

# The use or misuse of biomedical treatment approaches to autism

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## Abstract

**Introduction:** The need for evidence based recommendations regarding biomedical approaches to autism was felt in view of the significant number of autistic children presenting within the Child Development Assessment Unit, Malta and the interest shown in these approaches by their families and local nongovernmental organisations.

**Aim:** To establish the medical basis of biomedical approaches to treating autism, by establishing which of these approaches are of reported proven efficacy, effectiveness and safety and hence offer recommendations for their use.

**Methods:** An electronic literature search was carried out for supporting evidence-based biomedical approaches in autism, particularly mainstream authoritative national guidelines.

**Results:** No strong recommendation was found to *support* any of the biomedical approaches to autism addressed in

10 authoritative national guidelines from 1999 to 2011. The evidence and recommendations were *against* using chelation, immunoglobulin therapy, secretin, amantadine, antifungal/yeast therapies, naltrexone, dimethylglycine, vancomycin, digestive enzyme supplements and donepezil.

Melatonin for sleep disturbances and to a lesser degree, Omega-3 fatty acids for hyperactivity had enough support to consider their use in autism. The recommendations for gluten/casein diets, and Vitamin B6/magnesium were mostly either indeterminate or negative. Iron, vitamin C, piracetam, pentoxifylline, ketogenic diets, L-carnosine and hyperbaric oxygen therapy could not be safely recommended.

**Conclusion:** The evidence-based literature does not support most biomedical approaches to autism. There is limited support for melatonin and Omega-3 use.

## Keywords

Autism-treatment-guidelines

## Introduction

Autism/Autism Spectrum Disorder (ASD) is a spectrum of neurodevelopmental disorders diagnosed on the basis of a behavioural phenotype in children presenting before 3 years of age showing impairment in socialization, communication as well as restricted, repetitive and stereotyped patterns of behaviour, interests, and activities (DSM-IV-TR).<sup>1</sup>

The reported current rate of diagnosis of autism may be as high as 1 in every 100 children.<sup>2</sup> 26% of all children first presenting to the author within the Child Development Assessment Unit, CDAU St. Luke's Hospital, Malta present with communication difficulties. 27% of these meet the DSM-IV-TR criteria for Autistic Disorder.

An ever increasing number of parents of children with autism presenting within the CDAU, as well as local nongovernmental organisations are interested in biomedical approaches to autism besides the conventional approaches of speech and language

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therapy, occupational therapy, and early educational intervention.

It is felt that local medical professionals should be knowledgeable about such biomedical approaches and thus be able to provide parents with unbiased evidence-based opinions. This prompted the review being presented here.

### Aim

To establish the medical basis of biomedical approaches to treating autism, by establishing which of these approaches are of reported proven efficacy, effectiveness and safety and hence offer recommendations for their use.

### Objectives

To summarise the established authoritative national recommendations addressing biomedical approaches to autism published for the period 1999-2011, and set forth recommendations regarding the use of specific biomedical approaches.

### Method

An electronic search was made for the literature supporting evidence-based biomedical approaches in autism. This was mainly through using internet searches of terms "biomedical treatments in autism"/ "therapy in

autism"/"management of autism spectrum disorders" and related search terms on Google, and a wide expanse of medical websites including PubMed, MERK, MedlinePlus, UpToDate, DL+, ScienceDirect, Medscape, MD Consult, MeSH, WebMD, HealthCentral, WD Medical Dictionary, OpenMED@NIC, CureResearch, Diseases database, WHO, MayoClinic, NIH, bmj Group, JAMA, NEJM, journal watch, Ovid MEDLINE, Oxford Journals and Springer. The focus was on the management, treatment or therapy in autism. Priority was given primarily to mainstream authoritative national guidelines addressing biomedical approaches to autism published from 1999 to 2011. Specific papers and international recommendations regarding hyperbaric oxygen therapy for autism were also focused upon for the period 2009-2011.

### Results

#### *Authoritative national guidelines and sources addressing biomedical approaches to autism: 1999 - 2011*

Ten authoritative national guidelines addressing biomedical approaches to autism were located. Eight were published between 1999-2011.<sup>3,4,5,6,7,8,9,10</sup> Three guidelines addressing hyperbaric oxygen therapy, were published between 2009-2011.<sup>3,11,12</sup>

	2011 USA AHRQ <sup>3</sup>	2008 New Zealand <sup>4</sup>	2007 USA AAP <sup>5</sup>	2007 UK SIGN <sup>6</sup>	2006 Spain <sup>7</sup>	2004 Australia <sup>8</sup>	2003 Canada <sup>9</sup>	1999 USA <sup>10</sup>
Melatonin	+	++	++	++	-			
Omega-3 fatty acids	+	-	+					
gluten/casein free diets	0	-	0	0	-	0	-	-
Iron	+							
Vitamin B6 and magnesium	+	0	-	0	-	+	-	-
Vitamin C			+					
Amantadine /antiviral agents	-	-	-	-				
Vancomycin				-				
Immunoglobulin	-	-	0		-		-	--
Dimethylglycine	-	-	-		-			
Naltrexone		-			-			
Antifungal/ yeast							0	-
Secretin	-	-	-	-	-	-	-	-
Chelation	-	--	--		-			

