Bibliography – Pediatric Migraine
December 5, 2007

1. Annequin, D., Tourniaire, B., and Massiou, H. Migraine and headache in childhood and adolescence. *Pediatr Clin North Am* 47**:** 617-631, 2000.

2. Brna, P., Dooley, J., Gordon, K., and Dewan, T. The prognosis of childhood headache: a 20-year follow-up. *Arch Pediatr Adolesc Med* 159**:** 1157-1160, 2005.

3. Damen, L., Bruijn, J., Verhagen, A.P., Berger, M.Y., Passchier, J., and Koes, B.W. Prophylactic treatment of migraine in children. Part 2. A systematic review of pharmacological trials. *Cephalalgia* 26**:** 497-505, 2006.

4. Damen, L., Bruijn, J.K., Verhagen, A.P., Berger, M.Y., Passchier, J., and Koes, B.W. Symptomatic treatment of migraine in children: a systematic review of medication trials. *Pediatrics* 116**:** e295-302, 2005.

5. Eiland, L.S., Jenkins, L.S., and Durham, S.H. Pediatric migraine: pharmacologic agents for prophylaxis. *Ann Pharmacother* 41**:** 1181-1190, 2007.

6. Evers, S. Controlled trials in pediatric migraine: crossover versus parallel group. *Curr Pain Headache Rep* 11**:** 241-244, 2007.

7. Hamalainen, M.L. Migraine in children and adolescents: a guide to drug treatment. *CNS Drugs* 20**:** 813-820, 2006.

8. Kienbacher, C., Wober, C., Zesch, H.E., Hafferl-Gattermayer, A., Posch, M., Karwautz, A., Zormann, A., Berger, G., Zebenholzer, K., Konrad, A., and Wober-Bingol, C. Clinical features, classification and prognosis of migraine and tension-type headache in children and adolescents: a long-term follow-up study. *Cephalalgia* 26**:** 820-830, 2006.

9. Lewis, D., Ashwal, S., Hershey, A., Hirtz, D., Yonker, M., and Silberstein, S. Practice parameter: pharmacological treatment of migraine headache in children and adolescents: report of the American Academy of Neurology Quality Standards Subcommittee and the Practice Committee of the Child Neurology Society. *Neurology* 63**:** 2215-2224, 2004.

10. Lewis, D.W., and Winner, P. The pharmacological treatment options for pediatric migraine: an evidence-based appraisal. *NeuroRx* 3**:** 181-191, 2006.

11. Lipton, R.B., and Bigal, M.E. Migraine: epidemiology, impact, and risk factors for progression. *Headache* 45 Suppl 1**:** S3-S13, 2005.

12. Maneyapanda, S.B., and Venkatasubramanian, A. Relationship between significant perinatal events and migraine severity. *Pediatrics* 116**:** e555-558 2005.

13. Pakalnis, A. Pediatric migraine: new diagnostic strategies and treatment options. *Expert Rev Neurother* 6**:** 291-296, 2006.

14. Pakalnis, A. Current therapies in childhood and adolescent migraine. *J Child Neurol* 22**:** 1288-1292, 2007.

15. Winner, P., and Hershey, A.D. Diagnosing migraine in the pediatric population. *Curr Pain Headache Rep* 10**:** 363-369, 2006.

16. Winner, P., and Hershey, A.D. Epidemiology and diagnosis of migraine in children. *Curr Pain Headache Rep* 11**:** 375-382, 2007.

17. Winner, P., Linder, S.L., Lipton, R.B., Almas, M., Parsons, B., and Pitman, V. Eletriptan for the acute treatment of migraine in adolescents: results of a double-blind, placebo-controlled trial. *Headache* 47**:** 511-518, 2007.

18. Yonker, M.E. Pharmacologic treatment of migraine. *Curr Pain Headache Rep* 10**:** 377-381, 2006.

Autism and Autism Spectrum Disorders – Treatment
Reviews
July 23, 2010
87 citations with abstracts

1. Aman, M.G. Stimulant drug effects in developmental disorders and hyperactivity--toward a resolution of disparate findings. *J Autism Dev Disord* 12**:** 385-398, 1982.

   An attempt is made to integrate data from a variety of clinical populations and from the animal literature. Evidence is presented suggesting that mentally retarded and autistic children generally show a poor response to stimulant medication, whereas hyperactive and normal children respond beneficially. Cognitive research in mentally retarded and autistic children is reviewed, and it is suggested that both diagnostic groups suffer from attentional difficulties, the mechanisms of which may be very similar. The literature on stimulant-induced stereotypy in animals is discussed, with emphasis on the clinical implications for autism and mental retardation. An attentional model is proposed to account for type of therapeutic response to stimulant medication. This is followed by a possible method for testing the model and by specific predictions relating to subject characteristics and response.

2. Aman, M.G., Farmer, C.A., Hollway, J., and Arnold, L.E. Treatment of inattention, overactivity, and impulsiveness in autism spectrum disorders. *Child Adolesc Psychiatr Clin N Am* 17**:** 713-738, vii, 2008.

   We reviewed the recent literature on medicines used to manage inattention, impulsiveness, and overactivity in children with pervasive developmental disorders (autistic disorder, pervasive developmental disorder not otherwise specified, Asperger's disorder) using computer searches of pharmacologic studies. A substantial number of reports were identified and summarized. The literature tends to be dominated by uncontrolled studies, although the number of controlled trials is growing. Findings are described for psychostimulants, noradrenergic reuptake inhibitors, antipsychotics, alpha adrenergic agonists, antidepressants, anxiolytics, cholinesterase inhibitors, N-methyl-D-aspartate receptor blockers, and antiepileptic mood stabilizers. Evidence for a positive effect is strongest for psychostimulants, noradrenergic reuptake inhibitors, antipsychotics, and alpha adrenergic agonists. Evidence for efficacy seems weakest for newer antidepressants, anxiolytics, and mood stabilizers.

3. Aman, M.G., and Kern, R.A. Review of fenfluramine in the treatment of the developmental disabilities. *J Am Acad Child Adolesc Psychiatry* 28**:** 549-565, 1989.

   Fenfluramine, a serotonin reducing agent, has been the subject of intense research effort in recent years. A variety of biochemical studies summarized

suggest that some autistic children and many nonautistic severely retarded individuals have elevated blood serotonin concentrations. The research on fenfluramine's clinical efficacy is thoroughly reviewed from a methodological perspective. All studies assessing the drug's effects on blood serotonin have observed reductions in whole blood serotonin to about 50% of baseline concentrations. Although there were early reports of drug enhancement of IQ, there is no good evidence that this is the case. However, there are data to suggest that fenfluramine may enhance social relatedness, reduce stereotypic behavior, lessen overactivity, and improve attention span in some autistic children, although these results do not appear consistently across studies. The animal literature on the neurotoxicity of fenfluramine is reviewed, and a number of limitations in this research are identified that raise questions about its relevance to the pharmacotherapy of children.

4. Anderson, G.M., Zimmerman, A.W., Akshoomoff, N., and Chugani, D.C. Autism clinical trials: biological and medical issues in patient selection and treatment response. *CNS Spectr* 9**:** 57-64, 2004.

   Biomedical measures are critical in the initial patient-screening and -selection phases of a clinical trial in autism and related disorders. These measures can also play an important role in the assessment and characterization of response and can provide an opportunity to study underlying etiologic and pathophysiologic processes. Thus, biomedical measures, including clinical laboratory analyses, metabolic screening, and chromosomal analysis, are used to screen for potential safety-related problems, to decrease biological and genetic heterogeneity, and to define subgroups. Neurobiological measures can be examined as possible predictors, modifiers or surrogates of therapeutic response, and adverse effects. Neurobiological research measures can also be used to study mechanisms and extent of drug action and to perform baseline and longitudinal investigations of possible pathophysiologic alterations. The potential utility and desirability of specific measures are considered and the general approach to choosing measures for incorporation is discussed.

5. Aneja, A., and Tierney, E. Autism: the role of cholesterol in treatment. *Int Rev Psychiatry* 20**:** 165-170, 2008.

   Cholesterol is essential for neuroactive steroid production, growth of myelin membranes, and normal embryonic and fetal development. It also modulates the oxytocin receptor, ligand activity and G-protein coupling of the serotonin-1A receptor. A deficit of cholesterol may perturb these biological mechanisms and thereby contribute to autism spectrum disorders (ASDs), as observed in Smith-Lemli-Opitz syndrome (SLOS) and some subjects with ASDs in the Autism Genetic Resource Exchange (AGRE). A clinical diagnosis of SLOS can be confirmed by laboratory testing with an elevated plasma 7DHC level relative to the cholesterol level and is treatable by dietary cholesterol supplementation. Individuals with SLOS who have such cholesterol treatment display fewer autistic

behaviours, infections, and symptoms of irritability and hyperactivity, with improvements in physical growth, sleep and social interactions. Other behaviours shown to improve with cholesterol supplementation include aggressive behaviours, self-injury, temper outbursts and trichotillomania. Cholesterol ought to be considered as a helpful treatment approach while awaiting an improved understanding of cholesterol metabolism and ASD. There is an increasing recognition that this single-gene disorder of abnormal cholesterol synthesis may be a model for understanding genetic causes of autism and the role of cholesterol in ASD.

6. Angley, M., Semple, S., Hewton, C., and Paterson, F. Children and autism--Part 2--management with complementary medicines and dietary interventions. *Aust Fam Physician* 36**:** 827-830, 2007.

   BACKGROUND: Complementary and alternative medicines (CAMs) and dietary interventions are widely used in the management of autistic disorders as pharmacological treatments offered by mainstream medicine are limited and often associated with significant adverse effects. OBJECTIVE: In this article, the rationale, safety and efficacy of a range of CAMs and dietary interventions used in the management of autistic disorders are discussed. DISCUSSION: Despite many anecdotal reports supporting the efficacy of CAMs, evidence for their use in autistic disorders is either unclear or conflicting, and available data comes from a limited number of small studies. Large randomised controlled trials have not yet been conducted to examine efficacy in this population. Although most interventions are associated with only mild adverse effects, there is a lack of long term safety data. General practitioners need to be aware that the use of CAMs in autism is not risk free and often lacks sound clinical evidence. On the other hand, there may be subtle benefits to the child, especially if interventions are coupled with intensive behavioural and/or educational intervention.

7. Angley, M., Young, R., Ellis, D., Chan, W., and McKinnon, R. Children and autism--Part 1--recognition and pharmacological management. *Aust Fam Physician* 36**:** 741-744, 2007.

   BACKGROUND: Autism is a neurodevelopmental disorder characterized by complex aetiology, variable presentation and widely divergent outcomes. It is clear that an individual's intrinsic genetic susceptibility, health, nutritional status and environmental exposures all contribute to the aetiology of autism. OBJECTIVE: This article aims to assist the general practitioner in recognizing and managing a child with an autistic disorder. DISCUSSION: Screening for autism by the GP can lead to referral for a formal diagnosis, enabling much needed support at an early stage of development, which can improve outcomes for the individual. Currently, evidence for psychotropic use and awareness of adverse effects in young people with autism is limited. Antipsychotic medications are increasingly used in people with autism and the importance of monitoring for adverse effects is paramount. Primary strategies for dealing with children with

autism are understanding, environmental modification and behavioural interventions. Combined with these, pharmacological interventions may have benefits for children with autism with extreme or challenging behaviours.

8. Arnold, L.E., Aman, M.G., Martin, A., Collier-Crespin, A., Vitiello, B., Tierney, E., Asarnow, R., Bell-Bradshaw, F., Freeman, B.J., Gates-Ulanet, P., Klin, A., McCracken, J.T., McDougle, C.J., McGough, J.J., Posey, D.J., Scahill, L., Swiezy, N.B., Ritz, L., and Volkmar, F. Assessment in multisite randomized clinical trials of patients with autistic disorder: the Autism RUPP Network. Research Units on Pediatric Psychopharmacology. *J Autism Dev Disord* 30**:** 99-111, 2000.

   Assessment of autistic disorder (autism) symptoms, primary and secondary, poses more challenging problems than ordinarily found in multisite randomized clinical trial (RCT) assessments. For example, subjects may be uncommunicative and extremely heterogeneous in problem presentation, and current pharmacological treatments are not likely to alter most core features of autism. The Autism Research Units on Pediatric Psychopharmacology (RUPP Autism Network) resolved some of these problems during the design of a risperidone RCT in children/adolescents. The inappropriateness of the usual anchors for a Clinical Global Impression of Severity (CGI-S) was resolved by defining uncomplicated autism without secondary symptoms as a CGI-S of 3, mildly ill. The communication problems, compromising use of the patient as an informant, were addressed by several strategies, including careful questioning of care providers, rating scales, laboratory tests, and physical exams. The broad subject heterogeneity requires outcome measures sensitive to individual change over a wide spectrum of treatment response and side effects. The problems of neuropsychologically testing nonverbal, lower functioning, sometimes noncompliant subjects requires careful instrument selection/adaptation and flexible administration techniques. The problems of assessing low-end IQs, neglected by most standardized test developers, was resolved by an algorithm of test hierarchy. Scarcity of other autism-adapted cognitive and neuropsychological tests and lack of standardization required development of a new, specially adapted battery. Reliability on the Autism Diagnostic Interview (currently the most valid diagnostic instrument) and other clinician instruments required extensive cross-site training (in-person, videotape, and teleconference sessions). Definition of a treatment responder required focus on individually relevant target symptoms, synthesis of possible modest improvements in many domains, and acceptance of attainable though imperfect goals. The assessment strategy developed is implemented in a RCT of risperidone (McDougle et al., 2000) for which the design and other methodological challenges are described elsewhere (Scahill et al., 2000). Some of these problems and solutions are partially shared with RCTs of other treatments and other disorders.

9. Barnard, L., Young, A.H., Pearson, J., Geddes, J., and O'Brien, G. A systematic review of the use of atypical antipsychotics in autism. *J Psychopharmacol* 16**:** 93-

101, 2002.

Conventional antipsychotic medication is commonly prescribed to patients with autistic spectrum disorder. However, a high incidence of severe adverse reactions highlights the need to find more favourable treatments. Atypical antipsychotics may combine efficacy in ameliorating some autistic symptoms with a lower incidence of some adverse reactions. This article reviews the use of atypical antipsychotics in autistic disorder, with particular focus on behaviour, cognition and physical well-being. Thirteen studies using risperidone, three using olanzapine, one using clozapine, one using amisulpride and one using quetiapine were identified. Few firm conclusions can be drawn due to the limitations of the studies; however, there is an indication that risperidone may be effective in reducing hyperactivity, aggression and repetitive behaviours, often without inducing severe adverse reactions. Olanzapine and clozapine may also be effective; however, there is little evidence for using amisulpride or quetiapine in this population. Randomized trials are required to clarify the effectiveness of these agents.

10. Bent, S., Bertoglio, K., and Hendren, R.L. Omega-3 fatty acids for autistic spectrum disorder: a systematic review. *J Autism Dev Disord* 39**:** 1145-1154, 2009.

We conducted a systematic review to determine the safety and efficacy of omega-3 fatty acids for autistic spectrum disorder (ASD). Articles were identified by a search of MEDLINE, EMBASE, and the Cochrane Database using the terms autism or autistic and omega-3 fatty acids. The search identified 143 potential articles and six satisfied all inclusion criteria. One small randomized controlled trial (n = 13) noted non-significant improvements in hyperactivity and stereotypy. The remaining five studies were small (n = 30, 22, 19, 9, and 1) with four reporting improvements in a wide range of outcomes including language and learning skills, parental observations of general health and behavior, a clinician-administered symptom scale, and clinical observations of anxiety. Due to the limitations of evidence from uncontrolled studies and the presence of only one small randomized controlled trial, there is currently insufficient scientific evidence to determine if omega-3 fatty acids are safe or effective for ASD.

11. Bethea, T.C., and Sikich, L. Early pharmacological treatment of autism: a rationale for developmental treatment. *Biol Psychiatry* 61**:** 521-537, 2007.

Autism is a dynamic neurodevelopmental syndrome in which disabilities emerge during the first three postnatal years and continue to evolve with ongoing development. We briefly review research in autism describing subtle changes in molecules important in brain development and neurotransmission, in morphology of specific neurons, brain connections, and in brain size. We then provide a general schema of how these processes may interact with particular emphasis on neurotransmission. In this context, we present a rationale for utilizing

pharmacologic treatments aimed at modifying key neurodevelopmental processes in young children with autism. Early treatment with selective serotonin reuptake inhibitors (SSRIs) is presented as a model for pharmacologic interventions because there is evidence in autistic children for reduced brain serotonin synthesis during periods of peak synaptogenesis; serotonin is known to enhance synapse refinement; and exploratory studies with these agents in autistic children exist. Additional hypothetical developmental interventions and relevant published clinical data are described. Finally, we discuss the importance of exploring early pharmacologic interventions within multiple experimental settings in order to develop effective treatments as quickly as possible while minimizing risks.

