Complementary Therapies and Autism Spectrum Disorder

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Abstract

While recent studies have suggested that autism spectrum disorder (ASD) is the result of genetic predisposition with environmental influences, conventional interventions usually focus on overall skills and function, using behavioral, communication, educational and pharmacologic methods. Conventional treatments are intense, complex and resource heavy, but may not target specific symptoms which have great impact on family life. As a result, families may seek non-standard treatments they perceive to treat the cause(s) of their child's symptoms and/or ASD. These novel therapies, also known as complementary, and/or alternative medical (CAM) or integrative treatments, are frequently promoted in the public domain and proof for effectiveness may not include scientific evidence. This paper describes commonly used CAM therapies and summarizes a framework for evaluating the claims of effectiveness, potential harm and how to work with families who may elect to pursue them.

Introduction

The most commonly used conventional interventions for children and youth with autism spectrum disorder (ASD) focus on social skills, communication, educational curricula, behavioral intervention and/or pharmacologic treatments. These treatments promote development of new social, academic or communication skills, improve attention and may ameliorate challenging behaviors. However, they do not provide a "cure" and many challenging symptoms may persist. Families often pursue as yet unproven therapies to address purported "biologic" causes of the symptoms they believe are not being addressed by conventional interventions. Up to three quarters of families report that they use, or have used, additional therapies to complement those or as an alternative to treatments recommended by their physician or treatment team (1-3). Targets of treatment with CAM include over-awareness and under-awareness of sensory input, agitation, gastrointestinal symptoms and proposed biologic causes for the symptoms of autism.

The most frequent sources of information families use to learn about complementary and alternative medical (CAM) therapies are the internet, other parents, and therapists other than their healthcare provider (HCP). Many families do not report CAM use to their HCP because they do not think it is relevant or of interest to the clinician (1). However, given the potential for pharmacologic interactions or adverse effects from supplements an open dialogue between clinician and family/patient will promote coordination of care and improved outcome. An internet survey has reported that children with ASD are treated with a mean of 7 different interventions (4) often to address different symptoms. The clinician needs to understand the potential impact of these interventions on general health, conventional treatment, and the cost to the family.

This paper provides an overview of commonly used complementary and alternative therapies for ASD, reviews potential for harm of treatments, and suggests approaches to counseling and collaborating with families. An overview of common CAM interventions is presented in Table 1. It summarizes the evidence documenting the benefit, or lack thereof, and risk of each intervention. Additional

information on these topics is available in recent published reviews (5-7), and on the following websites:

- National Center for Complementary and Alternative Medicine (NCCAM) of the NIIH
  - www.nccam.org
- American Academy of Pediatrics, Section on Integrative Medicine
  -www2.aap.org/sections/chim/
- IAN (Interactive Autism Network)
  - www.ianproject.org

What is CAM?

Complementary and alternative therapies may be classified by three types of approaches, including the following.

- Natural products (e.g., supplements that may be ingested or applied locally).
- Other biomedical approaches (e.g., off-label use of medication or medical procedures).
- Mind and body practices (such as relaxation or meditation or physical manipulation).

Natural products

Natural products are the most commonly used form of complementary therapy for children with ASD. Supplements are given to 28-74% of children with ASD (3). A natural product that has been adequately studied and is used in conventional practice is melatonin, a naturally occurring hormone sold as a nutritional supplement in the US. It may be effective in regulating sleep in some individuals with ASD. Supportive evidence includes randomized trials demonstrating effect and scientific understanding of the regulation of sleep (8). A double-blind randomized control trial using melatonin and placebo in children with neurodevelopmental disorders, showed that on average, melatonin improved mean total sleep time only by 23 minutes but time taken to fall asleep was reduced by 45 minutes (9).

There is insufficient data to support the use of other common supplements such as omega 3 fatty acids (for repetitive behavior or hyperactivity) (10) or vitamin B6 with or without magnesium (for hyperactivity or language promotion) (11;12) due to small and methodologically compromised clinical trials. There has not been adequate study to evaluate efficacy of supplementation with vitamin B12, vitamin C, dimethylglycine, or carnosine (13;14) for symptoms of ASD. No studies have been published on the behavioral effects of probiotics, amino acids, or coenzyme Q (to decrease oxidative stress), amongst others, to guide use in this population. While the role of immune regulation and oxidative stress in the ongoing symptoms of ASD are being studied, none of the interventions reviewed in Table 1 has been demonstrated to impact symptoms of ASD in clinical trials that would support recommending their use (13;14).