**Table 1** Relative recommendations of authoritative national guidelines addressing biomedical approaches to autism: 1999 - 2011:

- ++ Relatively good support for (but still not licensed),
- + Limited/weak support for, or guarded recommendation,
- 0 No recommendation for/against,
- Evidence/recommendation against,
- Strong evidence/ recommendation against: dangerous.

Table 1 indicates the relative recommendations of each national authority vis-à-vis specific biomedical approaches to autism, as reported by their respective published guidelines. Besides the data shown, the 2011 USA AHRQ guidelines also singularly include recommendations on piracetam (with risperidone), pentoxifylline (with risperidone), ketogenic diets, and L-carnosine (all with + limited/weak support for or guarded recommendation); cholinesterase inhibitors (donepezil), and digestive enzyme supplements (Peptizyde) (both with - negative evidence/recommendation). These guidelines also report "some promise for future research" for melatonin and omega-3 fatty acids.<sup>3</sup> The USA AAP also noted similar promise of omega 3 fatty acids for hyperactivity in autistic children.<sup>5</sup>

Table 2 indicates the relative support of authoritative inter/national guidelines specifically addressing hyperbaric oxygen therapy in autism.

2011: USA: AHRQ <sup>3</sup>	2011: European Committee for Hyperbaric Medicine (ECHM). <sup>11</sup>	2009: UHMS Position paper <sup>12</sup>
+	-	-

**Table 2** Relative recommendations of authoritative guidelines addressing hyperbaric oxygen therapy in autism:

- + Limited support for,
- Evidence/recommendation against

## Discussion

It is notable that the primary focus of all available guidelines concerning therapies in autism is *not* on biomedical treatments but on the conventional medical, allied medical, multidisciplinary educational and behavioural management approaches to this condition. This is understandable as the conventional diagnosis of autism is basically defined as a behavioural phenotype and not by specific biomedical physiological parameters. Moreover, most of the guidelines remark that despite the ever increasing popularity of biomedical approaches amongst parents of children with autism, varying from 11 - 70% of children,<sup>13</sup> the published evidence for these approaches is limited. In fact, the strongest evidence for or against any medical approach is present in mainstream medical treatments in which pharmaceutical companies have an interest and provide funding for such studies.<sup>3</sup> Thus, risperidone and aripiprazole have the strongest support for their indicated use in autism and are recommended for the control of irritability, with a

cautionary note about their potential harm of weight gain, sedation, extrapyramidal effects and hyperprolactinaemia. Risperidone and aripiprazole are in fact the only drugs licensed and approved by the FDA (US Food and Drug Administration) for the treatment of irritability in children with autism.<sup>3</sup>

This review focused on the limited sections of these guidelines discussing published evidence and offering recommendations regarding the biomedical approaches towards autism.

### **Chelation: dangerous**

The strongest evidence and recommendations that these guidelines give are actually negative ones *against* chelation therapy in autism, the American Association of Pediatrics<sup>5</sup> and the New Zealand Ministry of Health<sup>4</sup> stressing on the serious risks of renal damage and mortality apart from the evidence against its effectiveness in autism in all of the four guidelines which address the issue. (2011 USA AHRQ<sup>3</sup>, 2008 New Zealand<sup>4</sup>, 2007 AAP<sup>5</sup> and 2006 Spain<sup>7</sup>).

Biomedical approaches advocate the use of intravenous or oral chelation therapy on the purported basis that heavy metal poisoning due to mercury is a cause of the symptoms of autism.<sup>14</sup> There is no evidence to support this claim, nor the association of mercury and thiomersal in vaccines and the development of autism.<sup>5</sup> The 2010 Childhood Autism Risks from Genetics and Environment CHARGE study, showed no difference in total blood mercury levels in 249 children with autism compared to 143 controls.<sup>15</sup> Chelation therapy is licensed by the FDA for *lead* poisoning but not for mercury poisoning.<sup>16</sup> The FDA strongly cautions against the use of chelation therapy for unapproved indications like autism, in view of the risks of "dehydration, kidney failure and even death".<sup>17</sup> Three deaths have been reported in the USA, associated with hypocalcaemia from chelation therapy.<sup>18</sup> One of these children was a 5 year old child being treated with intravenous EDTA for autism. In 2008 the US National Institute of Mental Health (NIMH) actually withdrew its support for a study on chelation in view of the absence of clear evidence of the effectiveness of chelation and its associated risks.<sup>19</sup> Two years later the FDA also warned against over-the-counter chelating agents being sold on-line.<sup>17</sup>

### **Secretin: ineffective**

Secretin is the single most biomedical therapy which has consistently been reported to show *no* effectiveness in autism and have recommendations *against* its use throughout all eight available

authoritative guidelines. The senior author of the last guidelines published, those of the US AHRQ feels that "this is the final word"<sup>20</sup> on the ineffectiveness of secretin. After anecdotal reports of its use and its popularity amongst biomedical practitioners it has been extensively studied and found to be ineffective in autism. There is criticism that this illustrates how so much effort and resources may be spent by individual families as well as the medical community on an approach which in the end proves to be ineffective.

