Pilot Study of Sleep Therapy and Biomarkers in Children with Autism Spectrum Disorders

Principal Investigator: Jill Miller-Horn

Co-investigator: Dennis Choi

NCT: NCT02487082

Clinicaltrials.gov Protocol ID 65709

Document Date: 3/23/2020

Background

Autism Spectrum Disorder (ASD) refers to a range of neurodevelopmental disorders involving social impairments, communication difficulties, and restricted, repetitive, and stereotyped behaviors (2009). ASD has an enormous impact on affected families and upon society as a whole (Cidav et al. 2012; Mandell 2012; Mandell et al. 2012).

Studies have shown that the majority of individuals with ASD have problems with sleep (Richdale and Schreck 2009). Research indicates that sleep difficulty in children with ASD is more frequent than in typically developing children, or those with other forms of developmental delays (Richdale and Schreck 2009; Taylor et al. 2012). Compared with typically developing children, those with autism have a reduction in sleep time, and spend a higher percentage of that time in slow wave sleep, and a much lower percentage in rapid eye movement (REM) sleep (Buckley et al. 2010). Sleep related concerns in ASD children have been linked to behavioral difficulties and family stress (Richdale and Schreck 2009). Moreover, better sleep in these children has been associated with higher scores on measures of daily living, communication, cognition, social interaction and motor skills (Malow et al. 2006; Taylor et al. 2012).

Treatments to improve sleep could therefore have important implications for these children and their families. A consensus statement in the journal Pediatrics emphasized the need for clinical trials to improve sleep specifically for children in this population (Mindell et al. 2006). This pilot investigation will assess the combined benefit of two medicines that have each shown promise in treating sleep and behavior problems in children with autism: melatonin and donepezil.

Melatonin is a widely used neurohormone available without prescription in the United States. It plays a well-documented role in modulating sleep by helping regulate the circadian sleep-wake cycle (Tordjman et al. 2013). Recent research has identified abnormalities in melatonin physiology among individuals with ASD (Rossignol and Frye 2013) In addition, a number of small randomized clinical trials (RCT) in children with ASD have shown melatonin to be well tolerated and to increase total sleep time and decrease sleep latency (Garstang and Wallis 2006; Wasdell et al. 2008; Wirojanan et al. 2009; Wright et al. 2011; Tordjman et al. 2013). One RCT in ASD found that melatonin improved daytime behavior (Wasdell et al. 2008). Studies in other populations have found that the medication also increases REM sleep percentage and REM sleep continuity (Kunz et al. 2004).

Donepezil is another promising medication in ASD. It is an acetylcholinesterase inhibitor (AChEI) initially used to treat cognitive and behavioral symptoms in Alzheimer's disease (Rogers et al. 1998; Burns et al. 1999). Donepezil and other acetylcholinesterase inhibitors have also been examined in ASD in a number of small investigations and shown to be reasonably well tolerated (Hardan and Handen 2002; Chez et al. 2003; Hertzman 2003; Chez et al. 2004; Hohnadel et al. 2007; Yoo et al. 2007; Buckley et al. 2011; Handen et al. 2011; Srivastava et al. 2011; Sahu et al. 2012), though few of those were RCT (Chez et al. 2003; Handen et al. 2011; Ghaleiha et al. 2013). The results of these small RCTs are promising with regard to the behavioral impact of this class of medications. Along with its behavioral impact, a recent line of investigation led by NIH has documented that donepezil improves sleep in young ASD children (ages 2.5-6.9 years) (Buckley et al. 2011). They found it reduced REM latency, and increased the percent of sleep spent in REM, thus helping normalize this important aspect of sleep architecture (Buckley et al. 2011).

The goal of the present exploratory investigation is to see if there is a suggestion of a large additive or synergistic effect of melatonin and donepezil given together. Individually both medications improve sleep, but appear do so in different ways, with melatonin altering circadian rhythm and donepezil altering the characteristics of REM sleep. In this pilot investigation we will examine whether their combined effects on sleep lead to a large improvement in the behavior of children with ASD. Combined pharmacotherapy is very common in clinical practice, but is rarely studied in research (Comer et al. 2010). These two medications are both well tolerated and there is no negative drug interaction between the two. This investigation will use an RCT as well as a set of exploratory analyses to assess the combined effects of

these two medications compared to placebo in terms of behavioral and sleep measures. In addition we will collect exploratory biomarkers (e.g., digit ratio, the ratio of the lengths different fingers as a measure of the balance of sex hormones during embryonic development) to relate to the various sleep and behavioral measures. A positive signal from this study may be used to guide a follow-up study with greater numbers of study subjects and statistical power.

Methods

Subjects

Inclusion Criteria:

1. Both male and female children
2. Ages 4 to 17 1/2 years
3. Diagnosis with ASD on the basis of the clinical judgment of an autism specialist, preferably using the Autism Diagnostic Observation Schedule (ADOS) (Lord et al. 2000) or the Autism Diagnostic Interview-Revised (ADI-R) (Rutter et al. 2003).

Exclusion Criteria:

1. Abnormal EEG in the past month
2. Cardiovascular problems
3. Asthma
4. Respiratory disease
5. Peptic ulcer disease
6. Renal or hepatic dysfunction (abnormal BUN/creatinine or 2x elevated liver transaminases)
7. Urinary tract obstruction
8. Underweight (BMI < 5th percentile compared to age & sex matched population)
9. Other serious illness
10. Use of any of the following drugs that might interact with study medications (anticholinergics, systemic corticosteroids, phenobarbital, peginterferon, beta-blockers or any drug that may cause arrhythmias). Drugs that induce or inhibit CYP2D6 and CYP3A4 (enzymes important for drug metabolism) will be allowed because any effects of such medications are likely to be lost in individual variability due to genetic polymorphisms (Rahmioglu et al. 2011; Teh and Bertilsson 2012).
11. Use of medications affecting sleep with a half-life of 7 days or more. Children on medications affecting sleep with a half-life of less than 7 days (including melatonin and donepezil) are eligible if they agree to discontinue use for the duration of the trial.
12. Pregnancy and lactation

Recruitment

We will send "Dear Physician" letters to Stony Brook and local physicians who see children with ASD. The physicians will inform their appropriate eligible patients and their parents/legal guardians about this study and provide them with a flyer. Flyers will also be posted at the Stony Brook Neurology clinics and Stony Brook Pediatric clinics. We will ask local autism organizations to inform their members about this study. Interested patients and their parents/legal guardians can contact the study coordinator to find out more about the study and schedule a screening visit with Dr. Miller-Horn. We will also use ResearchMatch.org, a national electronic, web-based recruitment tool. An IRB-approved study recruitment message will be sent to potential study volunteers on ResearchMatch.org.

Screening visit

Parent/legal guardian and patient will meet with Dr. Miller-Horn and the study coordinator to discuss the study. If all agree to participate, the study coordinator will obtain 1) informed consent from parent/legal guardian for their participation, 2) permission from parent/legal guardian for the child's participation. Dr. Miller-Horn will assess the child's capacity to give assent. For patients aged 12-17.5 years old and deemed capable, a signed assent form will be obtained. For patients aged 4 to 11 years old and deemed capable, verbal assent will be obtained (written if capable). For patients that are not deemed capable of giving assent, only parental consent will be obtained. If patient does not have relevant blood work in the past month, venipuncture and blood tests are needed to determine renal/hepatic dysfunction. For female patients who have menses, urine will be collected for an over-the counter pregnancy test. By signing the consent

and assent forms, female patients agree to avoid any risk of conception during the study. If any patient becomes pregnant during the study, she will have to withdraw from the study immediately. Parents/legal guardians are health care proxies of their autistic child until 18 years old, thus they will have access to their child's medical information, including results of the pregnancy test. Parent/legal guardian will be notified by phone if the patient is still eligible for the study and if they are still interested in participation. If they are, a baseline visit will be scheduled.

Study Design

Table 1 – Study design and medication dosage (mg)

Week			Run-In (V0-V1)	Phase 1 (V1-V2)					Phase 2 (V2-V3)					Wash-Out (V3-V4)
			1 - 5	6	7	8	9	10	11	12	13	14	15	16 up to ≤ 27
Group A	Younger*	Donepezil	P	1.25	2.5	2.5	2.5	2.5	1.25	2.5	2.5	2.5	2.5	
		Melatonin	P	3	3	3	3	3	3	3	3	3	3	
	Older	Donepezil	P	2.5	5.0	5.0	5.0	5.0	2.5	5.0	5.0	5.0	5.0	
		Melatonin	P	3	3	3	3	3	3	3	3	3	3	
Group B	Younger*	Donepezil	P	P	P	P	P	P	1.25	2.5	2.5	2.5	2.5	
		Melatonin	P	P	P	P	P	P	3	3	3	3	3	
	Older	Donepezil	P	P	P	P	P	P	2.5	5.0	5.0	5.0	5.0	
		Melatonin	P	P	P	P	P	P	3	3	3	3	3	

Key: * Younger = children below 12 years of age or 80 lbs. weight, who start and end at a lower dose of donepezil, than the other Older children; P = Placebo

Table 2 – Visit procedures

Visit no.	Person in charge	Screening	Baseline (V0)	V1	V2	V3	V4
Study weeks		/	0	5	10	15	17 – 27
Incl/excl criteria*	Dr. Miller-Horn	X					
Pregnancy test (if applicable)**	CRC nurse	X					
Informed consent and assent	Study coordinator	X					
Aberrant Behavior Checklist	Parent		X	X	X	X	X
Child's Sleep Habits Questionnaire	Parent		X	X	X	X	X
Parent Global Impressions	Parent		X	X	X	X	X
Prenatal, developmental, neurological history	Dr. Miller-Horn		X				
Neurological exam	Dr. Miller-Horn		X	X	X	X	X
Clinical Global Impressions	Dr. Miller-Horn		X	X	X	X	X
Adverse event monitoring	Dr. Miller-Horn			X	X	X	X
Head circumference	CRC nurse		X				
D2/D4 finger length ratio	CRC nurse		X				
Dispense study drug	Dr. Miller-Horn		X	X	X		
Sleep hygiene education	Dr. Miller-Horn		X				
Study drug accountability	Study coordinator			X	X	X	

*Includes renal/hepatic function test if blood work was not done within the past month

** For female patients who have started menses

Patients will meet with Dr. Miller-Horn for 5 visits (baseline, follow up visit 1-4) every 5 weeks:

Phase 1 (between follow up visit 1 and 2) **–** The investigation will be conducted in 2 Phases as shown in Table 1. Phase 1 will be a double-blind randomized clinical trial using a parallel group design. It will assess the combined benefit of donepezil and melatonin in Group A versus placebo in Group B over 5 weeks.

Phase 2 (between follow up visit 2 and 3) **–** Phase 1 will be followed by an exploratory Phase 2 in which both groups (A & B) will be placed on the active medications for an additional 5 weeks. Phase 2 will allow us to explore whether Group A derives any additional benefit from 5 extra weeks of treatment with the active medications, and whether Group B obtains any benefit from switching from placebo to the active medications.

Run-In Phase (between visit 0/baseline and 1) **–** Phase 1 will be preceded by a Run-In Phase of 5 weeks where all subjects will receive placebo and instructions about how to improve sleep hygiene using the "Good Sleep Habits Checklist" (Durand 2014). Subjects and their families will be blinded to treatment during this phase, but investigators will not. The run-in will allow us to assess patient compliance with the study protocol. Only those who achieve compliance of at least 80% will be allowed to continue in the study and then be randomized to the two Groups. The Run-In will also allow us to control for any improvement due to better sleep hygiene. Finally, the Run-In will allow us to control for placebo effects, because the score obtained at the end of Run-In (possibly reflecting placebo effects) will be used as a baseline to which the scores at the end of each treatment phase can be compared.

Wash-Out Phase (between follow up visit 3 and 4) **–** A washout period of between 2 – 12 weeks will follow Phase 2, allowing us to explore any changes in both subject groups after active treatment has been withdrawn. The length of this period will vary in order to coincide with the next clinical visit of the patient with Dr. Miller-Horn, recognizing that this data is of lower priority.

