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Dietary supplements in child and adolescent psychiatry

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Complementary and alternative treatments, including dietary supplements, are very popular and increasingly used in developed countries. Some features such as accessibility, ease of use, the possibility of self-administration and the belief they are safe without side effects, have led to an increase in their consumption. However, there is limited evidence of the effectiveness and safety of these treatments because of methodological issues. The level of scientific evidence is particularly low and weak in the field of child and adolescent Psychiatry. The purpose of this article is to give an updated overview of dietary treatments in this area. We make a brief introduction about general questions, including legal aspects, and propose general practical recommendations for a proper management by the families that choose these treatments. We focus on reviewing the current state of research into dietary treatments in some childhood and juvenile psychiatric disorders, highlighting current evidence of specific treatments. The final purpose of this article is to describe the level of current evidence on dietary treatments and to provide professionals involved in the care of children and adolescents with a useful tool to help, guide and educate families about their use in order to achieve the greatest benefit to patients.

Keywords: Complementary and Alternative treatments, Dietary treatments, ADHD, ASD, Depression, Essential fatty acids, Micronutrients

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Suplementos nutricionales en psiquiatría del niño y del adolescente

Los tratamientos de la medicina complementaria y alternativa, incluyendo los tratamientos con suplementos nutricionales, son muy populares en los países desarrollados y su uso continúa creciendo. La facilidad de uso, su accesibilidad y posibilidad de autoadministración y la percepción como seguros y carentes de efectos secundarios han conducido a un incremento de su consumo. Sin embargo, la evidencia de la efectividad y seguridad de estos tratamientos es limitada a causa de los problemas metodológicos. En el caso de la psiquiatría del niño y del adolescente, el nivel de evidencia científica es particularmente escaso y débil. El propósito de este artículo es dar una visión general actualizada de los tratamientos nutricionales en psiquiatría del niño y del adolescente. Realizamos una breve introducción que expone cuestiones generales sobre este tema, incluyendo aspectos legales. Proponemos recomendaciones generales prácticas para un manejo adecuado de las familias que escogen estos tratamientos. Nos centramos en la revisión del estado actual de la investigación de los tratamientos nutricionales en varios trastornos psiquiátricos infanto-juveniles, y describimos la evidencia actual de tratamientos específicos. El objetivo último de este artículo es proporcionar a los profesionales implicados en la atención de niños y adolescentes la información sobre el nivel de la evidencia actual de los tratamientos nutricionales para que puedan orientar, ayudar y educar a las familias sobre su uso y procurar de esta manera el mayor beneficio de los pacientes.

Palabras clave: Tratamientos de medicina complementaria y alternativa, Tratamientos nutricionales, TDAH, TEA, Depresión, Ácidos grasos esenciales, Micronutrientes

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INTRODUCTION

Definitions

According to the World Health Organization (WHO), traditional medicine is defined as the combination of indigenous knowledge, beliefs and experiences of different cultures, explainable or not, used for the maintenance of health and for prevention, diagnosis or treatment of physical and mental diseases. When traditional medicine is used in non-native populations, as occurs in a developed country, it is then known as complementary and alternative medicine (CAM)[1] That which combines conventional medicine and CAM treatments is called Integrating or Integrative Medicine.[2]

El National Center for Complementary Medicine and Alternative Medicine (NCMAM) classifies the CAM practices into different types, including the so-called biological practices.[3] In the third Strategic Plan of NCCAM, the term natural product replaces biological based practices and several categories of natural products of CAM are differentiated, among them nutritional supplements.[4]

The terms nutritional supplement and dietary supplement are often used as synonyms. They are defined as products taken orally that contain a "dietary ingredient" aimed at supplementing the diet. These ingredients can be vitamins, minerals, herbs, plants, amino acids, and substances such as enzymes, tissues, glands and metabolites.[3]

A general view of CAM in Child and Adolescent Psychiatry

The limits between conventional medicine and CAM are arbitrary and porous. Treatments considered as non-conventional at one time become well-established treatments for a specific disease.[2]

Interest by the general population has been growing regarding the efficacy, safety of CAM treatments with nutritional supplements over recent years.[5]

The ease of using supplements, their accessibility and possibility of self-administrations as well as the perception of these products as natural and safe have led to an increase in their use for both prevention and treatment of acute and chronic diseases.[6,7]

The percentage of pediatric patients who take CAM treatments may be greater than 70% in children and families who suffer chronic, recurrent or fatal diseases, and included among the CAM therapies most sought are vitamins and minerals, herbal products and other nutritional supplements, special diets and mind-body interventions.[8] These treatments are more frequent if the parents also use CAM treatments.[5] The studies report that children with chronic diseases, such as cancer, asthma, rheumatoid arthritis, attention deficit hyperactivity disorder (ADHD), genetic disorders, cerebral palsy and other neurodevelopmental disorders are those having the highest rates of CAM (24-75%). Families of children having Autism spectrum disorder (ASD) have even higher levels (28-95%). Use is greater if comorbidity is associated or if the symptoms are severe.[5] Young persons with psychiatric disorders or other medical disorders tend to use more complementary interventions than other youths.[5]

The reasons for the use of these CAM treatments may be therapeutic, for the promotion of health or both simultaneously.[9] Other possible objectives are: relief of specific symptoms, improvement of side effects from conventional treatments, or the desire for better control on the management of one's own health. Many treatments are perceived as "natural" without the possible side effects of the conventional treatments.[5]

Many family do not report the use of these treatments to their medical professionals of reference, among other reasons because they are concerned about getting a possible negative opinion from the professional.[5]

Generally, the families obtain the information on these treatments from relatives or other members of the community, other non-medical professionals, Internet, press, books and food shops.[5,9] The low stigma and competiveness regarding the costs of some CAM treatments make them highly attractive to the children/adolescents and their parents.[2]

Because of the popularity of CAM and its growing use, the increasingly greater interest of the families for these interventions, the frequent simultaneous use of CAM with conventional medicine, risks of toxicity and interactions with other products or drugs, and the use and effectiveness of some CAM interventions, the professionals need to know the current status of research in this field to be able to adequately inform and orient the patients and families.[7,10]

This article aims to provide an updated general view of the CAM treatments with nutritional supplements of interest in Child and Adolescent Psychiatry. The most frequently used are mentioned in Table 1.

