Current treatments and therapies for Autism

Autism spectrum disorders (ASD) are reaching epidemic proportions. Autism is characterized by abnormalities in social interaction, impaired verbal and nonverbal communication, and repetitive, obsessive behaviour. Autism may vary in severity from mild to disabling and is believed to arise from genetic and environmental factors. While symptomology of Autism may be noted by caregivers around 12–18 months, definitive diagnosis generally occurs around 24–36 months.

Determination of Autism is performed using the DSM-5 or other questionnaires and tests.

Current treatments for Autism can be divided into behavioural, nutritional and medical approaches, although no clear golden standard approach exists. Behavioural interventions usually include activities designed to encourage social interaction, communication, awareness of self, and increase attention. Nutritional interventions aim to restrict allergy-associated dietary components, as well as to supplement minerals or vitamins that may be lacking.

Medical interventions usually treat specific activities associated with Autism. For example, serotonin reuptake inhibitors (SSRI's) such as fluoxetine, fluvoxamine, sertraline, and clomipramine, are used for treatment of anxiety and depression. Some studies have shown that SSRI's also have the added benefit of increasing social interaction and inhibiting repetitive behaviour. Typical antipsychotic drugs such as thioridazine, fluphenazine, chlorpromazine, and haloperidol have been showed to decrease behavioural abnormalities in Autism. Atypical antipsychotics such as risperidone, olanzapine and ziprasidone have also demonstrated beneficial effect at ameliorating behavioural problems. Autism associated seizures are mainly treated by administration of anticonvulsants such as carbamazepine, lamotrigine, topiramate, and valproic acid. Attention deficient/hyperactivity is treated by agents such as methylphenidate.

1. Stem Cell Therapy in Autism

Current hypothesis behind possible use of stem cell therapy in ASDs (in future):

1. **Administration of CD34+ umbilical cord cells and mesenchymal cells:**

   Children with Autism have been consistently shown to have impaired CNS perfusion. Defects include basal hypoperfusionand decreased perfusion in response to stimuli that under normal circumstances upregulates perfusion. In numerous studies the areas affected by hypoperfusion seem to correlate with regions of the brain that(those) are responsible for functionalities abnormal in Autism. For example temporal lobe areas associated with face recognition, social interaction and language comprehension; have been demonstrated to be hypoperfused in autistic but not control children.

   Therapeutic angiogenesis, the induction of new blood vessels from pre-existing arteries for overcoming ischemia, has been experimentally demonstrated in peripheral artery disease, myocardial ischemia, and stroke.

   There is one ongoing clinical trial in ASDs patients, investigators are looking for similar benefits in regional hypoperfusion recovery, immunoregulation and anti-inflammatory

benefits of Mesenchymal stem cell transplant.

2. **Neural Stem Cells (NSC) / Embryonic Stem Cell:** There are three main sources of human stem cells for neurotherapy: the brain itself, bone marrow or cord blood and preimplantation embryo. Neural stem cells have clone forming ability, self -renewal capacity and multipotency can be isolated from foetal, neonatal and adult human brain. Difficultiesare:
    - Survival of transplanted cells in vivo
    - Migration of stem cellsto area of injury
    - Delineation into required cell type
    - Tumour formation

3. **Induced Pluripotent Stem Cells(iPSC):**
   The derivation of iPSC from specific individuals and their differentiation into neural cells provides the first opportunity to correlate individual genetic variation with patterns of gene expression and specific processes of neurodevelopment. Immediate and long-term goals are to use iPSCs to understand aspects of the neurobiology of neuropsychiatric disorders and their genetics on the individual patient level, as well as develop novel diagnostic tools and pharmacological interventions.

Research suggests that immunological processes may play a role in the etiology/ cause of Autism. However, current knowledge does not support the use of stem cell therapy as a treatment modality at this time. Here is an additional reference:
International Society of Stem Cell Research:
http://www.sciencebasedmedicine.org/index.php/cracking-down-on-stem-cell-tourism/

References:

- *Charles Arber andMeng Li "Cortical interneurons from human pluripotent stem cells: prospects for neurological and psychiatric disease" Frontiers in Cellular Neuroscience; www.frontiersin.org; March 2013 | Volume 7 | Article 10*
- *"China's stem-cell rules go unheeded" Health ministry's attempt at regulation has had little effect. 12 APRIL 2012 | VOL 484 | NATURE | 149*
- *Diseases"Guo-Li Ming, Oliver Bru¨stle "Cellular Reprogramming : Recent Advances in Modeling Neurological The Journal of Neuroscience, November 9, 2011 • 31(45):16070 –16075*
- *Flora M. Vaccarino, Hanna E. Stevens, ArifKocabas "Induced pluripotent stem cells: a new tool to confront the challenge of neuropsychiatric disorders" Neuropharmacology. 2011 June ; 60(7-8): 1355–1363. doi:10.1016/j.neuropharm.2011.02.021.*
- *Flora M. Vaccarino, Alexander Eckehart Urban "The promise of stem cell research for neuropsychiatric disorders" J Child Psychol Psychiatry. 2011 April ; 52(4): 504–516. doi:10.1111/j.1469-7610.2010.02348.x.*
- *Philip H Schwartz "The potential of stem cell therapies for neurological diseases" Expert Review of Neurotherapeutics, February 2006, Vol. 6, No. 2 : Pages 153-161 Read More: http://informahealthcare.com/doi/pdf/10.1586/14737175.6.2.153*