12. Blatt, S.D., Meguid, V., and Church, C.C. Sudden infant death syndrome and secretin treatment for autism. *Curr Opin Pediatr* 12**:** 179-183, 2000.

    The Back to Sleep Campaigns remain the greatest influence on the reduction of sudden infant death syndrome. Blatt and Meguid review updates on the effectiveness of these campaigns in reducing sudden infant death syndrome. They also review studies on why parents do not follow this proven advice. The contribution of the risks of other environmental factors are also reviewed. Also discussed are commentaries from a study reviewed last on the link between a prolonged QT electrocardiogram interval and sudden infant death syndrome. Church provides a cogent and timely review of the reported effectiveness of hormone secretin effectiveness in treating children with autism. This newly proposed treatment has been in the spotlight of the lay public, the popular media, and the scientific community. In short order, secretin as a treatment for autism has moved from a chance observation to the subject of a double-blind, placebo-controlled study.

13. Blatt, S.D., Meguid, V., Church, C.C., Botash, A.S., Jean-Louis, F., Siripornsawan, M.P., and Weinberger, H.L. Sudden infant death syndrome, child sexual abuse, and child development. *Curr Opin Pediatr* 11**:** 175-186, 1999.

    Since the introduction of the Back to Sleep Campaigns, there has been a dramatic reduction in sudden infant death syndrome in this country. Steven Blatt and Victoria Meguid review the literature surrounding sleep position. Investigators have continued efforts to find other modifiable risk factors of sudden infant death syndrome. A prospective study of more than 33,000 neonates found a link between a prolonged QT electrocardiogram interval and sudden infant death syndrome. Also discussed are investigations seeking to explain the relationship between smoking and sudden infant death syndrome. Ann Botash, Florence Jean-Louis and Mongkae Ploy Siripornsawan review the latest thinking on genital warts and their relation to specific viral etiologies and child sexual abuse. Other symptoms and signs of sexual abuse are the focus of a number of articles that can help the practitioner care for these unfortunate children. Catherine Church reviews medication options for children diagnosed with

pervasive developmental disorders or autism spectrum disorders. Finally, in this article, risperidone, fluoxetine and naltrexone are reviewed.

14. Bostic, J.Q., and King, B.H. Autism spectrum disorders: emerging pharmacotherapy. *Expert Opin Emerg Drugs* 10**:** 521-536, 2005.

    Autism, Asperger and other pervasive developmental disorders (PDDs) are an increasingly commonly identified group of conditions wherein patients experience significant difficulty in social interactions, communicating with others, and inflexible adherence to unusual, unhelpful and frequently stereotyped routines and behaviour. These autism spectrum disorders are now being diagnosed earlier in life (approximately 15 months), and often remain a chronic, daily burden for those afflicted. In addition to the often profound impact on an individual's quality of life, the familial, social and economic burdens of PDDs can be enormous. No treatments are curative, and most pharmacological treatments are employed to treat specific troubling symptoms rather than the core features of the disorder itself. Therefore, more effective pharmacotherapies are desperately needed. This review describes current and emerging pharmacotherapies that may advance care of people with PDDs.

15. Broadstock, M., Doughty, C., and Eggleston, M. Systematic review of the effectiveness of pharmacological treatments for adolescents and adults with autism spectrum disorder. *Autism* 11**:** 335-348, 2007.

    The variable expression of autism over the lifespan is likely to lead to different symptoms and support requirements, and to distinct responses to pharmacotherapy treatment, in older patients compared to children. This systematic review considers the effectiveness of pharmacological treatment in managing autism spectrum disorder in adolescents and adults. Following a comprehensive search of literature published in English from 1980, methodological criteria were applied to identify studies designed to reliably assess treatment effectiveness. Only five double-blind, randomized controlled trials were eligible for appraisal. All had small sample sizes (mean = 30) and brief treatment duration of no more than 12 weeks. The paucity of trials and their methodological limitations means that there is only preliminary evidence about the short-term effectiveness of a few drug treatments for this age group. There was also a lack of reliable data reported on drug safety profiles. Methodological challenges and directions for future research are discussed.

16. Buitelaar, J.K., and Willemsen-Swinkels, S.H. Medication treatment in subjects with autistic spectrum disorders. *Eur Child Adolesc Psychiatry* 9 Suppl 1**:** I85-97, 2000.

    Autism is a pervasive developmental disorder that is aetiologically and clinically heterogeneous. Twin and family genetic studies provide evidence for strong genetic components. An international consortium using an affected sib pair

strategy has found a promising linkage to a region on chromosome 7. In 10-15 % of the cases autism is due to associated medical conditions that affect normal brain functioning. Post-mortem studies on small case series report cellular abnormalities in the limbic system and cerebellum. Between 10 and 20 % of subjects with autism have macrocephalia, which is in accordance with MRI findings of an increased total brain tissue volume and enlargement most prominent in the occipital and parietal lobes. The most robust and well-replicated neurobiological abnormality in autism is an elevation of whole blood serotonin found in over 30% of the patients. Pharmacological interventions with serotonin reuptake blockers or with atypical neuroleptics that block both dopamine (D2) and serotonin (5-HT2) receptors seem to offer clinical benefit and merit further study.

17. Buitelaar, J.K., and Willemsen-Swinkels, S.H. Autism: current theories regarding its pathogenesis and implications for rational pharmacotherapy. *Paediatr Drugs* 2**:** 67-81, 2000.

    Autism is a pervasive developmental disorder that is aetiologically and clinically heterogeneous. Twin and family-genetic studies provide evidence for strong genetic components. An international consortium using an affected sib pair strategy has found a promising linkage to a region on chromosome 7. In 10 to 15% of cases autism is due to associated medical conditions that affect normal brain functioning. Postmortem studies on small case series report cellular abnormalities in the limbic system and cerebellum. Between 10 and 20% of individuals with autism have macrocephalia, which is in accordance with magnetic resonance imaging (MRI) findings of an increased total brain tissue volume and enlargement most prominent in the occipital and parietal lobes. The most robust and well replicated neurobiological abnormality in autism is an elevation of whole blood serotonin (5-hydroxytryptamine; 5-HT) found in over 30% of patients. Pharmacological interventions with serotonin reuptake inhibitors or with atypical neuroleptics that block both dopamine (D2) and serotonin (5-HT2) receptors seem to offer clinical benefit and merit further study.

18. Campbell, M., and Cueva, J.E. Psychopharmacology in child and adolescent psychiatry: a review of the past seven years. Part I. *J Am Acad Child Adolesc Psychiatry* 34**:** 1124-1132, 1995.

    OBJECTIVE: To present a critical overview of the literature published in the past 7 years on the efficacy and safety of psychoactive agents in mental retardation with associated psychiatric disorders, autistic disorder, Tourett's disorder, and attention-deficit/hyperactivity disorder. METHOD: Double-blind and placebo-controlled clinical trials and open studies were reviewed and selected reports presented. RESULTS: The literature review reveals that progress has been made in the psychopharmacological treatment of the above conditions. This is partly because more studies use larger sample sizes and a narrower age range of diagnostically homogeneous patients and use a more sophisticated

methodology than in previous years. Greater attention is being paid to a critical assessment of psychoactive agents and to their safety, to the efficacy as well as to the effectiveness of drugs. The 5-year National Plan for Research on Child and Adolescent Mental Disorders (1991) based on the Institute of Medicine Report (1989) already has had a significant impact on psychophamacology research. CONCLUSIONS: Advances in methodology, initiatives of the National Institute of Mental Health, and the advent of DSM-IV should continue to enhance research and improve pharmacotherapy in clinical practice.

19. Campbell, M., Kafantaris, V., Malone, R.P., Kowalik, S.C., and Locascio, J.J. Diagnostic and assessment issues related to pharmacotherapy for children and adolescents with autism. *Behav Modif* 15**:** 326-354, 1991.

    Autism involves not only developmental delays but also aberrant behavior, both of which change in nature over time. Rating instruments may be useful to assess maladaptive and adaptive behaviors of autistic children in a standardized way and, perhaps, to measure change due to treatment. With the expansion of basic science, knowledge, and technology, there is increasing evidence that autism is etiologically heterogeneous. Currently, there is no biological marker specific to autism, although hyperserotonemia is a consistent finding in one third of autistic children. An aim of basic science research has been to develop a rational pharmacotherapy based upon the underlying neurochemistry. However, at the present time, this approach has not always been successful. It is expected that the development and use of more restrictive criteria, delineation of subtypes of autism, and interaction of descriptive, behavioral, clinical, and basic research will lead to more effective planning for treatment. The relationship of assessment to treatment response is presented and discussed.

20. Campbell, M., Schopler, E., Cueva, J.E., and Hallin, A. Treatment of autistic disorder. *J Am Acad Child Adolesc Psychiatry* 35**:** 134-143, 1996.

    OBJECTIVE: To present an overview of a variety of treatment approaches in individuals with autistic disorder. METHOD: Selected studies and articles are reviewed. RESULTS: In the past three decades, great progress has been made in the treatment of autistic disorder, particularly in the area of education and parental involvement, with the objective to transfer to home and in other situations learning acquired in school. A role for psychoactive agents, when combined with psychosocial treatments, has been identified. CONCLUSIONS: Although considerable advances have been made in a variety of interventions-educational, psychosocial, and biological-knowledge about the comparative and combined efficacy of the various treatment modalities is lacking. From the parents' perspective, particularly, support and continuity of services require improvement.

21. Carlsson, M.L. Hypothesis: is infantile autism a hypoglutamatergic disorder? Relevance of glutamate - serotonin interactions for pharmacotherapy. *J Neural*

Transm 105**:** 525-535, 1998.

Based on 1) neuroanatomical and neuroimaging studies indicating aberrations in brain regions that are rich in glutamate neurons and 2) similarities between symptoms produced by N-methyl-D-aspartate (NMDA) antagonists in healthy subjects and those seen in autism, it is proposed in the present paper that infantile autism is a hypoglutamatergic disorder. Possible future pharmacological interventions in autism are discussed in the light of the intimate interplay between central glutamate and serotonin, notably the serotonin (5-HT) 2A receptor. The possible benefit of treatment with glutamate agonists [e.g. agents acting on the modulatory glycine site of the NMDA receptor, or so-called ampakines acting on the alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptor] is discussed, as well as the potential usefulness of a selective 5-HT2A receptor antagonist.

22. Carr, J.E., and LeBlanc, L.A. Autism spectrum disorders in early childhood: an overview for practicing physicians. *Prim Care* 34**:** 343-359; abstract viii, 2007.

Autism spectrum disorders (ASDs) affect approximately 1 in 166 children in the United States, making it likely for the average physician to encounter patients with ASDs in his or her practice. In particular, pediatricians and developmental neurologists play a critical role in early identification, resource referrals, and management of a variety of comorbid physical and medical concerns. This article reviews the current literature on ASDs and provides recommendations for practice in areas critical to the provision of medical services.

23. Chabane, N., Leboyer, M., and Mouren-Simeoni, M.C. Opiate antagonists in children and adolescents. *Eur Child Adolesc Psychiatry* 9 Suppl 1**:** I44-50, 2000.

Naltrexone a pure opioid antagonist, well tolerated in young patients, has been found to be an interesting treatment in some disorders in children and adolescents. Naltrexone has been first tried in mental retardation and autism disorders in children and adolescents. Symptoms like self-injury behaviours, hyperactivity, stereotyped and ritualistic conducts appear to be improved in a subgroup of children with the opiate antagonist. But new controlled studies still need to be done before recommending naltrexone in autism. Preliminary results in the treatment of alcoholic adolescents seem to support the efficacy of naltrexone on abstinence when combined with a supportive psychotherapy. In adults, results found with the use of naltrexone in eating disorders are different, when considering the duration and the dosage of the treatment and the kind of eating disorder (bulimia, binge eating or anorexia nervosa). Studies in children and adolescents are needed before proposing naltrexone in eating disorders. We resumed here the results found with this treatment in these indications.

24. Charles, J.M., Carpenter, L.A., Jenner, W., and Nicholas, J.S. Recent advances in autism spectrum disorders. *Int J Psychiatry Med* 38**:** 133-140, 2008.

OBJECTIVE: This review article provides an overview of the most recent developments in the literature regarding autism spectrum disorders including epidemiology, etiology, assessment, and management/treatment. METHOD: A review of the recent literature was conducted using Medline and the search term "Autism Spectrum Disorders." RESULTS: Autism Spectrum Disorders are more common than previously believed (1 in 166), and etiology appears to be multifaceted including both heritable and non-heritable factors. State of the art treatment includes comprehensive medical monitoring as well as behavioral intervention. CONCLUSIONS: Current and anticipated federal funding, policy changes, and large scale research projects provide promise for increasing knowledge about Autism Spectrum Disorders.

25. Chavez, B., Chavez-Brown, M., and Rey, J.A. Role of risperidone in children with autism spectrum disorder. *Ann Pharmacother* 40**:** 909-916, 2006.

OBJECTIVE: To review the clinical trials investigating the efficacy and safety of risperidone in the treatment of children with autism spectrum disorder (ASD). DATA SOURCES: Searches of MEDLINE/PubMed (1992-February 2006) were conducted, as well as an extensive manual review of journals, using the key words autism and risperidone. STUDY SELECTION AND DATA EXTRACTION: Only double-blind, placebo-controlled trials were included for review. DATA SYNTHESIS: ASD is the most common of the pervasive developmental disorders. The main characteristics (core symptoms) of autism are impairment in social skills, problems communicating, and stereotypical movements. Behavioral manifestations or maladaptive behaviors include aggression, irritability, hyperactivity, inattention, impulsivity, tantrums, and self-injurious behavior. CONCLUSIONS: Based on the data examined, risperidone appears efficacious and safe for treating certain behavioral aspects of autism including irritability, aggression, hyperactivity, and stereotypy. It does not appear to be as effective for the treatment of the core symptoms of autism.

26. Cormier, E., and Elder, J.H. Diet and child behavior problems: fact or fiction? *Pediatr Nurs* 33**:** 138-143, 2007.

Dietary treatment of children with behavioral disorders has had wide public appeal and been a source of controversy since the 1920's. Yet, to date, there is little empirical evidence supporting the effectiveness of dietary restrictions in treating child psychiatric disorders, in particular, autism and attention deficit hyperactivity disorder (ADHD). Thus, the purpose of this article is (a) to provide historical background information regarding dietary treatment in children with behavioral disorders, (b) review the evidence-based literature for common dietary interventions, (c) discuss limitations in the research, including challenges inherent in conducting well-controlled dietary studies, and (d) provide recommendations regarding how nurses in primary care settings can assist families in making informed decisions.

27. De Ocampo, A.C., and Jacobs, J.M. Medical management of autism. *J S C Med Assoc* 102**:** 274-276, 2006.

The primary care physician should be knowledgeable about the medical issues that children with ASD encounter and also be aware of available treatment options. Included among these are: identification of seizures, treatment of sleep problems, aggressive management of chronic constipation and GERD as well as timely referral for preventive dental care. Due to the scarcity of sub-specialists (Pediatric Neurologist, Developmental Pediatrician, Child Psychiatrist/ Psychologist) managing children with ASD, the primary care physician should likewise be familiar with medication options for challenging behaviors. More importantly, there needs to be a close collaboration and communication between the family, the sub-specialist and the child's primary care physician.

28. DeLong, R. Autism and familial major mood disorder: are they related? *J Neuropsychiatry Clin Neurosci* 16**:** 199-213, 2004.

Family history studies of autism consistently reveal a large subgroup with a high incidence of major mood disorder in family members, suggesting the two entities are related clinically and genetically. This review examines this concept, comparing current clinlical and biological knowledge of autism and major mood disorder, and advances the hypothesis that this subgroup of autism represents an early-life phenotype of major mood disorder. If confirmed, this hypothesis would suggest that the basic biological defects determining major mood disorders may have prominent neurodevelopmental and cognitive dimensions. Testing of the hypothesis will depend on genetic studies.

29. Di Martino, A., and Tuchman, R.F. Antiepileptic drugs: affective use in autism spectrum disorders. *Pediatr Neurol* 25**:** 199-207, 2001.

Antiepileptic drugs are widely administered to individuals with autistic spectrum disorders. There are several reasons for the use of antiepileptic drugs in autistic spectrum disorders, including the high incidence of epilepsy in these individuals, the anecdotal reports suggesting an improvement of communication and behavior in autistic subjects with epileptic discharges, and the increased awareness that some disruptive behaviors may be manifestations of an associated affective disorder. In this study, data on the current use of antiepileptic drugs in the treatment of autism, and on the association of affective disorders with epilepsy and autism, are reviewed. The evidence supporting the hypothesis that there may be a subgroup of autistic children with epilepsy and affective disorders that preferentially respond to antiepileptic drugs is still very preliminary, and further investigations with double-blind controlled studies are needed. Although the role of antiepileptic drugs at the present time is not established, there is evidence that autism, epilepsy, and affective disorders commonly co-occur, and that they may share a common neurochemical

substrate, which is the common target of the psychotropic mechanism of action of different antiepileptic drugs.