Treatment

Melatonin– Melatonin is categorized by the US Food and Drug Administration (FDA) as a dietary supplement. It is widely available in the US without prescription. The dose of melatonin will be fixed at 3 mg for all participants, a level well tolerated in previous studies in this population of children (Tordjman et al. 2013). Adverse effects of melatonin have been found to be minimal to none in twenty small treatment studies in ASD (Rossignol and Frye 2013; Tordjman et al. 2013). None of the seven placebo-controlled trials of melatonin have found any increased risk of side effects (McArthur and Budden 1998; Garstang and Wallis 2006; Wasdell et al. 2008; Wirojanan et al. 2009; Wright et al. 2011; Cortesi et al. 2012; Gringras et al. 2012; Tordjman et al. 2013). Most other small studies of children with ASD taking melatonin also report no side effects (Jan et al. 1994; Horrigan and Barnhill 1997; Hayashi 2000; Jan et al. 2004; Gupta and Hutchins 2005; Giannotti et al. 2006; Galli-Carminati et al. 2009; Tordjman et al. 2013). Side effects, when noted in the other ASD melatonin studies tended to be mild and included: tiredness, daytime sleepiness, fogginess, awakening in the middle of sleep, excitement after awakening and before going to sleep, headaches, bed-wetting, and diarrhea (Ishizaki et al. 1999; Paavonen et al. 2003; Andersen et al. 2008; De Leersnyder et al. 2011; Malow et al. 2012; Tordjman et al. 2013). Dose timing is important for melatonin, and in keeping with earlier investigations (Wasdell et al. 2008; Wirojanan et al. 2009; Wright et al. 2011), parents/legal guardians will be instructed to administer it (12 ml) 30 minutes before a consistent desired bedtime. We will use supplemental melatonin in liquid form (Natrol®) as used in a previous study that obtained IND approval from the FDA for use in children with autism (Malow et al. 2012).

Donepezil– Donepezil, which is regulated by the FDA as a pharmaceutical drug, is also well tolerated in this population (Hardan and Handen 2002; Chez et al. 2003; Buckley et al. 2011; Handen et al. 2011; Srivastava et al. 2011). Related studies using other acetylcholinesterase inhibitors, including rivastigmine (Chez et al. 2004) and galantamine (Ghaleiha et al. 2013) have also shown that this class of medications is well tolerated in ASD children. Studies of donepezil in related pediatric clinical populations, such as fragile X (Sahu et al. 2013) and general Pervasive Developmental Disorder (Doyle et al. 2006) have found similar levels of tolerance. To maximize tolerance, the dosage will be titrated, as is commonly done in clinical trials with autistic children (Hardan and Handen 2002; Buckley et al. 2011; Handen et al. 2011). Parents/legal guardians will be instructed to administer the donepezil (1 capsule) with the melatonin, 30 minutes before a consistent desired bedtime.

Drug compounding –Pine Pharmaceuticals will repackage the liquid melatonin from Natrol® and compound the liquid placebo. The Stony Brook Pharmacy will repackage 5 mg generic donepezil into 1.25 and 2.5 mg gelatin capsules and compound the placebo in identical gelatin capsules. Patients will be given 40 days' worth of study medication.

Treatment Randomization – Patients who agree to participate after they pass the screening will be assigned a study ID. After the run-in phase, study subjects will be randomly assigned to Group A or B using a computer-generated randomization plan with blocking and stratification by gender and age group (Younger: children below 12 years of age or 80 lbs. weight; Older: $\geq$ 12 years or $\geq$ 80 lbs.).

Treatment Blinding – The study pharmacists at Stony Brook and at Pine Pharmaceuticals will be the only individuals informed of the randomization assignments and will be responsible for labeling study drug and maintaining a master list linking patients with treatment assignments. All other research staff and participants will be masked regarding treatment assignment. Masking of active and placebo treatments will be preserved by creating liquids and capsules and containers that appear identical.

Study Medication Accountability – Study medication used and unused will be monitored through a drug accountability form completed at visit 1, 2, and 3.

Outcome Measures

Neurological Exam. At the Baseline visit and study visits V1-V4, a neurological exam will be performed, using the following template.

General Appearance: Is the child/adolescent well appearing? Are there any neurocutaneous lesions and/or dysmorphic features?

Neurologic: Cranial Nerve Exam:
CN II - Optic fundi and pupils are examined with response to light.
CN III, IV, VI - Extraocular movements are examined for dysconjugate movements and nystagmus.
CN V - Facial sensation is not tested.
CN VII - Is there facial weakness or asymmetry?
CN VIII - Is hearing intact to voice?
CN IX-XII - Is the palate was up-going, and the tongue was midline?
SENSATION: Overall not tested.
MOTOR SYSTEM: Muscle bulk, tone, and strength is tested by a combination of functional and manual tests for symmetry.
CEREBELLAR: Fine movements and movements of the limbs are assessed. The gait and the ability to tandem walk is assessed.
DEEP TENDON REFLEXES: Are reflexes normally active and symmetric?

Lethargy/Social Withdrawal Subscale of the Aberrant Behavior Checklist (ABC-Social) – the primary outcome measure will be the parent/legal guardian completed ABC-Social subscale (Aman et al. 1985a; Aman et al. 1985b). The ABC includes 58 items divided into five subscales (Irritability/Agitation, Lethargy/Social Withdrawal, Stereotypic Behavior, Hyperactivity/Noncompliance, and Inappropriate Speech) and requires approximately 10-15 minutes to administer. The ABC is a well-regarded measure that is widely used in ASD treatment studies and has good reliability and validity (Aman et al. 1985b; Rojahn et al. 2011; Kaat et al. 2013). The ABC has been used in a number of previous AChEI treatment studies, though most were open label trials (Hardan and Handen 2002; Niederhofer et al. 2002; Doyle et al. 2006; Nicolson et al. 2006; Niederhofer 2007; Ghaleiha et al. 2013). The ABC-Social subscale in particular has been found to be a useful and sensitive measure of treatment effects in this population (Scahill et al. 2013).

Stereotypic Behavior subscale of the ABC (ABC – Stereotypic) The ABC will also provide a secondary outcome for the study, the Stereotypic Behavior subscale. This subscale is a well-regarded outcome measure of the restrictive and repetitive behaviors that are among the core symptoms of autism (Aman 2012).

Children's Sleep Habits Questionnaire (CSHQ) – This secondary outcome measure will assess sleep, using a brief seven item questionnaire adapted from the Children's Sleep Habits Questionnaire (CSHQ) (Owens et al. 2000). This parental questionnaire assesses sleep behaviors in children (Owens et al. 2000). It has been validated in children with ASD, correlates with polysomnographic recordings, and has been used successfully in previous studies of melatonin with such children (Malow et al. 2006; Leu et al. 2011; Goldman et al. 2012). The CSHQ items chosen for this study come from the subscales found to be most often disturbed in children with autism: Sleep Duration, Sleep Onset Delay, and Night Wakings (Goldman et al. 2012).

Clinical Global Impressions (CGI) –The blinded treating neurologist will complete this secondary outcome in order to assess overall clinical impressions of global improvement and medication efficacy (Guy 1976).

Parent Reported Global Impressions (PRGI) – Modeled on the CGI, parents/legal guardians will complete this secondary outcome in order to their overall impressions of global improvement and medication efficacy.

Biomarkers – A variety of convenient, non-invasive, and safe biomarkers will also be collected in order to better characterize the sample and to relate to baseline behavioral and sleep measures: prenatal history (including stressors and history of exposure to selective serotonin reuptake inhibitors or terbutaline), developmental neurological history and neurological exam, D2/D4 finger length ratio (from xerox of hand), and head circumference.

Data safety and monitoring plan

Dr. Rebecca Spiegel, who is unaffiliated with the current study, has volunteered to serve as our data safety monitor. Dr. Spiegel is an associate professor in the Neurology Department here at Stony Brook who is board certified by American Board of Sleep Medicine and the American Board of Psychiatry and Neurology. Dr. Spiegel will periodically randomly audit the protocol documentation with the first audit occur by the enrollment of the fifth subject in order to check the quality control of the investigation early in the process, and additional audits occurring an average of every 10 subjects. Among the important goals of the audits will be to ensure that adverse events are reported, protocol amendments are filed with the IRB, inclusion/exclusion criteria are followed, and the number of patient visits do not exceed the protocol guidelines.

Analysis

Power – This is an exploratory study. It will be powered only to detect a large superiority (d = 0.9) of the combined medication treatment as compared to placebo on the primary outcome (ABC-Social) in Phase 1 of the study. With a proposed sample size of 60 (30 in each group) and 10% subject attrition, there will be 54 completers (27 in each group), and power is estimated to be 91.1% (2-sided test, 5% type 1 error rate)

Statistical Analysis - All statistical analyses will be performed according to an intention-to-treat principle on the full sample. A last-observation-carried-forward imputation strategy will be used for missing data. The primary analysis will consist of an independent samples *t*-test on the normally distributed ABC Social change score in Phase 1. This will be followed by an analysis of covariance (ANCOVA) controlling for any variables on which the two drug groups are found to differ at baseline. Analyses of other continuous outcome variables in Phase 1 will use a similar approach. Group differences on categorical outcomes (e.g., CGI) will be analyzed by Chi Square test. Exploratory analyses for within group changes in Phase 2 (e.g., testing whether Group A derives additional benefit from 5 extra weeks of active treatment, or whether Group B obtains any benefit from the change from placebo to active treatment) and during the Washout Phase (e.g., testing whether the effects of the medications do washout when withdrawn) will be analyzed by means of a paired sample t-test on the outcome variables of interest. All tests will be 2-tailed, with a p = .05 considered significant, with no correction for multiple analyses in this exploratory study. Correlation coefficients will be used to explore the relation of biomarkers to baseline behavioral and sleep measures, again using p = .05. All analyses will be performed using SPSS 21.0 statistical software. There will be no interim analysis.

References

(2009). "Autism fact sheet." from http://www.ninds.nih.gov/disorders/autism/detail_autism.htm.

Aman, M. G. (2012). "Aberrant behavior checklist: Current identity and future developments." Clinical and Experimental Pharmacology **2**(3).

Aman, M. G., N. N. Singh, A. W. Stewart and C. J. Field (1985a). "The aberrant behavior checklist - a behavior rating-scale for the assessment of treatment effects." American Journal of Mental Deficiency **89**(5): 485-491.

The development of a scale to assess drug and other treatment effects on severely mentally retarded individuals was described. In the first stage of the project, an initial scale encompassing a large number of behavior problems was used to rate 418 residents. The scale was then reduced to an intermediate version, and in the second stage, 509 moderately to profoundly retarded individuals were rated. Separate factor analyses of the data from the two samples resulted in a five-factor scale comprising 58 items. The factors of the Aberrant Behavior Checklist have been labeled as follows: (I) Irritability, Agitation, Crying; (II) Lethargy, Social Withdrawal; (III) Stereotypic Behavior; (IV) Hyperactivity, Noncompliance; and (V) Inappropriate Speech. Average subscale scores were presented for the instrument, and the results were compared with empirically derived rating scales of childhood psychopathology and with factor analytic work in the field of mental retardation.

Aman, M. G., N. N. Singh, A. W. Stewart and C. J. Field (1985b). "Psychometric characteristics of the aberrant behavior checklist." American Journal of Mental Deficiency **89**(5): 492-502.

Andersen, I. M., J. Kaczmarska, S. G. McGrew and B. A. Malow (2008). "Melatonin for insomnia in children with autism spectrum disorders." Journal of Child Neurology **23**(5): 482-485.