- *Siniscalco D, Sapone A, Cirillo A, Giordano C, Maione S, Antonucci N. Autism spectrum disorders: is mesenchymal stem cell personalized therapy the future? J Biomed Biotechnol. 2012.*
- *Careaga M, Van de Water J, AshwoodP(2010). Immune dysfunction in Autism: a pathway to treatment. Neurotherapeutics. 2010 Jul;7(3):283-92.*
- *Michael G. Chez* and Natalie Guido-Estrada (2010)Immune Therapy in Autism: Historical Experience and Future Directions with Immunomodulatory Therapy. Neurotherapeutics: The Journal of the American Society for Experimental NeuroTherapeutics.*
- *Ghanizadeh A. c-Kit+ cells transplantation as a new treatment for Autism, a novel hypothesis with important research and clinical implication. J Autism DevDisord. 2011 Nov;41(11):1591-2.*
- *Ichim TE, Solano F, Glenn E, Morales F, Smith L, Zabrecky G, Riordan NH. Stem cell therapy for Autism. J Transl Med. 2007 Jun 27;5:30.*
- *Stéphane D. Girard. Arnaud Devéze, Emmanuel Nivet, Bruno Gepner5, François S. Roman, François Féron; Isolating Nasal Olfactory Stem Cells from Rodents or Humans. Journal of Visual Experiments; August 2011 | 54 | e2762 | Page 2 of 5*

2. Hyperbaric Oxygen Therapy (HBOT) in Autism

Hyperbaric oxygen therapy (HBOT) is suggested for treating some medical problems, such as air or gas embolism, carbon monoxide poisoning, intracranial abscess, and radiation injury; however, its mechanism of action is not clear. It is suggested that HBO increases the production of reactive oxygen species. Moreover, HBO is a safe intervention and middle ear barotraumas is one of its common adverse effects.

Autism is a complex neurodevelopmental disorder with an increasing prevalence which is characterized by three main symptoms, including impairments in socialization and communication, restricted interests, and repeated behaviours. Meanwhile, there is no curative treatment for Autism. Moreover, there are only two Food and Drug Administration (FDA) approved medications, including risperidone and aripiprazole for managing its symptoms. In recent years, HBO is investigated as an alternative treatment for Autism. Early uncontrolled studies reported the efficacy of HBO therapy. However, the results of later controlled-studies are controversial.

There are many reports about the possible role of neuro-inflammation in Autism. This neuro-inflammation can be a possible target for the treatment of some cases with Autism. Besides, the regional cerebral blood flow is decreased in the bilateral frontal lobe, temporal, limbic system, and basal ganglia in Autism spectrum disorders. Moreover, it is proposed that HBO may improve the cerebral hypoperfusion and decrease brain inflammation as well as oxidative stress in Autism.

Systematic review of two randomized and 7 non-randomized studies suggest that the results supporting the efficacy of HBO therapy are not replicated and further studies with rigorous methodology is required.

There is one controlled evaluation study of three children given HBOT. It was concluded that the form of HBOT provided to these participants did not improve task engagement or decrease

problem behaviour beyond that provided by ongoing behaviour analytic services. HBOT also was not associated with changes in spontaneous communication for two of the three participants. It was further added that research is needed to determine if HBOT is a viable treatment for Autism. A more intensive form of this therapy (e.g., higher oxygen concentrations, larger numbers or durations of dives) may produce beneficial outcomes.

One multicenter, randomized, double blind, controlled trial on 62 children (33 in treatment group and 29 controls) favours HBOT. In this study children with Autism who received hyperbaric treatment at 1.3 atm and 24% oxygen for 40 hourly sessions had significant improvements in overall functioning, receptive language, social interaction, eye contact, and sensory/cognitive awareness compared to children who received slightly pressurized room air.

References:

- *"Hyperbaric oxygen therapy for treatment of children with Autism: a systematic review of randomized trials". Ahmad Ghanizadeh Ghanizadeh Medical Gas Research 2012, 2:13 http://www.medicalgasresearch.com/content/2/1/13*
- *"Using Behaviour Analysis to Examine the Outcomes of Unproven Therapies: An Evaluation of Hyperbaric Oxygen Therapy for Children with Autism " Dorothea C. Lerman, Ph. D., TesaSansbury, Behaviour Analysis in Practice, 1(2), 50-58. 10/10/2008*
- *"The effects of hyperbaric oxygen therapy on oxidative stress, inflammation, and symptoms in children with Autism: an open-label pilot study " Daniel A Rossignol, Lanier W Rossignol, S Jill James. BMC Pediatrics2007, 7:36 doi:10.1186/1471-2431-7-36*
- *Research article "Hyperbaric treatment for children with Autism: a multicenter, randomized, double-blind, controlled trial " Daniel A Rossignol, Lanier W Rossignol, Scott Smith. BMC Pediatrics2009, 9:21 doi:10.1186/1471-2431-9-21*