30. du Verglas, G., Banks, S.R., and Guyer, K.E. Clinical effects of fenfluramine on children with autism: a review of the research. *J Autism Dev Disord* 18**:** 297-308, 1988.

A review of research studies published to date on the effects of fenfluramine on children with autism is presented. The current status of the fenfluramine research on children with autism is assessed. The review analyzed the methodological aspects of the research, the toxicity of fenfluramine, and the relationship between fenfluramine, neurotransmitter activity, cognitive ability, and subsequent behavioral change. The review of published data indicated that fenfluramine had positive effects on the reduction of hyperactivity and stereotypic behaviors in 33% of the subjects. The best responders were children with the highest baseline IQs. The conclusions address the need for appropriate subgrouping of autistic syndromes, which may lead to identification of responders to pharmacological treatments. The need for further study of the possible long-term adverse side effects of flenfluramine is noted. Further experimental research on the effects of fenfluramine on children with autism is endorsed.

31. Elchaar, G.M., Maisch, N.M., Augusto, L.M., and Wehring, H.J. Efficacy and safety of naltrexone use in pediatric patients with autistic disorder. *Ann Pharmacother* 40**:** 1086-1095, 2006.

OBJECTIVE: To review the efficacy and safety of naltrexone in pediatric patients with autistic disorder (AD). DATA SOURCES: Using the terms pediatric, child, naltrexone, autism, and autistic disorder, a literature search was performed using MEDLINE (1966-May 18, 2006) and the International Pharmaceutical Abstracts (1971-May 18, 2006) database. The references of these articles were scanned for additional relevant literature. STUDY SELECTION AND DATA EXTRACTION: All articles describing or evaluating the efficacy and/or safety of naltrexone in pediatric patients with AD were included in this review. Three case reports, 8 case series, and 14 clinical studies were identified as pertinent. DATA SYNTHESIS: Naltrexone has been used most commonly at doses ranging from 0.5 to 2 mg/kg/day and found to be predominantly effective in decreasing self-injurious behavior. Naltrexone may also attenuate hyperactivity, agitation, irritability, temper tantrums, social withdrawal, and stereotyped behaviors. Patients may also exhibit improved attention and eye contact. Transient sedation was the most commonly reported adverse event. Small sample size, short duration, and inconsistent evaluative methods characterize the available research. CONCLUSIONS: A child affected by AD may benefit from a trial of naltrexone therapy, particularly if the child exhibits self-injurious behavior and other attempted therapies have failed. Serious adverse effects have not been reported in short-term studies.

32. Esch, B.E., and Carr, J.E. Secretin as a treatment for autism: a review of the evidence. *J Autism Dev Disord* 34**:** 543-556, 2004.

Secretin is used in the United States for diagnosis of pancreatic gastrointestinal (GI) dysfunction and disease. Repeated therapeutic use has not been approved. Widespread interest in secretin as a treatment for autism followed media reports of behavioral improvements in an autistic child who received the hormone during a GI diagnostic procedure. International demand for secretin soared in the absence of experimental evidence of its efficacy for autism. This review presents a brief history of secretin's rise to popularity and summarizes research on secretin as a treatment for autism. Seventeen studies are reviewed comparing the effects of secretin forms, dosage levels, and dosing intervals on outcome measures with approximately 600 children. Twelve of 13 placebo-controlled studies failed to demonstrate the differential efficacy of secretin. Implications for advocating treatment in the absence of empirical evidence are discussed.

33. Findling, R.L. Pharmacologic treatment of behavioral symptoms in autism and pervasive developmental disorders. *J Clin Psychiatry* 66 Suppl 10**:** 26-31, 2005.

Autism and other pervasive developmental disorders (PDDs) are associated with various dysfunctional and problematic behaviors, in addition to the core features of language and social skills dysfunction that define these conditions. Although there is currently no pharmacologic cure for the core features of PDDs, some of the behavioral symptoms may be treated pharmacologically. In addition to relieving some of the daily stress in the lives of patients and their families, improvement of these behavioral symptoms, which include hyperactivity, aggression, tantrums, and self-injury, removes some of the hindrances to other rehabilitative efforts. This article discusses the efficacy and tolerability of various medications and alternative interventions in addressing the symptoms of autism and other PDDs.

34. Friedlander, A.H., Yagiela, J.A., Paterno, V.I., and Mahler, M.E. The pathophysiology, medical management, and dental implications of autism. *J Calif Dent Assoc* 31**:** 681-682, 684, 686-691, 2003.

Autism is a lifelong, severe, developmental disorder that appears initially in infancy and early childhood and impairs the acquisition of some of the most important skills in human life. The disease is characterized by impaired social interactions, verbal and nonverbal communication deficiencies, limited activities and interest, and repetitive behaviors. Often accompanying the disorder are behavioral disturbances, such as self-mutilation and aggression, psychiatric symptoms, and seizures, which necessitate the administration of multiple medications to help the affected individual participate effectively in the educational and rehabilitative process. Dentists caring for these people must be familiar with the manifestations of the disease and its associated features so that they can garner the maximum level of cooperation. They must also be familiar

with the medications used to treat the associated features of the disorder because many of these pharmaceuticals cause untoward orofacial and systemic reactions and may precipitate adverse interactions with dental therapeutic agents.

35. Friedlander, A.H., Yagiela, J.A., Paterno, V.I., and Mahler, M.E. The neuropathology, medical management and dental implications of autism. *J Am Dent Assoc* 137**:** 1517-1527, 2006.

BACKGROUND: A paucity of information exists in the dental literature about autism and its dental implications. TYPES OF STUDIES REVIEWED: The authors conducted a MEDLINE search for the period 2000 through 2006, using the term "autism," with the aim of defining the condition's clinical manifestations, dental and medical treatment and dental implications. RESULTS: Autism is a severe developmental brain disorder that appears in infancy, persists throughout life, and is characterized by impaired social interaction, abnormalities in communication (both verbal and nonverbal) and restricted interests. Often accompanying the disorder are behavioral disturbances - such as self-mutilation, aggression, psychiatric symptoms and seizures - that necessitate the administration of multiple medications to help the affected person participate effectively in the educational and rehabilitative process. CLINICAL IMPLICATIONS: Dentists caring for people with autism must be familiar with the manifestations of the disease and its associated features so that they can garner the maximum level of patient cooperation. They also must be familiar with the medications used to treat the associated features of the disorder because many of them cause untoward orofacial and systemic reactions and may precipitate adverse interactions with dental therapeutic agents.

36. Garreau, B., Herry, D., Zilbovicius, M., Samson, Y., Guerin, P., and Lelord, G. Theoretical aspects of the study of benzodiazepine receptors in infantile autism. *Acta Paedopsychiatr* 56**:** 133-138, 1993.

This paper is part of a special section on 'psychopharmacotherapy in children' and focuses on benzodiazepine receptors in autism. Infantile autism in an early and pervasive developmental disorder described by Kanner in 1943. Anatomical, pathological and magnetic resonance imaging studies have indicated changes in the cerebellum and hippocampus of autistic subjects. Given the numerical importance and diffuse benzodiazepine receptors, their study by functional brain imaging methods in vivo could be value in cases of infantile autism as a gauge of neuronal potentiality. The main data concerning benzodiazepine complex are presented. The relations between these data and the neurophysiological hypotheses of autism are discussed.

37. Gerlai, R., and Gerlai, J. Autism: a target of pharmacotherapies? *Drug Discov Today* 9**:** 366-374, 2004.

Autism is reaching epidemic proportions. The diagnosis can be made as early as 2 years of age, and autistic patients are expected to have a normal life span. Thus, in terms of the number of 'patient years', autism spectrum disorder (ASD) represents a market that is as large as that of the biggest neurological indication, Alzheimer's disease. However, despite the clear unmet medical need no effective treatment is yet available. This could be because the biology of ASD is not clearly understood and thus proper drug treatment has not been possible. However, significant advances are being made toward understanding the mechanisms of the disease. Here, we review the most recent preclinical advances in the hope that they will lead to a breakthrough in the near future.

38. Gilman, J.T., and Tuchman, R.F. Autism and associated behavioral disorders: pharmacotherapeutic intervention. *Ann Pharmacother* 29**:** 47-56, 1995.

OBJECTIVE: To review the literature on autism and pervasive developmental disorders (PDDs) as well as their respective pharmacotherapies. DATA SOURCES: An Index Medicus, MEDLINE, and bibliographic search of the literature pertaining to autism, PDDs, and respective treatments. STUDY SELECTION: Because of the paucity of literature on the treatment of autism and PDDs, the selection of reported data for this review included both controlled and uncontrolled studies, as well as case reports and any other information reported in the literature on the treatment of these disorders. DATA SYNTHESIS: Autism and PDDs are severe developmental disabilities defined by behavioral criteria. These disorders are lifelong in nature and present in varying severity of clinical manifestations. Behavioral manifestations of patients with autism include core deficits in social interaction, communication, and imaginative activities, with a restricted repertoire of activities and interests. The present understanding of the neurochemical basis of the disorder is limited. The role of pharmacotherapy in the management of autism and PDDs is to ameliorate behavioral symptoms that interfere with the patient's ability to participate in educational, social, work, and family systems. Agents that have shown positive clinical effects in the treatment of children with autism and PDDs are reviewed in this article. CONCLUSIONS: Autism is a complex developmental disorder representing a heterogeneous group of individuals with similar symptomatologies and multiple biologic etiologies. Present pharmacotherapeutic intervention seeks to resolve behavioral symptoms. Treatment of autism and PDDs requires appropriate delineation of the behaviors and neurobiologic disorders associated with each patient. No single therapeutic agent, or combination thereof, is appropriate for the treatment of all children and adults with autism or PDDs.

39. Gualtieri, C.T. The functional neuroanatomy of psychiatric treatments. *Psychiatr Clin North Am* 14**:** 113-124, 1991.

The attraction of this kind of model-building is its rigor. There is an unhealthy indiscipline to psychiatry as long as it remains purely phenomenologic. Clouds are described, then other clouds; then they are related, one to another; then new

clouds form, and they too are described. It is a process that could go on forever, but it is too nebulous to win support for very much longer. In contrast, psychiatry that is based on etiopathogenesis, on brain maps, has rigor. It is either true or untrue, like the three models presented above. If it is true, like the frontal lobe hypothesis of dopamine agonists, it will lead somewhere. If it is only a small part of the truth, like the kindling theory of temporal lobe drugs, it will be supplanted, before long, by a more cogent hypothesis. What is more attractive about this kind of thinking, however, is the practical side of it. The KBS hypothesis of autism is not simply an idle exercise. It is a guide to a specific approach to behavioral treatment and a warning to eschew the mindless search for a pharmacologic "bullet." Theories, like every other living thing, have to do something useful before they are ultimately set aside. At least this one lends some common sense to day-to-day events.

40. Hollander, E., Phillips, A., King, B.H., Guthrie, D., Aman, M.G., Law, P., Owley, T., and Robinson, R. Impact of recent findings on study design of future autism clinical trials. *CNS Spectr* 9**:** 49-56, 2004.

There are specific challenges to studying the design of pharmacologic trials in child/adolescent and adult autism, such as subject stratification and parallel versus crossover designs. This article describes how optimal study design is influenced by subject selection and outcome measures chosen. Lessons learned in study design from the Research Units on Pediatric Psychopharmacology Autism Network trial with risperidone, Seaver Center trials with fluoxetine and valproate, Dartmouth trials with amantadine, and National Institutes of Health secretin trials are highlighted. The Internet System for Assessing Autistic Children system for managing multicenter clinical trials in autism and statistical issues in autism research are also described.

41. Hunsinger, D.M., Nguyen, T., Zebraski, S.E., and Raffa, R.B. Is there a basis for novel pharmacotherapy of autism? *Life Sci* 67**:** 1667-1682, 2000.

No medication has yet been shown to consistently alter the symptoms or the course of autism in the majority of patients. The present pharmacotherapy is mainly palliative and sometimes effective in attenuating specific behaviors. The search for better treatment involves examination of the underlying pathophysiology, the genetic or environmental etiology (including possible iatrogenic causes), and assessment of the clinically-generated evidence of efficacy, including serendipitous or unexplained findings. Subtle neuroanatomic and neurochemical changes are being explored and there are anecdotal reports or limited clinical trials that suggest some therapy might be possible. Secretin is a surprising recent addition to the list of candidates. The pharmacologic mechanism by which these agents might provide such effect is not clear, but hypotheses are beginning to emerge. In addition, the prevention of some uncertain number of autism cases is being investigated by examination of certain vaccinations as putative causative or contributory factors. These topics are

reviewed in this article, which has the additional purpose of stimulating novel drug discovery efforts for this enigmatic disorder.

42. Jesner, O.S., Aref-Adib, M., and Coren, E. Risperidone for autism spectrum disorder. *Cochrane Database Syst Rev***:** CD005040, 2007.

BACKGROUND: Autistic spectrum disorder encompasses a wide variety of behavioural and communicative problems. Both the core features and non-core features of autism have been targeted in a variety of therapies. Atypical antipsychotic medications, including risperidone, have been used for symptom and behaviour improvement and have shown beneficial outcomes, particularly in certain aspects of the disorder. However, given the nature of the condition presenting in young patients, the risks of these potentially long term therapies must be weighed against the benefits. OBJECTIVES: To determine the efficacy and safety of risperidone for people with autism spectrum disorder. SEARCH STRATEGY: Electronic databases: CENTRAL (Cochrane Central Register of Controlled Trials) 2006 (Issue 3); MEDLINE (1966 to April 2006); EMBASE (1980 to April 2006);PsycINFO (1887 to April 2006); CINAHL (1982 to April 2006); LILACS (1982 to April 2006); Clinicaltrials.gov (USA) (accessed April 2006); ZETOC (1993 to April 2006); National Research Register (NRR) (UK) 2006 (Issue 1) were searched. In addition further data were retrieved through contact with pharmaceutical companies and authors of published trials. SELECTION CRITERIA: All randomised controlled trials of risperidone versus placebo for patients with a diagnosis of autism spectrum disorder. All trials had to have at least one standardised outcome measure used for both intervention and control group. DATA COLLECTION AND ANALYSIS: Data were independently evaluated and analysed by the reviewers. Data were evaluated at the end of each randomised controlled trial. Unpublished data were also considered and analysed. MAIN RESULTS: Only three randomised controlled trials were identified. Meta-analysis was possible for three outcomes. Some evidence of the benefits of risperidone in irritability, repetition and social withdrawal were apparent. These must however be considered against the adverse effects, the most prominent being weight gain. AUTHORS' CONCLUSIONS: Risperidone can be beneficial in some features of autism. However there are limited data available from studies with small sample sizes. In addition, there lacks a single standardised outcome measure allowing adequate comparison of studies, and long-term followup is also lacking. Further research is necessary to determine the efficacy pf risperidone in clinical practice.

43. Johnson, K.P., and Malow, B.A. Assessment and pharmacologic treatment of sleep disturbance in autism. *Child Adolesc Psychiatr Clin N Am* 17**:** 773-785, viii, 2008.

Like children with other developmental disabilities, children with autism spectrum disorders suffer with sleep problems at a higher rate than do typically developing children. There is a growing recognition that addressing these sleep problems

may improve daytime functioning and decrease family stress. Presented here is a discussion of the sleep problems experienced by children with autism spectrum disorders, focusing on appropriate assessment and pharmacologic treatment.

44. Kaminska, B., Czaja, M., Kozielska, E., Mazur, E., and Korzon, M. Use of secretin in the treatment of childhood autism. *Med Sci Monit* 8**:** RA22-26, 2002.

The paper presents current views concerning childhood autism. The authors present the concepts of etiology of this disorder, emphasizing the role of negative psychical stimuli in early childhood and the role of mother's contact with the child. Organic factors, including genetic background, developmental abnormalities of the nervous system, teratogenic factors and perinatal traumas are also taken into consideration. The role of metabolic factors and enterohormones, particularly those belonging to the secretin group and their effect on the function of the gastrointestinal tract and central nervous system is emphasized. We discuss signs which may be indicative of first symptoms of autism in different age groups. A typical symptom of autism is no development of speech, observed from infancy, taking the form of complete mutism at later stages. It has been emphasized that most pathologic symptoms result from altered perception of external stimuli, which arouse fear and anxiety. Autistic patients may suffer from gastrointestinal tract disturbances such as abdominal pains and diarrhea. Methods used hitherto in the therapy of childhood autism, mainly by psychologists and psychiatrists, as well as some attempts of pharmacological treatment, are presented. The structure and function of secretin, as well as its effects on the motor and secretory function of the stomach and the exocrine function of the pancreas are discussed. The role of secretin in diagnostic tests, among others in the diagnosis of gastrinoma, is emphasized. We also present the history of the application of secretin in the therapy of childhood autism.

45. Kern, J.K., Espinoza, E., and Trivedi, M.H. The effectiveness of secretin in the management of autism. *Expert Opin Pharmacother* 5**:** 379-387, 2004.