### ***Melatonin for sleep difficulties***

The latest four guidelines published, generally report relatively good support for the use of melatonin to alleviate sleep disturbances in children with autism.<sup>3,4,5,6</sup> In fact, this seems the only biomedical approach to be supported by mainstream medical literature as well as being strongly promoted by biomedical practitioners.<sup>21</sup> Children with ASD have been reported to show abnormalities of melatonin regulation.<sup>22,23</sup> Melatonin has been shown to be effective in improving onset of sleep in children with neurodevelopmental disabilities in general<sup>24,25</sup> and specifically in those with ASD.<sup>26</sup> However, the effect size may not be as appreciable as some claim. In 2011 the 'Melatonin for sleep disturbance in neurodevelopmental disorders' study, MENDS, reported that children (who included those with autism) given melatonin at bedtime slept from as little as 15 minutes to 60 minutes longer than their controls.<sup>27</sup> It is usually recommended after behavioural approaches to sleep disturbance have been introduced and failed. Though unlicensed for children, the British National Formulary for Children (BNFC) suggests that clinical experience indicates it may be of value, cautioning that it should be started and monitored by a specialist with the need to continue medication being reviewed every 6 months - the long-term circadian and hormonal effects being undefined.<sup>28</sup> The Martindale cites a report that there may be increased seizure activity when on melatonin,<sup>29</sup> and that it is not to be used in hepatic impairment.<sup>30</sup> Being an unlicensed medication the information that is available about its effectiveness and safety is limited.<sup>4</sup>

### ***Gluten/casein-free GFCF diets: Difficult to establish effectiveness in autism***

None of the guidelines supported the use of these diets in autism: four state that there is no evidence/recommendation for or against these diets, another four presenting evidence/recommendations against (Table 1).

A Cochrane review in 2008<sup>31</sup> had concluded that the current evidence was poor and called on the need for good quality RCTs (random controlled trials). A 2009 review by Mulloy A et al concluded that "the current corpus of research does not support the use of GFCF diets in the

treatment of ASD" (Autism Spectrum Disorders).<sup>32</sup> Controlled dietary studies are generally difficult and expensive to carry out. There were two such studies in 2010: The ScanBrit study published by Whiteley was a randomised controlled, single-blind study suggesting that "dietary intervention may positively affect developmental outcome for some children diagnosed with ASD." However, the paper acknowledges the limitation of the study "in the absence of a placebo condition."<sup>33</sup> The second study in 2010 was presented at the 9<sup>th</sup> Annual International Meeting For Autism Research (IMFAR) by Hyman S and Stewart PA.<sup>34</sup> It was a well-controlled double blind, placebo controlled challenge study using gluten and casein free diets. After a strict GFCF diet for 4 weeks preschool autistic children were given weekly challenges of wheat or milk, both, or neither over 12 weeks, the challenges being identical in taste and texture. There were 14 successful participants. There were no statistically significant changes in objective and parent/teacher/observer outcomes. Though the sample size was small it was well-controlled.

These diets may be associated with decreased bone mass and inadequate vitamin D, calcium and protein intake and thus merit monitoring.<sup>35</sup>

### ***Omega-3 fatty acids: some limited evidence***

Evidence, albeit limited, is presented by the two last US guidelines (2011 AHRQ, 2007 AAP) to support the use of Omega-3 fatty acids.<sup>3,5</sup> The 2008 New Zealand guideline reports that omega-3 fatty acids are unlikely to be useful.<sup>4</sup> The former guidelines refer to a sound pilot RCT of omega-3 fatty acids supplementation in children with autism which indicated a small, non-significant trend towards benefit in the hyperactivity and stereotypy subscales.<sup>36</sup> A similar effect on hyperactivity was also reported in another recent pilot RCT.<sup>37</sup> It is concluded that there is some early promise for future research in the use of omega-3 fatty acids in autism. However, the consensus is that there is a need for large well-conducted randomised controlled trials that examine both high and low functioning individuals with ASD, and that have longer follow-up periods.<sup>38</sup>