3. Dietary Therapy in Autism

- Gluten and casein free diet (GFCF):

Dietary intervention as a tool for maintaining and improving physical health and wellbeing is a widely researched and discussed topic. It has been suggested that a gluten-free (GF), casein-free (CF), or gluten- and casein-free diet (GFCF) can ameliorate core and peripheral symptoms and improve developmental outcome in some cases of Autism spectrum conditions. The majority of published studies indicate statistically significant positive changes to symptom presentation following dietary intervention. In particular, changes to areas of communication, attention, and hyperactivity are detailed, despite the presence of various methodological shortcomings.

Meta-analyses of the specific findings of the various trials of such dietary intervention for ASDs published in the peer reviewed scientific literature have been summarized by several authors (Knivsberget al., 2001; Mulloy et al., 2010, 2011) including the Cochrane Library of Systematic Reviews (Millwardet al., 2008). The main conclusions from such meta-analyses suggest

caution in the universal adoption of GFCF dietary intervention for ASCs whilst stressing the need for further controlled research to ascertain any significant effect. A thorough examination of the individual evidence included in these texts is beyond the scope of this document. Several pertinent and additional studies published after the Cochrane review (post-2009) do, however, necessitate further description.

One of the RCTs (ClinicalTrials.gov NCT00614198) published in 2010 (Whiteley*et al., 2010*) popularly known as "ScanBrit" used an adaptive study design responsive to intermediate analysis of results (a "drop-the-loser" design) to analyze any dietary effect (n = 72). The main findings indicated statistically significant changes to both core and peripheral behaviours in the diet group in the first 12 months of study followed by indications of a plateau effect of diet following 12 months further study. Results also indicated a substantial degree of variability in individual response to intervention.

Taking the various studies of GFCF diet into account, reported positive effects can be broadly categorized into several areas to include core Autism and peripheral symptoms:

- *Communication and use of language (Knivsberg**et al., 1990, 1995, 2002; Lucarelli et al., 1995; Whiteley et al., 1999, 2010a; Johnson et al., 2011).*
- *Attention and concentration (Knivsberg**et al., 1990, 1995, 2002; Lucarelli et al., 1995; Whiteley et al., 1999, 2010a).*
- *Social integration and interaction (Knivsberg**et al., 1990, 1995, 2002; Whiteley et al., 1999, 2010a).*
- *Self-injurious behaviour/altered pain perception (Knivsberg**et al., 1990, 1995; Lucarelli et al., 1995; Whiteley et al., 1999).*
- *Repetitive or stereotyped patterns of behaviour (Knivsberg**et al., 1990, 1995, 2002).*
- *Motor co-ordination (Knivsberg**et al., 1990, 1995; Whiteley et al., 1999).*
- *Hyperactivity (Whiteley**et al., 2010a; Johnson et al., 2011).*

There is a continued requirement for further study on the potential role of dietary intervention for ASDs. Future controlled trials including blinded and placebo elements are necessary carrying appropriate power of study by sample size and duration.

Based on the significant heterogeneity present in ASDs and the likelihood of various "Autisms" manifesting similar presentation, further thought should also be given to the concept of best and non-responders to this type of intervention. So for example, (1) screening for GI and/or potentially relevant pathogenic comorbidity, (2) measuring gut hyperpe-meability, (3) examining gut microbial populations and food-related enzyme activities, and (4) ascertaining the presence of inflammatory processes, either peripherally in GI tissue or more centrally, might all be included as parameters for future dietary investigations.

Strength of the evidence for other supplements:

Grade A (randomized controlled trials, reviews and/or meta-analyses)

Grade B (other evidence such as isolated well-designed controlled and uncontrolled studies)

Grade C (case reports or theories)

This grading refers to the strength of the evidence; evidence that supports or refutes the use of the intervention.

Dietary supplements

B6/Magnesium (Mg) - (Grade B)

Vitaminsupplements to improve symptoms of mental health disorders have been in use for over 50 years with B6 and Magnesium a popular treatment for Autism over the past 20 years. This treatment has been the subject of reviews by several authors. Due to the small number of studies, methodological deficits, small sample sizes meta-analysis could not be done and the evidence was not adequate to support use of this supplement.

The most recent Cochrane Review identified three studies completed between 1993 and 2002 which compared outcomes to either placebo or non-treated group. A total of 28 subjects were treated in these trials. Findling and colleagues studied 12 participants using a randomized, double blind placebo-controlled trial following a 2 weekpre-randomization placebo lead in period. No effects of treatment were seen in the 10 subjects who completed the study. More recently Kuriyamaand colleagues reported improvement in IQ and social quotient scores in 8 children treated with B6 and Mg. Despite the fact that these studies met criteria for Cochrane review, they all suffered from significant methodological weaknesses, including inadequate description of diagnosis and selection criteria and outcome measures. One additional study with similar methodological issues has been published since this review, describing an open study of 33 children with ASD who were reported to improve in symptoms after Mg-B6 treatment.