Autism is a complex neurological disorder that severely impacts a child's ability to communicate and interact socially. Many treatments have attempted to alleviate the symptoms of autism, but with limited success. After reports of improvements in autistic children who received secretin, this hormone became popular as a possible treatment for autism. Since then, the interest in secretin has greatly increased, as well as the demand for secretin by parents of autistic children. However, there is still limited experimental evidence that supports its effectiveness. Many biological studies and clinical trials were conducted to test the effectiveness of secretin in treating autism. This review discusses the autistic disorder, instruments used in the trials, and reports the findings of some of these studies.

46. King, B.H., and Bostic, J.Q. An update on pharmacologic treatments for autism spectrum disorders. *Child Adolesc Psychiatr Clin N Am* 15**:** 161-175, 2006.

Increasingly recognized over the past 20 years, autism spectrum disorders (ASD) are heterogeneous. Medication treatments remain fundamentally ameliorative, so prioritizing symptoms and matching medications to the patient's constellation of symptoms remains the psychopharmacologic approach to ASD. Atypical antipsychotic medications and glutamatergic agents are receiving increased attention, and antidepressants are being examined for specific symptoms and for younger patients who have autism. Large multisite networks (Research Units on Pediatric Psychopharmacology; Studies to Advance Autism Research and Treatment) have been constructed to expedite studies to elucidate effective treatments for ASD. Findings from these networks are coupled with those from recent independent trials.

47. Kolevzon, A., Mathewson, K.A., and Hollander, E. Selective serotonin reuptake inhibitors in autism: a review of efficacy and tolerability. *J Clin Psychiatry* 67**:** 407-414, 2006.

BACKGROUND: Awareness of the impact and prevalence of autism spectrum disorders has significantly increased in recent years. Given the dearth of reliable interventions, there is great interest in demonstrating efficacy of the various treatment options. A growing body of evidence links autism spectrum disorders to abnormalities in serotonin function, and the selective serotonin reuptake inhibitors (SSRIs) have been utilized to target various symptoms of the disorders. This article reviews the available data on the efficacy and tolerability of SSRIs in individuals with autism spectrum disorders. Objectives for future research in this area will also be suggested. DATA SOURCES AND STUDY SELECTION: The entire PubMed database including MEDLINE (1966-July 2005) was searched for English-language biomedical articles. Search terms included autism, autism spectrum disorder, citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, pervasive developmental disorder, selective serotonin reuptake inhibitors, and sertraline. All clinical trials evaluating treatment outcomes associated with the use of SSRIs in managing symptoms of autism that were identified in the search were reviewed. All randomized controlled trials and open-label trials were included in this review. Case reports and case series were excluded. DATA SYNTHESIS: We identified 3 randomized controlled trials and 10 open-label trials or retrospective chart reviews on the use of SSRIs in autism and autism spectrum disorders. The SSRIs that have been studied in autism spectrum disorders are citalopram, escitalopram, fluoxetine, fluvoxamine, and sertraline. Most studies demonstrate significant improvement in global functioning and in symptoms associated with anxiety and repetitive behaviors. While side effects were generally considered to be mild, increased activation and agitation occurred in some subjects. CONCLUSIONS: Although SSRIs may demonstrate therapeutic benefit in autism spectrum disorders, methodological weaknesses of many of the clinical trials suggest the need for additional randomized controlled trials. Furthermore, given the increased awareness of the dangers associated with SSRI-induced activation and agitation, the presence of these side effects in

the autistic population warrants closer attention to dosage, titration, and subject selection issues.

48. Leskovec, T.J., Rowles, B.M., and Findling, R.L. Pharmacological treatment options for autism spectrum disorders in children and adolescents. *Harv Rev Psychiatry* 16**:** 97-112, 2008.

    Autism and other pervasive developmental disorders (PDDs) are frequently associated with dysfunctional behaviors and are characterized by deficits in socialization, communication, and behavioral rigidity. Despite the absence of a pharmacological cure for PDDs, many of the dysfunctional, coinciding behaviors may be treated pharmacologically. This article reviews what is known about the efficacy and tolerability of pharmacological interventions for the treatment of children and adolescents suffering from autistic spectrum disorders.

49. Malone, R.P., Gratz, S.S., Delaney, M.A., and Hyman, S.B. Advances in drug treatments for children and adolescents with autism and other pervasive developmental disorders. *CNS Drugs* 19**:** 923-934, 2005.

    Autism is a disorder characterised by abnormalities in language and social development, and repetitive behaviours. Antipsychotics, including haloperidol and risperidone, are the most widely studied drugs for reducing symptoms in children and adolescents with autism. When administered at relatively low dosages, antipsychotics have been shown to reduce repetitive behaviours (stereotypies) and social withdrawal, as well as a number of related symptoms, such as hyperactivity, aggression, self-abusive behaviour, temper tantrums, lability of mood and irritability. Adverse effects of antipsychotics include sedation, dizziness, increased appetite, weight gain, changes in the electrocardiogram parameters, drooling, hyperprolactinemia and a risk of drug-related dyskinesias. Other agents have been less well studied for the treatment of autism, but there are suggestive data regarding their safety and efficacy. Of these agents, a number have been investigated, based on theories about the aetiology of autism, including SSRIs and naltrexone, although the efficacy of these agents has been limited. Stimulant drugs have been shown to reduce hyperactivity and improve focus, but they may cause behavioural worsening, weight loss and stereotypies de novo. Secretin is a treatment that has received much media attention after reports of efficacy from small open studies, but all controlled studies have failed to show any benefit. In autism, alternative treatments have also been used, but none have shown benefit in well-designed studies.

50. Malone, R.P., and Waheed, A. The role of antipsychotics in the management of behavioural symptoms in children and adolescents with autism. *Drugs* 69**:** 535-548, 2009.

    Autistic disorder or autism is a serious childhood-onset disorder that affects all areas of development, particularly in the areas of language, communication and

reciprocal social interaction. Patients with autistic disorder typically demonstrate repetitiveness and a restricted repertoire of behaviour. Additionally, they also have a number of disruptive symptoms that may be reduced by drug treatment, including severe tantrums, hyperactivity and lability. Antipsychotic drugs are the agents that are the most critically studied as treatments for reducing symptoms. Both first- and second-generation antipsychotics have shown safety and efficacy in short- and long-term studies in autism. The most studied antipsychotic drugs include haloperidol and risperidone, although studies of other antipsychotic drugs are underway. Safety concerns associated with treatment include the risk of drug-related dyskinesias, which is greater with the first-generation drugs, and the risk of weight gain and associated metabolic problems (i.e. increases in glucose and lipids), which is greater with second-generation agents. Prescription of antipsychotic drugs requires careful monitoring because of these safety risks and the likelihood of long-term use. Drug administration should be initiated at low dosages and subsequent dosage changes should be based on tolerability and clinical response.

51. McCracken, J.T. Safety issues with drug therapies for autism spectrum disorders. *J Clin Psychiatry* 66 Suppl 10**:** 32-37, 2005.

    Although currently no medication has been approved to treat autism spectrum disorders, survey data show that community practitioners are prescribing a broad range of medication treatments, including, but not limited to, antidepressants, stimulants, antipsychotics, alpha agonists, and anticonvulsants. Patients with autism spectrum disorders are also taking alternative treatments, including herbal remedies, immunologic treatments, and vitamin therapies, which may themselves produce side effects and/or create drug interactions with traditional medications. Although short-term data on the efficacy and safety of commonly prescribed treatments for autism spectrum disorders are increasing, few data are currently available on long-term treatment for autism spectrum disorders, but available studies and clinical experience can offer preliminary recommendations on the safety of and monitoring needs for the medications currently used for these disorders. Monitoring the safety and tolerability of drugs used in patients with these disorders should minimize the burden of side effects and optimize treatment outcome.

52. McDougle, C.J., Scahill, L., McCracken, J.T., Aman, M.G., Tierney, E., Arnold, L.E., Freeman, B.J., Martin, A., McGough, J.J., Cronin, P., Posey, D.J., Riddle, M.A., Ritz, L., Swiezy, N.B., Vitiello, B., Volkmar, F.R., Votolato, N.A., and Walson, P. Research Units on Pediatric Psychopharmacology (RUPP) Autism Network. Background and rationale for an initial controlled study of risperidone. *Child Adolesc Psychiatr Clin N Am* 9**:** 201-224, 2000.

    This article has reviewed the background and rationale for the choice of risperidone as the first drug to be studied by the RUPP Autism Network. Risperidone has potent effects on 5-HT and DA neuronal systems, both of which

have been implicated in the pathophysiology of autism. Unlike the typical antipsychotics, haloperidol and pimozide, which have been shown to be effective for reducing many of the maladaptive behaviors associated with autism, risperidone's 5-HT2A/DA D2 ratio of receptor blockade appears to produce a lower risk of acute and chronic extrapyramidal side effects, as well as enhanced efficacy for the "negative" symptoms of autism. Indirect clinical and preclinical evidence supports the use of risperidone to treat impaired social behavior, interfering repetitive phenomena, and aggression, targets of pharmacotherapy for many patients with autism. Numerous published open-label trials in children and adolescents with autism and related PDDs and one double-blind, placebo-controlled study in adults suggest that risperidone has promise for the treatment of children and adolescents with autism. Because most of these studies have been short-term, open-label trials in small samples, however, a large-scale controlled study of risperidone in children and adolescents with autism is needed to confirm these results. Finally, because it is likely that children who demonstrate short-term benefit from risperidone will remain on the medication indefinitely, the longer-term effectiveness and safety of risperidone in this population also needs to be determined. The design of this study and the assessments used are described separately.

53. McDougle, C.J., Stigler, K.A., Erickson, C.A., and Posey, D.J. Atypical antipsychotics in children and adolescents with autistic and other pervasive developmental disorders. *J Clin Psychiatry* 69 Suppl 4**:** 15-20, 2008.

    Atypical antipsychotics are emerging as the first-line pharmacologic treatment for irritability (i.e., aggression, self-injurious behavior, and severe tantrums) in children and adolescents with autistic and other pervasive developmental disorders. Results from placebo-controlled and open-label studies of clozapine, risperidone, olanzapine, quetiapine, ziprasidone, and aripiprazole in this subject population are reviewed. Additional placebo-controlled trials and studies of longer-term safety and tolerability are needed.

54. McDougle, C.J., Stigler, K.A., and Posey, D.J. Treatment of aggression in children and adolescents with autism and conduct disorder. *J Clin Psychiatry* 64 Suppl 4**:** 16-25, 2003.

    The optimal clinical management of aggression in children and adolescents involves both behavioral and pharmacologic intervention strategies. This article reviews medication treatments for youngsters with autistic disorder and conduct disorder, conditions for which the pharmacologic management of aggression is often necessary. Efficacy results and associated adverse effects from selected clinical trials of most classes of psychotropic medications are discussed. While preliminary progress has been made in the development of medication treatments for these serious disorders of youth, additional controlled research and longitudinal studies are needed to better understand the efficacy and tolerability of currently available compounds within each diagnostic group.

55. McGinnis, W.R. Oxidative stress in autism. *Altern Ther Health Med* 10**:** 22-36; quiz 37, 92, 2004.

STATEMENT OF PURPOSE: Indirect markers are consistent with greater oxidative stress in autism. They include greater free-radical production, impaired energetics and cholinergics, and higher excitotoxic markers. Brain and gut, both abnormal in autism, are particularly sensitive to oxidative injury. Higher red-cell lipid peroxides and urinary isoprostanes in autism signify greater oxidative damage to biomolecules. A preliminary study found accelerated lipofuscin deposition--consistent with oxidative injury to autistic brain in cortical areas serving language and communication. Double-blind, placebo-controlled trials of potent antioxidants--vitamin C or carnosine--significantly improved autistic behavior. Benefits from these and other nutritional interventions may be due to reduction of oxidative stress. Understanding the role of oxidative stress may help illuminate the pathophysiology of autism, its environmental and genetic influences, new treatments, and prevention. OBJECTIVES: Upon completion of this article, participants should be able to: 1. Be aware of laboratory and clinical evidence of greater oxidative stress in autism. 2. Understand how gut, brain, nutritional, and toxic status in autism are consistent with greater oxidative stress. 3. Describe how anti-oxidant nutrients are used in the contemporary treatment of autism.

56. McQueen, J.M., and Heck, A.M. Secretin for the treatment of autism. *Ann Pharmacother* 36**:** 305-311, 2002.

OBJECTIVE: To evaluate the role of secretin in the treatment of children with autism. DATA SOURCE: Literature was assessed through MEDLINE, EMBASE, BIOSIS (November 1998-August 2001), and the World Wide Web. Literature included scientific studies, anecdotal reports, and meeting abstracts. Key search terms included autism and secretin. DATA SYNTHESIS: Autism is a pervasive developmental disorder. Although several treatments exist, no cure has been identified. New information suggests that secretin may be beneficial for this disorder. A critical evaluation of current information about the use of secretin in autism was conducted. CONCLUSIONS: Currently, several anecdotal reports and a few controlled trials with conflicting results have been published regarding the use of secretin in autism. Further studies should be conducted to determine the safety and efficacy of secretin for autism.

57. Mikhail, A.G., and King, B.H. Autism spectrum disorders: update of evaluation and treatment. *Curr Psychiatry Rep* 3**:** 361-365, 2001.

Autistic spectrum disorders are a group of neurodevelopmental conditions that are increasingly capturing the attention of clinicians and investigators. New insights from genetics and neuropathophysiology of autism will increasingly inform treatment. Presently, individualized treatment approaches typically include

a mix of behavioral and, occasionally, pharmacotherapeutic strategies. Concerning the latter, exquisite sensitivity to medication is not uncommon in some children with autism.

58. Moore, M.L., Eichner, S.F., and Jones, J.R. Treating functional impairment of autism with selective serotonin-reuptake inhibitors. *Ann Pharmacother* 38**:** 1515-1519, 2004.

OBJECTIVE: To review literature describing use of selective serotonin-reuptake inhibitors (SSRIs) in the management of functional impairments associated with autistic disorder. DATA SOURCES: EMBASE (1980-3rd quarter of 2003), International Pharmaceutical Abstracts (1970-August 2003), and MEDLINE (1966-August 2003) were searched. Search terms included autism, autistic disorder, citalopram, fluoxetine, fluvoxamine, paroxetine, selective serotonin-reuptake inhibitors, and sertraline. DATA SYNTHESIS: Studies and case reports evaluating treatment outcomes associated with the use of SSRIs in managing impairments of autism were reviewed. Multiple SSRI dosing ranges were evaluated in autistic patients of different ages with various functional impairments. No specific SSRI or dose range has been shown to improve a specific autistic symptom although some patients have demonstrated improvements. CONCLUSIONS: Benefits with SSRIs in treating functional impairments in autism have been observed. Response to therapy and adverse effects are individualized. Current evidence does not support selection of one SSRI over another for any impairment associated with autism.

59. Myers, S.M. The status of pharmacotherapy for autism spectrum disorders. *Expert Opin Pharmacother* 8**:** 1579-1603, 2007.

The use of pharmacologic agents as a component of treatment for children and adults with autism spectrum disorders is common and a substantial body of literature describing controlled and open-label clinical trials now exists to guide clinical practice. Empiric evidence of efficacy of risperidone, methylphenidate and some selective serotonin re-uptake inhibitors for maladaptive behaviors commonly associated with autism spectrum disorders has increased substantially in recent years. Preliminary controlled trials of valproate, atomoxetine, alpha-2 adrenergic agonists and olanzapine are promising. In addition to traditional psychotropic medications, investigators have examined the potential role of a variety of agents with glutamatergic or cholinergic mechanisms, and the results warrant further investigation. Although psychotropic medications are effective in treating some important associated behaviors, evidence of significant impact on the core features of autism spectrum disorders is very limited.

60. Nye, C., and Brice, A. Combined vitamin B6-magnesium treatment in autism spectrum disorder. *Cochrane Database Syst Rev***:** CD003497, 2002.

BACKGROUND: The use of mega-vitamin intervention began in the early 1950's

with the treatment of schizophrenic patients. Pyroxidine (vitamin B6) was first used with children diagnosed with "autism syndrome" when speech and language improvement was observed in some children as a result of large doses of B6. A number of published studies attempted to assess the effects of vitamin B6-Mg (Mg was found to reduce undesirable side effects from B6) on a variety of characteristics such as verbal communication, non-verbal communication, interpersonal skills, and physiological function, in individuals with autism. OBJECTIVES: To determine the efficacy of vitamin B6 and magnesium (B6-Mg) for treating social, communication and behavioural responses of children and adults with autism. SEARCH STRATEGY: We searched the Cochrane Controlled Trials Register (Cochrane Library, Issue 2, 2002), MEDLINE (1966- January 2002), EMBASE (1980-January 2002), PsychINFO (1887 - January 2002), Dissertation Abstracts International (1861 - January 2002). The search engine FirstSearch was also used (January 2002). Reference lists for all the obtained studies and other review articles were examined for additional studies. SELECTION CRITERIA: All studies in which the participants were randomly allocated prior to intervention and in which outcomes were compared to either a placebo or non-treated group were included. DATA COLLECTION AND ANALYSIS: Two reviewers independently evaluated all potential studies identified as indicated above for inclusion. MAIN RESULTS: Two trials were included in the review. Both studies used a double-blind crossover design. One study (Tolbert 1993) provided insufficient data to conduct an analysis. The senior author was contacted for supporting data but was unable to provide the needed information. The remaining study (Findling, 1997) yielded no significant differences between treatment and placebo group performances following the B6 intervention on measures of social interaction, communication, compulsivity, impulsivity, or hyperactivity. REVIEWER'S CONCLUSIONS: Due to the small number of studies, the methodological quality of studies, and small sample sizes, no recommendation can be advanced regarding the use of B6-Mg as a treatment for autism.