Dietary Interventions

Dietary interventions constitute another common category of biomedical intervention for symptoms of ASD. Up to 40% of children with ASD are reported to have gastrointestinal symptoms, predominantly constipation and food refusal (15), so a role for food intolerance has been hypothesized. A gluten and casein free diet is trialed by at least 17% of families (3). While it was initially hypothesized that absorption of opiate-like peptides caused symptoms of ASD, this has not been confirmed with more specific characterization of peptides (16). Two single-blind trials suggest there might be improvement in language; however, smaller double-blind trials have not demonstrated improvement (17;18). If children are not given dairy products they need to be provided with adequate amounts of calcium and vitamin D from supplements or plant based beverages (19).

Some families may elect to trial the elimination of artificial food colorings and preservatives to decrease hyperactivity, although this has never been studied in children with ASD (20). There is no evidence to support the elimination of sugar or treatment with anti-yeast agents.

Other/ Biomedical interventions

Conventional medical practices may be used in a non-standard or off-label way to treat symptoms of ASD. The best known example is secretin, an intestinal hormone used to evaluate pancreatic function. Over 800 children have participated in controlled trials which have demonstrated that it is not effective (21).

There is conflicting evidence for other practices such as hyperbaric oxygen treatment. In this case, the potential for adverse effects and discordance with the scientific understanding of the disorder argue against its use (22). Studies continue to test new uses of existing medications such as N-Acetylcysteine (an anti-oxidant), but methodological problems (e.g., small sample size) imply that there is inadequate evidence to allow them to be recommended for use (23). Chelation has been proposed to treat symptoms of ASD, based on the unproven assumption of heavy metal exposure as a risk factor for ASD. However, chelating agents are potentially dangerous since many enzyme systems depend on the presence of heavy metals (24) and at present there are no clinical trials in the peer reviewed literature to support this practice.

Mind and Body Practices

As evidence is collected, interventions that were once considered unproven, like Applied Behavioral Analysis, are shown to be effective in clinical trials and become accepted as conventional therapy. Others like auditory integration training where children are exposed to altered sound through earphones in a systematic fashion, do not demonstrate improvement in symptoms and are not recommended in conventional practice (25). Emerging neurobiologic understanding of sensory processing in individuals with ASD suggests that some interventions that do not currently have the scientific support for intervention, may have some basis for continued study such as music therapy (26;27). Other nonbiologic interventions with emerging data that are not sufficient for endorsement include yoga, acupuncture, and hippotherapy (28-30). Sensory integration therapy in conventional forms including brushing, joint compression and use of weighted vests are often used in school programmes but do not yet have a robust evidence base (31). Sensory integration therapies should not substitute for effective educational or behavioral interventions. Increasing understanding of sensory processing is likely to inform future interventions that will address specific abnormalities.

Where to Start

Working with families

Since families may not tell a clinician about therapies that they are obtaining from other sources, it is important that direct questioning about CAM use be part of the history taken at medical visits. Families can be reluctant to volunteer this information because they may feel that the physician might not approve of or know about such therapies. To work effectively with families, clinicians should be respectful of family concerns and beliefs, be knowledgeable about how to evaluate the literature examining novel therapies and maintain a dialogue with the family. Even if the family and clinician do not agree on the use of novel therapies, this dialogue is important for the promotion of safe and effective care for the child (32;33).

Knowledge about CAM

Physicians report that their most frequently used sources for updating their medical information are the peer reviewed print literature (68%), colleagues (60%), medical conferences (42%) and web-based information for physicians (42%). All of these sources are increasingly providing information on CAM. Of note, 42% of physicians report frequently using general internet sites for medical information (34). Almost two thirds of patients report using the internet to obtain health information. Clinicians need to help families interpret the claims regarding novel therapies and understand the quality of data that ranges from anecdotal reports in commercial materials to peer-reviewed articles in scientific journals. Scientific reports should include a discussion of how the participants were recruited and characterized, if group assignment was random, if outcome evaluations were valid and treatments were both double blind and using consistent dosing (35).

How to monitor treatment

Whether a new intervention is complementary or conventional, the family should be counseled regarding the importance of identifying target symptoms that relate to the anticipated effect. To ascribe the results of a trial properly, families should be counseled on changing one intervention at a time. In addition, families should understand the length of time necessary for a treatment to reach the anticipated outcome. If an intervention requires a long trial, based on the proposed mechanism, a brief exposure may result in abandoning a potentially useful intervention. The converse may be true as well. For example, the long time frame that advocates of the gluten and casein free diet (18) claim is necessary to see maximal effect may occur in parallel with the improvement seen in many children with maturation and conventional intervention (36). Both the family and clinician need to monitor for adverse effects with introduction of a new treatment. Careful, data-driven monitoring is important to help families, and clinicians, to recognize the interventions that are or are not effective for a given child.

