


Biomedical and Vocational Interventions for Adults with Autism

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Integration of Adults with Autism into the Whole of Society
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Primary Care for Adults with ASD

- Individuals' **challenges fall along multiple axes** (spoken language, written communication, performance on daily living activities, need for consistency, sensory sensitivity, emotional regulation)
- Adults with ASD have **increased rates of chronic medical illness**, including epilepsy, GI disorders, feeding and nutritional problems, metabolic syndrome, anxiety, depression, and sleep disturbances
- Group differences in **sociocommunicative ability and school participation** mediated the relationship between ASD and less thriving

GI = gastrointestinal. Nicolaidis C, et al. *Med Clin North Am.* 2014;98(5):1169-1191. Weiss JA, et al. *J Autism Dev Disord.* 2015;[Epub ahead of print].

Physician Perspectives on Providing Primary Medical Care to Adults with ASD

- Challenges to Providing Care
 - **shortage** of medical and non-medical services and providers for youth and adults with ASD
 - **Financial disincentives** (issues of time, reimbursement, and the need for additional staff)
 - **Complexity** of family involvement
 - **Barriers to communicating** with patients during visit
 - **Lack of formal education or training**

Warfield ME, et al. *J Autism Dev Disord.* 2015;[Epub ahead of print].



Autism Comorbidity

ASD Comorbidities

- GI abnormalities (30%–70%)
- Seizure disorder (30%)
- Mental retardation (70% of full syndrome)
- Mitochondrial disorders
- Higher than expected rates of other medical conditions – eczema, allergies, asthma, ear and respiratory infections, headache

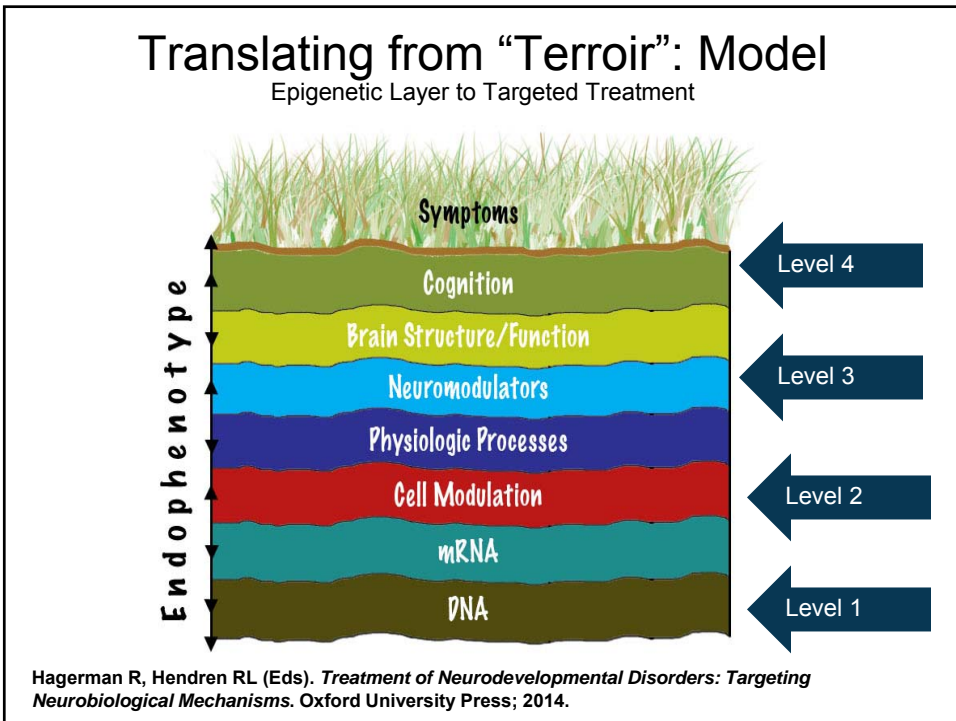
Werner E, et al. *Arch Gen Psychiatry*. 2005;62(8):889-895. Buie T, et al. *Pediatrics*. 2010;125 Suppl 1:S1-S18. Tharp B. In: Ozonoff S, et al (Eds). *Autism Spectrum Disorders: A Research Review for Practitioners*. Arlington, VA: American Psychiatric Publishing, Inc; 2003. Task Force on DSM-IV. *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (Textbook Revision)*. Arlington, VA: American Psychiatric Association; 2000. McDougle CJ, et al. *J Clin Psychiatry*. 2005;66 Suppl:9-18. Frye RE, et al. *Pediatr Res*. 2011;69(5 Pt 2):41R-47R. Kohane IS, et al. *PLoS One*. 2012;7(4):e33224.