SPECIFIC QUESTIONS

Change of paradigm

The idea that nutritional supplements can reduce psychopathology generates controversy and great skepticism.[11]

Table 1 CAM treatments with dietary supplements used in Child and Adolescent Psychiatry in developed countries*

Treatment	Indications
St. John's Wort *(Hypericum Perforatum)*	Depression Anxiety ADHD
Omega 3- Fatty Acids	Depression ADHD Bipolar D. Schizophrenia
Kava *(Piper methysticum)*	Anxiety
Valerian *(Valeriana officinalis)* Limon balm *(Melissa officinalis)*	Anxiety
Exclusion/elimination diets · Elimination of colorings/ preservatives · Food restriction (oligoantigenic) Healthy diet	ADHD
Gluten-casein free diet Healthy diet	ASD
Other treatments: · Vitamins · Minerals (Magnesium, Zinc, Iron, Calcium) · Amino acids · Other herbal treatments · Homeopathic treatments	No pathology defined Proposals for different disorders

** Adapted from Soh NL, Walter G. Traditional and alternative medicine treatments in child and adolescent mental health. In Rey JM (ed), IACAPAP e-Textbook of Child and Adolescent Mental Health. Geneva: International Association for Child and Adolescent Psychiatry and Allied Professions 2012.*

According to the of the International Society for in Nutritional Psychiatry Research Statement,[12] nutrition and nutraceuticals should be considered as mainstream elements of the psychiatric practice, following an integrative psychiatry model, diet being a key element. The selective use of evidence based nutrient prescriptions should be the main treatment measure whether in monotherapy, principally in cases of less severe mental disorders, non-tolerance to the medication, nutritional deficiencies or in the case of choice or preference of the patient, or as coadjuvant treatment with psychotropic drugs to increase treatment efficacy.

Negative attitudes or prejudices must be avoided because they can prevent better knowledge of CAM.[13] Integration of safe and effective therapies with conventional medical treatments can give rise to better results for the patient.[5] Placing oneself in extreme positions needs to be avoided and we must resist the tendency to dogmatize or simplify excessively.[14]

The evidence of complementary therapies in child and adolescent psychiatry is fragmented and there are very few well-designed and adequate clinical trials that incorporate control groups.[5]

It is necessary to advance in evidence of the complementary treatments with nutritional supplements regarding safety, efficacy, interactions, age-based dosing and clarification regarding indications and contraindications for the treatment.[4,5]

Future works, with better methodological quality, will make it possible to adopt an intermediate position between dogmatic investigators and those who excessively simplify the relationship between nutrition and behavior.[11]

Safety and efficacy evidence of CAM treatments

In a systematic general view/synthesis of Cochrane reviews of the CAM in Pediatrics between 1995 and 2012 in which 135 reviews were included and that evaluated efficacy, the clinical implications and limitations of CAM in children, only 5/135 (3.7%) of the reviews indicated a recommendation in favor of a specific intervention. Ninety five reviews (79.3%) were non-conclusive. The main criticisms on quality of the studies were: need for more research, low methodology quality and a small number of participants in the study.[15]

Few studies are available on the efficacy and safety of nutritional supplements in children and adolescents.[5,9] The data come from small, open, inadequately controlled trials or case studies.[5] However, many of these products are promoted as effective treatments for anxiety, depression, ADHD, autism and sleep disorders.[5] Many studies lack the sufficient size or necessary rigor to evaluate safety or effectiveness. Consequently, the evidence base for almost all the treatments with nutritional supplements is minimum.[7] The possible adverse effects or interactions they have must also be considered.[5,9] The tendency is to believe that natural remedies, because they are such, are safe and this often is not true. Nutritional supplements are exposed to a greater risk of contamination, substitution, adulteration, incorrect packaging and storage, wrong dosing, inappropriate labeling and warnings.[10] Figure 1 gives the details on the precaution to consider when using nutritional supplements in children.

In the case of child and adolescent psychiatry, scientific evidence of efficacy and safety of CAM treatments is especially scarce and weak, partially because of the ethical problems when developing clinical trials of quality in this age group.[1] In spite of this, there is sufficient data on some treatments that may be useful for the investigators and clinicians, and beneficial for children and adolescents, as coadjuvant treatment or monotherapy.[2]

Criteria for the management of CAM treatments in the clinical practice

Given that there is no conclusive evidence for most of the CAM treatments, such as that derived from randomized, placebo-controlled clinical trials, their clinical application should depend on other criteria in most of the cases.[16] The professionals should help the families to select the most promising treatments, which have a justification for their

Product purity problem. Risk of the presence of unidentified substances and contamination due to pesticides, herbicides, other pharmaceutical products, heavy metals and excipients. Especially in the case of products imported from developing countries

Problem of product reliability, in regards to variability of the presence and concentration of active ingredients, conditions of growth, processing and storage

Unstudied effectiveness of active ingredients of the product

Unknown short term safety and toxicity of use in children

Unknown long term (chronic use) safety and toxicity in children

Lack of knowledge of the possible interactions with other medications and treatments

Lack of knowledge of the metabolism of these products in children with renal, hepatic or other disorders

Cost of the products not necessarily related with the quality, purity or concentration of the active ingredients

** Adapted from Kemper KJ. Overview of complementary and alternative medicine in pediatrics. Uptodate 2017 (updated Sept 15, 2016; cited 9 March 2017). Available at www.uptodate.com*

Figure 1 | *Precautions to consider with herbal products and dietary supplements when they are used in children**

use, that adjust to the family values and have evidence of safety and possible efficacy. That is, that these treatments are safe, simple, inexpensive and reasonable.[16]

The clinical professionals needs to have knowledge about the CAM treatments and to maintain an open, receptive attitude, regarding the knowledge and incorporation of these treatments into their usual practice, the same as they do when faced with learning about a new conventional treatment.[2]

The recommendations of the American Academy of Pediatrics for the professionals who discuss CAM treatments with the families are indicated in Table 2,[17] similar to those stated in other works.[9,18,19]

A summary of practical recommendations for discussion with the families on the CAM treatments are shown in Table 3.