### ***Vitamin B6 and magnesium: limited evidence for***

All eight guidelines address this biomedical approach. The 2011 AHRQ and 2004 Australian guidelines present some limited evidence to support this.<sup>3,8</sup> The 2008 New Zealand and 2007 Scottish guidelines give no recommendations against or in favour,<sup>4,6</sup> while the other four give evidence/recommendations against their use in

autism.<sup>5,7,9,10</sup> Megadoses of Vitamin B6 (>100mg/day) may cause neuropathy.<sup>35,39</sup>

### **Other approaches which are not recommended in view of lack of evidence of effectiveness**

#### ***Immunoglobulin treatment***

Only the 2007 AAP guideline indicates that there is no recommendation for or against this treatment.<sup>5</sup> Five other guidelines are against with the 1999 New York State Department of Health guideline strongly recommending against in view of the absence of evidence showing effectiveness, and the associated risks of transmitting blood born infections.<sup>3,4,7,9,10</sup>

#### ***Anti-fungal/yeast treatment***

Though the 2003 Canadian guidelines had no recommendation for or against anti-fungal treatment four other guidelines including the 2007 AAP ones recommend against its use in autism.<sup>9,5,7,8,10</sup>

#### ***Amantadine (antiviral), dimethylglycine (neuroinhibitor), naltrexone (opioid antagonist)***

These have been addressed by four of the guidelines and recommendations are against their use.<sup>3,4,5,6</sup>

#### ***Vancomycin, peptizyde (digestive enzyme supplement) and donepezil (cholinesterase inhibitor)***

These have only been addressed by single guidelines, with negative recommendations.<sup>6,3</sup>

#### ***Vitamin C, piracetam (with risperidone), pentoxifylline (with risperidone), L-carnosine (dipeptide) and ketogenic diets***

There is limited/weak evidence for the above treatment presented mainly in the latest 2011 AHRQ guideline.<sup>3</sup> The vitamin C evidence was reported in the 2007 AAP guideline document.<sup>5</sup>

#### ***Autism is not an acceptable indication for hyperbaric oxygen treatment***

Some evidence for the effectiveness of hyperbaric oxygen was reported in the latest 2011 AHRQ guidelines.<sup>3</sup> They refer to the study by Rossignol DA et al in 2009.<sup>40</sup> This was a multicenter, randomized, double-blind, controlled trial reporting significant improvements in overall functioning, receptive language, social interaction, eye contact, and sensory/cognitive awareness. The study has been criticized for conflicts of interest and basic scientific issues.<sup>41</sup> A review of this paper and three case series by the Undersea and Hyperbaric Medical Society (UHMS) again criticised the methodology of Rossignol's paper, suggested the need for replication, and could not recommend the routine treatment of autism using this

modality.<sup>12</sup> The UHMS indications are those upheld by the FDA.<sup>42</sup> Rossignol's results could not be replicated by Granpeesheh's randomized, double-blind placebo controlled trial in 2010,<sup>43</sup> nor could the effectiveness of this treatment be established by trials in 2011 by Jepson and Granpeesheh<sup>44</sup> and Bent S, Bertoglio K, et al.<sup>45</sup> In June 2011 the European Committee for Hyperbaric Medicine (ECHM) updated its 2010 recommended indications for hyperbaric oxygen by weighing the current clinical evidence: It has maintained that hyperbaric oxygen therapy is not indicated in autism.<sup>11</sup>

### ***Conclusion and recommendations***

It is felt that none of the evidence and recommendations found throughout the above literature review *strongly* support any of the biochemical approaches. Except for risperidone and aripiprazole none of the medical and biomedical medications, therapies or supplements are licensed for use in children with autism.

In considering the application of biomedical treatments for autism the following recommendations are being forwarded:

1. Melatonin may be considered in children with autism with sleep disturbance unresponsive to behavioural approaches alone.
2. Omega-3 supplementation may be considered especially in autistic children who are hyperactive.
3. All doctors caring for children with autism should be aware that these children may be on gluten/casein-free diets and be able to monitor possible nutritional deficiencies and their effects, and advise accordingly.
4. Vitamin B6 and magnesium supplementation should be avoided.
5. Iron, vitamin C, piracetam (as an add-on to risperidone), pentoxifylline (as an add-on to risperidone), ketogenic diets, L-carnosine are not recommended.
6. Secretin, chelation, immunoglobulin, amantadine, antifungal/yeast therapies, naltrexone, dimethylglycine, vancomycin, digestive enzyme supplements and donepezil are strongly *not* recommended and should be discouraged. Chelation and immunoglobulin therapy are particularly *not* recommended in view of the risks associated with them.
7. Hyperbaric oxygen therapy in autism is not effective and should not be recommended.
8. Paediatricians, family doctors and other medical professionals should be aware of the various biomedical therapies which parents of children

with autism may be interested in, and have an understanding of the scientific evidence in favour of or against such approaches.

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