61. Nye, C., and Brice, A. Combined vitamin B6-magnesium treatment in autism spectrum disorder. *Cochrane Database Syst Rev***:** CD003497, 2005.

BACKGROUND: The use of mega-vitamin intervention began in the 1950s with the treatment of schizophrenic patients. Pyroxidine (vitamin B6) was first used with children diagnosed with "autism syndrome" when speech and language improvement was observed in some children as a result of large doses of B6. A number of studies attempted to assess the effects of vitamin B6-Magnesium (Mg) was found to reduce undesirable side effects from B6) on characteristics such as verbal communication, non-verbal communication, interpersonal skills, and physiological function, in individuals with autism. OBJECTIVES: To determine the efficacy of vitamin B6 and magnesium (B6-Mg) for treating social, communication, and behavioural responses of children and adults with autism. SEARCH STRATEGY: We searched the Cochrane Controlled Trials Register (Cochrane Library, Issue 2, 2002), MEDLINE (1966 to January 2002), EMBASE

(1980 to January 2002), PsycINFO (1887 to January 2002), Dissertation Abstracts International (1861 to January 2002). The search engine FirstSearch was also used (January 2002). All searches were updated in April 2005. Reference lists for all the obtained studies and other review articles were examined for additional studies. SELECTION CRITERIA: All studies in which the participants had been diagnosed with autistic spectrum disorder were randomly allocated prior to intervention and in which outcomes were compared to either a placebo or non-treated group were included. DATA COLLECTION AND ANALYSIS: Two reviewers independently evaluated and extracted data from all potential studies identified for inclusion. MAIN RESULTS: This update includes a new trial (Kuriyama 2002) to bring the total of included studies to three (total n=33). One study, which used a cross-over design (Tolbert 1993) provided insufficient data to conduct an analysis. Another crossover study (Findling 1997) yielded no significant differences between treatment and placebo group performances following the B6 intervention on measures of social interaction, communication, compulsivity, impulsivity, or hyperactivity. The latest study (Kuriyama 2002) was motivated by evidence from epilepsy research and was focussed on a subgroup of children with pervasive developmental disorders (PDDs) who exhibited clinical features similar to those with pyroxidine-dependent epilepsy. This small study (n=8) only measured IQ and 'Social Quotient' and found a statistically significant benefit for IQ (5.2, 95% CI = [0.2 to 10.3]) when in the treated group, by using change scores. AUTHORS' CONCLUSIONS: Due to the small number of studies, the methodological quality of studies, and small sample sizes, no recommendation can be advanced regarding the use of B6-Mg as a treatment for autism.

62. Palermo, M.T., and Curatolo, P. Pharmacologic treatment of autism. *J Child Neurol* 19**:** 155-164, 2004.

Autism is a chronic and lifelong pervasive developmental disorder for which there is yet no effective cure, and medical management remains a major challenge for clinicians. In spite of the possible similarities with conditions that have an established pharmacotherapy, and despite improvements in some associated "problematic behaviors" following the use of available medications, effective medical treatment for the core symptoms involving language and social cognition remains elusive. The purpose of the present article is to review current biologic knowledge about autism in an attempt to correlate clinical trials with known mechanisms of disease. In addition, the need for controlled studies and for the creation of homogeneous subgroups of patients based on clinical and genetic characteristics is emphasized. The application of molecular genetic investigations and pharmacogenetics in the diagnostic work-up of autistic patients can lead to more effective individualized medical care.

63. Parikh, M.S., Kolevzon, A., and Hollander, E. Psychopharmacology of aggression in children and adolescents with autism: a critical review of efficacy and tolerability. *J Child Adolesc Psychopharmacol* 18**:** 157-178, 2008.

BACKGROUND: Autism is characterized by a clinical triad of symptoms that affect social, language, and behavioral domains. Aggression and self-injury may be associated symptoms of autism and can result in significant harm to those affected as well as marked distress for their families. The precise nature of the relationship between aggressive or self-injurious behavior (SIB) and autism remains unclear and as a result, these symptoms are treated with a broad range of pharmacological approaches. This review seeks to systematically and critically examine the evidence for the pharmacological management of aggression and SIB in children with autism spectrum disorders. METHOD: The entire PubMed database was searched for English language biomedical articles on clinical trials with medication in autism spectrum disorders. Studies were selected based on the following inclusion criteria: (1) randomized placebo-controlled trials; (2) a sample population that included children and adolescents; (3) at least one standardized assessment of aggression as a primary outcome measure of the study. RESULTS: Twenty one trials with 12 medications were identified. Five medications produced significant improvement as compared to placebo, including tianeptine, methylphenidate, risperidone, clonidine, and naltrexone. Only risperidone and methylphenidate demonstrate results that have been replicated across at least two studies. CONCLUSIONS: Although many medications have been studied under placebo-controlled conditions, few produce significant improvement. Additional placebo-controlled trials are needed to increase the number of therapeutic options available in the treatment of aggression in autism.

64. Patel, N.C., Yeh, J.Y., Shepherd, M.D., and Crismon, M.L. Secretin treatment for autistic disorder: a critical analysis. *Pharmacotherapy* 22**:** 905-914, 2002.

We assessed evidence of the effects of secretin on behavior in individuals with autistic disorder. Articles were obtained through a MEDLINE search of the English-language literature from January 1966-November 2001; all investigations and case reports on the topic were included. Press releases obtained from the World Wide Web also were included. Secretin, a gastrointestinal hormone, is suggested to improve autistic symptoms, particularly social function and communication. Two formulations, porcine and synthetic human secretin, were evaluated in humans. A small body of literature and popular belief in autistic disorder communities supported the agent's efficacy. A number of controlled clinical trials did not show improvement in autistic symptoms with secretin compared with placebo, possibly indicating no role for the drug in autistic disorder.

65. Pfeiffer, S.I., Norton, J., Nelson, L., and Shott, S. Efficacy of vitamin B6 and magnesium in the treatment of autism: a methodology review and summary of outcomes. *J Autism Dev Disord* 25**:** 481-493, 1995.

Pauling's orthomolecular hypothesis appeared in 1968, stating that some forms

of mental illness and disease are related to biochemical errors in the body. Vitamin therapy is believed to be a means of compensating for such errors. There have been few empirical studies on vitamin therapy in individuals with autism. This article presents a critical analysis of the 12 published studies located through an extensive computerized search. Studies were systematically evaluated to provide an objective assessment of empirical evidence supporting the efficacy of vitamin treatment. The majority of studies report a favorable response to vitamin treatment. However, interpretation of these positive findings needs to be tempered because of methodological shortcomings inherent in many of the studies. For example, a number of studies employed imprecise outcome measures, were based on small samples and possible repeat use of the same subjects in more than one study, did not adjust for regression effects in measuring improvement, and omitted collecting long-term follow-up data. Recommendations are offered to assist researchers in designing future investigations.

66. Posey, D.J., Erickson, C.A., and McDougle, C.J. Developing drugs for core social and communication impairment in autism. *Child Adolesc Psychiatr Clin N Am* 17**:** 787-801, viii-ix, 2008.

There are many challenges to studying drug effects on core social and language impairment in autism. Drugs such as fenfluramine, naltrexone, and secretin do not appear to be efficacious for these core symptoms. Risperidone has led to improvement in some aspects of social relatedness when used to treat irritability in autism. More research is needed on the utility of selective serotonin reuptake inhibitors, cholinergic drugs, glutamatergic drugs, and oxytocin for core autistic symptoms.

67. Posey, D.J., Erickson, C.A., Stigler, K.A., and McDougle, C.J. The use of selective serotonin reuptake inhibitors in autism and related disorders. *J Child Adolesc Psychopharmacol* 16**:** 181-186, 2006.

This paper reviews the published literature on the use of selective serotonin reuptake inhibitors (SSRIs) for the treatment of symptoms associated with autistic disorder and other pervasive developmental disorders (PDDs) in both children and adults. To date, placebocontrolled studies of SSRIs have involved only fluvoxamine (in children and adults) and fluoxetine (in children). Open-label and retrospective studies of all other SSRIs in PDDs have also been published that suggest effectiveness. Despite these positive reports, there continues to be questions about the tolerability and appropriate dosing of SSRIs in children with PDDs. Because of the limited number of placebo-controlled studies, definitive conclusions about the role SSRIs should play in the clinical treatment of children with PDDs cannot be drawn. Larger, placebo-controlled studies of SSRIs are needed to guide clinical treatment.

68. Posey, D.J., and McDougle, C.J. The pharmacotherapy of target symptoms

associated with autistic disorder and other pervasive developmental disorders. *Harv Rev Psychiatry* 8**:** 45-63, 2000.

Research into the pharmacotherapy of autistic disorder has steadily increased over the past two decades. Several psychoactive medications have shown efficacy for selected symptoms of autistic disorder and can be used to augment critical educational and behavioral interventions that are the mainstays of treatment. A comprehensive review of medication trials conducted in individuals with autistic disorder and other pervasive developmental disorders is presented. The typical antipsychotic haloperidol is the best-studied medication in autistic disorder but is associated with a high rate of dyskinesias. Investigations to date suggest that the atypical antipsychotics such as risperidone have efficacy for certain symptoms of autistic disorder and may be better tolerated than typical antipsychotics. Preliminary results from trials with serotonin-reuptake inhibitors are favorable, although efficacy has not been demonstrated in younger age groups. Recent controlled studies of nalfrexone suggest that the drug has minimal efficacy. In two small controlled investigations, clonidine was more effective than placebo for a variety of symptoms, including hyperactivity and irritability; in one of these studies, however, the majority of patients relapsed within several months. Psychostimulants reduced hyperactivity and irritability in one small double-blind crossover study in children with autistic disorder, although these agents are frequently reported to exacerbate irritability, insomnia, and aggression in clinical populations. Recent controlled trials of secretin have not shown efficacy compared to placebo. Several other medications, including buspirone, mood stabilizers, and beta-blockers, have produced symptom reduction in some open-label studies and may warrant controlled investigation.

69. Posey, D.J., and McDougle, C.J. Pharmacotherapeutic management of autism. *Expert Opin Pharmacother* 2**:** 587-600, 2001.

There are no medications that are specifically marketed for the treatment of autism. There does exist, however, an extensive body of literature describing both open-label and controlled studies of medications in the treatment of both children and adults with autism. Some of the better-studied medications (including haloperidol and risperidone) are often efficacious in treating associated symptoms of autism but can also cause unacceptable adverse effects. Early studies of serotonin re-uptake inhibitors appear promising but may not be indicated for all age groups. Small, controlled studies of methylphenidate and clonidine indicate a possible role for these medications in the treatment of hyperactivity in autism. No medications have been proven to be efficacious in the treatment of the core social or communication impairment seen in autism. Current pharmacological management is best aimed at target symptoms that have been demonstrated to respond to medication in treatment studies.

70. Posey, D.J., and McDougle, C.J. The pathophysiology and treatment of autism. *Curr Psychiatry Rep* 3**:** 101-108, 2001.

This article critically reviews research done in the past 2 years concerning the pathophysiology and treatment of autism. Recent research in genetics, neuroimaging, neurochemistry, and pharmacologic treatment has advanced the body of knowledge about the pathophysiology of autism. Relatively new imaging technologies (eg, positron emission tomography) are increasingly being applied to the study of subjects with autism and have produced promising results that await replication. Neurochemical and challenge studies continue to suggest a role for 5-HT dysregulation in autism. Additional research is needed to determine the role of neuroendocrine and autoimmune factors in autism. Significant gains have been made in determining which pharmacologic treatments are efficacious in autism. Additional research is needed on agents that might ameliorate the core and associated symptoms of autism.

71. Posey, D.J., and McDougle, C.J. Risperidone: a potential treatment for autism. *Curr Opin Investig Drugs* 3**:** 1212-1216, 2002.

Autistic disorder (autism) is a neuropsychiatric syndrome characterized by marked deficits in reciprocal social relatedness, communication impairment and a narrow range of interests and/or repetitive behaviors. Autism is frequently associated with, but distinct from, mental retardation. It is classified as a subtype of pervasive developmental disorder (PDD) along with 'PDD not otherwise specified' (NOS) and Asperger's disorder. These disorders have in common marked impairments in social relatedness. Individuals with autism may also have other symptoms that become the primary focus of psychiatric treatment. These associated symptoms include aggression, self-injury, irritability and anxiety.

72. Posey, D.J., Stigler, K.A., Erickson, C.A., and McDougle, C.J. Antipsychotics in the treatment of autism. *J Clin Invest* 118**:** 6-14, 2008.

Atypical antipsychotics have become indispensable in the treatment of a variety of symptoms in autism. They are frequently used to treat irritability and associated behaviors including aggression and self injury. They may also be efficacious for hyperactivity and stereotyped behavior. This review presents the rationale for the use of this drug class in autism and reviews the most important studies published on this topic to date. Significant adverse effects, including weight gain and the possibility of tardive dyskinesia, are reviewed. Future research directions are discussed.

73. Rimland, B. Controversies in the treatment of autistic children: vitamin and drug therapy. *J Child Neurol* 3 Suppl**:** S68-72, 1988.

A survey of approximately 4,000 questionnaires completed by parents of autistic children provided ratings on a variety of treatments and interventions. Among the biomedical treatments, the use of high-dosage vitamin B6 and magnesium (n = 318) received the highest ratings, with 8.5 parents reporting behavioral

improvement to every one reporting behavioral worsening. Deanol (n = 121) was next most highly rated, with 1.8 parents reporting improvement to each one reporting worsening. Fenfluramine (n = 104) was third, with a ratio of 1.5:1. Thioridazine hydrochloride (Mellaril), by far the most often used drug on the list (n = 724), was fourth with a helped-worsened ratio of 1.4:1. The research literature on the use of vitamin B6-magnesium is briefly reviewed, and mention is made of recent findings regarding high-dosage folic acid in autism and biotin in Rett syndrome.

74. Scahill, L., and Koenig, K. Pharmacotherapy in children and adolescents with pervasive developmental disorders. *J Child Adolesc Psychiatr Nurs* 12**:** 41-43, 1999.

Children with autism and the related PDDs may benefit from serotonin reuptake inhibitors such as clomipramine, fluoxetine, fluvoxamine, and sertraline for targeting repetitive thoughts and behaviors, anxiety, and depressed mood. To date, however, there are few controlled studies of these agents in children with PDD, so definitive evidence is lacking. Despite preliminary results in favor of naltrexone, neuroleptic medication appears to be effective for reducing aggression, self-injurious behavior, agitation, and stereotypies. The primary drawback with traditional neuroleptics is risk of short- and long-term side effects. The newer atypical neuroleptics have the potential for benefit with fewer extrapyramidal side effects, but more study is needed to establish their efficacy and safety. Children on neuroleptic medications should be started at the lowest possible dose, with gradual increases until clinical benefit is observed. The likelihood of untoward side effects is increased if the medication dose is increased rapidly. Baseline measurement of target behaviors can be aided by using standardized scales. The presence of abnormal movements should be assessed before initiating treatment and at regular intervals during the course of treatment--including after medication withdrawal. Weight gain is emerging as a recurrent side effect with the atypical neuroleptics. Thus, weight should be monitored, and the family should be advised about a diet baseline. As with all treatments of children with severe behavioral difficulties, pharmacotherapy should be instituted in the context of an integrated treatment plan.

75. Scott, L.J., and Dhillon, S. Risperidone: a review of its use in the treatment of irritability associated with autistic disorder in children and adolescents. *Paediatr Drugs* 9**:** 343-354, 2007.

Risperidone (Risperdal), a psychotropic atypical antipsychotic agent, is thought to act via dopamine D(2) and serotonin (5-HT [5-hydroxytryptamine])(2A) receptor antagonism. The clinical efficacy of oral risperidone in the treatment of bipolar mania and schizophrenia in adult patients is well established. In the US, risperidone is also approved for the treatment of irritability associated with autistic disorder in children and adolescents aged 5-16 years, for the treatment of schizophrenia in adolescents aged 13-17 years and, as monotherapy, for the

short-term treatment of acute manic and mixed episodes associated with bipolar I disorder in children and adolescents aged 10-17 years. Oral risperidone treatment was better than placebo treatment in reducing irritability and other behavioral symptoms associated with autistic disorder in children and adolescents in two well designed short-term trials, with these benefits maintained in those receiving risperidone for up to 6 months. The drug had a clinically manageable tolerability profile, with most adverse events being of mild to moderate intensity. There are some aspects of treatment, such as weight gain, somnolence, and hyperglycemia, that require monitoring, and the long-term safety of risperidone in children and adolescents with autistic disorder remains to be fully determined. With these issues in mind, risperidone offers a valuable emerging option for the treatment of irritability associated with autistic disorder in children and adolescents.