Legal aspects

Table 4 includes the general medical-legal considerations in the use of complementary therapies in children and adolescents.[17]

The following aspects must be taken into consideration.[20] The CAM treatments that are recommended in the safest way are those having evidence of safety and efficacy in publications. Both the patient and his/her caregivers should have extensive information on the risks and benefits in order to make an informed decision. All the treatments should be carried out for the best benefit of the minor. Treatment must always be supervised. Any discussion on CAM treatments should be documented in the medical records. Once a CAM treatment demonstrates its safety and efficacy and great acceptance, it is obligatory to report it as an alternative to the conventional treatment.

An open and informed attitude of the professional may allow for better knowledge of the interests and beliefs of the patients, better education of the patient and better results.[13]

Table 2 Recommendation of the American Academia of Pediatrics for the professionals who discuss CAM therapies with the families*

- Learn about information and be prepared and in condition to share it with the families
- Evaluate the scientific evidence of the different therapeutic interventions
- Identify risks and potential harmful effects
- Provide the family with information on a range of treatment options
- Educate the families on how to evaluate the information on the different treatments
- Avoid taking an attitude that transmits lack of sensitivity or concern/interest/respect for the viewpoint of the patient and family
- If the family chooses a CAM treatment, offer to monitor the response to the treatment
- Actively listen in the case of families of children with chronic diseases
- It is recommended that the clinical professionals use a structured approach when discussing the therapeutic options, including the complementary therapies, with their patients and families
- The medical-legal aspects must always be taken into account

Kemper KJ. Overview of complementary and alternative medicine in pediatrics. Uptodate 2017 (updated Sep 15, 2016; cited 9 March 2017). Available at www.uptodate.com

SPECIFIC DISORDERS

Attention deficit and hyperactivity disorder (ADHD)

Exclusion of artificial colorings and food preservatives

A meta-analysis of 20 studies on restriction diets found a small effect size (0.18) based on the records of the parents, but this decreased to 0.12 when the possible publication bias was considered.[21] The effect on the records of the professors and observation measures was not significant.[21] Another meta-analysis of 8 studies found a similar effect size (0.32 to 0.42 depending the informer). The effect size was not significant when the analysis was limited to studies will few or no medications.[22] There are no long-term studies.

A meta-analysis review of controlled, randomized trials of exclusion of artificial food colorings in the treatment of ADHD suggests small but significant effects on the ADHD symptoms, although the patients had shown some degree of previous intolerance in most of the trials.[23]

This may be a useful coadjuvant treatment in some cases,[24] although these diets are difficult to perform and are expensive.[24]

Food restriction diets (Oligoantigenic diets)

In accordance with the IgG-ADHD theory, those foods associated to an increase in IgG levels would determine a significant deterioration in the behavior when these foods are eaten while this would not occur in the case of foods

Table 3 Recommendation for discussion with the families on CAM treatment*

- Speak about the different types of therapies the families have done to help the child/adolescent. Evaluate in a routine and structured way
- Do not wait for the family to bring up the subject. They generally do not inform about it unless directly asked about it
- Ask with an open, not critical attitude. Avoid using derogatory terms such as "not tested" or "not conventional" or "alternative". Do not judge
- Obtain information on specific therapies. Herbal products, dietary, other therapies. Assure that the possible side effects are evaluated. The families generally assume that there are no adverse effects or that they are very limited
- Obtain information on the values, beliefs, reasons for the search for CAM treatments of the patient and his/her family (family advise; cultural, spiritual or religious beliefs; preference for natural products; fear of the side effects of the conventional treatments)
- Whenever possible, seek agreement and association with the parents, be their allies
- Before giving an opinion, ask what the family thinks about the therapies that have been useful and those that have not been useful
- Offer the possibility to coordinate any of the professionals who are involved in the child's care
- Offer the families additional information and resources where to go to ask questions on the CAM therapies. Orient and educate the families

**Kemper KJ. Overview of complementary and alternative medicine in pediatrics. Uptodate 2017 (updated Sep 15, 2016; cited 9 March 2017). Available at www.uptodate.com*

Table 4 Medical-legal considerations in the use of complementary and alternative treatments in children and adolescents*

- Situation of the minor (seriousness/life threatening) and need for immediate treatment with conventional treatments
- Does the use of CAM treatments keep the child away from the immediately necessary conventional treatment?
- Is scientific evidence known on the efficacy and safety of the CAM therapies selected?
  - Medical evidence that supports efficacy and safety: therapy can be recommended
  - Medical evidence supports safety, but with non-conclusive efficacy: therapy can be tolerated Medical evidence supports efficacy, but the safety data are not conclusive: the therapy should be closely monitored or be advised against and avoided
  - Medical evidence indicates lack of efficacy and elevated risk: the treatment should be avoided and forbidden
  - The products can change category based on the new information available
- Is there consent by the interested parties for the use of CAM treatments?
- Is the risk/benefit ratio of the therapy proposed acceptable and reasonable, as in a similar clinical situation, and does the treatment have at least a minimum acceptance and support in the medical literature?