We describe our experience in using melatonin to treat insomnia, a common sleep concern, in children with autism spectrum disorders. One hundred seven children (2-18 years of age) with a confirmed diagnosis of autism spectrum disorders who received melatonin were identified by reviewing the electronic medical records of a single pediatrician. All parents were counseled on sleep hygiene techniques. Clinical response to melatonin, based on parental report, was categorized as (1) sleep no longer a concern, (2) improved sleep but continued parental concerns, (3) sleep continues to be a major concern, and (4) worsened sleep. The melatonin dose varied from 0.75 to 6 mg. After initiation of melatonin, parents of 27 children (25%) no longer reported sleep concerns at follow-up visits. Parents of 64 children (60%) reported improved sleep, although continued to have concerns regarding sleep. Parents of 14 children (13%) continued to report sleep problems as a major concern, with only 1 child having worse sleep after starting melatonin (1%), and 1 child having undetermined response (1%). Only 3 children had mild side-effects after starting melatonin, which included morning sleepiness and increased enuresis. There was no reported increase in seizures after starting melatonin in children with pre-existing epilepsy and no new-onset seizures. The majority of children were taking psychotropic medications. Melatonin appears to be a safe and well-tolerated treatment for insomnia in children with autism spectrum disorders. Controlled trials to determine efficacy appear warranted.

Azevedo Marques, L., M. Giera, H. Lingeman and W. M. Niessen (2011). "Analysis of acetylcholinesterase inhibitors: Bioanalysis, degradation and metabolism." Biomedical Chromatography **25**(1-2): 278-299.

Alzheimer's is a neurodegenerative disease. Its symptoms are attributed to a deficiency of cholinergic neurotransmission. The drugs of choice for the treatment of Alzheimer's disease are acetylcholinesterase (AChE) inhibitors. Starting in the 1980's from non-specific AChE inhibitors, the first-generation drugs such as physostigmine, a second generation of more selective and better tolerated products has been developed. Methods to detect and quantify these drugs and their metabolites in biological samples have been developed for analysis in plasma, blood, urine and cerebrospinal fluid. Diverse detection techniques have been used, such

as ultraviolet, fluorescence, electrochemical and mass spectrometry. In this review, the methods applied to the analysis of these drugs and their metabolites in different biological matrices are reviewed and discussed. The stability of these drugs in biological matrices and under stress-conditions is also included in the discussion.

Buckley, A. W., A. J. Rodriguez, K. Jennison, J. Buckley, A. Thurm, S. Sato and S. Swedo (2010). "Rapid eye movement sleep percentage in children with autism compared with children with developmental delay and typical development." Archives of Pediatrics and Adolescent Medicine **164**(11): 1032-1037.

OBJECTIVE: To compare objective polysomnographic parameters between 3 cohorts: children with autism, typical development, and developmental delay without autism. DESIGN: Overnight polysomnographic recordings were scored for sleep architecture according to American Academy of Sleep Medicine criteria by a board-certified sleep medicine specialist blind to diagnosis for studies collected between July 2006 and September 2009. SETTING: Subjects were evaluated in the pediatric ward in the Clinical Research Center of the National Institutes of Health. PARTICIPANTS: First 60 consecutive children with autism, 15 with typical development, and 13 with developmental delay matched for nonverbal IQ to the autism group, ranging in age from 2 to 13 years, selected without regard to the presence or absence of sleep problem behavior. MAIN OUTCOME MEASURES: Total sleep time, latencies to non-rapid eye movement (REM) and REM sleep, and percentages of total sleep time for stages 1 and 2 sleep, slow-wave sleep, and REM sleep. RESULTS: There were no differences between the typical vs developmental delay groups. Comparison of children with autism vs typical children revealed shorter total sleep time (P = .004), greater slow-wave sleep percentage (P = .001), and much smaller REM sleep percentage (14.5% vs 22.6%; P < .001). Comparison of children with autism vs children with developmental delay revealed shorter total sleep time (P = .001), greater stage 1 sleep percentage (P < .001), greater slow-wave sleep percentage (P < .001), and much less REM sleep percentage (14.5% v 25%; P < .001). CONCLUSION: A relative deficiency of REM sleep may indicate an abnormality in neural organization in young children with autism that is not directly associated with or related to inherent intellectual disability but may serve as a window into understanding core neurotransmitter abnormalities unique to this disorder.

Buckley, A. W., K. Sassower, A. J. Rodriguez, K. Jennison, K. Wingert, J. Buckley, A. Thurm, S. Sato and S. Swedo (2011). "An open label trial of donepezil for enhancement of rapid eye movement sleep in young children with autism spectrum disorders." Journal of Child and Adolescent Psychopharmacology **21**(4): 353-357.

BACKGROUND: Rapid eye movement (REM) sleep is greatest in the developing brain, is driven by acetylcholine, and may represent a protected time for neuroplasticity. Recently published data from our lab observed that children with autism spent significantly less time in this state during a single night recording than did typically developing children and those with developmental delay without autism. The objective of this study was to determine whether or not donepezil can increase the REM % in children with diagnosed autism spectrum disorder (ASD) found to have REM % values of at least two standard deviations below expected for age. METHODS: Five subjects found to have an ASD (ages 2.5-6.9 years) and demonstrated deficits in REM sleep compared with within-lab controls were enrolled in a dose finding study of donepezil. Each subject was examined by polysomnography for REM sleep augmentation after drug administration. RESULTS: REM sleep as a percentage of Total Sleep Time was increased significantly and REM latency was decreased significantly after drug administration in all subjects. No other observed sleep parameter was changed significantly. CONCLUSIONS: Donepezil can increase the amount of time that children with an ASD spend in the REM sleep state. A double-blind, placebo-controlled trial is needed to assess the association between REM sleep augmentation and learning, cognition, and behavior in such children.

Burns, A., M. Rossor, J. Hecker, S. Gauthier, H. Petit, H. J. Moller, S. L. Rogers and L. T. Friedhoff (1999). "The effects of donepezil in alzheimer's disease - results from a multinational trial." Dementia and Geriatric Cognitive Disorders **10**(3): 237-244.

Donepezil has been shown to be well tolerated and to improve cognition and global function in patients with mild to moderately severe Alzheimer's disease (AD). The current trial was undertaken to investigate further the

efficacy and safety of donepezil, in a multinational setting, in patients with mild to moderately severe AD. This 30-week, placebo-controlled, parallel-group study consisted of a 24-week, double-blind treatment phase followed by a 6-week, single-blind, placebo washout. Eight hundred and eighteen patients with mild to moderately severe AD were randomly allocated to treatment with single, daily doses of 5 or 10 mg donepezil, or placebo. The two primary efficacy measures were: a cognitive performance test, the Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog) and a global evaluation, the Clinician's Interview-Based Impression of Change with caregiver input (CIBIC plus). Secondary outcome measures included the Sum of the Boxes of the Clinical Dementia Rating Scale (CDR-SB), a modified Interview for Deterioration in Daily living activities in Dementia (IDDD) and a patient rated quality of life assessment. Statistically significant improvements in cognitive and global function were observed, as evaluated by ADAS-cog and CIBIC plus, respectively, in both the 5 and 10 mg/day donepezil groups, compared with placebo. Treatment-associated changes were also observed in functional skills, as shown by improved scores on the CDR-SB and the complex-tasks component of the IDDD. A dose-response effect was evident, with the 10 mg/day donepezil group demonstrating greater benefits in all outcome measures than the 5 mg/day group. Donepezil was well tolerated by this patient population and did not produce any clinically significant laboratory test abnormalities. The results of this study confirm that donepezil is effective and well tolerated in treating the symptoms of mild to moderately severe AD.

Chez, M. G., M. Aimonovitch, T. Buchanan, S. Mrazek and R. J. Tremb (2004). "Treating autistic spectrum disorders in children: Utility of the cholinesterase inhibitor rivastigmine tartrate." Journal of Child Neurology **19**(3): 165-169.

Rivastigmine tartrate is a dual-action cholinesterase inhibitor shown to improve language, cognition, and global functioning in patients with Alzheimer's disease, likely via increased availability of cerebral acetylcholine. Because cholinergic receptor abnormalities can contribute to the neuropathology of autistic spectrum disorders, rivastigmine tartrate could prove to be an effective therapy for affected children. Observations of improved behavior and language output from prior open-label and double-blind treatment of autistic children with donepezil, another cholinesterase inhibitor, prompted this 12-week open-label study with rivastigmine tartrate of 32 autistic patients. Therapeutic indices were the Childhood Autistic Rating Scale, Gardner's Expressive and Receptive One-Word Picture Vocabulary tests, and the Conners' Parent Rating Scale. Testing administered at baseline, 6 weeks, and 12 weeks showed gains in both expressive speech and overall autistic behavior over baseline. These improvements were statistically significant and supported the hypothesis that treatment with cholinergic enhancing drugs in autistic spectrum disorders yields positive therapeutic effects.

Chez, M. G., T. M. Buchanan, M. Becker, J. Kessler, M. C. Aimonovitch and S. R. Mrazek (2003). "Donepezil hydrochloride: A double-blind study in autistic children." Journal of Pediatric Neurology **1**(2): 83-88.

Recent studies in autistic brain samples have shown diminished acetylcholine and nicotinic receptor activity. We hypothesized that acetylcholinergic enhancement may pharmacologically improve some autistic characteristics. Donepezil hydrochloride, an acetylcholinesterase inhibitor, was studied previously in two open label studies which showed improvement in the expressive and receptive speech and aberrant behaviors of autistic children. We therefore undertook a double-blind placebo controlled study to confirm these findings. Forty-three patients (35 males, 8 females, average age 6.8 yrs, range 2.1-10.3 yrs), with diagnoses of Autistic Spectrum Disorders enrolled in a randomized six-week, double-blind, placebo-controlled trial of donepezil hydrochloride, with an additional six weeks of open-label treatment. Change was evaluated by the Childhood Autistic Rating Scale, Gardner's Expressive One-Word Picture Vocabulary Test, Revised, and Gardner's Receptive One- Word Picture Vocabulary Test. Testing was administered at baseline, six-week, and twelve week follow-up. Expressive and receptive speech gains, as well as decreases in severity of overall autistic behavior, were documented after 6-weeks for the treatment group. These improvements were statistically significant when compared to placebo, and were clinically meaningful as assessed over time. Donepezil hydrochloride appears to improve expressive and receptive language as well as overall autistic features, consistent with the hypothesis of acetylcholinergic enhancement.

Cidav, Z., S. C. Marcus and D. S. Mandell (2012). "Implications of childhood autism for parental employment and earnings." Pediatrics **129**(4): 617-623.

OBJECTIVE: To examine changes in parental labor force participation, hours of work, and annual earnings associated with childhood autism spectrum disorders (ASD). METHODS: We used the 2002-2008 Medical Expenditure Panel Survey to examine parental labor market outcomes of children with ASD relative to children with another health limitation and children without health limitations. A logit model was used to estimate parental labor force participation. A tobit model was used to estimate parental hours of work and earnings. RESULTS: On average, mothers of children with ASD earn 35% ($7189) less than the mothers of children with another health limitation and 56% ($14 755) less than the mothers of children with no health limitation. They are 6% less likely to be employed and work 7 hours less per week, on average, than mothers of children with no health limitation. There were no statistically significant differences in fathers' labor market outcomes across 3 groups. On average, children with ASD are 9% less likely to have both parents working. Family earnings of children with ASD are 21% ($10 416) less than those of children with another health limitation and 28% ($17 763) less than those of children with no health limitation. Family weekly hours of work are an average of 5 hours less than those of children with no health limitation. CONCLUSIONS: Families of children with ASD face significant economic burden. Given the substantial health care expenses associated with ASD, the economic impact of having lower income in addition to these expenses is substantial. It is essential to design universal health care and workplace policies that recognize the full impact of autism.

Comer, J. S., M. Olfson and R. Mojtabai (2010). "National trends in child and adolescent psychotropic polypharmacy in office-based practice, 1996-2007." Journal of the American Academy of Child and Adolescent Psychiatry **49**(10): 1001-1010.