DMG - Grade B—Dimethylglycine (DMG) and a related compound, trimethyl glycine (TMG), are commonly used nutritional supplements. An older case series suggested improvement in language and attention in a group of children with intellectual disability treated with DMG. Two small, double blind studies of DMG have not demonstrated positive effects on symptoms of Autism compared to placebo.

Vitamin C - Grade B—VitaminC is not commonly used as an isolated treatment but is frequently added to vitamin mixtures used by children with ASD. Dolske and colleagues reported positive results of decreased stereotyped behaviour in a 30 week double-blind/ placebo controlled trial in 18 children with ASD. To date this study has not been replicated. Other reports have implicated vitamin C in its role with oxidative stress.

Omega 3 fatty acids - Grade B—Polyunsaturatedfatty acids, in particular Omega 3 fatty acids, are crucial for brain development and cannot be manufactured in the body. Dietary consumption occurs through ingestion of fish or fish oils. Oral supplementation with essential fatty acids has become popular for children with developmental differences including Autism and ADHD. Studies have examined differences in plasma levels of children with Autism which are decreased compared to typical volunteerswithout clinical correlations. Recently, Amminger and colleagues reported improvement in behaviour following a randomized double-blind placebo-controlled 6 week pilot trial of oral supplementation in 13 children with ASD with severe behaviour difficulties. No side effects were noted beyond gastrointestinal symptoms.

Enzyme Supplement

In a Randomized, double-blind placebo-controlled trial, Munasinghe et al (2010), examined the effects of a digestive enzyme supplement in improving expressive language, behaviour

and other symptoms in children with ASD. No clinically significant improvement of Autism symptoms with enzyme was found in this trial.

References:

- *Paul Whiteley1, Paul Shattock, Ann-Mari Knivsberg"Gluten- and casein-free dietary intervention for Autism spectrum conditions". Frontiers in Human Neuroscience www.frontiersin.org January 2013 | Volume 6 | Article 344 | 1*
- *M. Mousain-Bosc, M. Roche, A. Polge. "Improvement of neurobehavioural disorders in children supplemented with magnesium-vitamin B6 II. Pervasive developmental disorder-Autism" Magnesium Research 2006; 19 (1): 53-62 ORIGINAL ARTICLE*
- *James B Adams, TapanAudhya, Sharon McDonough-Means.*
- *Adams et al "Effect of a vitamin/mineral supplement on children and adults with Autism"BMCPediatrics 2011, 11:111 http://www.biomedcentral.com/1471-2431/11/111*
- *Susan E. Levy, M.D. and Susan L. Hyman, M.D."Complementaryand Alternative Medicine Treatments for Children with Autism Spectrum Disorders" Child AdolescPsychiatrClin N Am. 2008 October ; 17(4): 803–ix. doi:10.1016/j.chc.2008.06.004.*
- *Nye C, Brice A. Combined vitamin B6-magnesium treatment in Autism spectrum disorder. Cochrane Database Syst Rev 2005:CD003497. [PubMed: 16235322]*
- *Nye C, Brice A. Combined vitamin B6-magnesium treatment in Autism spectrum disorder. Cochrane Database Syst Rev 2002:CD003497. [PubMed: 12519599] Millward C, Ferriter M, Calver SJ, Connell-Jones GG*
- *"Gluten- and casein-free diets for autistic spectrum disorder" (Review) Copyright © 2009 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.*
- *Williams K, Marraffa C (2012). No evidence yet to support omega-3 fatty acids as a treatment for Autism. J Paediatr Child Health. 2012 Jun; 48(6):534-6.*
- *James S, Montgomery P, Williams K (2011). Omega-3 fatty acids supplementation for Autism spectrum disorders (ASD). Cochrane Database* ***Syst Rev.*** *2011 Nov 9;(11).*
- *Munasinghe SA, Oliff C, Finn J, Wray JA (2010). Digestive enzyme supplementation for Autism spectrum disorders: a double-blind randomized controlled trial. J Autism DevDisord. 2010 Sep;40(9):1131-8.*

4. Yoga in Autism

Yoga - Grade C

Decreasing anxiety through nonpharmacologic techniques has great attraction to both families and clinicians. Yoga is a mind-body approach that enjoys popular practice for increasing the sense of wellbeing and control with the potential to decrease anxiety. A trial of yoga for symptoms of ADHD was underpowered to demonstrate effect, but suggested some benefit in children on medication. Relaxation therapy decreased symptoms of anxiety in inpatients with anxiety on a child psychiatry service and in children with mental retardation. No studies have yet been published related to symptoms of Autism and response to yoga techniques.

- *"Complementary and Alternative Medicine Treatments for Children with Autism*

Spectrum Disorders" Susan E. Levy, M.D. and Susan L. Hyman, M.D. Child AdolescPsychiatrClin N Am. 2008 October ; 17(4): 803–ix. doi:10.1016/j.chc.2008.06.004.

