'existe pas de traitement pharmacologique approuvé par la FDA américaine (Food and Drug Administration) pour les symptômes fondamentaux du TSA, mais on trouve dans la littérature un soutien croissant en faveur de la prise en charge des symptômes comportementaux associés à ce trouble du développement, en particulier l'irritabilité et l'hyperactivité. L'aripiprazole et la rispéridone sont actuellement approuvés par la FDA pour le traitement de l'irritabilité chez les jeunes ayant un TSA. Non approuvés par la FDA, le méthylphénidate et la guanfacine sont cependant efficaces pour la prise en charge de l'hyperactivité chez les enfants ayant un TSA. Les inhibiteurs sélectifs de la recapture de la sérotonine sont souvent utilisés en pratique clinique pour cibler l'anxiété et les compulsions, mais il y a peu de données en faveur de leur utilisation dans cette population. Il faudrait d'autres études sur la sécurité d'emploi et l'efficacité des traitements psychotropes existants chez les jeunes ayant un TSA, et il faudrait développer de nouvelles modalités de traitement pour les symptômes comportementaux fondamentaux et associés.