OBJECTIVE: To examine patterns and recent trends in multiclass psychotropic treatment among youth visits to office-based physicians in the United States. METHOD: Annual data from the 1996-2007 National Ambulatory Medical Care Surveys were analyzed to examine patterns and trends in multiclass psychotropic treatment within a nationally representative sample of 3,466 child and adolescent visits to office-based physicians in which a psychotropic medication was prescribed. RESULTS: There was an increase in the percentage of child visits in which psychotropic medications were prescribed that included at least two psychotropic classes. Across the 12 year period, multiclass psychotropic treatment rose from 14.3% of child psychotropic visits (1996-1999) to 20.2% (2004-2007) (adjusted odds ratio [AOR] = 1.89, 95% confidence interval [CI] = 1.22-2.94, $p < .01$). Among medical visits in which a current mental disorder was diagnosed, the percentage with multiclass psychotropic treatment increased from 22.2% (1996-1999) to 32.2% (2004-2007) (AOR = 2.23, 95% CI = 1.42-3.52, $p < .001$). Over time, there were significant increases in multiclass psychotropic visits in which ADHD medications, antidepressants, or antipsychotics were prescribed, and a decrease in those visits in which mood stabilizers were prescribed. There were also specific increases in co-prescription of ADHD medications and antipsychotic medications (AOR = 6.22, 95% CI = 2.82-13.70, $p < .001$) and co-prescription of antidepressant and antipsychotic medications (AOR = 5.77, 95% CI = 2.88-11.60, $p < .001$). CONCLUSIONS: Although little is known about the safety and efficacy of regimens that involve concomitant use of two or more psychotropic agents for children and adolescents, multiclass psychotropic pharmacy is becoming increasingly common in outpatient practice.

Cortesi, F., F. Giannotti, T. Sebastiani, S. Panunzi and D. Valente (2012). "Controlled-release melatonin, singly and combined with cognitive behavioural therapy, for persistent insomnia in children with autism spectrum disorders: A randomized placebo-controlled trial." Journal of Sleep Research **21**(6): 700-709.

Although melatonin and cognitive-behavioural therapy have shown efficacy in treating sleep disorders in children with autism spectrum disorders, little is known about their relative or combined efficacy. One hundred and sixty children with autism spectrum disorders, aged 4-10 years, suffering from sleep onset insomnia and impaired sleep maintenance, were assigned randomly to either (1) combination of controlled-release melatonin and cognitive-behavioural therapy; (2) controlled-release melatonin; (3) four sessions of cognitive-behavioural

therapy; or (4) placebo drug treatment condition for 12 weeks in a 1 : 1 : 1 : 1 ratio. Children were studied at baseline and after 12 weeks of treatment. Treatment response was assessed with 1-week actigraphic monitoring, sleep diary and sleep questionnaire. Main outcome measures, derived actigraphically, were sleep latency, total sleep time, wake after sleep onset and number of awakenings. The active treatment groups all resulted in improvements across all outcome measures, with moderate-to-large effect sizes from baseline to a 12-week assessment. Melatonin treatment was mainly effective in reducing insomnia symptoms, while cognitive-behavioural therapy had a light positive impact mainly on sleep latency, suggesting that some behavioural aspects might play a role in determining initial insomnia. The combination treatment group showed a trend to outperform other active treatment groups, with fewer dropouts and a greater proportion of treatment responders achieving clinically significant changes (63.38% normative sleep efficiency criterion of >85% and 84.62%, sleep onset latency <30 min). This study demonstrates that adding behavioural intervention to melatonin treatment seems to result in a better treatment response, at least in the short term.

De Leersnyder, H., N. Zisapel and M. Laudon (2011). "Prolonged-release melatonin for children with neurodevelopmental disorders." Pediatric Neurology **45**(1): 23-26.

Previous studies demonstrated the efficacy and safety of prolonged-release melatonin in children and adolescents with neurodevelopmental and behavioral disorders. The long-term effectiveness and safety of prolonged-release melatonin treatment were assessed in 88 children (42 girls and 46 boys) with neurodevelopmental disorders. These patients participated in a compassionate-use program with the drug Circadin (2 mg; Neurim Pharmaceuticals, Tel Aviv, Israel) in France, and received treatment in the context of regular care by a specialized physician. The study involved a structured questionnaire for the parents, comprising a combination of multiple-choice and numeric questions addressing sleep onset/offset, sleep quality problems, and mood. The dose of melatonin ranged from 4-6 mg, and treatment duration ranged from 6-72 months. Within 3 months, sleep latency with prolonged-release melatonin decreased by 44.0% ($P < 0.001$), sleep duration increased by 10.1% ($P < 0.001$), the number of awakenings decreased by 75% ($P < 0.001$), and sleep quality improved by 75%, compared with baseline ($P < 0.001$). No serious adverse events or treatment-related comorbidities were reported. Prolonged-release melatonin remains a safe, effective therapy for the long-term treatment of sleep disorders in children with neurodevelopmental disorders.

Doyle, R. L., J. Frazier, T. J. Spencer, D. Geller, J. Biederman and T. Wilens (2006). "Donepezil in the treatment of adhd-like symptoms in youths with pervasive developmental disorder: A case series." J Atten Disord **9**(3): 543-549.

BACKGROUND: Recent studies reported ADHD-like symptoms and cognitive deficits in pervasive developmental disorder (PDD). Because work in dementia documents improvement in executive function deficits with the acetylcholinesterase inhibitor donepezil, the authors reason that similar benefits could be obtained in PDD. METHOD: The authors describe eight cases of PDD youth ages 10 to 17 treated with donepezil targeting ADHD-like symptoms associated with PDD. RESULTS: Most participants improve ADHD-like symptomatology. In addition, improvement in communication and socialization is noted. CONCLUSION: Donepezil may have a role in treating ADHD-like symptoms in children with PDD.

Durand, V. M. (2014). Sleep better! A guide to improving sleep for children with special needs. Baltimore, MD, Brookes Publishing Co.

Galli-Carminati, G., N. Deriaz and G. Bertschy (2009). "Melatonin in treatment of chronic sleep disorders in adults with autism: A retrospective study." Swiss Medical Weekly **139**(19-20): 293-296.

BACKGROUND: Melatonin may be used to treat sleep disorders in both children and adults with intellectual disability. The evidence for its efficacy, potential adverse effects and drug interactions are reviewed in the context of prescription of melatonin to patients with autism. METHODS: This study presents the use of melatonin to treat severe circadian sleep-wake disturbances in 6 adults with autism. Melatonin was initiated at a

daily dose of 3 mg at nocturnal bedtime. If this proved ineffective, the melatonin dose was titrated over the following 4 weeks at increments of 3 mg/2 weeks up to a maximum of 9 mg, unless it was tolerated. Assessments included Clinical Global Impression-Severity (CGI-S) and CGI-Improvement (CGI-I). RESULTS: Melatonin administered in the evening dramatically improved the sleep-wake pattern in all patients. Melatonin appears to be effective in reducing sleep onset latency and is probably effective in improving nocturnal awakenings and total sleep time in adults with autism. Its effectiveness remained stable for the 6-month period of administration. Melatonin was well tolerated in all patients and no side effects were noted during the therapy. CONCLUSIONS: Melatonin appears to be promising as an efficient and seemingly safe alternative for treatment of severe circadian sleep disturbances in adults with autism. There may be heterogeneity of response depending on the nature of the sleep problem and cause of the intellectual disability or associated disabilities. Further studies are necessary before firm conclusions can be drawn and guidelines for the use of melatonin in people with autism formulated.

Garstang, J. and M. Wallis (2006). "Randomized controlled trial of melatonin for children with autistic spectrum disorders and sleep problems." Child: Care, Health and Development **32**(5): 585-589.

BACKGROUND: Melatonin is often used for autistic children with sleep disorders, despite a lack of published evidence in this population. METHODS: A randomized, placebo-controlled double-blind crossover trial of melatonin was undertaken in 11 children with autistic spectrum disorder (ASD). RESULTS: Seven children completed the trial. Sleep latency was 2.6 h [95% confidence intervals (CI) 2.28-2.93] baseline, 1.91 h (95% CI 1.78-2.03) with placebo and 1.06 h (95% CI 0.98-1.13) with melatonin. Wakings per night were 0.35 (95% CI 0.18-0.53) baseline, 0.26 (95% CI 0.20-0.34) with placebo and 0.08 (95% CI 0.04-0.12) with melatonin. Total sleep duration was 8.05 h (95% CI 7.65-8.44) baseline, 8.75 h (95% CI 8.56-8.98) with placebo and 9.84 h (95% CI 9.68-9.99) with melatonin. CONCLUSIONS: Although the study was small owing to recruitment difficulties, it still provides evidence of effectiveness of melatonin in children with sleep difficulties and ASD, which we predict a larger study would confirm.

Ghaleiha, A., M. Ghyasvand, M. R. Mohammadi, M. Farokhnia, N. Yadegari, M. Tabrizi, R. Hajiaghaee, H. Yekehtaz and S. Akhondzadeh (2013). "Galantamine efficacy and tolerability as an augmentative therapy in autistic children: A randomized, double-blind, placebo-controlled trial." J Psychopharmacol.

The role of cholinergic abnormalities in autism was recently evidenced and there is a growing interest in cholinergic modulation, emerging for targeting autistic symptoms. Galantamine is an acetylcholinesterase inhibitor and an allosteric potentiator of nicotinic receptors. This study aimed to evaluate the possible effects of galantamine as an augmentative therapy to risperidone, in autistic children. In this randomized, double-blind, placebo-controlled, parallel-group study, 40 outpatients aged 4-12 years whom had a diagnosis of autism (DSM IV-TR) and a score of 12 or higher on the Aberrant Behavior Checklist-Community (ABC-C) Irritability subscale were equally randomized to receive either galantamine (up to 24 mg/day) or placebo, in addition to risperidone (up to 2 mg/day), for 10 weeks. We rated participants by ABC-C and a side effects checklist, at baseline and at weeks 5 and 10. By the study endpoint, the galantamine-treated patients showed significantly greater improvement in the Irritability ($P = 0.017$) and Lethargy/Social Withdrawal ($P = 0.005$) subscales than the placebo group. The difference between the two groups in the frequency of side effects was not significant. In conclusion, galantamine augmentation was shown to be a relatively effective and safe augmentative strategy for alleviating some of the autism-related symptoms.

Giannotti, F., F. Cortesi, A. Cerquiglini and P. Bernabei (2006). "An open-label study of controlled-release melatonin in treatment of sleep disorders in children with autism." Journal of Autism and Developmental Disorders **36**(6): 741-752.

Long-term effectiveness of controlled-release melatonin in 25 children, aged 2.6-9.6 years with autism without other coexistent pathologies was evaluated openly. Sleep patterns were studied using Children's Sleep Habits Questionnaire (CSHQ) and sleep diaries at baseline, after 1-3-6 months melatonin treatment and 1 month after discontinuation. Sleep diary and CSHQ showed a more problematic sleep in autistic children compared with

controls. During treatment sleep patterns of all children improved. After discontinuation 16 children returned to pre-treatment score, readministration of melatonin was again effective. Treatment gains were maintained at 12 and 24-month follow-ups. No adverse side effects were reported. In conclusion, controlled-release melatonin may provide an effective and well-tolerated treatment for autistic children with chronic sleep disorders.

Goldman, S. E., A. L. Richdale, T. Clemons and B. A. Malow (2012). "Parental sleep concerns in autism spectrum disorders: Variations from childhood to adolescence." Journal of Autism and Developmental Disorders **42**(4): 531-538.

Sleep problems of adolescents and older children with Autism Spectrum Disorder (ASD) were compared to toddlers and young children in 1,859 children. Sleep was measured with the Children's Sleep Habits Questionnaire. Total sleep problems were significant across all age groups, however the factors contributing to these problems differed. Adolescents and older children had more problems with delayed sleep onset, shorter sleep duration, and daytime sleepiness; while younger children had more bedtime resistance, sleep anxiety, parasomnias, and night wakings. The results suggest that sleep problems persist through adolescence in ASD with differences in types of problems experienced and emphasize the need for clinicians to address sleep behaviors not only in young children with ASD but throughout the age span.