76. Stachnik, J.M., and Nunn-Thompson, C. Use of atypical antipsychotics in the treatment of autistic disorder. *Ann Pharmacother* 41**:** 626-634, 2007.

OBJECTIVE: To review clinical trials and reports describing the efficacy and safety of atypical antipsychotics (olanzapine, ziprasidone, quetiapine, aripiprazole) in the treatment of autistic or other pervasive developmental disorders. DATA SOURCES: English-language publications from the MEDLINE database (1966-February 2007) including clinical trials, case reports, and retrospective series were reviewed. STUDY SELECTION AND DATA EXTRACTION: Relevant data were extracted from studies of selected atypical antipsychotics in the treatment of autistic disorder in children, adolescents, and adults. Most literature found was in the form of case reports or case series; however, several open-label and double-blind trials were also identified. DATA SYNTHESIS: Autistic disorder is a chronic neurodevelopmental disorder with limited treatment options. Nonpharmacologic approaches may be the most beneficial, but pharmacologic agents are needed for some patients with significant behavioral manifestations of the disorder. The atypical antipsychotics (olanzapine, ziprasidone, quetiapine, aripiprazole) have shown some efficacy in improving certain behavioral symptoms of autistic disorder--primarily aggressiveness, hyperactivity, and self-injurious behavior. Efficacy was based on observation or changes from baseline in behavioral rating scores. Data appear to be strongest for olanzapine compared with quetiapine, with several open-label trials suggesting its efficacy. Weight gain and sedation were frequently reported adverse events with both agents. Aripiprazole has demonstrated efficacy in limited case series, with minimal adverse effects reported. CONCLUSIONS: Atypical antipsychotics represent a treatment option for symptoms associated with autistic disorder. However, these drugs do not affect the core symptoms of autistic disorder and are associated with potentially significant adverse effects. In addition, there is a lack of randomized controlled trials to determine the true efficacy and long-term safety of these agents in the pediatric population.

77. Stigler, K.A., and McDougle, C.J. Pharmacotherapy of irritability in pervasive

developmental disorders. *Child Adolesc Psychiatr Clin N Am* 17**:** 739-752, vii-viii, 2008.

Children and adolescents diagnosed with autism and related pervasive developmental disorders (PDDs) often sustain irritability, including aggression, self-injurious behavior, and tantrums. Research to date supports the use of the atypical antipsychotics as a first-line pharmacologic treatment for this target symptom domain in PDDs. Currently, the atypical antipsychotic risperidone is the only medication approved by the US Food and Drug Administration for irritability in youth with autism. Additional large-scale, placebo-controlled studies of other medications are needed to determine their efficacy for the treatment of irritability in this diagnostic group.

78. Sturmey, P. Secretin is an ineffective treatment for pervasive developmental disabilities: a review of 15 double-blind randomized controlled trials. *Res Dev Disabil* 26**:** 87-97, 2005.

In 1998, Horvath et al. [Horvath, K., Stefanatos, G., Sokolski, K. N., Wachtel, R., Nabors, L., & Tildon, J. T. (1998). Improved social and language skills after secretin administration in patients with autism spectrum disorders. Journal of the Association of the Academy of Minority Physicians, 9, 9-15] reported an uncontrolled trial of secretin with three participants with autism, which apparently resulted in significant behavioral improvement. Subsequently, secretin was widely used. Sandler et al. [Sandler, A. D., Sutton, K. A., SeWeese, J., Girardi, M. A., Sheppard, V., & Bodfish, J. W. (1999). Lack of benefit of a single dose of synthetic human secretin in the treatment of autism and pervasive and developmental disorder. The New England Journal of Medicine, 341, 1801-1806] reported the first double-blind trial of secretin with negative results. This article is a review of 15 double-blind trials of secretin. Almost none of the studies reported any significant effects and none concluded that secretin was effective. Transient effects of secretin, including both minor benefits and behavioral deterioration were reported, probably due to multiple statistical tests. Four papers reported data on differential responding in sub-groups of participants, including those with gastrointestinal symptoms. These effects were not replicable. At this time there is no robust evidence that secretin is an effective treatment for pervasive developmental disorders.

79. Theoharides, T.C., Doyle, R., Francis, K., Conti, P., and Kalogeromitros, D. Novel therapeutic targets for autism. *Trends Pharmacol Sci* 29**:** 375-382, 2008.

Autism spectrum disorders (ASDs) are pervasive neurodevelopmental disorders, diagnosed in early childhood when acquired skills are lost or the acquisition of new skills becomes delayed. ASDs are associated with varying degrees of dysfunctional communication and social skills, in addition to repetitive and stereotypic behaviors. The diagnosis has increased considerably to approximately one in 180 people, but it is not clear whether this is because of a

higher prevalence of the disorder, improved awareness by clinicians or a combination of both. There are no defined mechanisms of pathogenesis or curative therapy presently available. Oxidative stress, overactivation of the hypothalamic-pituitary-adrenal axis and increased gut-blood-brain-barrier permeability might be involved. The scope of this article is to integrate these findings and present the opinion that non-allergic activation of gastrointestinal and brain mast cells could contribute to many of the pathologic findings and provide unique targets for ASD therapy. We make suggestions for new research directives and possible novel therapies from readily available molecules.

80. Tsai, L.Y. Psychopharmacology in autism. *Psychosom Med* 61**:** 651-665, 1999.

Autism is a neurobiological disorder. The core clinical features of autism include impairment in social interaction, impairments in verbal and nonverbal communication, and restricted, repetitive, and stereotyped patterns of behavior, interests, and activities. Autism often has coexisting neuropsychiatric disorders, including seizure disorders, attention deficit hyperactivity disorder, affective disorders, anxiety disorder, obsessive-compulsive disorder, and Tourette disorder. No etiology-based treatment modality has been developed to cure individuals with autism. However, comprehensive intervention, including parental counseling, behavior modification, special education in a highly structured environment, sensory integration training, speech therapy, social skill training, and medication, has demonstrated significant treatment effects in many individuals with autism. Findings from preliminary studies of major neurotransmitters and other neurochemical agents strongly suggest that neurochemical factors play a major role in autism. The findings also provide the rationale for psychopharmacotherapy in individuals with autism. This article reviews studies of neurochemical systems and related psychopharmacological research in autism and related neuropsychiatric disorders. Clinical indications for pharmacotherapy are described, and uses of various medications are suggested. This article also discusses new avenues of investigation that may lead to the development of more effective medication treatments in persons with autism.

81. Tuchman, R. AEDs and psychotropic drugs in children with autism and epilepsy. *Ment Retard Dev Disabil Res Rev* 10**:** 135-138, 2004.

The efficacy of antiepileptic drugs (AEDs) and psychotropic medications in children with autism is limited to the treatment of seizures or to specific behaviors such as irritability, impulsivity, hyperactivity, repetitive behaviors, or aggression. The reliability and value of the available data--to determine the efficacy of these medications in autism--are limited by lack of controlled clinical trials, the small number of subjects, the heterogeneity of the population studied, and the brief duration of most drug trials. Indeed, few controlled clinical trials using AEDs in autism, with or without seizures, have been conducted. Because some AEDs also have a positive effect on mood, the benefits that children with autism sometimes obtain from these medications may not be due to the treatment of the

abnormal electrical activity or the seizures per se but to an effect on common neuronal systems responsible for both behavior and epilepsy. The relationship between epilepsy and autism, and specifically the effects that abnormal electrical activity may have on the developing brain, may provide some valuable insights into the type of studies that are needed to help us understand the pathophysiology of autism.

82. Volkmar, F.R. Pharmacological interventions in autism: theoretical and practical issues. *J Clin Child Psychol* 30**:** 80-87, 2001.

Focused on issues of drug treatment in relation to autism. Pharmacological treatment studies in autism are complicated by various factors including a tremendous range of syndrome expression, a lack of robust animal models of the disorder, and various methodological problems. Theories have tended to follow treatments, and various neurochemical systems have been the focus of study. Neurochemical systems potentially implicated include those involving dopamine, norepinephrine, serotonin, and neuropeptides. The dopaminergic system has been the most extensively studied. Treatments developed are effective relative to certain disabling symptoms but "core" problems (e.g., in social relatedness and communication) appear less responsive to medications. The development of new approaches to assessment, including integration of behavioral and pharmacological approaches, is an important research priority.

83. Walker, M.A. Treatment of autism spectrum disorders: neurotransmitter signaling pathways involved in motivation and reward as therapeutic targets. *Expert Opin Ther Targets* 12**:** 949-967, 2008.

BACKGROUND: There is a growing body of literature describing the etiology of autism spectrum disorders (ASD). Some of the targets suggested belong to neurochemical transmitter pathways implicated in the behavior and motivation reward pathway. OBJECTIVE: To examine data linking potential targets to ASD and the feasibility of developing drugs targeting these pathways. While the inhibitors are mostly being developed for other indications, it is beneficial to examine them to determine the responsiveness of the targets to small-molecule modulation. METHODS: A search in Medline and Scifinder for articles concerning relevant targets in the context of ASD and their relation to the reward signaling pathway. RESULTS: There is evidence suggesting that behaviors controlled by these targets are related to behaviors exhibited by individuals with ASD. The targets appear to be involved in neurotransmitter pathways controlling motivation and reward, further implicating this system in ASD. Sufficient research has been conducted to identify lead compounds for discovering agents for treatment of ASD.

84. West, L., Brunssen, S.H., and Waldrop, J. Review of the evidence for treatment of children with autism with selective serotonin reuptake inhibitors. *J Spec Pediatr Nurs* 14**:** 183-191, 2009.

PURPOSE: To review the potential role of serotonin dysregulation in autism and the efficacy of selective serotonin reuptake inhibitors (SSRIs) in treating core deficits and associated symptoms of autism in children. The literature was searched for reports of SSRI use in children with autism. Data are presented from prospective clinical trials that evaluated treatment outcomes. CONCLUSIONS: Some SSRIs show moderate success in managing specific behaviors. Only fluoxetine shows evidence of decreasing global autism severity. PRACTICE IMPLICATION: Definitive conclusions concerning selection criteria, dosage, safety, and efficacy cannot be drawn given the current state of evidence.

85. West, L., and Waldrop, J. Risperidone use in the treatment of behavioral symptoms in children with autism. *Pediatr Nurs* 32**:** 545-549, 2006.

The overall goal of autism treatment is to help the individual function normally or near normal in society (NICHD, 2004). Children and adolescents with autism can display disruptive behaviors, which has created challenges and barriersfor teachers, caretakers, and medical professionals. In an attempt to control these behaviors, medical providers are prescribing psychotropic drugs that have not been approved by the United States Food and Drug Administration for the treatment of autism in children. Conventional neuroleptics have been used to treat the more aggressive and violent behaviors associated with autism, but many healthcare professionals and families consider their side effects unacceptable. As a result, atypical antipsychotic drugs, such as risperidone, are being studied as off-label medications to treat autism because of their increased safety and efficacy over conventional neuroleptics. This article will discuss the use of risperidone as a potentially safe and effective treatment for disruptive behavioral symptoms in children with autism.

86. Wheeler, G. RG-1068 RepliGen. *Curr Opin Investig Drugs* 4**:** 66-71, 2003.

RG-1068 is a synthetic form of the natural human hormone secretin under development by RepliGen for the potential treatment of autism. RG-1068 received Fast Track designation for the treatment of pediatric autism in September 2001, and in February 2002, it entered phase III clinical trials.

87. Williams, K.W., Wray, J.J., and Wheeler, D.M. Intravenous secretin for autism spectrum disorder. *Cochrane Database Syst Rev***:** CD003495, 2005.

BACKGROUND: Secretin is a gastro-intestinal hormone which has been presented as an effective treatment for autism based on anecdotal evidence. OBJECTIVES: To determine if intravenous secretin:1. improves the core features of autism (social interaction, communication and behaviour problems); 2. improves the non-core aspects of behaviour or function such as self injurious behaviour;3. improves the quality of life of affected individuals and their carers; 4. has short term and long term effects on outcome; 5. causes harm. SEARCH

STRATEGY: Results of electronic searches of CENTRAL, MEDLINE, EMBASE, PsycINFO, CINAHL, ERIC, HealthStar and Sociofile (1998 - March 2005) were independently examined by two authors. Reference lists of trials and reviews were searched; experts and trialists were contacted to find unpublished studies. SELECTION CRITERIA: Randomised controlled trials of intravenous secretin comparing secretin with a placebo treatment in children or adults diagnosed with autism spectrum disorders, where at least one standardised outcome measure was reported. DATA COLLECTION AND ANALYSIS: Fourteen studies met inclusion criteria. All outcome data were continuous. Where trials used cross-over designs, analysis was conducted on results from first treatment phase, allowing combined analysis with parallel design trials. Where standardised assessment tools generated scores as outcome measures, comparisons were made between means of these scores. Where baseline means were reported, differences between treatment and control were determined to assess possible bias. Where mean change from baseline was reported, this was used in preference to post-treatment scores for meta-analyses or forest plots. As meta-analysis was possible for only one outcome (Childhood Autism Rating Scale), it was impossible to use sensitivity or subgroup analyses to assess impact of study quality, clinical differences in the intervention, or clinically relevant differences between groups, such as age or presence of gastrointestinal symptoms. MAIN RESULTS: Twenty-five established standardised outcome measures were reported to assess core features of autism, communication, behaviour, visio-spatial skills, affect and adverse events within fourteen included studies. No more than four studies used any one outcome measure similarly. Outcomes were reported between three and six weeks. RCTs of efficacy of secretin in autism have not shown improvements for core features of autism. AUTHORS' CONCLUSIONS: There is no evidence that single or multiple dose intravenous secretin is effective and as such it should not currently be recommended or administered as a treatment for autism. Further experimental assessment of secretin's effectiveness for autism can only be justified if methodological problems of existing research can be overcome.

88. Yoo, J.H., Valdovinos, M.G., and Williams, D.C. Relevance of donepezil in enhancing learning and memory in special populations: a review of the literature. *J Autism Dev Disord* 37**:** 1883-1901, 2007.

This review discusses the laboratory and clinical research supporting the rationale for the efficacy of donepezil (Aricept USA) in enhancing cognition in autism, Alzheimer disease, Down syndrome, traumatic brain injury, Attention Deficit Hyperactivity Disorder (ADHD), and schizophrenia. While preliminary animal models have shown effective, human studies exclusive of Alzheimer disease are sparse. Although attention and memory are unlikely a sole operation of the cholinergic system, evidence indicates a promising direction for further examination of this hypothesis in autism. Studies that examine changes in operationally defined behaviors and reliable and valid measure of changes in attention and memory are needed.

Bibliography–Pediatric Anesthesia Toxicities

1. Haberny, K.A., Paule, M.G., Scallet, A.C., Sistare, F.D., Lester, D.S., Hanig, J.P., and William Slikker, Jr.: Ontogeny of the N-methyl-D-aspartate (NMDA) receptor system and susceptibility to neurotoxicity, Tox. Sci. 68: 9-17, 2002.

2. Wang, C., Sadovova, N., Hotchkiss, C., Fu, X., Schmued, L., Scallet, A., Patterson, T., Hanig, J., Paule, M., and Slikker, W., Jr.: Blockade of n-methyl-d-aspartate (NMDA) receptors by ketamine produces loss of postnatal day 3 (PND-3) monkey frontal cortical neurons in culture. Tox. Sci. 91(1): 192-201, 2006.

3. Wang, C., Sadovova, N., Ali, S.F., Fu, X., Scallet, A.C., Patterson, T.A., Paule, M.G., and Slikker, W., Jr.: L-carnitine protects neurons from 1-methyl-4-phenylpyridinium (MPP+)-induced neuronal apoptosis in rat forebrain culture. Neuroscience 144: 46-55, 2007.

4. Slikker, W., Jr., Zou, X., Hotchkiss, C.E., Divine, R.L., Sadovova, N., Twaddle, N.C., Doerge, D.R., Scallet, A.C., Patterson, T.A., Hanig, J.P., Paule, M.G., and Wang, C.: Ketamine-induced neurodegeneration in the perinatal rhesus monkey. Tox. Sci., 98(1): 145-158, 2007.

5. Zou, X., Sadovova, N., Patterson, T.A., Divine, R.L., Hotchkiss, C.E., Ali, S.F., Hanig, J.P., Paule, M.G., Slikker, W., Jr., Wang, C.: The effects of L-carnitine on the combination of inhalation anesthetic-induced developmental neuronal apoptosis in the rat frontal cortex. Neuroscience 151: 1053-1065, 2008.