Only one study (Indian):

- *ShanthaRadhakrishna. Application of integrated yoga therapy to increase imitation skills in children with Autism spectrum disorder. Int J Yoga.2010 Jan-Jun; 3(1): 26–30. PMCID: PMC2952122 doi: 10.4103/0973-6131.66775*

Parents and six children with ASD participated in a 10-month program of 5-weekly sessions and regular practice at home. Pre, mid and post treatment assessments included observers and parent ratings of children's imitation skills in tasks related to imitation skills such as gross motor actions, vocalization, complex imitation, oral facial movements and imitating breathing exercises.

Results:

Improvement in children's imitation skills, especially pointing to body, postural and oral facial movements. Parents reported change in the play pattern of these children with toys, peers and objects at home.

Conclusions:

This study indicates that Yoga Therapy may offer benefits as an effective tool to increase imitation, cognitive skills and social-communicative behaviours in children with ASD. In addition, children exhibited increased skills in eye contact, sitting tolerance, non-verbal communication and receptive skills to verbal commands related to spatial relationship.

5. AUTISM-TREATMENT OPTIONS (Supplements)

In present scenario only risperidone (atypical antipsychotic) is approved by FDA for use in Autism.Rossignol DA et al have conducted a systemic review on novel and emerging treatments in Autism and grade them according to the evidence till date.

Grade¶	**Treatment options**¶
Grade A (supported by least 2 prospective randomized controlled trials (RCTs) or 1 systematic review)	melatonin, acetylcholinesterase inhibitors, naltrexone, and **music** therapy.
Grade B (Supported by at least 1 prospective RCT or 2 nonrandomized controlled trials.)	Carnitine, tetrahydrobiopterin, vitamin C, alpha-2 adrenergic agonists, oxytocin, hyperbaric oxygen treatment, immunomodulation and anti-inflammatory treatments, , and vision therapy
Grade C	

(Supported by at least 1 nonrandomized controlled trial or 2 case series)	Carnosine, multivitamin/mineral complex, piracetam, polyunsaturated fatty acids, vitamin B6/magnesium, elimination diets, chelation, cyproheptadine, famotidine, glutamate antagonists, acupuncture, auditory integration training, massage, and neurofeedback.

¶*RossignolDA,Novel and emerging treatments for Autism spectrum disorders: a systematic review,AnnClin Psychiatry. 2009 Oct-Dec;21(4):213-36.*

Complementary and Alternative medicine (CAM):-

Complementary and alternative medicine is defined by the National Center for Complementary and AlternativeMedicine (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).
Although current data is insufficient to make guidelines but Paediatricians and other healthcare professionals need to be aware and to help families negotiate the many available CAM treatments and make decisions based on current safety and efficacy data.CAM treatments used in ASD are organized by NCCAM in following classification domains

- Mind-body therapies
- Biologically based therapies
- Manipulative and body based therapies
- Energy medicine
- Whole medicine systems.

Melatonin.-Rossignol and Frye published a review and meta-analysis of 35 studies.Unfortunately, small sample sizes, variability in sleep assessments, and lack of follow-up limit the conclusivenessof these studies but, overall, melatonin is one of the best studied CAMs for ASD.Short term release products are recommended for children with difficulty initiating sleep and long-term releaseproducts recommended for children with difficulty maintaining sleep. Melatonin appears well toleratedupto 7.5mg dose.

Vitamin B6 and Magnesium(Mg)
The evidence for B6 and Mg from over 25 studies remains rather equivocal, a bit more positive than negative. Open studies are with more positive outcomes but RCTs failed to produce similar results.Daily doses of B6 should not go beyond a gram and those of Mg beyond 300 g. higher doses risk neuropathy from B6 or diarrhoea from Mg.

Methyl B12
Use is based on indications of impaired methylation in a subset of children with ASD.Only one RCT published regarding use of methyl B12 in Autism showing response to methyl B12 of a subgroup of children with Autism in terms of behavioural scores but on statistical difference in terms of GSH(Gluathione) concentrations.

Multivitamin/Mineral Supplements
Although being used widespread, there is limited evidence for the efficacy of vitamin and mineral supplements for ASD. The promising results from the open label and twoRCTswarrant larger, placebo-controlled RCTs with pre- and post-measures of vitamin, mineral, and metabolic status. It is recommended for those with a restricted or idiosyncratic diet and those with poor appetite, and is acceptable for all others.

Folic Acid
Folic acid has been considered because a polymorphism in the gene for methylenetetrahydrofolatereductase(MTHFR C677T) doubles the risk of Autism. An open trial of folinic acid and B12 in children with ASD and antibodies to the cerebral folate receptor showed significant improvement in receptive and expressive language. It is not clear whether folate or folinate would be the preferred supplement or whether adjunctive B12 is needed.In view of lack of evidence if it is tried then one should monitor closely for possible unexpected side effects.

Probiotics and GI Medication
There is increasing evidence for a gut-brain connection associated with at least some cases of ASD. A double-blind placebo-controlled trial using crossover design over 6 months for 43 children with ASD, aged 3–8years did not show any clinically significant improvement of ASD symptoms with enzyme use. While there is no published evidence that probiotics or digestive enzymes are effective in treating ASD, their use for treating GI symptoms and their safety profile suggest that they might be considered in treating ASD individuals with GI symptoms.