Gringras, P., C. Gamble, A. P. Jones, L. Wiggs, P. R. Williamson, A. Sutcliffe, P. Montgomery, W. P. Whitehouse, I. Choonara, T. Allport, A. Edmond, R. Appleton and M. S. Group (2012). "Melatonin for sleep problems in children with neurodevelopmental disorders: Randomised double masked placebo controlled trial." BMJ **345**: e6664.

OBJECTIVE: To assess the effectiveness and safety of melatonin in treating severe sleep problems in children with neurodevelopmental disorders. DESIGN: 12 week double masked randomised placebo controlled phase III trial. SETTING: 19 hospitals across England and Wales. PARTICIPANTS: 146 children aged 3 years to 15 years 8 months were randomised. They had a range of neurological and developmental disorders and a severe sleep problem that had not responded to a standardised sleep behaviour advice booklet provided to parents four to six weeks before randomisation. A sleep problem was defined as the child not falling asleep within one hour of lights out or having less than six hours' continuous sleep. INTERVENTIONS: Immediate release melatonin or matching placebo capsules administered 45 minutes before the child's bedtime for a period of 12 weeks. All children started with a 0.5 mg capsule, which was increased through 2 mg, 6 mg, and 12 mg depending on their response to treatment. MAIN OUTCOME MEASURES: Total sleep time at night after 12 weeks adjusted for baseline recorded in sleep diaries completed by the parent. Secondary outcomes included sleep onset latency, assessments of child behaviour, family functioning, and adverse events. Sleep was measured with diaries and actigraphy. RESULTS: Melatonin increased total sleep time by 22.4 minutes (95% confidence interval 0.5 to 44.3 minutes) measured by sleep diaries (n=110) and 13.3 (-15.5 to 42.2) measured by actigraphy (n=59). Melatonin reduced sleep onset latency measured by sleep diaries (-37.5 minutes, -55.3 to -19.7 minutes) and actigraphy (-45.3 minutes, -68.8 to -21.9 minutes) and was most effective for children with the longest sleep latency (P=0.009). Melatonin was associated with earlier waking times than placebo (29.9 minutes, 13.6 to 46.3 minutes). Child behaviour and family functioning outcomes showed some improvement and favoured use of melatonin. Adverse events were mild and similar between the two groups. CONCLUSIONS: Children gained little additional sleep on melatonin; though they fell asleep significantly faster, waking times became earlier. Child behaviour and family functioning outcomes did not significantly improve. Melatonin was tolerable over this three month period. Comparisons with slow release melatonin preparations or melatonin analogues are required. TRIAL REGISTRATION: ISRCT No 05534585.

Gupta, R. and J. Hutchins (2005). "Melatonin: A panacea for desperate parents? (hype or truth)." Archives of Disease in Childhood **90**(9): 986-987.

Sleep disorders are common in children with neurodevelopmental disorder and are a major source of stress for the whole family. In children with neurodevelopmental disabilities the prevalence may be as high as 80%. The current literature is suggestive of circadian rhythm dysfunction, social difficulties, and abnormal melatonin levels in children with autism. Hypnotics and sedatives can produce side effects and tolerance, so is melatonin the

answer in children with sleep problems associated with severe developmental difficulties of social and communicating nature, which have not responded to behavioural and social measure? Previous studies and case reports have suggested that melatonin could be effective. We retrospectively reviewed cases of nine autistic children with chronic sleep disorder, who were attending the Child Developmental Centre at Windmill Lodge. The age range of these children was 2–11 years. No additional non-pharmacological sleep intervention was instituted. They were started on 2.5–5 mg melatonin 45 minutes before their sleeping time. In four of these patients sleep latency was reduced. Our own experience of reduction in sleep latency is in accordance with literature. Five parents reported improvement in total duration of sleep. In three patients medication was stopped within a week because of no response. Four patients are still on melatonin for over a year without any side effects. We could not find the cause in non-responders. To find out the real benefit of melatonin, the dose, short and long term side effects, and group of patients who will respond to melatonin, several authors have already identified the need for a double blind crossover study. Previous studies have reported response rates of up to 80%, but it is seems likely that studies which group together children with ‘‘neurodevelopmental disorders’’ in a generic manner will not furnish the answer as to the true place of melatonin in the management of disturbed sleep patterns.

Guy, W. (1976). Ecdeu assessment manual for psychopharmacology – revised (dhew publ no adm 76-338). E. US Department of Health, and Welfare; Public Health Service; Alcohol, Drug Abuse, and Mental Health Administration, NIMH Psychopharmacology Research Branch; Division of Extramural Research Programs. Rockville, MD**:** 218-222.

Handen, B. L., C. R. Johnson, S. McAuliffe-Bellin, P. J. Murray and A. Y. Hardan (2011). "Safety and efficacy of donepezil in children and adolescents with autism: Neuropsychological measures." Journal of Child and Adolescent Psychopharmacology **21**(1): 43-50.

OBJECTIVE: There has been recent interest in the use of cognitive enhancing drugs, such as cholinesterase inhibitors, as a possible treatment for executive functioning (EF) deficits in autism spectrum disorder (ASD). The goal of this study was to assess the tolerability, safety, and efficacy of donepezil on EF in a sample of children and adolescents with ASD. METHOD: Thirty-four children and adolescents with ASD (age range 8-17 years; IQ >75) were enrolled in a 10-week, double-blind, placebo-controlled trial of donepezil (doses of 5 and 10 mg), followed by a 10-week open label trial for placebo nonresponders. RESULTS: The effect of donepezil treatment on EF was examined. Despite improvement on a number of EF measures, no statistically significant between-group differences were found (with gains observed for both the placebo and donepezil groups). CONCLUSIONS: The results suggest that short-term treatment with donepezil may have limited impact on cognitive functioning in ASD. Future controlled trials may need to consider a longer treatment period to detect significant gains on EF measures.

Hardan, A. Y. and B. L. Handen (2002). "A retrospective open trial of adjunctive donepezil in children and adolescents with autistic disorder." Journal of Child and Adolescent Psychopharmacology **12**(3): 237-241.

In light of the recently reported neuropathologic and neurochemical abnormalities of the cholinergic pathways in autism, donepezil, a cholinesterase inhibitor, is a potentially useful agent in the treatment of cognitive and behavioral symptoms observed in this disorder. A retrospective pilot study was conducted to determine whether donepezil is effective in the treatment of children and adolescents with autism. Eight patients (mean age = 11.0 +/- 4.1 years; range 7-19 years) who met Diagnostic and Statistical Manual of Mental Disorders (4th edition) criteria for autistic disorder were openly treated with donepezil. All patients were on concomitant psychoactive medications. Four of these patients (50%) demonstrated significant improvement as assessed by the Aberrant Behavior Checklist and the Clinical Global Impression Scale. Decreases in the Irritability and Hyperactivity subscales were observed, but no changes in the Inappropriate Speech, Lethargy, and Stereotypies subscales were noted. Limited and transient side effects were reported, with one patient experiencing gastrointestinal disturbances and another reporting mild irritability. Double-blind, placebo-controlled

investigations are needed to provide further evidence of the potential benefits of donepezil to patients with autistic disorder.

Hayashi, E. (2000). "Effect of melatonin on sleep-wake rhythm: The sleep diary of an autistic male." Psychiatry and Clinical Neurosciences **54**(3): 383-384.

This study reports on melatonin treatment in autism. A 14-year-old autistic male with severe mental retardation was given melatonin at a dose of 6 mg at 9:00 pm (C1) or 11:00 pm (C2). His parents kept a sleep diary. In C1, he often experienced early morning waking and fragmented night sleep but in C2, night sleep was prolonged and sleep-wake rhythm was improved. Suitable medication time, therefore, improved the sleep-wake rhythm.

Hertzman, M. (2003). "Galantamine in the treatment of adult autism: A report of three clinical cases." International Journal of Psychiatry in Medicine **33**(4): 395-398.

OBJECTIVE: To study the usefulness of galantamine, a competitive, reversible acetylcholinesterase inhibitor (AChEI), in adults diagnosed with autism (in accordance with DSM-IV-TR Axis I clinical criteria) before age three years. METHODS: To promote verbalization and meaningful speech sound production through biochemical enhancement of the serotonergic subsystem of the central nervous system (CNS), galantamine 4 mg qhs was administered, with indicated dose increases. RESULTS: Verbal fluency increased in all patients, according to their caregivers. One patient developed a macular rash that abated when the medication was discontinued. After one month on donepezil 5 mg qhs, verbal and behavioral regression again led to discontinuation. Doses for the other patients have been escalated by 4 mg daily each month to a maximum of 12 mg, with improvement following each increase. CONCLUSIONS: Cholinergic stimulation of the CNS serotonergic subsystem with galantamine may enhance expressive language and communication in autistic adults. Clinical trials are needed to study adjuvant therapy with galantamine in such patients.

Hohnadel, E., K. Bouchard and A. V. Terry, Jr. (2007). "Galantamine and donepezil attenuate pharmacologically induced deficits in prepulse inhibition in rats." Neuropharmacology **52**(2): 542-551.

Acetylcholinesterase inhibitors (AChEIs) are currently being evaluated as adjunctive therapy for the cognitive dysfunction of schizophrenia. This core symptom of schizophrenia has often been attributed to impaired attention and abnormal sensory motor gating, features that are also found in Huntington's Disease, autism, and several other psychiatric and neurological disorders. The ability to improve prepulse inhibition (PPI) of the acoustic startle response may predict the efficacy of compounds as cognitive enhancers. In this study, PPI was disrupted in Wistar rats in three pharmacologic models: dopamine receptor agonism by apomorphine, NMDA receptor antagonism by MK801, or muscarinic acetylcholine receptor antagonism by scopolamine. We then evaluated the commonly used AChEIs, donepezil (0.5, 1.0, or 2.0mg/kg) and galantamine (0.3, 1.0, or 3.0mg/kg) for the capacity to improve PPI in each model. Under vehicle conditions, the prepulse stimuli (75, 80 and 85dB) inhibited the startle response to a 120dB auditory stimulus in a graded fashion. Galantamine (depending on dose) improved PPI deficits in all three PPI disruption models, whereas donepezil ameliorated PPI deficits induced by scopolamine and apomorphine, but was not effective in the MK801 model. These results indicate that some AChEIs may have the potential to improve cognition in schizophrenia by improving auditory sensory gating.

Horrigan, J. P. and L. J. Barnhill (1997). "More on melatonin." Journal of the American Academy of Child and Adolescent Psychiatry **36**(8): 1014.