6. Wang, C., Sadovova, N., Patterson, T.A., Zou, X., Fu, X., Hanig, J.P., Paule, M.G., Ali, S.F., Zhang, X., and Slikker W., Jr.: Protective effects of 7-nitroindazole on ketamine-induced neurotoxicity in rat forebrain culture. NeuroToxicology 29: 613-620, 2008.

7. Wang, C., Zhang, X., Zou, X., Paule, M.G., and Slikker, W., Jr. Ketamine and glutamate receptors: potential toxicity of general anesthetics during rapid brain development. C. N. S. Agents Med. Chem. 8: 85-91, 2008.

8. Zou, X., Patterson, T.A., Sadovova, N., Twaddle, N.C., Doerge, D.R., Zhang, X., Fu, X., Hanig, J.P., Paule, M.G., Slikker, W., and Wang, C.: Potential Neurotoxicity of Ketamine in the Developing Rat Brain, Tox. Sci. 108: 149-158, 2009.

9. Zou, X., Patterson, T.A., Divine, R.L., Sadovova, N., Zhang, X., Hanig, J.P., Paule, M.G., Slikker, W., Jr. and Wang, C.: Prolonged exposure to ketamine increases neurodegeneration in the developing monkey brain, Intl. J. Develop. Neurosci. 27: 727-731, 2009.

10. Zhang, X., Paule, M.G., Newport, G.D., Zou, X., Sadovova, N., Berridge, M.S., Apana, S.M., Hanig, J.P., Slikker, W., Jr. and Wang, C.: A Minimally-invasive, translational biomarker of ketamine-induced neuronal death in rats: microPET imaging using [18F]-Annexin-V, Tox Sci 111: 355-361, 2009.

11. Shi, Q., Guo, L., Patterson, T.A., Dial, S., Li, Q., Sadovova, N.., Zhang, X., Paule, M.G., Slikker, W., Jr., and Wang, C.: Gene expression profiling in the developing rat brain exposed to ketamine. Neuroscience 166(3): 852-863, 2010.

12. X. Zhang, X., Paule, M.G., Newport, G.D., Sadovova, N., Berridge, M.S., Apana, S.M., Kabalka, G., Miao, M., Slikker, W., Jr. and Wang, C.: MicroPET imaging of ketamine-induced neuronal apoptosis with radiolabeled DFNSH. Submitted, Neuroscience 2010.

Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD)
Obstetric and Pediatric Pharmacology Branch (OPPB)
Best Pharmaceuticals for Children Act (BPCA)

Selected Citations–Cyproheptadine

1. **Akhondzadeh, S., S. Erfani, M.R. Mohammadi, M. Tehrani-Doost, H. Amini, S.S. Gudarzi, and M.T. Yasamy. "Cyproheptadine in the treatment of autistic disorder: a double-blind placebo-controlled trial." _Journal of Clinical Pharmacy and Therapeutics_ 29.2 (2004): 145-150.**

Abstract
OBJECTIVE: Autism is a childhood-onset disorder of unknown, possibly of multiple aetiologies. The core symptoms of autism are abnormalities in social interaction, communication and behaviour. The involvement of neurotransmitters such as 5-HT has been suggested in neuropsychiatric disorders and particularly in autistic disorder. Increased platelet 5-HT levels were found in 40% of the autistic population, suggesting that hyperserotonaemia may be a pathologic factor in infantile autism. Therefore, it is of interest to assess the efficacy of cyproheptadine, a 5-HT2 antagonist in the treatment of autistic disorder. In this 8-week double-blind, placebo-controlled trial, we assessed the effects of cyproheptadine plus haloperidol in the treatment of autistic disorder.
METHODS: Children between the ages 3 and 11 years (inclusive) with a DSM IV clinical diagnosis of autism and who were outpatients from a specialty clinic for children at Roozbeh Psychiatric Teaching Hospital were recruited. The children presented with a chief complaint of severely disruptive symptoms related to autistic disorder. Patients were randomly allocated to cyproheptadine + haloperidol (Group A) or haloperidol + placebo (Group B) for an 8-week, double-blind, placebo-controlled study. The dose of haloperidol and cyproheptadine was titrated up to 0.05 and 0.2 mg/kg/day respectively. Patients were assessed by a third-year resident of psychiatry at baseline and after 2, 4, 6 and 8 weeks of starting medication. The primary measure of the outcome was the Aberrant Behaviour Checklist-Community (ABC-C) and the secondary measure of the outcome was the Childhood Autism Rating Scale (relating to people and verbal communication). Side effects and extrapyramidal symptoms were systematically recorded throughout the study and were assessed using a checklist and the Extrapyramidal Symptoms Rating Scale, administered by a resident of psychiatry during weeks 1, 2, 4, 6 and 8.
RESULTS: The ABC-C and the Childhood Autism Rating Scale scores improved with cyproheptadine. The behaviour of the two treatments was not homogeneous across time (groups-by-time interaction, Greenhouse-Geisser correction; $F = 7.30$, d.f. = 1.68, $P = 0.002$; $F = 8.21$, d.f. = 1.19, $P = 0.004$ respectively). The difference between the two treatments was significant as indicated by the effect of group, and the between-subjects factor ($F = 4.17$, d.f. = 1, $P = 0.048$; $F = 4.29$, d.f. = 1, $P = 0.045$ respectively). No significant difference was observed between the two groups in terms of extrapyramidal symptoms ($P = 0.23$). The difference between the two groups in the frequency of side effects was not significant.
CONCLUSION: The results suggest that the combination of cyproheptadine with a conventional antipsychotic may be superior to conventional antipsychotic alone for children with autistic disorder. However the results need confirmation by a larger randomized controlled trial.

2. **Andersen, J.M., K.S. Sugerman, J.R. Lockhart, and W.A. Weinberg. "Effective prophylactic therapy for cyclic vomiting syndrome in children using amitriptyline or cyproheptadine." _Pediatrics_ 100.6 (1997): 977-981.**

Abstract
OBJECTIVE: To evaluate our experience using the antimigraine prophylactic drugs, amitriptyline and cyproheptadine, for the prophylactic management of cyclic vomiting syndrome (CVS) in children.
METHODS AND PATIENTS: Twenty-seven patients (16 males) ranging in age from 2 to 16 years at diagnosis, fulfilling the diagnostic criteria for CVS and treated prophylactically with either amitriptyline (22) or/and cyproheptadine (6) were identified through retrospective chart review. Individual patient

data were corroborated by the attending physician and/or interviews with patients and families. Minimum follow-up time before entry into the study group was 5 months. Patients were stratified according to three treatment outcomes: 1) complete response-no attacks, 2) partial response-50% or greater reduction in frequency of attacks, and 3) no response-less than 50% decrease in frequency of attacks.
RESULTS: Of the 22 patients treated with amitriptyline, 16 (73%) had a complete response while 4 (18%) had a partial response. Of the 6 patients treated with cyproheptadine, 4 (66%) had a complete response and 1 (17%) had a partial response. Thus, 91% of the amitriptyline group and 83% of the cyproheptadine group had at least a partial response to therapy. No patients experienced significant side effects to either medication.
CONCLUSION: The antimigraine prophylactic drugs, amitriptyline and cyproheptadine, represent effective prophylactic agents for the management of CVS in the vast majority of patients fulfilling the diagnostic criteria for this syndrome.

3. **Arisaka, O., N. Shimura, Y. Nakayama, and K. Yabuta. "Cyproheptadine and growth."** ***American Journal of Diseases of Children*** **142.9 (1988): 914-915.**
(No Abstract Available)

4. **Balottin, U., and C. Termine. "Recommendations for the management of migraine in paediatric patients."** ***Expert Opinion on Pharmacotherapy*** **8.6 (2007): 731-744.**

Abstract
Migraine is a common and disabling condition in children and adolescents. The complexity of migraine on a pathogenetic and clinical level results from the interaction between biological, psychological and environmental factors. Appropriate management requires an individually tailored strategy giving due consideration to both pharmacological and non-pharmacological measures. Ibuprofen (7.5-10.0 mg/kg) and acetaminophen (15 mg/kg) are safe and effective, and should be considered for symptomatic treatment. Sumatriptan nasal spray (5 and 20 mg) is also likely to be effective, but at the moment, should be considered for the treatment of adolescents only. With reference to prophylactic drug treatment, the available data suggest that flunarizine (5 mg/day) is likely to be effective and pizotifen and clonidine are likely to be ineffective. The efficacy data regarding propranolol, nimodipine and trazodone are conflicting. Insufficient evidence is available on cyproheptadine, amitriptyline, divalproex sodium, topiramate, levetiracetam, gabapentin or zonisamide. The management of migraine in children needs an individualised therapeutic approach, directed to the whole person of the child, taking into account the developmental perspective and the high rate of psychiatric comorbidities. It is the authors' opinion that for the prophylaxis of migraine, interventions such as identification and avoidance of trigger factors, regulation of lifestyle, relaxation, biofeedback, cognitive behavioural treatment and psychological or psychotherapeutic interventions (e.g., psychodynamics) could be much more effective than pharmacotherapy.

5. **Calka, O., A. Metin, H. Dülger, and R. Erkoç. "Effect of cyproheptadine on serum leptin levels."** ***Advances in Therapy*** **22.5 (2005): 424-428.**

Abstract
Leptin is a 167 amino acid protein encoded by the obesity gene that is synthesized in adipose tissue and interacts with receptors in the hypothalamus linked to the regulation of appetite and metabolism. It is known to suppress appetite and increase energy expenditure. Cyproheptadine is a piperidine antihistamine that increases appetite through its antiserotonergic effect on 5-HT2 receptors in the brain. Although both leptin and cyproheptadine are effective in controlling appetite, their interaction has not been addressed in clinical studies. This study evaluated serum leptin concentrations in patients who received cyproheptadine to treat a variety of disorders. Sixteen patients aged 7 to 71 years (mean, 26.25 years) were given cyproheptadine 2 to 6 mg/day for a minimum of 7 days. Body weight was measured and blood samples were obtained at baseline and after 1 week of treatment. Serum leptin levels were determined by leptin radioimmunoassay. The mean body weight at baseline (52.59 kg) did not differ significantly from that at 1 week after treatment (52.84 kg; $P > .05$), but the mean leptin level after 1 week of treatment with cyproheptadine (3.14 ng/mL) was 14.2% higher than

that at baseline (2.75 ng/mL; P < .05). This increase may suggest that both leptin and cyproheptadine may affect appetite via similar receptors and that cyproheptadine does not impair leptin activity through these receptors. Further study will be necessary to clarify this relationship.

6. **Couluris, M., J.L. Mayer, D.R. Freyer, E. Sandler, P. Xu, and J.P. Krischer. "The effect of cyproheptadine hydrochloride (periactin) and megestrol acetate (megace) on weight in children with cancer/treatment-related cachexia."** ***Journal of Pediatric Hematology/Oncology*** **30.11 (2008): 791-797.**

Abstract
BACKGROUND: Children with cancer frequently have associated cachexia and malnutrition. Failure to thrive affects nearly 40% of oncology patients with advanced or progressive disease. Malnutrition can erode quality of life and adversely impact disease prognosis. Appetite stimulation and increased food intake is 1 approach to combat cancer-related cachexia.
MATERIALS AND METHODS: Cyproheptadine hydrochloride (CH), an appetite stimulant, was administered to children with cancer-associated cachexia to prevent further weight loss. All participants started CH and were evaluated for response after 4 weeks. Efficacy of megestrol acetate (MA) was evaluated in patients who did not respond to CH. Medical evaluation, weight measurements, prealbumin, and serum leptin levels were preformed at follow-up visits.
RESULTS: Seventy patients were enrolled. Of the 66 evaluable patients, 50 demonstrated a response to CH (average weight gain 2.6 kg and mean weight-for-age z-score change of 0.35, P=0.001). Seven of the 16 nonresponders received MA. Six patients completed 4 weeks of MA, 5 responded (average weight gain of 2.5 kg). The most commonly reported side effect of CH was drowsiness. One patient on MA developed low cortisol levels and hyperlipidemia.
CONCLUSIONS: This study demonstrates that CH is a safe and effective way to promote weight gain in children with cancer/treatment-related cachexia.

7. **Daviss, W.B., and J. Scott. "A chart review of cyproheptadine for stimulant-induced weight loss."** ***Journal of Child and Adolescent Psychopharmacology*** **14.1 (2004): 65-73.**

Abstract
Youths with attention deficit hyperactivity disorder often experience weight loss on stimulants, which may limit optimal dosing and compliance. Cyproheptadine has been shown in medical samples to stimulate weight gain. We conducted a retrospective chart review of 28 consecutive pediatric psychiatry outpatients prescribed cyproheptadine for weight loss or insomnia while on stimulants. Of these, 4 patients never took cyproheptadine consistently, and 3 discontinued it within the first 7 days due to intolerable side effects. Data were analyzed for 21 other patients (age range 4-15 years) who continued with 4-8 mg of cyproheptadine nightly (mean final dose = 4.9 mg/day) for at least 14 days (mean duration = 104.7 days). Most had lost weight on stimulant alone (mean weight loss was 2.1 kg, mean weight velocity was -19.3 g/day). All 21 gained weight taking concomitant cyproheptadine, with a mean gain of 2.2 kg (paired t = 6.87, p < 0.0001) and a mean weight velocity of 32.3 g/day. Eleven of 17 patients who had reported initial insomnia on stimulant alone noted significant improvements in sleep with cyproheptadine added. We conclude that concomitant cyproheptadine may be useful in youths with attention deficit hyperactivity disorder for stimulant-induced weight loss, pending future randomized controlled trials.

8. **Eiland, L.S., L.S. Jenkins, and S.H. Durham. "Pediatric migraine: pharmacologic agents for prophylaxis."** ***The Annals of Pharmacotherapy*** **41.7 (2007): 1181-1190.**

Abstract
OBJECTIVE: To identify and evaluate the data regarding medication use for migraine prophylaxis in the pediatric population.
DATA SOURCES: Literature was obtained through searches in PubMed (Mid 1950s-March 2007), Iowa Drug Information Service/Web (1966-February 2007), International Pharmaceutical Abstracts (1970-February 2007), and the Cochrane Library. The terms migraine, prophylaxis, child, and children

were used and cross referenced with all drug names. Reference citations from publications identified were also reviewed and included.
STUDY SELECTION AND DATA EXTRACTION: Only trials that evaluated migraine headaches in the pediatric population were included. Trials including adolescent and adult populations are briefly listed, but not reviewed. Trials involving non-prescription medication were also included in the evaluation. Due to the limited information, all clinical trials, retrospective reviews, and abstracts evaluated were included in this review.
DATA SYNTHESIS: Few controlled clinical trials regarding prophylaxis therapy are available. Currently, no medications are approved by the Food and Drug Administration for prophylaxis of migraines in children. Seventeen drugs were identified and included in the review. Of the drugs with available data, topiramate, valproic acid, flunarizine, amitriptyline, and cyproheptadine have shown efficacy in decreasing migraine frequency and duration in children. However, larger clinical trials are necessary to validate the utility of these agents. Conflicting data exist for propranolol and pizotifen, and additional data are needed for gabapentin, levetiracetam, zonisamide, naproxen, and trazodone. In clinical trials, nimodipine, clonidine, and natural supplements have shown a lack of efficacy versus placebo for prophylaxis of migraines in children.
CONCLUSIONS: Topiramate, valproic acid, and amitriptyline have the most data on their use for prophylaxis of migraines in children. Numerous agents have limited data in this population and several agents lack efficacy. Prospective, well designed, controlled clinical trials that include quality-of-life and functional outcomes are needed for guiding therapy of migraine prophylaxis for children.

9. **Goldberg, S.C., E.D. Eckert, K.A. Halmi, R.C. Casper, J.M. Davis, and M. Roper. "Effects of cyproheptadine on symptoms and attitudes in anorexia nervosa."** ***Archives of General Psychiatry*** **37.9 (1980): 1083.**
   (No Abstract Available)

10. **Hikita, T., H. Kodama, N. Nakamoto, F. Kaga, K. Amakata, K. Ogita, S. Kaneko, Y. Fujii , and Y. Yanagawa. "Effective prophylactic therapy for cyclic vomiting syndrome in children using valproate."** ***Brain & Development*** **31.6 (2009): 411-413.**

    Abstract
    This trial sought to evaluate our experience using the antimigraine prophylactic drug, use of valproate for the prophylactic management of cyclic vomiting syndrome (CVS) in children. Thirteen children diagnosed with severe CVS were enrolled. Prophylactic therapy consisted of valproate administered at a dose of 10-40 mg/kg/day. Upon enrollment in the study, all patients underwent diagnostic tests to rule out organic causes of their symptoms. Vomiting was severe enough in all patients to cause dehydration requiring hospitalization for intravenous rehydration. Nine of 13 patients did not respond to numerous previous medical therapies like propranolol, amitriptyline, cyproheptadine, phenobarbital, phenytoin, and carbamazepine. Three of 13 patients required combination therapy with valproate and phenobarbital. Of the 13 patients, two showed complete resolution of their symptoms, nine had marked improvement in their symptoms, as evidenced by infrequent attacks of reduced severity, and two failed to respond to valproate therapy. Four patients experienced relapse with a decreased dosage of valproate. Side effects associated with long-term valproate administration were not observed. Valproate appears to be effective for the prophylactic management of severe CVS, with 85% of all patients achieving at least a reduction in the frequency of attacks.

