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Medical treatment overview: traditional and novel psycho-pharmacological and complementary and alternative medications

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Abstract

Purpose of review—Up to 35% of children and youth with autism spectrum disorder (ASD) receive at least one psychotropic medication. 50–70% of this population also receives biologically based complementary and alternative medicine (CAM). The data evaluating such practices are being reviewed.

Recent findings—There are accumulating data to suggest that atypical antipsychotics and stimulants may be useful for the treatment of irritability and hyperactivity in children and youth with ASD. The data for the use of selective serotonin reuptake inhibitors are less promising. New avenues of pharmacologic research targeting molecular targets identified by genomics, animal models and neuropathology are being evaluated. Areas of interest include glutamate/gamma-aminobutyric acid systems, neuropeptides such as oxytocin, and immune dysfunction, among others. In the case of biologically based CAM, a few compounds have been shown to be well tolerated, although efficacy is still being evaluated, such as melatonin, certain vitamins, and omega 3 fatty acids. Others have safety concerns without demonstrated efficacy, such as chelation therapies.

Summary—Accumulating data suggest a series of existing medications may be useful in ASD and large randomized clinical trials are necessary to evaluate safety and efficacy of both pharmaceuticals and alternative treatments.

Keywords

autism; complementary and alternative medicine; medication; pharmacology

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Conflicts of interest

There are no conflicts of interest.

Introduction

Although autism spectrum disorders (ASDs) are defined by social communication deficits and repetitive behaviors, children seek medical intervention for a variety of symptoms often associated with ASD, although not part of the diagnostic triad. Up to 35% of children and youth with ASD use at least one psychotropic medication [1•] and 50–70% receive biologically based complementary and alternative medicine (CAM) therapies [2,3]. The most common approach to studying psychotropic medications in autism has been based on the assumption that overlapping symptoms between disorders must share common neurobiology and therefore medications useful in other disorders may be useful in autism if they target such domains. Several classes of medications have been studied following this approach and using randomized clinical trial designs. Overall, most data supporting the use of medications in this population target associated symptom domains of ASD, such as irritability/aggression and hyperactivity/inattention. We will review data generated in randomized clinical trials for both psychotropic medications and CAM therapies over the past decade in children and youth with ASD, and suggest a model for discussing treatment decisions with families based on safety and efficacy information.

Psychopharmacology

There are three classes of medications that have been evaluated in adequate clinical trials: atypical neuroleptics, stimulants and selective serotonin reuptake inhibitors (SSRIs). Other agents have been evaluated in smaller studies and will also be briefly reviewed.

Atypical neuroleptics

The most robust evidence of efficacy of any class of medications in ASD exists for the use of atypical antipsychotics for the treatment of irritability/aggression in this population. Although open-label studies exist for almost all atypical antipsychotics on the market, large randomized controlled trials (RCTs) are available for risperidone and aripiprazole.

A recent meta-analysis identified six randomized clinical trials of atypical antipsychotics that randomized 30 or more participants in the past decade [4••]. Four of these studies used risperidone, two used aripiprazole [5–10], and all but one [7] were 8 weeks long. All reported significant improvements in irritability/aggression, as measured by the Aberrant Behavior Checklist (ABC)-Irritability subscale, as well as repetitive behaviors. Side effects reported were similar between the two medications and included somnolence and weight gain. A trend for more extrapyramidal symptoms was seen in the risperidone/aripiprazole arms vs. placebo. Elevation of prolactin was reported in the Research Units on Pediatric Psychopharmacology (RUPP) network study of risperidone, although the clinical significance of such a finding is not known. Decreased prolactin was reported in the case of aripiprazole. These findings are consistent with the literature for the use of these drugs in other populations. They highlight that atypical antipsychotics are effective for the treatment of irritability/aggression and possibly repetitive behaviors in children and youth with ASD, but that the side effect profile is not benign and there are no long-term studies. Individualized decisions need to be made regarding the risk-to-benefit ratio for each patient.

Stimulants

There is only one large clinical trial of stimulants in ASD. The RUPP network ran a randomized, placebo-controlled, crossover trial of methylphenidate (three doses) vs. placebo in children and adolescents with ASD [11]. All three doses performed better than placebo in the case of hyperactivity, as measured by the ABC-hyperactivity subscale, although the highest dose produced worsening in withdrawal/lethargy as reported by the parents. Irritability was the most frequent side effect leading to discontinuation. In addition, appetite loss, insomnia, mood changes, headaches, and diarrhea were also reported.