**Cohen M, Natbony SR, Abbott RB. Complementary and Alternative Medicine in Child and Adolescent Psychiatry: Legal considerations. Child Adolesc Psychiatric Clin N Am 22 (2013)493-507 http://dx.doi.org/10.1016/j.chc.2013.03.005*

associated to low IgG levels. There is no current evidence to corroborate this hypothesis.[25]

A meta-analysis of 6 controlled trials found an effect size of 0.29.[21] Another one estimated an effect size of 1.48 in the evaluation by the person who applied the treatment. The effect decreased to 0.51 when blind raters were used.[22] There is great heterogeneity in the studies due to the different designs and the more or less strict elimination diet. There are no studies that show middle and long-term effectiveness and cost-effectiveness.[24]

The children and parents who want to carry out an elimination diet should be closely supervised since the development of the diet requires much effort and dedication by the child and his/her whole family.[24]

The Clinical Guidelines of the American Academy of Pediatrics, the American Academia of Allergy, Asthma and Immunology and the NICE do not recommend the restriction diet in a routine way for the treatment of ADHD.[26]

Supplementation with omega 3 and omega 6 fatty acids

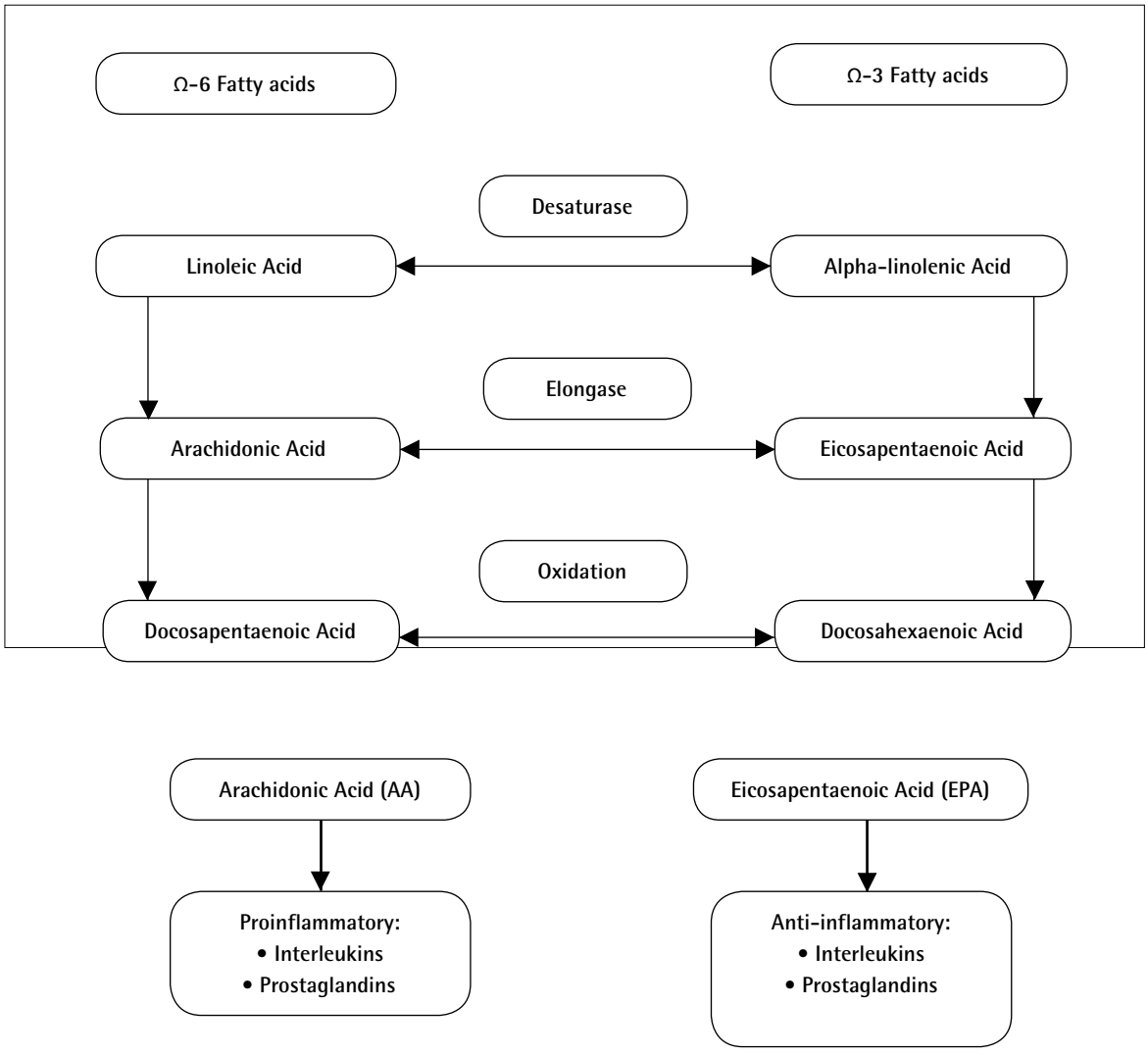
The synthesis pathway of the Fatty Acids is described in Figure 2.[24]

Some studies have reported lower concentrations of omega 3 fatty acids in plasma and in the erythrocyte membranes in children and adults with ADHD.[24] A recent study has concluded that children and young persons with ADHD have an elevated proportion of omega-6/omega-3 and more specifically Arachidonic Acid/Eicosapentaenoic Acid (AA/EPA) compared with controls.[27]

There are many commercial products (gels, capsules, liquids) available as supplements in the omega 3 fatty acids diet. Most satisfy EPA and DHA up to ten times. Many products also have other micronutrients or vitamins that are postulated to be deficient in patients with behavior disorders.[24]