Melatonin supplementation has received increased attention in the media and the lay literature over the past few years because of its potential role as a treatment for insomnia (Sahelian, 1995). However, the scientific literature dealing with melatonin has lagged behind, and the reports that have been issued have offered mixed findings and recommendations (Lamberg, 1996). On the basis of melatonin's putative role in the body as a

hormone and as a circadian pacemaker, it has been applied in special populations that have demonstrated low or irregular melatonin production, such as the blind (Jan et al., 1994). A computerized search of the medical literature revealed no reports on the use of melatonin supplementation in Asperger's disorder, a close relative to autism, which can often be accompanied by poor sleep hygiene (K1in, 1994). Accordingly, we report here the use of melatonin as a corrective sleep aid in the treatment of a young man with this disorder, who was seen in our outpatient neuropharmacology clinic. B.L., a 17-year-old male with Asperger's disorder, also met formal DSM-IV criteria for primary insomnia. Poor sleep hygiene (difficulty falling asleep as well as frequent nocturnal awakenings) had been problematic since early childhood. A variety of prescription (hydroxyzine, trazodone, and lorazepam) as well as nonprescription (diphenhydramine, chamomile, and valerian root) approaches had been explored by his parents and physicians since his early teenage years, when the sleep problems worsened. None of these approaches offered sustained success, despite various dosing strategies. B.L. complained of increasing problems with afternoon fatigue and a ready tendency to fall asleep as he progressed through his high school years (phenomena such as narcolepsy and sleep apnea had been ruled out). His parents continued their search for "natural" approaches. B.L. ultimately began a trial of melatonin tablets, obtained over the counter from a specialty health food store. The melatonin was manufactured by a U.S. laboratory with a consistent reputation for putting into their products precisely what the label states. The initial dose given to B.L. was 3 mg at 9 P.M., and essentially from the first night onward he slept through the night (with sleep onset at approximately 10:30 P.M., and minimal or no nocturnal awakenings thereafter). These benefits continued for the next 12 weeks. An attempt to lower the melatonin dose to 1.5 mg led to a resurgence of the previous problems, which attenuated once again, almost entirely, after returning to the original dose of 3 mg. No side effects were reported at either dose, and B.L.'s academic performance improved (his grade point average advanced by 0.5 over the next semester) while his level of alertness during the afternoon showed a similar improvement. In this instance, the melatonin appeared to be quite helpful across a sustained period of time, with essentially no side effects. It is possible that the patient, because of biological aberrations associated with his Asperger's disorder, had chronically deficient melatonin production which accounted for his poor sleep hygiene. The supplement may have produced a nocturnal boost in the amount of melatonin in his central nervous system, a phenomenon that appears to be critical to maintenance of normal sleep patterns in human subjects (Hajak et al., 1995). Key factors that require further elaboration in the scientific literature include the proper timing and appropriate dose of melatonin, as well as the differential absorption rates of the various preparations of melatonin that are commonly available (e.g., sublingual versus sustained release versus "regular" tablets). Another critical issue is the potential inconsistency of the product because melatonin is available over the counter in the United States and thus is subject to the whims of any laboratory that might choose to manufacture and market it. Accordingly, while this initial report suggests that there may be a role for nocturnal melatonin supplementation in conditions such as Asperger's disorder, suitable caution must be exercised by any clinician tempted to "prescribe" it.

Ishizaki, A., M. Sugama and N. Takeuchi (1999). "[usefulness of melatonin for developmental sleep and emotional/behavior disorders--studies of melatonin trial on 50 patients with developmental disorders]." No to Hattatsu **31**(5): 428-437.

We studied the usefulness of melatonin for sleep disorders and emotional/behavior disturbances of patients with developmental disorders. The efficacy and side effects of melatonin at bedtime were evaluated in 50 children and young adults with sleep disorders (3-28 years old, 41 males and 9 females, autism [AU] in 27 patients, mentally retardation [MR] in 20 patients, and severe motor and intellectual disability [SMID] in 3 patients). The sleep disorders consisted of various types of insomnia in 44 patients and of circadian rhythm sleep disorders in 6 patients. Thirty nine of the insomnia patients and 3 of the circadian rhythm sleep disorder patients experienced improvement in response to melatonin. In some cases, the efficacies were diminished after the daily medication of melatonin. With the emotional/behavior disturbances, excitabilities were often improved in cases whose sleep disorders were also improved. There was almost no change in contrariness, stereotyped behavior and in school/workshop refusal. Melatonin at bedtime was efficacious in 42 of the 50 patients with sleep disorders. In 17 patients, there were side effects (residual drowsiness on the next morning, awakening in the middle of sleep, excitement after awakening and before going to sleep, etc.). But these side effects were not serious. The effects of melatonin were influenced by the type of sleep disturbances, the factors of the

environment and the mental conditions. Taking side effects into account, we judged melatonin to be useful in 34 patients.

Jan, J. E., H. Espezel and R. E. Appleton (1994). "The treatment of sleep disorders with melatonin." Developmental Medicine and Child Neurology **36**(2): 97-107.

Fifteen children (most of whom were neurologically multiply disabled) with severe, chronic sleep disorders were treated with 2 to 10mg of oral melatonin, given at bedtime. Nine had fragmented sleep patterns, three had delayed sleep onset and three others had non-specific sleep disturbance of unclear aetiology; all had failed to respond to conventional management. Nine patients had ocular or cortical visual impairment. The health, behavioural and social benefits of treatment were significant, and there were no adverse side-effects. While the response was not always complete, the study clearly showed that melatonin has an important role in the treatment of certain types of chronic sleep disorders.

Jan, J. E., R. D. Freeman, M. B. Wasdell and M. M. Bomben (2004). "'A child with severe night terrors and sleep-walking responds to melatonin therapy'." Developmental Medicine and Child Neurology **46**(11): 789.

SIR–Night terrors (pavor nocturnus) occur in up to 6% of children. The onset of this parasomnia tends to be between 2 to 4 years of age and rarely persists into adulthood. The clinical presentation is striking. Usually 1–2 hours after falling asleep the affected child will suddenly sit up with their eyes wide open. They are confused, and scream and struggle; it is impossible to reason with them, and their speech is unintelligible. There is rapid heart rate and respiration, profuse sweating, and extreme anxiety. When they walk during these episodes (somnambulism) they bump into objects and often sustain injuries. Generally these episodes last from 10–15 minutes and there is no subsequent recall of these events by the child. Specific treatment is not required in milder cases. Parents are reassured and requested to protect, but not awaken, their children. In more severe cases, behavioural management techniques and low doses of benzodiazepines are used for night sedation. A 12-year-old male with Asperger syndrome and marked chronic sleep-phase onset delay was referred for melatonin therapy. He also had severe coexistent night terrors and sleepwalking for several years. These episodes occurred 2–3 times almost every night. His sleep disorder affected his parents so much that they said they could no longer cope. The child was also regularly sustaining cuts and bruises. Oral administration of controlled release melatonin (5mg), 30 minutes before the desired bed time, corrected the sleep phase onset within two days. The night terrors and the sleep-walking episodes abruptly disappeared and have not recurred for over six months. Melatonin therapy for sleep-phase onset delay is well described in the literature. Night terrors and sleep-walking episodes are both due to a faulty transition from slow wave to REM sleep state. This process is executed by complex neuronal and hormonal mechanisms. The exact pathophysiology of these parasomnias is unclear. It is known, however, that deep sleep predisposes children to these events, which is why they tend to occur most frequently 1–2 hours after falling asleep at night when the slow wave sleep cycle is deepest. Due to our patient’s severe sleep deprivation, he slept deeply. With melatonin therapy his sleep deprivation was corrected, which may explain the abrupt disappearance of his parasomnia. It is also quite likely that melatonin, in some way, corrects the faulty process of transition from slow wave to REM sleep in the brainstem, where this change occurs. Over the years we have heard anecdotal reports of children whose night terrors subsided with melatonin therapy. We have also corresponded with paediatric sleep pathologists who have had similar observations (personal communication, Dr. M Davey 2004). We believe that well-designed melatonin trials for night terrors and sleep-walking episodes should be undertaken. As melatonin is remarkably free from adverse effects, it offers significant advantages over the use of benzodiazepines in severe cases.

Johnson, C. E., M. P. Cober, T. Thome and E. Rouse (2011). "Stability of an extemporaneous alcohol-free melatonin suspension." American Journal of Health-System Pharmacy **68**(5): 420-423.

Purpose. The stability of alcohol-free oral suspensions of melatonin 1 mg/mL, extemporaneously prepared from two commercially available melatonin tablet products, was studied.

Methods. Four 1-mg/mL melatonin suspensions were prepared. Formulations A and B contained 20 crushed 3-mg tablets of melatonin combined with a 1:1 mixture of Ora-Plus and either Ora-Sweet or Ora-Sweet SF to produce a volume of 60 mL. Formulations C and D were prepared by crushing 20 combination tablets containing melatonin 3 mg and pyridoxine hydrochloride 10 mg and then combining the powder with a 1:1 mixture of Ora-Plus and either Ora-Sweet or Ora-Sweet SF to produce a 60-mL volume. The suspensions were prepared in triplicate and stored at room temperature in amber plastic prescription bottles. Immediately after preparation and on days 7, 15, 30, 60, and 90, the samples were assayed in duplicate by stability-indicating high-performance liquid chromatography (HPLC). The samples were also evaluated for any changes in color, odor, and taste.

Results. HPLC analysis demonstrated that at least 94% of the initial melatonin concentration in formulations A and B, and at least 98% of that in formulations C and D, remained throughout the 90-day study period. Detectable changes in color, odor, or taste occurred in all of the formulations.

Conclusion. Extemporaneously prepared, alcohol-free, 1-mg/mL suspensions of melatonin and melatonin pyridoxine hydrochloride in a 1:1 mixture of Ora-Plus and either Ora Sweet or Ora Sweet SF were stable for at least 90 days when stored in 2-oz amber plastic bottles at room temperature.

Kaat, A. J., L. Lecavalier and M. G. Aman (2013). "Validity of the aberrant behavior checklist in children with autism spectrum disorder." Journal of Autism and Developmental Disorders.

The Aberrant Behavior Checklist (ABC) is a widely used measure in autism spectrum disorder (ASD) treatment studies. We conducted confirmatory and exploratory factor analyses of the ABC in 1,893 children evaluated as part of the Autism Treatment Network. The root mean square error of approximation was .086 for the standard item assignment, and in exploratory factor analysis, the large majority of items continued to load on the originally assigned factors. Correlations between the ABC subscales and multiple external variables including the Child Behavior Checklist and demographic variables supported the convergent and divergent validity of the ABC as a measure of behavior problems in ASD. Finally, we examined the impact of participant characteristics on subscale scores and present normative data.

Kunz, D., R. Mahlberg, C. Müller, A. Tilmann and F. Bes (2004). "Melatonin in patients with reduced rem sleep duration: Two randomized controlled trials." The Journal of Clinical Endocrinology & Metabolism **89**(1): 128-134.

Recent data suggest that melatonin may influence human physiology, including the sleep-wake cycle, in a time-dependent manner via the body's internal clock. Rapid-eye-movement (REM) sleep expression is strongly circadian modulated, and the impact of REM sleep on primary brain functions, metabolic processes, and immune system function has become increasingly clear over the past decade. In our study, we evaluated the effects of exogenous melatonin on disturbed REM sleep in humans. Fourteen consecutive outpatients (five women, nine men; mean age, 50 yr) with unselected neuropsychiatric sleep disorders and reduced REM sleep duration (25% or more below age norm according to diagnostic polysomnography) were included in two consecutive, randomized, double-blind, placebo-controlled, parallel design clinical trials. Patients received 3 mg melatonin daily, administered between 2200 and 2300 h for 4 wk. The results of the study show that melatonin was significantly more effective than placebo: patients on melatonin experienced significant increases in REM sleep percentage (baseline/melatonin, 14.7/17.8 vs. baseline/placebo, 14.3/12.0) and improvements in subjective measures of daytime dysfunction as well as clinical global impression score. Melatonin did not shift circadian phase or suppress temperature but did increase REM sleep continuity and promote decline in rectal temperature during sleep. These results were confirmed in patients who received melatonin in the second study (REM sleep percentage baseline/placebo/melatonin, 14.3/12.0/17.9). In patients who received melatonin in the first study and placebo in the second, the above mentioned effects outlasted the period of melatonin administration and diminished only slowly over time (REM sleep percentage baseline/melatonin/placebo, 14.7/17.8/16.2). Our findings show that exogenous melatonin, when administered at the appropriate time, seems to normalize circadian variation in human physiology. It may, therefore, have a strong impact on general health, especially in the elderly and in shift workers.

Leu, R. M., L. Beyderman, E. J. Botzolakis, K. Surdyka, L. Wang and B. A. Malow (2011). "Relation of melatonin to sleep architecture in children with autism." Journal of Autism and Developmental Disorders **41**(4): 427-433.

Children with autism often suffer from sleep disturbances, and compared to age-matched controls, have decreased melatonin levels, as indicated by urine levels of the primary melatonin metabolite, 6-sulfatoxymelatonin (6-SM). We therefore investigated the relationship between 6-SM levels and sleep architecture in children with autism spectrum disorders (ASD). Twenty-three children, aged 4-10 years, completed two nights of polysomnography and one overnight urine collection for measurement of urinary 6-SM excretion rate. Parents completed the Children's Sleep Habits Questionnaire. We found that higher urinary 6-SM excretion rates were associated with increased N3 sleep, decreased N2 sleep, and decreased daytime sleepiness. The results warrant further examination to examine the effects of supplemental melatonin on sleep architecture and daytime sleepiness.