Table 1: Guidance for review of novel therapies for autism spectrum disorder

Intervention	Evidence	Risk	Benefits
Natural Products			
Melatonin (Andersen, et al, 2008; Malow et al., 2012; Wright et al., 2011; Appleton, et al, 2012)	Small RCTs support retrospective clinical data analyses	Low	Proven effective
Omega 3 Fatty Acids (Amminger et al., 2007; Bent, Bertoglio, Ashwood, Bostrom, & Hendren, 2011)	Small RCTs (n=13, n=27) suggested potential for benefit in hyperactivity and/or stereotyped behavior that was not clinically significant	Low	Unproven
B6 +/-Magnesium (James, Montgomery et al. 2011)	Small RCT high and low dose	Moderate	Unproven
Vitamin B12 (Bertoglio, Jill James, Deprey, Brule, & Hendren, 2010)	Small RCT, overall no impact but perhaps benefit in subset with increased glutathione (GSH) and increased redox ratio	Low	Unproven
Vitamin C (Dolske, Spollen, McKay, Lancashire, & Tolbert, 1993)	Small trial, possible benefit	Low	Unproven
Dimethylglycine (Bolman & Richmond, 1999)	Small trials, methodological problems	Unknown	Unproven
Carnosine (Chez et al., 2002)	One RCT (n=31) with improvement in symptoms of autism and language	Unknown	Unproven
Probiotics (Critchfield, van Hemert, Ash, Mulder, & Ashwood, 2011)	Unstudied in behaviors of autism	Low	Unproven
Coenzyme Q (no references)	Unstudied in behaviors of autism	Unknown	Unproven
Immune therapy (Hsiao, 2013)	Observational studies of different modalities, few controlled studies	High	Unproven
Gluten Free Casein Free Diet (Millward, Ferriter et al. 2008, Whiteley, Shattock et al. 2012)	2 small DB RCTs (no benefit); 2 single blind RCTs (benefit). Proponents suggest benefit with GI symptoms, as yet not studied	Low-Moderate	Unproven

Intervention	Evidence	Risk	Benefits
Nonstandard Use of Medications			
Secretin (Williams, Wray, et al., 2012)	Multiple RCTs, no benefit	High	Proven ineffective
Hyperbaric Oxygen (Jepson, Granpeesheh et al. 2011	2 RCTs, conflicting results	Moderate	Unproven
N-Acetylcysteine (Hardan, Fung, et al., 2012)	Pilot RCT (n=29) with improved irritability	Unknown	Unproven
Chelation (Hendren, 2013; Mitka, 2008)	No adequate studies	High	Unproven
Non-biologic			
Auditory Integration Therapy (Sinha, Silove, Hayen, & Williams, 2011)	6 RCTs with only two suggesting positive effect	Low	Unproven
Music Therapy (Sandiford, Mainess, & Daher," 2013; Simpson & Keen, 2011)	Small studies, case reports with methodologic challenges	Low	Unproven
Yoga (Koenig, Buckley-Reen, & Garg, 2012)	School based pre/post assessment of yoga suggest impact on behavior	Low	Unproven
Acupuncture (Lee, Choi, Shin, & Ernst, 2012)	Controlled trials, methodological issues in	Low-moderate	Unproven
Hippotherapy (Ward, Whalon, Rusnak, Wendell, & Paschall, 2013)	Observational, non-controlled trials	Low	Unproven
Sensory Integration (Zimmer et al., 2012)	Small studies and case reports with methodologic challenges	Low	Unproven

GP Comment.

What have I learned from this paper?

1. Parents of children with ASD are often keen to try anything that might help their child, including therapies for which there is no reliable evidence base.

2. There is a difference between the US and the UK with regard to the status of melatonin. This hormone can be prescribed in the UK, although it is discussed in this paper (written by authors from the US) as an alternative treatment. There is some evidence for melatonin, at least for helping children to fall asleep, although it is not so effective in keeping them asleep.

3. Assessment of whether any treatment, including an alternative treatment, is effective, needs to be carried out carefully to avoid misleading conclusions.

4. This paper, especially the table, is useful because it summarises the evidence, or rather the lack of evidence, for a variety of alternative therapies.

5. Some alternative therapies could do harm. NICE advises against their use. In the absence of good evidence, they should not be recommended and those that might cause harm should be avoided.

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