Two meta-analyses concluded that supplements with fatty acids were associated with a small but reliable effect of reduction of ADHD symptoms, with effect sizes between 0.18 and 0.31.[22,28] A third meta-analysis did not find significant differences in the ADHD symptoms scores in parents and professors among those who received supplements and those who took placebo.[29] None of the studies measured plasma levels of free fatty acids. Methodological limitations of the studies imply that the results should be carefully interpreted.[26] There are no long-term effectiveness and cost-effectiveness studies.[24]

In the 2014 Stevenson review,[23] a small but significant and highly consistent effect was identified in children with



**Adapted from Ferrin M, Sonuga-Barke E, Daley D, Danckaerts M, Van der Oord S, Buitelaar JK. Non-pharmacologic Treatments for ADHD. In Rey JM (ed.), IACAPAP e-Textbook of child and adolescent mental health. Geneva: International Association for child and adolescent Psychiatry and Allied Professions 2016*

Figure 2 | *Fatty Acids Synthesis Pathway**

ADHD and supplementation with omega 3 polyunsaturated fatty acids (PUFA). It can be a coadjuvant treatment of the conventional treatments or for patients with subclinical or prodromic presentations.[22]

In the Rainee study,[30] which had a double blind placebo controlled designed, the effects of a relatively high dose of PUFA versus placebo was compared in a sample of a general population during a 6-month period of treatment and a subsequent follow-up of 6 more months. At the end of the 12-month period, the effects were substantial, with a greater effect size than in the Stevenson study. In addition, the improvements included both externalizing and internalizing problems, with the strongest and most consistent effects in the scores of the parents. These results must be considered with care and require new replications.

Some investigators have suggested that supplementation with fatty acids may be useful in children having a partial response to the medication.[31] The side effects are less and include a fish favor and smell, gastric malaise, soft stools and nauseas.

Supplementation with micronutrients

The evidence of supplementation with micronutrients continues to be limited and inconsistent because of lack of good quality studies.[22]

The results of the trials with micronutrients vary because most of them have focused on a single nutrient, such as iron, magnesium or zinc. The works have demonstrated modest or negligible effects.[32-34] A randomized, blind, well-designed clinical trial showed improvements in the ADHD symptoms in adults after a "wide spectrum" treatment with minerals and vitamins.[35] An open pilot trial using the same micronutrient formula in 14 children with ADHD recorded a significant improvement in the ADHD symptoms.[36]

There are many commercial products with a "wide spectrum" approach in which supplements with multiple ingredients or multivitamins were provided. They are promoted as effective in the treatment of ADHD and other disorders such as bipolar disease, anxiety disorders and depression.[22]

No safety problems have appeared in the studies performed, however high doses may lead to toxicity without adding more benefit, as has been demonstrated in previous studies in which megadoses were used.[22]

Combined view of the nutritional treatments in ADHD

Recommendations and observations of the different complementary/alternative treatments in ADHD are indicated in Table 5.

The studies suggest that the dietary treatments play a statistically significant role, but with limited clinical value, the results being far from those of the promoters of the diet-behavior hypothesis. However, they are better than expected by the skeptics of this paradigm.[22]

Most of the complementary/alternative nutritional treatments for ADHD have a non-conclusive evidence base. However, some are sufficiently safe, easy, inexpensive and sensitive to be used while the research is undergoing.[16]

Most of the complementary/alternative treatments con be used together with the established conventional treatment.[16]

A "western" nutritional pattern, associated with an ADHD diagnosis, has been described in some studies. This pattern included an elevated intake of fat, above all saturated fats, refined sugars, salt and deficient intake of omega 3 fatty acids, fiber and folate and a healthy nutritional pattern, not associated with ADHD diagnosis, which implies a diet rich in fish, fruits, vegetables and cereals, breads, pasta and brown rice.[31,37]

Absence of response to pharmacological treatment or appearance of side effects, preference of the patient or parents, presence of signs or symptoms of mineral deficiency or need to replace an "Western" diet," of risk for ADHD for a healthy, non-associated ADHD diet, may be indications of nutritional treatment in ADHD.[31]

Finally, homeopathy has been used to treat ADHD. However, a 2009 Cochrane review concluded that there was no evidence that this intervention had any significant impact on ADHD diagnosed children.[1]

Autism Spectrum Disorder (ASD)

In spite of the limited evidence on its efficacy, the prevalence of complementary and alternative treatments in ASD is elevated,[38] above all in children with more severe pictures, those diagnosed at an earlier age and those with gastrointestinal symptoms or crisis. Vitamins, nutritional supplements, special diets and body based therapies are those used most.[39]

Different biological hypothesis of ASD have been proposed to justify treatment with complementary and alternative treatments[39] and it has been proposed that different epigenetic processes may be a therapeutic target.[40]

Safety and efficacy data have been shown for melatonin, omega 3 fatty acids and micronutrients in at least one randomized controlled trial. Other promising agents are N-Acetylcysteine and Methylcobalamin, digestive enzymes and memantine.[40]