Selective serotonin reuptake inhibitors

Although early data supported the use of SSRIs for the treatment of repetitive behaviors in ASD [12], a recent large randomized controlled clinical trial of citalopram in this population showed no separation between active drug and placebo in either global impression or repetitive behavior measures [13]. One secondary measure, the ABC-Irritability subscale, showed improvements in the citalopram arm vs. placebo, although the effect size was at best moderate. There was clearly an increase in prevalence of side effects in the citalopram group. Side effects included ‘activation syndrome’, which included symptoms such as increased energy, disinhibition, and insomnia. Many commentaries have been published since then related to this study. Although there is no argument that this was a negative clinical trial, and the largest randomized clinical trial to date in ASD, questions remain whether certain subgroups of children have repetitive behaviors that may still respond to these medications, and whether better stratification might have revealed a subgroup more likely to respond. In addition, this study questioned the much used strategy of choosing medications successful in treating overlapping disorders (in this case obsessive compulsive disorder), based on the assumption that phenotypic similarity is associated with shared neurobiology.

Other agents

Data from small clinical trials suggest that there are other medications with potential to improve associated symptoms of ASD. A small randomized trial of atomoxetine in ASD produced significant improvement on the ABC-Hyperactivity subscale [14]. The medication was well tolerated, suggesting future trials in this area are warranted. Anticonvulsant medications have long been used as mood stabilizers and the high prevalence of both abnormal electroencephalograms and mood instability in ASD suggest the need for further study. Valproic acid has been shown in one small randomized study to significantly improve irritability/aggression [15•], although a previous shorter trial [16] was negative. Both levetiracetam and lamotrigine have been evaluated in small randomized trials, but did not show advantage over placebo [17,18]. However, in the case of the lamotrigine trial, the placebo response was higher than 50%, suggesting this was a failed trial. Two small randomized trials of clonidine [19,20] suggested improvements in irritability/impulsivity. Side effects included sedation, hypotension and decreased activity. Open label data also suggest that guanfacine may be a reasonable alternative, but large randomized trials are pending [21].

Future directions in psychopharmacology of autism spectrum disorders

The current approach to psychopharmacology of ASD is symptom-based: symptom domains in ASD that seem to be in a phenotypic continuum with symptoms of other neurodevelopmental disorders have been assumed to share neurobiology and as such to be likely to respond to similar treatments. The approach has been productive in the case of atypical antipsychotics and stimulants, but not with SSRIs. As the fields of genomics and molecular neuroscience advance, we are for the first time in a position to identify molecular targets for treating core ASD symptoms.

In the case of the glutamate/gamma-aminobutyric acid systems, a series of studies have documented abnormalities in candidate genes (e.g. SHANK3, neuroligins) [22•], peripheral markers [23,24], animal models (e.g. Fragile X) [25] and neuropathology [26,27] that implicate this system in the pathophysiology of ASD. Medications affecting the *N*-methyl *D*-aspartate receptor, such as amantadine [28], dextromethorphan [29–31] and memantine [32–35], have preliminary evidence to support further studies in this system. Metabotropic glutamate receptor 5 (mGluR5) inhibitors are in phase II and early phase III trials. Further well controlled studies in this area are necessary.

The neuropeptide oxytocin has been linked to modulation of social cognition and function in multiple animal models and in humans. The data for oxytocin involvement in the pathophysiology of autism are still limited, but there exist both genomics and peripheral biomarker data to suggest that, at least in a subgroup, this system may be implicated in the neurobiology of the disorder [36–40]. Early studies in ASD have provided proof of concept for the potential therapeutic role of oxytocin in facilitating social cognition in ASD [41].

Lastly, ongoing neuroinflammatory processes in the cortex, white matter and cerebellum have been reported in post-mortem brain tissue of individuals with ASD. The abnormalities included microglia and astroglia [42], both of which are integrally involved in cortical organization, neuronal transmission, and synaptic plasticity. Increases in cerebrospinal fluid proinflammatory factors have been reported [43–45], suggesting a dysregulated immune response. There are multiple agents available that may modulate the immune system of children with ASD; however, the evidence for any of these is preliminary, and well controlled, randomized trials are urgently needed.

Complementary and alternative medicine

Despite significant progress in the development of evidence-based treatment strategies for both core and associated symptoms of ASD, the use of CAM remains common [2,3]. Most families report using CAM for health maintenance as well as to treat a wide variety of symptoms that are not core to ASD, such as moodiness and irritability, aggression, hyperactivity, gastrointestinal symptoms and sleep difficulties [45]. Unfortunately, the majority of parents of children receiving CAM do not share this with their physician [46], which undermines the ability of the healthcare provider to understand the concerns and challenges faced by the family and to help them make the best decisions regarding both conventional and CAM therapies.

Complementary and alternative medicine is defined by the National Center for Complementary and Alternative Medicine (NCCAM) as ‘a group of diverse medical and healthcare systems, practices and products that are not generally considered part of conventional medicine’ (http:www.nccam.nih.gov). Most have little evidence base to support their use, and new CAM therapies are introduced into the ASD community at a rapid rate. Pediatricians and other healthcare professionals need strategies and tools to help families negotiate the many available CAM treatments and make decisions based on current safety and efficacy data.