ASD Differential Diagnosis or Comorbidity

- ADHD
- OCD
- Tics and Tourette's
- Overanxious Disorder
- Bipolar Disorder
- Depressive Disorder
- Psychotic Disorder
- Aggression – 53% – younger; associated with medical comorbidities

ADHD = attention-deficit/hyperactivity disorder; OCD = obsessive-compulsive disorder. Hendren RL. In: Ozonoff S, et al (Eds). *Autism Spectrum Disorders: A Research Review for Practitioners*. Arlington, VA: American Psychiatric Publishing, Inc; 2003. Mazurek MO, et al. *Res Autism Spectr Disord*. 2013;7(3):455-465.

Autism Interventions



Level-Based Interventions

Level 4 – Behavioral interventions, family support, structure

Level 3-4 – Speech and language, OT, therapy, CBT

Level 2-3 – Pharmacotherapy

Level 2 – Biomedical/epigenetic

Level 1 – Gene modification

CBT = cognitive-behavioral therapy; OT = occupational therapy.

Stimulants and ASD

- Evidence for effectiveness mixed with less information for amphetamines
- Early studies suggest ineffectiveness and poor tolerability
- RUPP – DBPC study of 72 youth using methylphenidate suggest improvement in some, but with lower rates of improvement and more adverse events than in children with ADHD without ASD
- Atomoxetine – small studies suggest improvement, but less than children with ADHD without ASD

– ATX + Parent Training for ASD + ADHD – better side effect profile

RUPP = Research Units on Pediatric Psychopharmacology; DBPC = double-blind, placebo-controlled.

Campbell M. *Biol Psychiatry*. 1975;10(4):399-423. Aman MG. *J Autism Dev Disord*. 1982;12(4):385-398. Research Units on Pediatric Psychopharmacology Autism Network. *Arch Gen Psychiatry*. 2005;62(11):1266-1274. Arnold LE, et al. *J Am Acad Child Adolesc Psychiatry*. 2006;45(10):1196-1205.; Handen et al., JAACAP 2015

SSRIs and Autism

- Serotonin consistently shown to be dysregulated in ASD
- Fluvoxamine and sertraline demonstrate improvement in aggression and social relations
- Retrospective review of 15 children treated with citalopram reported improvement in anxiety and mood in 11 with mild adverse effects in 5
- Perhaps improved language and correlation with family history of affective disorder
- DBPC trial of fluoxetine in adults found significant improvement in repetitive behaviors

*Black Box Warning. SSRI = selective serotonin reuptake inhibitor.
 Cook EH Jr, et al. *Mol Psychiatry*. 1997;2(3):247-250. McDougle CJ, et al. *Arch Gen Psychiatry*. 1996;53(11):1001-1008.
 McDougle CJ, et al. *J Clin Psychopharmacol*. 1998;18(1):62-66. Namerow LB, et al. *J Dev Behav Pediatr*. 2003;24(2):104-108.
 DeLong GR, et al. *Dev Med Child Neurol*. 2002;44(10):652-659. Hollander E, et al. *Neuropsychopharmacology*.
 2005;30(3):582-589. Posey DJ, et al. *J Child Adolesc Psychopharmacol*. 2006;16(1-2):181-186.

Alpha-2 Adrenergic Agonists

- Clonidine – 2 DBPC trials
 - Modest benefit for overactivity, sensory responses, decreased irritability, stereotypy, and oppositional behavior
 - Sedation, fatigue, decreased activity
- Guanfacine
 - retrospective (N = 80), prospective (N = 11)
 - Decreased hyperactivity
 - Sedation, constipation, sleep disruption, irritability
 - Multisite RCT (N=62) ER for 8 weeks; modal dose 3mg
 - 43.6% decline in ABC- Hyperactivity active vs 13.2% placebo
 - CGI-I 50% vs 9.4%

Jaselskis CA, et al. *J Clin Psychopharmacol*. 1992;12(5):322-327. Fankhauser MP, et al. *J Clin Psychiatry*. 1992;53(3):77-82. Posey DJ, et al. *J Child Adolesc Psychopharmacol*. 2004;14(2):233-241.
 Handen BL, et al. *J Dev Behav Pediatr*. 2008;29(4):303-308; Scahill et al, *AM J Psychiatry* 2015

Antipsychotics and ASD

- A Double-Blind Placebo Controlled Trial of Risperidone in Autistic Disorder
 - 8 weeks of treatment associated with statistically significant decrease in self-injury, aggression, agitation, stereotypy and hyperactivity
- Aripiprazole in the Treatment of Irritability in Youth with Autism
 - 8 week DBPC fixed and flexible dose study of over 300 children & adolescents 6 to 17 yrs
 - 85% completion; Average dose 8.1mg; 50 – 52% responders based on ABC-I and CGI-I of much or very much improve

McCracken JT et al. *N Engl J Med*. 2002;347:314-321.

Marcus RN et al. *J Am Acad Child Adolesc Psychiatry*. 2009;48:1110-1119; Owen R et al. *Pediatrics*. 2009;124(6):1533-1540.