Iron Supplementation
Iron supplementation is safe and sensible for those ASD children with low serum ferritin, easy and cheap, and is therefore recommended for this subgroup. It also would be reasonable to screen children with ASD for iron insufficiency. At the current state of knowledge; it should not be used above the RDA amount without evidence of low iron.

L-Carnosine
L-Carnosine has been considered neuro-protective or improve function of frontal lobes. In an 8-week double-blind RCT with 31 children aged 3–12 with ASD, l-carnosine (800 mg/day) but not placebo showed statistically significant improvements on the Gilliam Autism Rating Scale.Hyperactivity and excitability were the main side effects. This is the only study of l-carnosine for the Tx of Autism. It would be towards the bottom of a preference list and if tried, it should be monitored closely.

Ascorbic Acid.
One RCT not yet replicated is suggesting reduced stereotyped behaviours in ASD; there have been reports of scurvy in children with ASD from restricted dietary intake. Due to this safety issue (as well as efficacy) ascorbicacid in these megadoses requires further study, currently is not recommended.

Immune Therapies
Currently there are six published open-label trials of IVIG Tx with ASD.They showed mixed and inconclusive reports of their effects in ASD. Therefore, IVIG therapy is not recommended

for the Tx of ASD. Other immune boosting therapies may be of benefit but have not been adequately studied.

6. CHELATION

Chelation is a process for removing heavy metals from the blood and is used in treating ASD based on the unproven theory that ASD is caused by heavy metal toxicity. The accumulation of heavy metals, particularly mercury, is theoretically due to either the body's inability to clear the heavy metals or to increased exposure or both.Two studies have been published involving 65 children with ASD who received one round of DMSA (3 days) and based on those who had high urinary excretion of toxic metals, 49 were randomly assigned to a double-blind design to receive either 6 additional rounds of DMSA or placebo. DMSA was reportedly well tolerated and resulted in high excretion of heavy metals, normalization of red blood cell glutathione, and possibly improved ASD symptoms.However, excretion of heavy metals and improvement only occurred after one round of DMSA with the additional six rounds being no better than placebo.Clearly, further studies, including randomized, placebo-controlled trials, are indicated to confirm these results.
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. Most common side effects are diarrhoea and fatigue. Less common side effects includemineral abnormalities, seizures, sulphur smell, regression, GI symptoms and rash. Therefore, we only recommend chelation for ASD if heavy metal toxicity is confirmed.The Food and Drug Administration has recently warned consumers that many chelating agents being currently marketed were developed for industrial use andhave never been tested in humans or animals.

7. MUSIC THERAPY

Currently one of the most sought emerging and one of the promising harmless treatment option for ASD individuals. It has multisystem effects almost improving all the developmental domains performance form improvement in communication and joint attention to refinement of gross and fine motor skills. Following figure is illustrative version of various effects of music therapy.