Table 5 Complementary/alternative treatments in ADHD*

Treatment	Quality of evidence/Clinical Recommendation	Observations
Elimination diet	Regular to good/Recommended in case of patients with documented sensitivity or reaction to foods, additives and preservatives. Acceptable for patients without documented reaction	Acceptable in short test or trial in patients without documented reaction. Monitor nutrition Supervise family stress derived from establishment of the diet
Sugar restriction	Good/Acceptable, especially if suspicion of prediabetes or daytime pattern of symptoms	Research does not suggest that elimination of sugar eliminates ADHD symptoms. However, reduction of sugar in all cases can be recommended for benefit of general health Monitor parent-child relationship. A strict restriction can lead to conflict
Breakfast that contains protein/ low sugar	Poor/Recommended	Recommended for all children Breakfast with milk and cereals can help to maintain attention during the day. Breakfast with high amount of sugar can cause a decrease in attention
Amino acids supplements	Poor/Recommended against	Not supported by research. Metabolic risks
Polyunsaturated fatty acids	Good/Strongly recommended	Recommended for everyone who does not eat fresh oily fish at least three times a week. Reasonable indication for all patients due to the benefits on the general health Concern due to mercury contamination It may require several months to observe effects
Megadoses of vitamins and minerals	Regular/Recommendation against	Not recommended. Risk of toxicity
Supplementation of multivitamins/minerals, according to recommended daily intake (RDI/RDA)	Regular/Recommended	Recommended for all children with ADHD, especially for children who are picky eaters or who have decreased appetite due to stimulant medication
Zinc supplementation	Regular/Recommended for cases of documented Zinc deficiency	Monitor treatment
Magnesium supplementation	Regular/Recommended for cases of documented Magnesium deficiency	Monitor possible toxicity It can cause diarrhea
Iron supplement	Regular/Recommended for documented cases of Iron deficiency or insufficiency	Monitor toxicity Do not indicate a dose above the recommended dietary intake It can cause constipation
Melatonin	Good/Recommended for treatment of sleep problems, not for ADHD core symptoms	It improves sleep, but there is not evidence that it improves ADHD symptoms It may be pre-seizure in children with epilepsy

Table 5 Continuation

Treatment	Quality of evidence/Clinical Recommendation	Observations
Supplementation with Thyroid Hormone	Regular/Recommended as treatment in case of hypothyroidism	Monitor the treatment
Ginkgo biloba	Regular/Recommendation against	Risk of bleeding (ocular, subdural)
St. John's Wort	Regular/Recomendación en contra	Risk of sensitivity to sunlight and Serotoninergic Syndrome It is not useful for ADHD
Other herbs (valerian, kava-kava, camomile)	No data/Recommendation against	Not recommended. Risk of cardiac and hepatic toxicity It can contain contaminants
Hemeopathic treatments	Regular/Neutral	Risk of onset in treatment tested. Long term need

[*] *Adapted from Arnold LE, Hurt E, Lofthouse N. Attention-Deficit/Hyperactivity Disorder: Dietary and Nutritional Treatments. Child Adolesc Psychiatr Clin N Am. 2013 Jul;22(3):381-402, v. doi: 10.1016/j.chc.2013.03.001. Epub 2013 May 17. Review.*

The 2011 Cochrane review included 2 trials and concluded that the evidence of effectiveness of omega 3 supplements in the treatment of the core symptoms of ASD is not sufficient.[41]

According to the 2006 Clinical Practice Guideline for the treatment of ASD, secretin is a non-recommended treatment, without any support of effectiveness evidence. Vitamins and nutritional supplements, gluten free diets and casein are only recommended in controlled research studies, given the limited or weak evidence of their effectiveness.[42]

There is good quality of evidence in the studies on melatonin, recommended for sleep disorders.[40] The methodological problems limit the value of the studies to support its use, however their is justification for its use, and it is reasonable, easy, inexpensive and safe.[38,40]

With only two small randomized clinical trials (RCT), the evidence is small for the use of omega 3 supplements (EPA and DHA) in ASD. The possible benefit can be derived from the small, although questionable effect, in the improvement of the hyperactivity. In spite of the weak evidence and limited effect, a logical basis exists for its use. It is reasonable, simple, not expensive and safe.[38,40]

In spite of the limited evidence of the efficacy of vitamin and mineral supplements in autism, its use is widespread. The promising results derived from 2 RCT suggest a benefit, it also being a safe, simple and non-expensive agent.[40]

A healthy life style (healthy diet, regular exercise, adequate sleep, stress management, social support, neurotoxin avoidance) should always be recommended.[39]

Both the clinician and family should evaluate if treatment with therapies that have unknown benefit are worthwhile compared to their potential risks, including their "competition" with validated treatments in time, effort and economic resources.[39]

A classification of the complementary and alternative treatments in ASD in accordance with the risks and benefits is shown in Figure 3.[39]

Table 6 shows the most relevant data of the available evidence for the different treatments.[43]

Depressive disorders

One review indicates physical exercise, light therapy, hypericum, SAMe and 5- Hydroxytryptophan as CAM antidepressant treatments that seem to show promising data, based on few controlled trials.[44]