Summary of Conventional Medications for Autism (Level 2)

- Stimulants: works for some; start low and go slow
- Antidepressants: maybe for anxiety; OCD and ASD negative in children but 1 positive study in adults
- Alpha-adrenergic agonists: worth a try for anxiety but limited studies
- Anticonvulsants: ? mood dysregulation + neurologic abnormalities; limited studies
- Antipsychotics: indication for risperidone and aripiprazole (Level 1), but adverse effects. ? asenapine, negative lurasidone study in children

Risperidone and aripiprazole (irritability) are the only FDA-approved medications or biomedical agents for treating autism.

Handen BL, et al. *Int J Adolesc Med Health*. 2011;23(3):167-173. Anagnostou E, et al. *Curr Opin Pediatr*. 2011;23(6):621-627. Correll CU, et al. *J Clin Psychiatry*. 2011;72(5):655-670. Kaplan G, et al. *Pediatr Clin North Am*. 2012;59(1):175-187.

Melatonin

- Endogenous neurohormone causes drowsiness, establishes circadian rhythms and synchronization of peripheral oscillators, and is produced from serotonin
- Review and meta-analysis of 35 studies reported that of 18 treatment studies, there were 5 RCTs (N = 61, 2 to 10 mg/day) where sleep duration (44 min, ES = .93) was increased, sleep onset latency was decreased (39 min, ES = 1.28), but nighttime awakenings were unchanged
- Adverse effects were minimal to none
- May also benefit social communication impairments and stereotyped behaviors or interests

Tordjman S, et al. *Int J Mol Sci.* 2013;14(10):20508-20542. Rossignol DA, et al. *Dev Med Child Neurol.* 2011;53(9):783-792.

Vitamin D Vitamin D Council

- “Ecological Evidence” – Northern latitudes, rainfall, skin pigment. Low levels of vitamin D reported
- Vitamin D activates serotonin-synthesizing gene
- Vitamin D is a “potent neurosteroid”
- UCSF study
 - 25(OH)D at or below 30 ng/mL
 - Initial loading dose of 10,000 IU of D3, then 300/IU/kg of vitamin D3
 - Target level 90 ng/mL
 - Safety measured by 25(OH)D and calcium level, tremor, weakness, fatigue, diarrhea, anorexia, headache, confusion,

Jia et al. *Pediatrics*, 2014; Patrick RP, et al. *FASEB J.* 2014;28(6):2398-2413. McGrath J, et al. *Trends Neurosci* 2010;33(11):570-572.

NAC with Autism

- NAC is an glutamatergic modulator and an antioxidant
- 12-week, double-blind, randomized, placebo-controlled study of NAC in children with autistic disorder
- NAC was initiated at 900 mg daily for 4 weeks, then 900 mg twice daily for 4 weeks, and 900 mg 3 times daily for 4 weeks
- 33 patients (31 male, 2 female; aged 3.2 to 10.7 years) were randomized
- Oral NAC was well tolerated with limited adverse effects
- Compared with placebo, NAC resulted in significant improvements on ABC-I ($F = 6.80$; $P < .001$; $d = .96$)

Hardan AY, et al. *Biol Psychiatry*. 2012;71(11):956-961.

UCSF-IAN Omega-3 Results

- 863 e-mail invitations
- 118 responded
- 57 met eligibility criteria from 28 states
- Recruitment completed in 6 weeks
- 57 teachers contacted and agreed to participate
- 100% completion rate, study finished in 12 weeks
- Results
 - Omega-3: ABC-H: -5.3 points
 - Placebo: ABC-H: -3.4 points $P = .38$, $ES = .26$
- Implications
 - Internet is a powerful tool for clinical trials
 - Sample size insufficient to judge efficacy of omega-3

IAN = Interactive Autism Network.
Bent S, et al. *J Am Acad Child Adolesc Psychiatry*. 2014;53(6):658-666.

Vitamin/Mineral Supplement and ASD

- RCT of oral vitamin/mineral supplement for 3 months with 141 children and adults with ASD
- Improved the nutritional and metabolic status of children with autism, including improvements in methylation, GSH, oxidative stress, sulfation, ATP, NADH, and NADPH
- The supplement group had significantly greater improvements than did the placebo group on the Parental Global Impression-Revised Average Change ($P = .008$), Hyperactivity ($P = .003$), and Tantrumming ($P = .009$)

ATP = adenosine-5'-triphosphate; NADH = nicotinamide adenine dinucleotide; NADPH = nicotinamide adenine dinucleotide phosphate.
Adams JB, et al. *BMC Pediatr.* 2011;11:111.