11. **Hirfanoglu, T., A. Serdaroglu, O. Gulbahar, and A. Cansu. "Prophylactic drugs, cytokine, and leptin levels in children with migraine."** ***Pediatric Neurology*** **41.4 (2009): 281-287.**

    Abstract
    The study objective was to evaluate levels of the cytokines tumor necrosis factor alpha, interleukin-1beta, and interleukin-6 and of leptin, and then to determine the relationship between these levels and clinical responses in children with migraine after prophylactic therapy with one of four drugs. In all, 77 children who needed prophylactic drugs were treated with cyproheptadine, amitriptyline, propranolol, or flunarizine. Serum levels of the cytokines and leptin were measured before and 4 months after the treatment. Results were compared by drug for headache frequency, severity, and

duration, the PedMIDAS score, and levels of each cytokine and of leptin. Each of the four drugs not only decreased the frequency and duration but also the severity of headache, and the PedMIDAS score. None of the drugs was found to be superior to others in terms of reduction in cytokine levels ($P > 0.05$). Both cyproheptadine and flunarizine (but not amitriptyline and propranolol) caused an increase in leptin levels ($P < 0.05$). These data suggest that cytokine levels are related to clinical responses, and might help in objective evaluation of clinical response in migraine. To our knowledge, the present study is the first trial to compare the effects of prophylactic drugs, cytokine levels, and leptin levels in children with migraine.

12. **Homnick, D.N., J.H. Marks, K.L. Hare, and S.K. Bonnema. "Long-term trial of cyproheptadine as an appetite stimulant in cystic fibrosis." *Pediatric Pulmonology* 40.3 (2005): 251-256.**

    Abstract
    Appetite stimulants have been used to help overcome decreased appetite and malnutrition in children and adults with various chronic illnesses, including cystic fibrosis (CF). Stimulants have included megestrol acetate (MA), cyproheptadine hydrochloride (CH), cannabinoids, hydrazine sulfate, anabolic hormones, and growth hormone. Many of these, including MA, have substantial side effects and may not be suitable for prolonged use. We previously studied the effects of CH on weight gain in a short-term (12 week) trial in CF with good results compared to placebo. Side effects were few, and weight gain was significant. In this study, we sought to determine the effects of CH over a longer term in order to assess its suitability for prolonged use. Sixteen CF children and adults enrolled in the original short-term study subsequently entered this study, and 12 completed the 9-month trial. All patients receiving placebo in the original short-term study received CH 4 mg up to four times a day in the long-term study continuation, and those receiving CH in the short-term study continued on the drug. No pill counts were done, and patients were queried at quarterly visits as to their CH use. Anthropometrics and spirometry were also done quarterly, and antibiotic use was quantified. Subjects who had changed from placebo (CH2 group) gained weight significantly over 3-6 months, and those continuing on CH (CH1 group) generally maintained previously gained weight over the duration of the study. Select spirometric measures improved in both groups but not significantly, and side effects were mild. CH appears to be an effective appetite stimulant in CF, and generally maintains its effect over time with an acceptable side-effect profile.

13. **Lehrer, J.F.. "Cyproheptadine's antiserotonin effects are responsible for its antimigraine activity." *Headache* 44.9 (2004): 935.**
    (No Abstract Available)

14. **Lewis, D., S. Ashwal, A. Hershey, D. Hirtz, M. Yonker, S. Silberstein, American Academy of Neurology Quality Standards Subcommittee, and Practice Committee of the Child Neurology Society. "Practice parameter: pharmacological treatment of migraine headache in children, and adolescents: report of the American Academy of Neurology Quality Standards Subcommittee, and the Practice Committee of the Child Neurology Society." *Neurology* 63.12 (2004): 2215-2224. Print.**

    Abstract
    OBJECTIVE: To review evidence on the pharmacologic treatment of the child with migraine headache.
    METHODS: The authors reviewed, abstracted, and classified relevant literature. Recommendations were based on a four-tiered scheme of evidence classification. Treatment options were separated into medications for acute headache and preventive medications.
    RESULTS: The authors identified and reviewed 166 articles. For acute treatment, five agents were reviewed. Sumatriptan nasal spray and ibuprofen are effective and are well tolerated vs placebo. Acetaminophen is probably effective and is well tolerated vs placebo. Rizatriptan and zolmitriptan were safe and well tolerated but were not superior to placebo. For preventive therapy, 12 agents were evaluated. Flunarizine is probably effective. The data concerning cyproheptadine, amitriptyline, divalproex sodium, topiramate, and levetiracetam were insufficient. Conflicting data were found concerning propranolol and trazodone. Pizotifen, nimodipine, and clonidine did not show efficacy.

CONCLUSIONS: For children (>age 6 years), ibuprofen is effective and acetaminophen is probably effective and either can be considered for the acute treatment of migraine. For adolescents (>12 years of age), sumatriptan nasal spray is effective and should be considered for the acute treatment of migraine. For preventive therapy, flunarizine is probably effective and can be considered, but is not available in the United States. There are conflicting or insufficient data to make any other recommendations for the preventive therapy of migraine in children and adolescents. For a clinical problem so prevalent in children and adolescents, there is a disappointing lack of evidence from controlled, randomized, and masked trials.

15. **Lewis, D.W., M. Yonker, P. Winner, and M. Sowell. "The treatment of pediatric migraine." *Pediatric Annals* 34.6 (2005): 448-460.**

    Abstract
    The management of pediatric migraine requires a balance of biobehavioral measures coupled with agents for acute treatment and, if needed, daily preventive medicines. A recent American Academy of Neurology practice parameter has critically reviewed the limited data regarding the efficacy and safety of medicines for the acute and preventive therapy of pediatric migraine. The first step is to establish the headache frequency and degree to which the migraines impact upon lifestyle and performance. The next step is to institute nonpharmacologic measures such as regulation of sleep (improved sleep hygiene), moderation of caffeine, regular exercise, and identification of provocative influences (eg, stress, foods, social pressures). A wide variety of therapeutic options exist for patients whose migraine headaches occur with sufficient frequency and severity to produce functional impairment. The most rigorously studied agents for the acute treatment of migraine are ibuprofen, acetaminophen, and sumatriptan nasal spray, all of which have shown safety and efficacy in controlled trials. Daily preventive drug therapies are warranted in about 20% to 30% of young migraine sufferers. The particular drug selected for the individual patient requires an appreciation of comorbidities such as affective or anxiety disorders, co-existent medical conditions such as asthma or diabetes, and acceptability of potential toxicities such as weight gain, sedation, or tremor.

16. **Lewis, D.W., and P. Winner. "The pharmacological treatment options for pediatric migraine: an evidence-based appraisal." *Journal of the American Society for Experimental NeuroTherapeutics* 3.2 (2006): 181-191.**

    Abstract
    The treatment of children and adolescents who suffer from migraine headaches must be individually tailored, flexible, and balanced with a blend of bio-behavioral measures, agents for acute treatment and, if needed, daily preventive medicines. While controlled data is limited, there is now enough evidence available to provide a rational framework to build treatment plans appropriate for the pediatric population. Essentially, the pharmacological management of pediatric migraine divides into agents for the acute attacks and agents used daily to prevent or reduce the frequency of attacks. For the acute treatment, the most rigorously studied agents are ibuprofen, acetaminophen, and the nasal spray forms of sumatriptan and zolmitriptan, all of which have shown both safety and efficacy in controlled trials. For preventive treatment the calcium channel blocker flunarezine has the best efficacy profile in controlled trials, but is not available in the U.S. A growing body of data, mostly uncontrolled, is emerging regarding the use of several anti-epileptic agents (e.g. topiramate, disodium valproate, levateracetam), as well as the antihistamine cyproheptadine and the anti-depressant amitriptyline.

17. **Li, B.U., F. Lefevre, G.G. Chelimsky, R.G. Boles, S.P. Nelson, D.W. Lewis, S.L. Linder, R.M. Issenman, C.D. Rudolph, North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition. "North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition consensus statement on the diagnosis, and management of cyclic vomiting syndrome." *Journal of Pediatric Gastroenterology, and Nutrition* 47.3 (2008): 379-393.**

    Abstract

Cyclic vomiting syndrome (CVS) is a disorder noted for its unique intensity of vomiting, repeated emergency department visits and hospitalizations, and reduced quality of life. It is often misdiagnosed due to the unappreciated pattern of recurrence and lack of confirmatory testing. Because no accepted approach to management has been established, the task force was charged to develop a report on diagnosis and treatment of CVS based upon a review of the medical literature and expert opinion. The key issues addressed were the diagnostic criteria, the appropriate evaluation, the prophylactic therapy, and the therapy of acute attacks. The recommended diagnostic approach is to avoid "shotgun" testing and instead to use a strategy of targeted testing that varies with the presence of 4 red flags: abdominal signs (eg, bilious vomiting, tenderness), triggering events (eg, fasting, high protein meal), abnormal neurological examination (eg, altered mental status, papilledema), and progressive worsening or a changing pattern of vomiting episodes. Therapeutic recommendations include lifestyle changes, prophylactic therapy (eg, cyproheptadine in children 5 years or younger and amitriptyline for those older than 5), and acute therapy (eg, 5-hydroxytryptamine receptor agonists, termed triptans herein, as abortive therapy, and 10% dextrose and ondansetron for those requiring intravenous hydration). This document represents the official recommendations of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition for the diagnosis and treatment of CVS in children and adolescents.

18. **Mahachoklertwattana, P., S. Wanasuwankul, P. Poomthavorn, L. Choubtum, and A. Sriphrapradang. "Short-term cyproheptadine therapy in underweight children: effects on growth and serum insulin-like growth factor-I."** ***Journal of Pediatric Endocrinology & Metabolism*** **22.5 (2009): 425-432.**

Abstract
BACKGROUND: Cyproheptadine, an appetite stimulant, has been used in poor-appetite underweight children. Its beneficial effects on enhancing growth rate have been demonstrated. In contrast, an adverse effect on blunting growth hormone (GH) secretion has also been reported. To date, however, its effect on insulinlike growth factor-I (IGF-I), a GH-mediated growth factor, has not been documented.
AIM: To examine the effect of cyproheptadine therapy on growth and serum IGF-I in underweight children.
METHODS: Twenty-one underweight, otherwise healthy children were recruited. They were randomly assigned into cyproheptadine administration (n = 10) and placebo (n = 11) groups. The former received cyproheptadine for 4 months. Serum IGF-I levels were measured in both groups.
RESULTS: Weight and height velocities and IGF-I z-scores during cyproheptadine therapy were significantly greater in the intervention group than those of the placebo group.
CONCLUSION: Cyproheptadine therapy in underweight children increased caloric intake and serum IGF-I concentration and consequently enhanced growth velocity.

19. **Paton, D.M., and D.R. Webster. "Clinical pharmacokinetics of H1-receptor antagonists (the antihistamines)."** ***Clinical Pharmacokinetics*** **10.6 (1985): 477-497.**

Abstract
This article reviews clinical pharmacokinetic data on the H1-receptor antagonists, commonly referred to as the antihistamines. Despite their widespread use over an extended period, relatively little pharmacokinetic data are available for many of these drugs. A number of H1-receptor antagonists have been assayed mainly using radioimmunoassay methods. These have also generally measured metabolites to greater or lesser extents. Thus, the interpretation of such data is complex. After oral administration of H1-receptor antagonists as syrup or tablet formulations, peak plasma concentrations are usually observed after 2 to 3 hours. Bioavailability has not been extensively studied, but is about 0.34 for chlorpheniramine, 0.40 to 0.60 for diphenhydramine, and about 0.25 for promethazine. Most of these drugs are metabolised in the liver, this being very extensive in some instances (e.g. cyproheptadine and terfenadine). Total body clearance in adults is generally in the range of 5 to 12 ml/min/kg (for astemizole, brompheniramine, chlorpheniramine, diphenhydramine, hydroxyzine, promethazine and triprolidine), while their elimination half-lives range from about 3 hours to about 18 days [cinnarizine about 3 hours; diphenhydramine about 4 hours; promethazine 10 to 14 hours;

chlorpheniramine 14 to 25 hours; hydroxyzine about 20 hours; brompheniramine about 25 hours; astemizole and its active metabolites about 7 to 20 days (after long term administration); flunarizine about 18 to 20 days]. They also have relatively large apparent volumes of distribution in excess of 4 L/kg. In children, the elimination half-lives of chlorpheniramine and hydroxyzine are shorter than in adults. In patients with alcohol-related liver disease, the elimination half-life of diphenhydramine was increased from 9 to 15 hours, while in patients with chronic renal disease that of chlorpheniramine was very greatly prolonged. Little, if any, published information is available on the pharmacokinetics of these drugs in neonates, pregnancy or during lactation. The relatively long half-lives of a number of the older H1-receptor antagonists such as brompheniramine, chlorpheniramine and hydroxyzine suggest that they can be administered to adults once daily.

20. **Phan, H., M.L. Moeller, and M.C. Nahata. "Treatment of allergic rhinitis in infants and children: efficacy and safety of second-generation antihistamines and the leukotriene receptor antagonist montelukast." *Drugs* 69.18 (2009): 2541-2576.**

Abstract
Allergic rhinitis (AR) affects a large percentage of paediatric patients. With the wide array of available agents, it has become a challenge to choose the most appropriate treatment for patients. Second-generation antihistamines have become increasingly popular because of their comparable efficacy and lower incidence of adverse effects relative to their first-generation counterparts, and the safety and efficacy of this drug class are established in the adult population. Data on the use of the second-generation antihistamines oral cetirizine, levocetirizine, loratadine, desloratadine and fexofenadine, and the leukotriene receptor antagonist montelukast as well as azelastine nasal spray in infants and children are evaluated in this review. These agents have been found to be relatively safe and effective in reducing symptoms associated with AR in children. Alternative dosage forms such as liquids or oral disintegrating tablets are available for most agents, allowing ease of administration to most young children and infants; however, limited data are available regarding use in infants for most agents, except desloratadine, cetirizine and montelukast. Unlike their predecessors, such as astemizole and terfenadine, the newer second-generation antihistamines and montelukast appear to be well tolerated, with absence of cardiotoxicities. Comparative studies are limited to cetirizine versus ketotifen, oxatomide and/or montelukast. Although second-generation antihistamines and montelukast are deemed relatively safe for use in paediatric patients, there are some noteworthy drug interactions to consider when selecting an agent. Given the wide variety of available agents for treatment of AR in paediatric patients, the safety and efficacy data available for specific age groups, type of AR, dosage form availability and cost should be considered when selecting treatment for AR in infants and children.

21. **Rossignol, D.A.. "Novel and emerging treatments for autism spectrum disorders: a systematic review." *Annals of Clinical Psychiatry* 21.4 (2009): 213-236.**

Abstract
BACKGROUND: Currently, only one medication (risperidone) is FDA-approved for the treatment of autism spectrum disorders (ASD). Perhaps for this reason, the use of novel, unconventional, and off-label treatments for ASD is common, with up to 74% of children with ASD using these treatments; however, treating physicians are often unaware of this usage.
METHODS: A systematic literature search of electronic scientific databases was performed to identify studies of novel and emerging treatments for ASD, including nutritional supplements, diets, medications, and nonbiological treatments. A grade of recommendation ("Grade") was then assigned to each treatment using a validated evidence-based guideline as outlined in this review: A: Supported by at least 2 prospective randomized controlled trials (RCTs) or 1 systematic review. B: Supported by at least 1 prospective RCT or 2 nonrandomized controlled trials. C: Supported by at least 1 nonrandomized controlled trial or 2 case series. D: Troublingly inconsistent or inconclusive studies or studies reporting no improvements. Potential adverse effects for each treatment were also reviewed.
RESULTS: Grade A treatments for ASD include melatonin, acetylcholinesterase inhibitors, naltrexone, and music therapy. Grade B treatments include carnitine, tetrahydrobiopterin, vitamin C, alpha-2 adrenergic agonists, hyperbaric oxygen treatment, immunomodulation and anti-inflammatory

treatments, oxytocin, and vision therapy. Grade C treatments for ASD include 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.
CONCLUSIONS: The reviewed treatments for ASD are commonly used, and some are supported by prospective RCTs. Promising treatments include melatonin, antioxidants, acetylcholinesterase inhibitors, naltrexone, and music therapy. All of the reviewed treatments are currently considered off-label for ASD (ie, not FDA-approved) and some have adverse effects. Further studies exploring these treatments are needed. Physicians treating children with an ASD should make it standard practice to inquire about each child's possible use of these types of treatments.