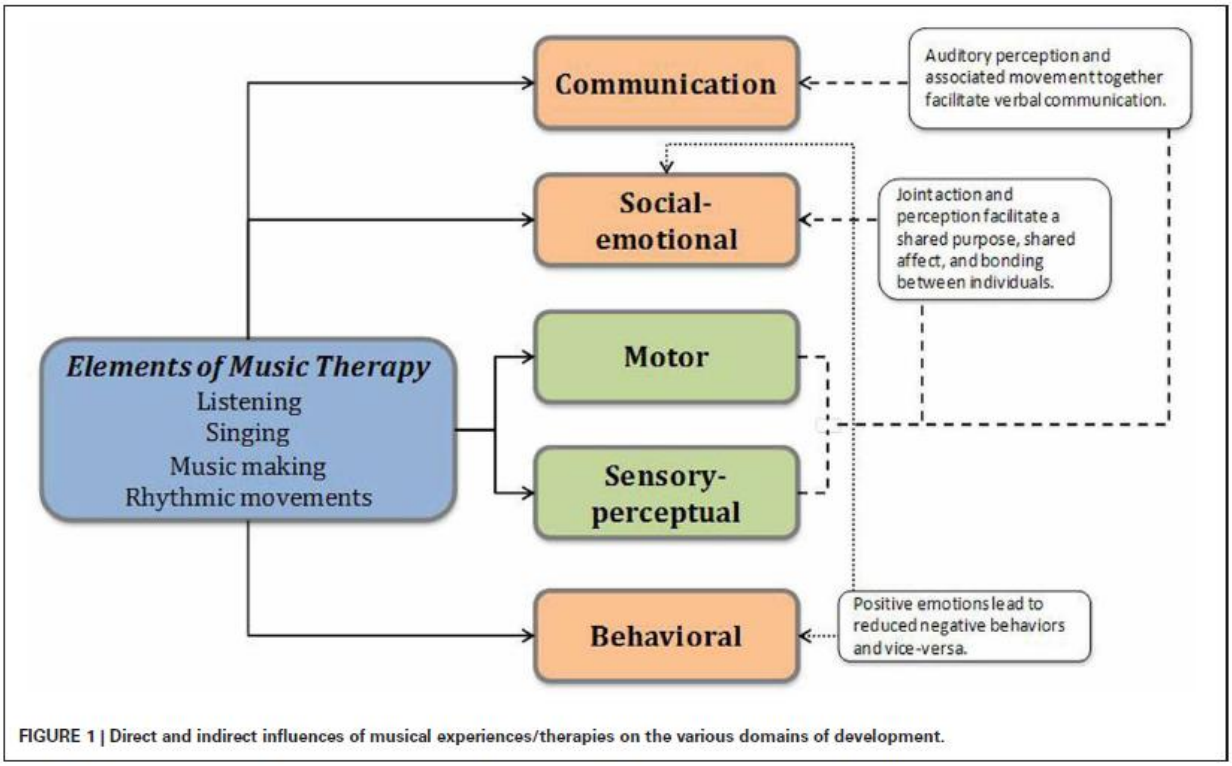

FIGURE 1 | Direct and indirect influences of musical experiences/therapies on the various domains of development.

CURRENT MUSIC THERAPY APPROACHES USED IN CHILDREN WITH AUTISM

Auditory Motor Mapping Training (AMMT) and Melodic Intonation Therapy (MIT)
Facilitate language production in non-verbal/low-verbal children by training an association between self-produced sounds (drum hit or finger tap) and articulatory movements or auditory-motor mapping. Non-verbal children with ASDs demonstrated improvements in their ability to articulate words and phrases following an 8-week intervention of AMMT. (Wan et al., 2011).
MIT which involves singing and associated gross motor tapping to mark the rhythm and stress of the intoned phrases was found to enhance phonation and speech production in children with apraxia (Roper, 2003; Norton et al., 2009).

Rhythm training
The multisensory experience focused on rhythm and timing facilitated the temporal processing skills of children with dyslexia and ASD.

Improvisational music therapy
An individualizedpatient- centered approach to facilitate socialengagement and verbal and non-verbal communication skills in children with ASDs (Kimetal, 2009). In this approach, the therapist uses improvised, shared music-making experiences to tune into thepatient'smusical and non-musical non- verbal behaviours. Such moment-by-moment musical attunement of the therapist to the patient helps develop a medium of communication between the two, which inturn facilitates socialskills such as turntaking, imitation and joint attention as well as verbal communication skills(Kimetal.,2008). This approach has been used to improve social communication skills in children with Autism(Kimetal.,2008,2009).

Evidence
On music therapy there are mainly case studies with only two randomized single-blind, repeated measures, within-subject comparison designs.These studies had a total of 20, 3-to-9

year-olds with ASD, with varied Txpresentations, given 1–20X/week for 1–12 weeks for 30 minutes. Significant results and potential clinical outcomes include improvement in imitating signs and words, longer and more eye contact and turn-taking, joint attention, nonverbal communication,longer and more “joy,” emotional synchronicity, initiating engagement and compliant behaviour. Research on music therapy for ASD lacks evidence-based assessment of ASD, large samples, RCTs, standardized protocols, use of standardTx outcome measures, follow-up. However,it appears safe, seems sensible, easy and cheap and is therefore acceptable and welcome.

Srinivasan and Bhat (2013), reviewed role of music therapy in ASD and found that though there is lack of systematic studies for the assessment and treatment of ASD using music therapy still rhythm-based, multisystem interventions based on singing, music-making, joint action, and social synchrony can be used to modify the social communication deficits and perceptuo-motor and behavioural problems of children with ASDs. Further systematic research is required to prove the effectiveness of music therapy.

In a systematic review, Brown and Jelloson (2012), on music research with children and youth published in peer reviewed journals for the years 1999 through 2009, found that music therapy is effective for social variables.

- *Srinivasan SM, Bhat AN (2013). A review of "music and movement" therapies for children with Autism: embodied interventions for multisystem development. Front IntegrNeurosci. 2013;7:22.*
- *Brown LS, Jellison JA. (2012). Music research with children and youth with disabilities and typically developing peers: a systematic review. J Music Ther. 2012 Autumn;49(3):335-64.*

8. Animal assisted therapy

AAT involves structured and supervised therapeutic interaction with animals(eg Horse riding), which are seen as transitional objects for initial bonding for individuals with ASD before generalizing this attachment to people. Although there are many case studies of AAT, only one RCT till date recently published involving 69, four to thirteen year olds, given AAT (horse riding) 15–60 minutes, 1-3X/week over 12–16 weeks. Reported results included significant improvement in playful mood, focus, awareness of social environment, use of language, social interaction, and motivation to interact with the environment, all of which are hoped to occur with clinical application of AAT for youth with ASD.AAT appears safe (if done under trained supervision) sensible and possibly easy but it may be expensive, so it is therefore potentially acceptable treatment option.