Lord, C., S. Risi, L. Lambrecht, E. H. Cook, Jr., B. L. Leventhal, P. C. DiLavore, A. Pickles and M. Rutter (2000). "The autism diagnostic observation schedule-generic: A standard measure of social and communication deficits associated with the spectrum of autism." Journal of Autism and Developmental Disorders **30**(3): 205-223.

The Autism Diagnostic Observation Schedule-Generic (ADOS-G) is a semistructured, standardized assessment of social interaction, communication, play, and imaginative use of materials for individuals suspected of having autism spectrum disorders. The observational schedule consists of four 30-minute modules, each designed to be administered to different individuals according to their level of expressive language. Psychometric data are presented for 223 children and adults with Autistic Disorder (autism), Pervasive Developmental Disorder Not Otherwise Specified (PDDNOS) or nonspectrum diagnoses. Within each module, diagnostic groups were equivalent on expressive language level. Results indicate substantial interrater and test-retest reliability for individual items, excellent interrater reliability within domains and excellent internal consistency. Comparisons of means indicated consistent differentiation of autism and PDDNOS from nonspectrum individuals, with some, but less consistent, differentiation of autism from PDDNOS. A priori operationalization of DSM-IV/ICD-10 criteria, factor analyses, and ROC curves were used to generate diagnostic algorithms with thresholds set for autism and broader autism spectrum/PDD. Algorithm sensitivities and specificities for autism and PDDNOS relative to nonspectrum disorders were excellent, with moderate differentiation of autism from PDDNOS.

Malow, B., K. W. Adkins, S. G. McGrew, L. Wang, S. E. Goldman, D. Fawkes and C. Burnette (2012). "Melatonin for sleep in children with autism: A controlled trial examining dose, tolerability, and outcomes." Journal of Autism and Developmental Disorders **42**(8): 1729-1737; author reply 1738.

Supplemental melatonin has shown promise in treating sleep onset insomnia in children with autism spectrum disorders (ASD). Twenty-four children, free of psychotropic medications, completed an open-label dose-escalation study to assess dose-response, tolerability, safety, feasibility of collecting actigraphy data, and ability of outcome measures to detect change during a 14-week intervention. Supplemental melatonin improved sleep latency, as measured by actigraphy, in most children at 1 or 3 mg dosages. It was effective in week 1 of treatment, maintained effects over several months, was well tolerated and safe, and showed improvement in sleep, behavior, and parenting stress. Our findings contribute to the growing literature on supplemental melatonin for insomnia in ASD and inform planning for a large randomized trial in this population.

Malow, B. A., M. L. Marzec, S. G. McGrew, L. Wang, L. M. Henderson and W. L. Stone (2006). "Characterizing sleep in children with autism spectrum disorders: A multidimensional approach." Sleep **29**(12): 1563-1571.

STUDY OBJECTIVES: To relate parentally reported sleep concerns in autism spectrum disorders (ASD) to polysomnographic (PSG) findings and measures of daytime behavior and autism symptomatology. DESIGN: Cross-sectional study involving validated questionnaires, sleep histories and diaries, 2 nights of PSG, and the Autism Diagnostic Observation Schedule (ADOS). SETTING: Vanderbilt University General Clinical Research

Center Sleep Core. PARTICIPANTS: 21 children with ASD and 10 typically developing (TD) children, aged 4-10 years. Children were free of psychotropic medications, with no history of mental retardation or epileptic seizures. INTERVENTIONS: N/A. MEASUREMENTS AND RESULTS: Children with ASD were defined as "good sleepers" (10 children) and "poor sleepers" (11 children) on the basis of parental report; the age-comparable TD children were all reported by their parents to be good sleepers. Poor sleepers with ASD showed prolonged sleep latency and decreased sleep efficiency on night 1 of PSG and differed on insomnia-related subscales of the Children's Sleep Habits Questionnaire (CSHQ; increased sleep onset delay and decreased sleep duration). The good sleepers with ASD did not differ from the TD children in sleep architecture or on CSHQ domains. As compared with ASD good sleepers, the ASD poor sleepers also had higher scores related to affective problems on the Child Behavior Checklist and more problems with reciprocal social interaction on the ADOS. CONCLUSIONS: Parentally reported sleep concerns of insomnia in children with ASD are substantiated by validated sleep questionnaires and by PSG. Furthermore, good sleepers with ASD showed fewer affective problems and better social interactions than ASD poor sleepers.

Mandell, D. S. (2012). "Understanding and addressing the impact of autism on the family." LDI Issue Brief **17**(7): 1-4.

Children and adults with autism spectrum disorders (ASDs) have needs that challenge our systems of care. A new study estimates ASDs cost more than $126 billion each year in the U.S.--an amount that reflects both the costs of providing educational and medical services as well as the costs of not intervening early and effectively enough to prevent lifelong disability. This Issue Brief summarizes the implications of childhood autism for parental employment and earnings, and analyzes whether community-based services can reduce costly, psychiatric hospitalizations of children with ASDs.

Mandell, D. S., M. Xie, K. H. Morales, L. Lawer, M. McCarthy and S. C. Marcus (2012). "The interplay of outpatient services and psychiatric hospitalization among medicaid-enrolled children with autism spectrum disorders." Archives of Pediatrics and Adolescent Medicine **166**(1): 68-73.

OBJECTIVE: To examine whether increased provision of community-based services is associated with decreased psychiatric hospitalizations among children with autism spectrum disorders (ASDs). DESIGN: Retrospective cohort study using discrete-time logistic regression to examine the association of service use in the preceding 60 days with the risk of hospitalization. SETTING: The Medicaid-reimbursed health care system in the continental United States. PARTICIPANTS: Medicaid-enrolled children with an ASD diagnosis in 2004 (N = 28 428). MAIN EXPOSURES: Use of respite care and therapeutic services, based on procedure codes. MAIN OUTCOME MEASURES: Hospitalizations associated with a diagnosis of ASD (International Classification of Diseases, 10th Revision, codes 299.0, 299.8, and 299.9). RESULTS: Each $1000 increase in spending on respite care during the preceding 60 days resulted in an 8% decrease in the odds of hospitalization in adjusted analysis. Use of therapeutic services was not associated with reduced risk of hospitalization. CONCLUSIONS: Respite care is not universally available through Medicaid. It may represent a critical type of service for supporting families in addressing challenging child behaviors. States should increase the availability of respite care for Medicaid-enrolled children with ASDs. The lack of association between therapeutic services and hospitalization raises concerns regarding the effectiveness of these services.

McArthur, A. J. and S. S. Budden (1998). "Sleep dysfunction in rett syndrome: A trial of exogenous melatonin treatment." Developmental Medicine and Child Neurology **40**(3): 186-192.

Nine girls with Rett syndrome (mean age, 10.1 years) were monitored 24 hours a day over a period of 10 weeks using wrist actigraphy. Baseline sleep-wake patterns were assessed for 1 week. Subsequently, patients underwent a 4-week melatonin treatment period in a double-blind, placebo-controlled, crossover protocol that employed a 1-week washout between treatment trials. Melatonin doses ranged from 2.5 to 7.5 mg, based upon individual body weight. Baseline sleep quality was poor compared with healthy children. At baseline the group demonstrated a low sleep efficiency (mean [+/- SE], 68.0+/-3.9%), long sleep-onset latency (42.1+/-12.0 minutes), and a short and fragmented total sleep time (7.5+/-0.3 hours; 15+/-2 awakenings per night).

Melatonin significantly decreased sleep-onset latency to (mean +/- SE) 19.1+/-5.3 minutes (P<0.05) during the first 3 weeks of treatment. While the variability of individual responsiveness was high, melatonin appeared to improve total sleep time and sleep efficiency in the patients with the worse baseline sleep quality. Finally, a 4-week administration of melatonin appears to be a safe treatment as no adverse side effects were detected, yet long-term effects of chronic melatonin use in pediatric patients are unknown at this time.

Mindell, J. A., G. Emslie, J. Blumer, M. Genel, D. Glaze, A. Ivanenko, K. Johnson, C. Rosen, F. Steinberg, T. Roth and B. Banas (2006). "Pharmacologic management of insomnia in children and adolescents: Consensus statement." Pediatrics **117**(6): e1223-1232.

OBJECTIVE: The purpose of this work was to develop a consensus statement on the current status and future role for pharmacologic management of insomnia in children and adolescents. METHOD: The National Sleep Foundation, in collaboration with Best Practice Project Management, Inc, convened expert representatives involved in the study and treatment of pediatric insomnia and conducted a 2-day conference to examine the role of pharmacologic management of pediatric insomnia and to make recommendations regarding the development of clinical trials in this area. After a series of presentations providing background on the current knowledge of pediatric insomnia and its treatment alternatives, workgroups provided recommendations for the evaluation of pharmacologic treatment of insomnia in specific populations of children and adolescents and developed guidelines for the core methodologic issues relevant to the design of clinical trials. The group developed consensus recommendations for clinical trials in this area encompassing: (1) high-priority patient populations for research, (2) inclusion/exclusion criteria, (3) outcome measures, (4) ethical considerations unique to clinical trials involving children and adolescents, and (5) priorities for future research that will enhance the understanding of pediatric insomnia. RESULTS: Conference participants unanimously agreed that there is a need for pharmacologic management of pediatric insomnia. Furthermore, the widespread use of "hypnotic" and psychotropic medications for children in the absence of safety and efficacy data indicates a knowledge gap about the best pharmacologic practices for management of pediatric insomnia. Attendees reached consensus on methodologic issues in the study of pharmacologic treatment of pediatric insomnia including agreeing on a definition of pediatric insomnia as "repeated difficulty with sleep initiation, duration, consolidation, or quality that occurs despite age-appropriate time and opportunity for sleep and results in daytime functional impairment for the child and/or family." It was agreed that priority should be given to insomnia studies in children with attention-deficit/hyperactivity disorder and those with pervasive developmental disorders/autism spectrum disorder. There was also agreement on the need for pharmacokinetic and pharmacodynamic studies to determine appropriate dose levels and to evaluate safety with a wide range of doses. CONCLUSIONS: The treatment of pediatric insomnia is an unmet medical need. Before appropriate pharmacologic management guidelines can be developed, rigorous, large-scale clinical trials of pediatric insomnia treatment are vitally needed to provide information to the clinician on the safety and efficacy of prescription and over-the-counter agents for the management of pediatric insomnia.

Nicolson, R., B. Craven-Thuss and J. Smith (2006). "A prospective, open-label trial of galantamine in autistic disorder." Journal of Child and Adolescent Psychopharmacology **16**(5): 621-629.

OBJECTIVE: Post-mortem studies have reported abnormalities of the cholinergic system in autism. The purpose of this study was to assess the use of galantamine, an acetylcholinesterase inhibitor and nicotinic receptor modulator, in the treatment of interfering behaviors in children with autism. METHODS: Thirteen medication-free children with autism (mean age, 8.8 +/- 3.5 years) participated in a 12-week, open-label trial of galantamine. Patients were rated monthly by parents on the Aberrant Behavior Checklist (ABC) and the Conners' Parent Rating Scale-Revised, and by a physician using the Children's Psychiatric Rating Scale and the Clinical Global Impressions scale. RESULTS: Patients showed a significant reduction in parent-rated irritability and social withdrawal on the ABC as well as significant improvements in emotional lability and inattention on the Conners' Parent Rating Scale--Revised. Similarly, clinician ratings showed reductions in the anger subscale of the Children's Psychiatric Rating Scale. Eight of 13 participants were rated as responders on the basis of their improvement scores on the Clinical Global Impressions scale. Overall, galantamine was well-tolerated, with no

significant adverse effects apart from headaches in one patient. CONCLUSION: In this open trial, galantamine was well-tolerated and appeared to be beneficial for the treatment of interfering behaviors in children with autism, particularly aggression, behavioral dyscontrol, and inattention. Further controlled trials are warranted.