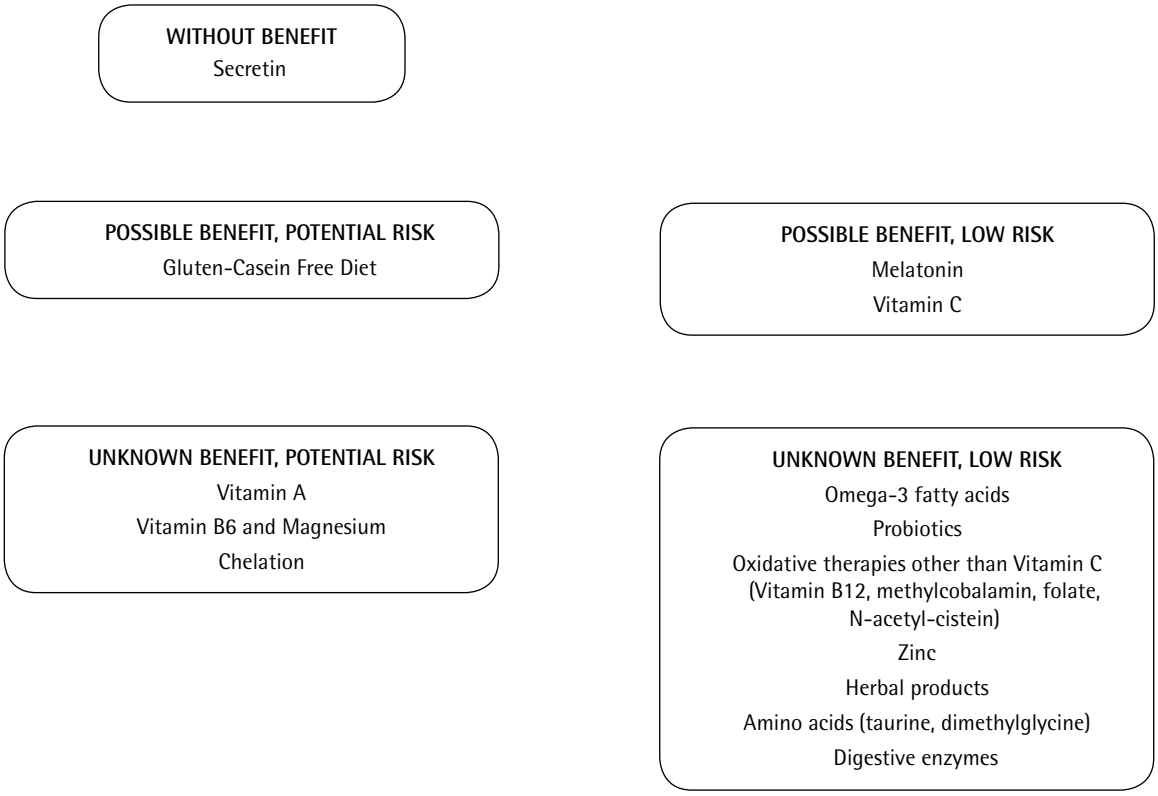
In regards to the St. John's wort *(hypericum)*, the most commonly prescribed antidepressant for children in Germany,[10] there are many randomized controlled trials in adults, mainly with mild depression. There are very limited data in children.[10,45] St. John's wort may be useful in mild depression,[1] when the parents or adolescents refuse to take medication, or if there has not been any benefit from conventional treatment, as long as the possible risks of the treatment have been discussed.[10] The St. John's wort requires

monitoring due to its possible interactions with other treatments, due to its induction of CYP 450[1], as oral contraceptives, serotoin reuptake selective inhibitors (risk of serotoninergic syndrome), anti-seizure medication and anticoagulants. It is generally well-tolerated by children,[1] although it may cause insomnia, vivid dreams, restlessness, agitation, gastrointestinal symptoms, dizziness, headache, photodermatitis and paresthesias.[7] Some of these effects (increased sensitivity to sunlight, gastrointestinal symptoms, fatigue, headache) are uncommon at therapeutic doses.[10] Hypericum is also a product having great variability and impredictability.[44] The quality of evidence is poor and the data are insufficient to recommend its use.[44]

There are several controlled randomized trials on the use of omega 3 fatty acids in depression in adults having diverse quality but there are very few studies in children. They show few and mild side effects.[45] In spite of the variable and heterogeneous results, extrapolating the effectiveness and safety data of the omega 3 effectiveness and safety data in adults, its use as a treatment of depression and bipolar disorder in children and adolescents seems to be justified for some authors.[10]

Although S-adenosylmethionin seems to be effective and well tolerated in adults, there is little data available in children and adolescents. This would require close supervision.[10]

Overall, these treatments should be reserved for those patients or families who do not want to take medication, those who demonstrate their preference for non-pharmacological treatments, those who have not responded to different conventional treatments, or for patients who lack the economic recourses to be able to maintain a conventional treatment.[44] The patient and their family should understand the significance of their decision to use a treatment with very limited and weak evidence instead of an already established treatment only when the seriousness and need for acute treatment are mild and the clinical situation of the patient permits delaying the initiation of the conventional treatment.[44]



[*] *Weissman L, Bridgemohan C. Autism Spectrum Disorder in children and adolescent: Complementary and Alternative Therapies. UptoDate 2017. (updated: Feb 16, 2017; cited 9 March 2017). Available at www.uptodate.com*

Figura 3 | *Complementary and Alternative Treatments in ASD in accordance with the risks and benefits*[*]

Table 6 Evidence of complementary and alternative treatments in children diagnosed of ASD*

Treatment	Evidence	Comments	Grade of evidence
Herbal products	No specific studies	No studies. No recommendation	D
Vitamins/minerals/ supplements	Double blind, placebo controlled randomized trials	Significant methodological problems	C
Vitamin A	No evidence Theories	No evidence of effectiveness. Significant possibility of harm	D
Vitamin C	2 double blind, placebo controlled trials	Some preliminary evidence. Non-significant toxicity	B
Vitamin D	Circumstantial evidence based treatment	Theories Methodological problems	D
Vitamins B6 and Magnesium	2005 Cochrane Review: No recommendation Update 2010: Same conclusion	Poor quality of the studies. No recommendation. Potential neurotoxicity of B6 and/or magnesium	D
Amino Acids	No peer review studies	Inadequate studies to make treatment recommendations	C
Omega-3 Fatty Acids	Several systematic reviews. Studies report benefits, but with many methodological problems	Absence of high quality evidence that shows effectiveness on the core symptoms and associated to ASD. Need for more studies based on promising effects in other populations	C
Vitamin B12	A small, open pilot study. No additional studies since 2008 review. 12-week double blind, placebo controlled study. Improvement in a subgroup	Need for more studies to define responders group	C+
Melatonin	Multiple studies	Good physiological evidence. Some observational and open studies of median quality	B
Probiotics	No specific studies	No recommendation	D+
Secretin	Many children evaluated in double blind, placebo controlled trials. No benefit	Product not approved by FDA No documented benefit	A
Gluten free diet/Casein free diet	Single blind trials that suggested potential benefit in 5-7 year old children with gastrointestinal symptoms. Double blind trial does not show benefit	Need for studies to clarify utility Risk of nutritional involvement. Supervision by specialist in nutrition	B