Huffman *et al.* [47•] completed a meta-analysis of studies on CAM treatments for ASD from 1994 to May 2007 in English language journals, using a framework consistent with the Cochrane Collaboration (http://www.cochrane.org/index.htm). They reviewed 26 articles addressing CAM, including 17 related to dietary supplements, six related to dietary modifications, two related to neurofeedback and one on hyperbaric oxygen. No empiric studies meeting their review criteria addressed antifungal agents or immune enhancers. The scientific merit of the studies ranged from weak to strong, with the strongest quality found for some of the dietary supplements (protein/amino acids, vitamins, iron), and weakest for digestive enzymes and neurofeedback. They reported marginal evidence of beneficial effect on socialization for proteins/amino acids such as carnosine and tetrahydrobiopterin, and inadequate studies addressing general core symptoms and associated maladaptive behavioral symptoms to draw conclusions about benefits of other CAM therapies.

Using an efficacy-safety model described by Kemper and Cohen [48], Akins *et al.* [49••] reviewed many of the most common CAM treatments used in ASD, organized by NCCAM classification domains (mind-body therapies, biologically based therapies, manipulative and body-based therapies, energy medicine and whole medicine systems). This model is helpful in discussions with families, as treatments with well supported efficacy and safety can be recommended, whereas treatments with little or no efficacy and high likelihood for harm should be discouraged. CAM therapies with little or no efficacy but few or no safety concerns can be accepted and monitored by the physician if chosen by the family. However, the redirection of limited time and resources from behavioral and educational interventions with proven efficacy should be avoided. A summary of the classifications for the biologically based CAM therapies reviewed is included below. For a more complete description of the basis for the ratings and recommen-dations, please refer to the review [49••].

Well tolerated, effective: encourage when indicated

There are very few biologically based CAM therapies that have evidence to support both efficacy and safety for treating ASD.

Melatonin – two small RCTs show efficacy in reducing sleep onset latency in children with ASD [50,51]. Short-term release products are recommended for children with difficulty initiating sleep and long-term release products recommended for children with difficulty maintaining sleep. Melatonin appears well tolerated up to 7.5 mg dose.

Well tolerated, unknown/inconclusive efficacy: tolerate, encourage objective monitoring

Whereas little or inconclusive efficacy data are available, these treatments have few safety concerns, except when used in doses many times over recommended levels.

Vitamin C – generally well tolerated at recommended doses and from dietary intake. One RCT [52] not yet replicated is suggesting reduced stereotyped behaviors in ASD; there have been reports of scurvy in children with ASD from restricted dietary intake.

Multivitamins – multivitamin formulations vary widely, in terms of the vitamins and minerals included as well as the doses of each. Dietary restrictions in children with ASD, either self-imposed or caretaker-imposed, can increase risk for nutritional deficiencies and many parents give their children standard, daily multivitamin preparations that are not specifically marketed for ASD for health maintenance purposes. However, some multivitamin formulations contain very high doses of some vitamins and many dietary supplements contain vitamin fortification, so careful monitoring of vitamin intake from various sources is required to avoid toxicity, particularly vitamins A, D, and E.

Gluten-casein-free diet – this is among the most common CAM treatments for ASD, based on an unproven rationale of incompletely digested proteins in gluten and casein being absorbed from the gastrointestinal tract and acting centrally as endogenous opioids in the brain.

Two RCTs failed to support efficacy [53]; three RCTs are currently underway. Bone loss has been reported in children in gluten-free/casein-free diet; calcium, vitamin D and protein adequacy of diet should be monitored closely.

Vitamin B6, magnesium – three small RCTs with little treatment effect. A Cochrane review concluded that there are insufficient data to make a recommendation in this area [54]. Adverse effects in high doses include neuropathy, skin and other allergic reactions, gastrointestinal symptoms, headache, hypotonia and seizures. The Institute of Medicine upper intake level for B6 in adults is 100 mg/day.

Carnosine (amino acids) – one RCT [55] showing improvements in receptive language and overall autism symptoms. Adverse effects include hyperactivity and irritability.

Essential fatty acids – omega 3 fatty acid supplementation in RCT showed nonsignificant decreases in hyperactivity and stereotypies [56,57].

Methyl B12 (methylcobalamin), folic acid, dimethylglycine, glutathione – based on indications of impaired methylation in a subset of children with ASD, but no RCTs indicating positive treatment effects.

Well tolerated, no evidence of efficacy: discourage

Although without safety concerns, there are no efficacy data to support use.