9. Acupuncture

Acupuncture involves the systematic insertion andmanipulation of thin needles into the body, via 400 acupoints, to improve health of body/mind by unblocking the flow of qi (“energy”). For ASD, there are 12 RCTs showing all these types of acupuncture were tolerated by >80%, with few or mild adverse-effects.Reported significant results and, therefore, expected

clinicaloutcomes for this Tx include improvement in attention,receptive language, self-care, language, overall functioning, and communication.

10. Exercise

In children with ASD, exercise may reduce hyperactive and repetitive behaviour through the release of certain neurotransmitters, such acetylcholine, or beta-endorphins. Eight within-subject studies (*N* = 36) compared the benefit of antecedent aerobic exercise (e.g., jogging, rangingfrom 6 to 20 minutes) to nonaerobic exercises antecedents (e.g., academic tasks, walking).Antecedentexercise seems sensible, cheap, safe, and easy and is therefore acceptable, before academics or play, if feasible for the child and setting, particularly those with significant repetitive behaviour.

- *Lofthouse, N. HendrenR , Hurt E, Arnold L. E., and Butter E ,A Review ofComplementary and Alternative Treatments for Autism Spectrum DisordersAutism Research and Treatment Volume 2012, Article ID 87039*
- *SrinivasanS.MandBhat A. N. A review of "music andmovement"therapies for children with Autism: embodied interventions for multisystem development,Frontiers in Integrative Neuroscience, April 2013, Volume7, and Article 22.*
- *AccordinoR.,ComerR.,Heller W.B., Searching for music's potential: A critical examination of research on music therapy with individuals with Autism,Research in Autism Spectrum Disorders 1 (2007) 101–115.*
- *Autism Research Institute. Treatment options for mercury/metal toxicity in Autism and related developmental disabilities: consensus position paper. San Diego: Autism Research Institute, 2005.*
- *Hardy W.M. and LaGasse B.A., Rhythm, movement and Autism :using rhythmic Rehabilitation research as a model for Autism;Frontiers in Integrative Neuroscience,March 2013 ,Volume 7 ,Article 19*

11. PHARMACOLOGICAL TREATMENT

A systematic review by McPheeters et al (2011) on medical treatment supports the benefit of risperidone and aripiprazole for challenging and repetitive behaviours in children with ASDs. But significant adverse effects of these medications may limit their use. Dove et al (2012), in a systematic review also found similar results.

Krishnaswami et al (2011), in systematic review reported no support for effectiveness of secretin for the treatment of ASD symptoms including language and communication impairment, symptom severity, and cognitive and social skill deficits.

Another systematic review by Hurwitz et al (2012), to determine if treatment with tricyclic antidepressants (TCA) improves the core features of Autism, non-core features such as challenging behaviours; comorbid states, such as depression and anxiety; and causes adverse effects. The authors concluded that there was little, limited and conflicting evidence of effect and the side effect profile, and further research is required before TCAs can be recommended for treatment of individuals with ASD.

Loy et al (2012) reviewed eight randomised controlled trials, spanning 2000 to 2008. Out of these, seven assessed risperidone and one assessed quetiapine. Reviewers found that there

is some limited evidence of efficacy of risperidone in reducing aggression and conduct problems in children aged 5 to 18 with disruptive behaviour disorders in the short term. They did not find evidence to support the use of quetiapine for disruptive behaviour disorders in children and adolescents.

Williams et al (2010), reviewed seven RCTs. There is no evidence of effect of specific serotonin receptor inhibitors (SSRIs) in children and emerging evidence of harm. There is limited evidence of the effectiveness of SSRIs in adults from small studies in which risk of bias is unclear.

Summary: There is some evidence that medications may prove useful for the treatment of specific symptoms of Autism, like aggression or difficulty in sleeping. However, there is *no medication that cures Autism.* Most medications also have side effects that need to be carefully considered, and monitored by the child's physician while prescribing them'

- *McPheeters ML, Warren Z, Sathe N, Bruzek JL, Krishnaswami S, Jerome RN, Veenstra-Vanderweele J. A systematic review of medical treatments for children with Autism spectrum disorders. Pediatrics. 2011 May; 127(5).*
- *Dove D, Warren Z, McPheeters ML, Taylor JL, Sathe NA, Veenstra-VanderWeele J. Medications for adolescents and young adults with Autism spectrum disorders: a systematic review. Pediatrics. 2012 Oct;130(4):717-26.*
- *Krishnaswami S, McPheeters ML, Veenstra-Vanderweele J.A systematic review of secretin for children with Autism spectrum disorders. Pediatrics. 2011 May; 127(5):e1322-5.*
- *Hurwitz R, Blackmore R, Hazell P, Williams K, Woolfenden S(2012). Tricyclic antidepressants for Autism spectrum disorders (ASD) in children and adolescents. Cochrane Database Syst Rev. 2012 Mar 14.*
- *Loy JH, Merry SN, Hetrick SE, StasiakK(2012). Atypical antipsychotics for disruptive behaviour disorders in children and youths. Cochrane Database Syst Rev. 2012 Sep.*
- *Williams K, Wheeler DM, Silove N, Hazell P.(2010) Selective serotonin reuptake inhibitors (SSRIs) for Autism spectrum disorders (ASD).Cochrane Database Syst Rev. 2010*