(Recommendations of the GRADE Work Group). A: More than one high quality study with consistent results or an extensive multicenter study. B: A high quality study or several studies with mild limitations. C: A study with important limitations. D: No evidence/Theories/multiple studies with very serious limitations

**Adapted from Levy SE, Hyman SL. Complementary and Alternative Medicine Treatments for Children with Autism Spectrum Disorders. Child Adolesc Psychiatric Clin N Am 2015; 24:117-143 http://dx.doi.org/10.1016/j.chc.2014.09.004*

CONSIDERATIONS ON SOME SPECIFIC TREATMENTS

Omega 3 Fatty Acids

A few controlled randomized trials have been conducted in children with depression or bipolar disorder, but only biologically active placebos were used. A modest improvement in those who received omega 3 supplements was observed.[1] A systematic review on the efficacy of omega 3 fatty acids for bipolar disorder found some positive benefits for the depressive symptoms, but not for mania, and no adverse event was reported.[46] More studies are required.[46]

The combined treatment of individual familial psychoeducation and supplementation with omega-3 fatty acids are well tolerated and can be effective in patients diagnosed of sub-syndromal bipolar disorder and cyclothymic disorder.[47] Supplementation with omega 3 can be a safe and coadjuvant intervention for the treatment of bipolar disorder in children and adolescents, even in the presence of psychotic symptoms and anxiety.[48]

In the randomized controlled trials of young persons at risk of psychotic disorder, it was demonstrated that those treated with omega 3 had a significant reduction of symptoms and their functioning compared with the placebo group.[1] In a 2008 review, it was concluded that the use of omega 3 polyunsaturated fatty acids for schizophrenia was still in an experimental phase and this review stressed the need for studies having a larger size, that were correctly designed, performed and reported.[49]

In the randomized controlled Vienna trial of omega-3 in subjects at high risk of psychosis, supplementation treatment with omega-3 polyunsaturated fatty acids reduced the risk of transition to acute psychosis and improved the symptoms and functioning of the high risk subjects without causing important side effects.[50] A very recent work showed the direct effects of omega-3 polyunsaturated fatty acids on the marker levels of the immune function in this high risk population of psychosis.[51] No evidence of the efficacy of omega-3 acids was found in a multicenter, randomized clinical trial published in this same year,[52] so that the results of the previous trial were not replicated.[53]

A randomized, double blind, placebo-controlled, stratified, group-parallel, trial shows results that can indicate initial evidence of the efficacy of omega-3 fatty acids in sustained reduction of the internalizing and externalizing problems in children and adolescents.[30]

A randomized, stratified, single blind, factorial clinical trial provides limited support regarding the efficacy of omega-3, vitamin and mineral supplements in reducing the aggressive behavior in children and makes up the first evaluation of the use of nutritional supplements together with cognitive-behavioral therapy.[54]

There is marginal evidence on the effect of omega-3 polyunsaturated fatty acids on cognition in those cases presenting omega-3 deficiency. However, there is no evidence on the effect in the general population or in those with neurodevelopment disorders, included patients with ADHD and related disorders.[55]

Omega-3 fatty acids are generally well tolerated by children and are even safe in high doses.[1] The adverse effects reported are relatively mild: gastrointestinal symptoms, fish taste/smell. Skin rashes and urinary problems are rare.[1] Risk of bleeding may be increased at high doses. Precaution must be taken in patients with a previous blood disorder[1] and the risk of contamination by heavy meters of omega-3 fatty acids of marine must be kept in mind.[1]

Vitamins and minerals

The preliminary evidence supporting the use of micronutrients in the treatment of psychiatric disorders is based mostly on studies that use formulas containing significantly larger doses of micronutrients than those found in the products on the market.[56]

Until recently, the investigators conducted studies with individual nutrients, with limited success, instead of using a wide spectrum approach with multi-ingredient formulae.[34]

Treatments with wide spectrum micronutrients seem to be effective in early controlled trials as treatment for ADHD, behavioral disorder and aggressiveness and mood disorders in young persons and adults.[56] However, the research is in its initial states and there is great variability in the ingredients and doses in the different studies, so that making comparisons between them is complicated.[34] In the case of bipolar depression and mania, effectiveness of the wide spectrum micronutrients seems comparable to the conventional medications, but with fewer side effects and possibly greater long-term stability.[57] There are promising works from various research groups on treatment with micronutrients of affective, anxiety and psychotic symptoms with complex formulae that seem to be safe and well tolerated.[58]

KEY POINTS

1. CAM treatments, including those with nutritional supplements, are very popular in developed countries and their use continues to go.

2. The evidence of the effectiveness and safety of these treatments is low due to the methodological problems. In the case of child and adolescent psychiatry, the level of scientific evidence is especially low and weak.

3. Professionals should know the research in this field due to the great popularity and growing use of these treatments, greater interest of the families, frequent simultaneous use of CAM with conventional medicine treatments, utility of some of these treatments, and the risk due to possible interactions with the pharmacological treatments.

4. Since most of the treatments do not have conclusive evidence, as that derived from placebo-controlled randomized clinical trials, the clinical application should depend on other criteria in most of the cases.

5. Professionals should help the families select the most promising treatments, which have a justification for their use, that adapt to the family values and have evidence of safety and possible efficacy. That is, that they are safe, simple, inexpensive and reasonable.

6. It is necessary to advance, using quality research, in the evidence of the complementary treatments with nutritional supplements in regards to safety, efficacy, interactions, dosing based on age and clarification in regards to indications and contraindications for the treatment.

CONFLICT OF INTERESTS

The authors declare they have no conflict of interests.

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