Diet

- Inconsistencies between parent reports and the results of clinical trials for a gluten-free casein-free diet in children with autism with no RCT showing benefit
- Several studies suggest a relationship between non-celiac gluten sensitivity and autism
- Detailed metabolic screening in a Greek cohort of ASD patients revealed biomarkers (urine 3-hydroxyisovaleric acid and serum b-OH-b) in 7% (13/187) of patients for whom biotin supplementation or institution of a ketogenic diet resulted in mild to significant clinical improvement in autistic feature
- Specific carbohydrate diet

Cheng JX, et al. *Adolesc Med State Art Rev.* 2013;24(2):446-464. Catassi C, et al. *Nutrients.* 2013;5(10):3839-3853. Spilioti M, et al. *Front Hum Neurosci.* 2013;7:858. Autism Network for Dietary Intervention. www.autismndi.com/news/advanced-dietary-interventions/the-specific-carbohydrate-diet-scd.html#U4NJisZ216k. Accessed June 25, 2014.

Hormones

- Oxytocin – Genetic studies of patients with autism show decreased expression of the oxytocin receptor
- RCT crossover study of intranasal oxytocin (12 IU BID) in 31 children with autism found improvement in caregiver-rated social responsiveness and behavioral and emotional difficulties
- Oxytocin significantly increased the correct rate in inferring others' social emotions. At the neural level, the peptide significantly enhanced the originally-diminished brain activity in the right anterior insula during inferring others' social emotions ($P = .004$).

Gregory SG, et al. *BMC Med.* 2009;7:62. Yatawara...Guastella, *Mol Psychiatry*, 2015; Tachibana M, et al. *J Child Adol Psychopharm.* 2013;23(2):123-127. Anagnostou E, et al. *Brain Res.* 2014;[Epub ahead of print]. Aoki Y, et al. *Brain.* 2014;137(Pt 11):3073-3086.

Adult Autism Tx Study

- **VANILLA** (*Vasopressin Antagonist to Improve Social Communication in Autism*) study (Level 3)
- Works by blocking a brain receptor of the vasopressin receptor that is associated with control of stress, anxiety, affection, and aggression
- Finished 4 stages with 154 high functioning ASD males ages 18 to 45 years. Participants take either 1.5 mg or 4 mg or 10 mg or placebo daily for 12 weeks

Presented at: 13th Annual International Meeting for Autism Research (IMFAR); May 17, 2014. Abstract 176.111.

Other Considerations for Adults with Autism

- Medical marijuana/THC/CBD and the endocannabinoid systems (Level 4)
- GABA-A (Level 3)
- Vitamins and Mineral Supplements (Level 2)
 - Relatively high doses of Vitamins B1, B2, B3, B5, B6, B12, biotin, folate, C, D, and K
 - MSM (a good source of sulfate which is low in many ASD)
 - Low-dose lithium (more than 100 × below the levels when it is used as a psychiatric medication)

THC = tetrahydrocannabinol; CBD = cannabidiol.

Hollander E, et al. *Am J Psychiatry*. 2012;169(3):292-299. Krueger DD, et al. *Neuron*. 2013;78(3):408-410. Han S, et al. *Nature*. 2012;489(7416):385-390. Adams JB. *Vitamins & Minerals*. 2015;4(1). <http://autismnrc.org/assets/images/PDF%20Files/vitaminmineral-supplements-for-children-and-adults-with-autism-2376-1318%201000127.pdf>. Accessed June 16, 2015.

Integrated Approach to Autism Treatment

- Medical – genetic, neurology, GI, other medical symptoms
- Ancillary – speech, OT
- Behavioral
- Treat associated symptoms – pharmacology
- Biomedical assessment and treatments – melatonin, omega-3, vitamin D3, probiotics, digestive enzymes

Hendren RL. *Child Adolesc Psychiatr Clin N Am*. 2013;22(3):443-456.

Postsecondary Employment Experiences among Young Adults with ASD

- Approximately **one-half (53.4%)** of young adults with **ASD had ever worked for pay** outside the home since leaving high school, the lowest rate among disability groups
- Young adults with an ASD **earned an average of \$8.10/hour**, significantly lower than average wages for young adults in the comparison groups, and held jobs that clustered within fewer occupational types.

Roux AM, et al. *J Am Acad Child Adolesc Psychiatry*. 2013;52(9):931-939.

Vocational Training Programs

- MERISTEM, in Fair Oaks, serves young adults on the autism spectrum by helping them develop practical life skills, increase social capacity, and transition to work and independence. Integrated with a teacher training college, farm apprenticeship program, community supported agriculture (CSA), and community workshops and events. Students develop skills through community integration and social inclusion.
- AUTISTRY STUDIOS, in San Rafael, is a pre-vocational program that promotes the growth of independence.
- PRIDE Industries in Northern California, delivers quality manufacturing, supply chain and facilities service solutions to businesses and government agencies nationwide, while creating meaningful jobs for people with disabilities.