Secretin – one of the most rigorously studied biological treatments in ASD. A recent systematic review in 2011 [58] concluded that there is no evidence that single or multiple doses of intravenous secretin are effective in treating ASD.

Unsafe/unknown safety, inconclusive or no efficacy: discourage

Complementary and alternative medicine therapies with known or unclear safety concerns and few or no efficacy data should be discouraged in discussions with families.

Chelation – on the basis of an unproven theory that some children with ASD have impaired elimination of mercury and other heavy metals that interfere with immune function and other biological systems; no studies demonstrating efficacy. Safety concerns include Stevens–Johnson syndrome, liver and kidney dysfunction, neutropenia, headache, neuralgia, and paresthesias; fatal hypocalcemia has been reported in three deaths attributed to chelation, including one child with autism [59]. The Food and Drug Administration has recently warned consumers that many chelating agents being currently marketed were developed for industrial use and have never been tested in humans or animals [60].

Hyperbaric oxygen therapy – randomized controlled trial study by Rossignol et al. [61] reported significant within-group improvements in overall functioning, receptive language, social interaction, eye contact, and cognitive awareness. However, the Undersea and Hyperbaric Medical Society (UHMS), which monitors the scientific validity of claims regarding the safety and efficacy of hyperbaric oxygen in specific conditions, refutes the findings based on concerns of ascertainment bias, loss of data, author conflict of interest and, most importantly, a concern that the very low oxygen pressures used in the ‘treatment’ arm did not actually constitute hyperbaric oxygen treatment [62]. Thus, it appears that both groups of children received placebo. Safety issues at therapeutic pressures include otic barotrauma, reversible myopia due to direct oxygen toxicity of the lens, seizures, hypoglycemia, and pulmonary complications.

Immune therapies – there are two RCTs of intravenous immunoglobulin (IVIg). The first [63] found no significant effects in clinician ratings but some improvements in parent and teacher reports. The second larger study [64] found no evidence of improvement in children with autism and gastrointestinal symptoms. Three to 15% of recipients exposed to IVIg experience a systemic reaction [65].

Antifungal agents – there are no RCTs showing efficacy of treating stool or urinary evidence of Candida overgrowth; safety concerns of antifungal treatment include toxicities of cardiac sudden death in individuals with prolonged QT syndrome, Stevens–Johnson syndrome, seizures, liver and bone marrow toxicity, and gastrointestinal symptoms.

Having access to reliable sources of information about efficacy and safety of specific CAM treatments is essential in order to make responsible, ethical and legally defensible decisions about CAM use with families. Discussing the available evidence that supports a treatment’s efficacy as well as potential for harm or injury with families makes it possible for joint decisions about CAM therapy to be made and effective monitoring to be established. Recommended resources include the National Institutes of Health National Center for

Complementary and Alternative Medicine (http://nccam.nih.gov/), which also has a toll free number for questions about specific CAM therapies in English or Spanish (888-644-6226 in USA, 866-464-3615 for deaf and hard of hearing callers) and a downloadable toolkit for healthcare providers to facilitate discussions about CAM with patients (http://nccam.nih.gov/timetotalk/). The US National Library of Medicine provides information about the ingredients in dietary supplements (Dietary Supplements Labels Database at http://dietarysupplements.nlm.nih.gov/dietary/)

Conclusion

Despite widespread use of both pharmacological agents and CAM therapies, efficacy data remain extremely sparse. Efficacy has been well demonstrated with three psychopharmacological agents in large RCTs, but it is important to note that these were in treating ancillary symptoms (irritability/aggression and hyperactivity/ inattention), not core deficits in ASD. The research in biologically based alternative treatments is really only just now emerging, and large randomized clinical trials are urgently needed. It is clear that the side effect profiles of these drugs and other therapies are not trivial and the risk-to-benefit ratio should be carefully evaluated with every patient. However, practitioners should be encouraged that studies using genomic techniques, animal models and neuropathological investigation are starting to identify novel molecular targets. This suggests we have reached the point when basic science findings can start to be translated into novel treatments targeting the core features of ASD.

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References and recommended readings

Papers of particular interest, published within the annual period of review, have been highlighted as:

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• • of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 703).

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Key points

- There is evidence for efficacy of atypical neuroleptics for the treatment of irritability and repetitive behaviors in autism spectrum disorder (ASD).
- There is evidence for efficacy of stimulants for the treatment of attention deficit-hyperactivity disorderlike symptoms in ASD.
- There are emerging data to suggest potential new molecular targets for drug development based on the maturing fields of genomics and molecular neuroscience.
- There are emerging data for safety and some early efficacy of alternative compounds, but randomized trials are urgently needed.
- It is important to have accessible resources for updated information on efficacy/safety data for psychopharmacologic and CAM therapies in ASD, as well as a framework for discussing therapeutic decision making with families based on this information.