Niederhofer, H. (2007). "Treating autism pharmacologically: Also tacrine might improve symptomatology in some cases." Journal of Child Neurology **22**(8): 1054.

Comments on an article by M. G. Chez et al. (see record 2004-13641-002). In 2004, Chez et al. published an open-label study demonstrating that rivastigmine leads to gains in overall autistic behavior and expressive speech. We did not find any data with regard to tacrine's efficacy for those patients. For that reason, we checked this substance in an open trial for 3 patients without medical or neurological illnesses, suffering from autistic disorder, diagnosed by ICD-10 criteria, which had been medication-free for at least 2 weeks, completed an open trial of Tacrine. Written informed consent was obtained. Tacrine was the first Acetylcholinesterase-inhibotor, developed for treating Alzheimer's disease. It seems to be effective in treating Alzheimer's disease and may also be modestly effective in the short-term treatment of irritability in children with autistic disorder. Tacrine cannot be recommended as an helpful drug for patients suffering from autism, mainly because of its proven hepatotoxicity. (PsycINFO Database Record (c) 2013 APA, all rights reserved)

Niederhofer, H., W. Staffen and A. Mair (2002). "Galantamine may be effective in treating autistic disorder." BMJ **325**(7377): 1422.

Owens, J. A., A. Spirito and M. McGuinn (2000). "The children's sleep habits questionnaire (cshq): Psychometric properties of a survey instrument for school-aged children." Sleep **23**(8): 1043-1051.

STUDY OBJECTIVES: To present psychometric data on a comprehensive, parent-report sleep screening instrument designed for school-aged children, the Children's Sleep Habits Questionnaire (CSHQ). The CSHQ yields both a total score and eight subscale scores, reflecting key sleep domains that encompass the major medical and behavioral sleep disorders in this age group. DESIGN: Cross-sectional survey. SETTING: Three elementary schools in New England, a pediatric sleep disorders clinic in a children's teaching hospital. PARTICIPANTS: Parents of 469 school-aged children, aged 4 through 10 years (community sample), and parents of 154 patients diagnosed with sleep disorders in a pediatric sleep clinic completed the CSHQ. INTERVENTIONS: N/A. MEASUREMENTS AND RESULTS: The CSHQ showed adequate internal consistency for both the community sample (p=0.68) and the clinical sample (p=0.78); alpha coefficients for the various subscales of the CSHQ ranged from 0.36 (Parasomnias) to 0.70 (Bedtime Resistance) for the community sample, and from 0.56 (Parasomnias) to 0.93 (Sleep-Disordered Breathing) for the sleep clinic group. Test-retest reliability was acceptable (range 0.62 to 0.79). CSHQ individual items, as well as the subscale and total scores were able to consistently differentiate the community group from the sleep-disordered group, demonstrating validity. A cut-off total CSHQ score of 41 generated by analysis of the Receiver Operator Characteristic Curve (ROC) correctly yielded a sensitivity of 0.80 and specificity of 0.72. CONCLUSIONS: The CSHQ appears to be a useful sleep screening instrument to identify both behaviorally based and medically-based sleep problems in school-aged children.

Paavonen, E. J., T. Nieminen-von Wendt, R. Vanhala, E. T. Aronen and L. von Wendt (2003). "Effectiveness of melatonin in the treatment of sleep disturbances in children with asperger disorder." Journal of Child and Adolescent Psychopharmacology **13**(1): 83-95.

Sleep disturbances are common in patients with Asperger disorder. Although these sleep problems are often persistent and may significantly impair the child's daytime well-being, no treatment studies have been reported. In this open clinical trial, the effectiveness of melatonin was studied in a sample of 15 children with Asperger disorder (13 boys, 2 girls) aged 6-17 years using several questionnaires and actigraph measurements. They included assessments of sleep quality, tiredness, and behavior. Melatonin (3 mg/day) was used for 14 days. All the measurements were made three times: before the treatment period, during the treatment (days 12-14), and

3 weeks after the discontinuation of the treatment. The sleep patterns of all the children improved, and half of them displayed excellent responses to melatonin. In particular, actigraphically measured sleep latency decreased from 40.02 +/- 24.09 minutes to 21.82 +/- 9.64 minutes (p = 0.002), whereas sleep duration remained steady at 477.40 +/- 55.56 minutes and 480.48 +/- 50.71 minutes. Despite the short duration of the treatment, behavioral measures also displayed a significant improvement, and most of the effect disappeared after the discontinuation of the melatonin (p = 0.001). In conclusion, melatonin may provide an interesting new and well-tolerated treatment option for children with Asperger disorder suffering from chronic insomnia. However, these results must be confirmed in a controlled study.

Rahmioglu, N., J. Heaton, G. Clement, R. Gill, G. Surdulescu, K. Zlobecka, D. Hodgkiss, Y. Ma, R. C. Hider, N. W. Smith and K. R. Ahmadi (2011). "Genetic epidemiology of induced cyp3a4 activity." Pharmacogenetics and Genomics **21**(10): 642-651.

AIM: The cytochrome P450 3A4 (CYP3A4) enzyme is implicated in the metabolism of more than 50% of all prescribed medications and its activity - including induced or inhibited activity - is deemed to be a crucial determinant of interindividual variability in drug disposition, poor therapeutic efficacy, and adverse response to medication. METHODS: We used the classical twin model in conjunction with an induction experiment to uncover the relative contribution of genetic and environmental factors to interindividual variation in induced CYP3A4 activity. A total of 367 healthy twins participated in the study. Each volunteer was administered a potent inducer of CYP3A4 (St John's Wort) for 14 days and the activity of CYP3A4 was quantified through the metabolism of the exogenously administered probe drug quinine sulfate. RESULTS: Baseline and induced CYP3A4 activity were highly variable with a seven-fold and 11-fold difference among our population, respectively. Alcohol consumption, BMI, and smoking were significantly associated with induced CYP3A4 activity, collectively explaining 20% of the variation (P<1x10(-4)). The narrow-sense heritability of induced CYP3A4 activity was estimated at 66%, whereas the remainder of the variation was attributed to unique environmental factors. CONCLUSION: To our knowledge, this is the first genetic epidemiological study of induced CYP3A4 activity. Our results motivate further research to identify common and rarer genetic variants that underpin the heritable component of variation in induced CYP3A4 activity.

Richdale, A. L. and K. A. Schreck (2009). "Sleep problems in autism spectrum disorders: Prevalence, nature, & possible biopsychosocial aetiologies." Sleep Medicine Reviews **13**(6): 403-411.

As considerably more people are diagnosed with an autism spectrum disorder (ASD), interest in the associated behaviours, including sleep problems has increased. This has resulted in a subsequent increase in the research related to the sleep problems occurring in people with an ASD. This article summarizes and evaluates the current literature related to a) the higher prevalence of a sleep problem compared to typically developing children, b) the specific types of sleep problems for people with an ASD, and c) the possible aetiology of sleep problems in the ASDs within a biopsychosocial framework. It is concluded that recent studies confirm that the majority of this population are likely to experience sleep difficulties, with settling issues in children with an ASD the most commonly reported. However, exploration of the types of sleep difficulties and associated aetiological factors in the ASDs is still in its infancy.

Rogers, S. L., M. R. Farlow, R. S. Doody, R. Mohs and L. T. Friedhoff (1998). "A 24-week, double-blind, placebo-controlled trial of donepezil in patients with alzheimer's disease. Donepezil study group." Neurology **50**(1): 136-145.

The efficacy and safety of donepezil as a treatment for patients with mild to moderate Alzheimer's disease (AD) was investigated in a multicenter, double-blind study. Patients were randomly assigned to treatment with placebo (n = 162), 5 mg/d donepezil (n = 154), or 10 mg/d donepezil (n = 157) for 24 weeks followed by a 6-week, single-blind placebo washout. The primary efficacy measures were the cognitive portion of the Alzheimer's Disease Assessment Scale (ADAS-cog) and the Clinician's Interview Based Assessment of Change-Plus (CIBIC plus), with the Mini-Mental State Examination (MMSE), Clinical Dementia Rating Scale-Sum of the Boxes (CDR-SB), and patient rated Quality of Life (QoL) used as secondary measures. Cognitive function, as measured

by the ADAS-cog, was significantly improved in the 5- and 10-mg/d donepezil groups as compared with the placebo group at weeks 12, 18, and 24. Clinician's global ratings on the CIBIC plus also improved in both the 5- and 10-mg/d donepezil groups relative to placebo. At the end of the 6-week placebo washout phase, ADAS-cog scores and CIBIC plus ratings were not significantly different for the three groups. Significant treatment benefits were also observed consistently in both the 5- and 10-mg/d groups on the MMSE and the CDR-SB, but there was no consistent effect on the patient-rated QoL. Cholinergic side effects (primarily diarrhea, nausea, and vomiting) were reported more often in the 10-mg/d group than either the 5-mg/d or placebo groups. Side effects were transient and generally mild in severity. These data indicate that donepezil is a well-tolerated drug that improves cognition and global function in patients with mild to moderate AD.

Rojahn, J., E. W. Rowe, S. Kasdan, L. Moore and D. J. van Ingen (2011). "Psychometric properties of the aberrant behavior checklist, the anxiety, depression and mood scale, the assessment of dual diagnosis and the social performance survey schedule in adults with intellectual disabilities." Research in Developmental Disabilities **32**(6): 2309-2320.

Progress in clinical research and in empirically supported interventions in the area of psychopathology in intellectual disabilities (ID) depends on high-quality assessment instruments. To this end, psychometric properties of four instruments were examined: the Aberrant Behavior Checklist (ABC), the Assessment of Dual Diagnosis (ADD), the Anxiety, Depression and Mood Scale (ADAMS), and the Social Performance Survey Schedule (SPSS). Data were collected in two community-based groups of adults with mild to profound ID (n = 263). Subscale reliability (internal consistency) ranged from fair to excellent for the ABC, the ADAMS, and the SPSS (mean coefficient alpha across ABC subscales was .87 (ranging from fair to excellent), the ADAMS subscales .83 (ranging from fair to good), and the SPSS subscales .91 (range from good to excellent). The ADD subscales had generally lower reliability scores with a mean of .59 (ranging from unacceptable to good). Convergent and discriminant validity was determined by bivariate Spearman p correlations between subscales of one instrument and the subscales of the other three instruments. For the most part, all four instruments showed solid convergent and discriminant validity. To examine the factorial validity, Confirmatory Factor Analyses (CFA) were attempted with the inter-item covariance matrix of each instrument. Generally, the data did not show good fits with the measurement models for the SPSS. ABC, or the ADAMS (CFA analyses with the ADD would not converge). However, most of the items on these three instruments had significant loadings on their respective factors.

Rossignol, D. A. and R. E. Frye (2013). "Melatonin in autism spectrum disorders." Current Clinical Pharmacology.

Melatonin is an endogenous neurohormone produced predominantly in the pineal gland. Recent studies have implicated abnormalities in melatonin physiology and the circadian rhythm in individuals with autism spectrum disorders (ASD). These physiological abnormalities include lower nighttime melatonin or melatonin metabolite concentrations in ASD compared to controls. These abnormalities in melatonin concentrations may be directly attributed to variations in melatonin pathway physiology as both functional and genetic variations in this pathway have been reported in children with ASD. Four studies have observed a correlation between abnormal melatonin concentrations and the severity of autistic behaviors. Twenty clinical studies have reported improvements in sleep parameters with exogenous melatonin supplementation in ASD, including longer sleep duration, less nighttime awakenings and quicker sleep onset. A recent meta-analysis of five randomized, double-blind, placebo-controlled crossover trials examining exogenous melatonin supplementation in ASD reported significant improvements with large effect sizes in total sleep duration and sleep onset latency compared to both baseline and placebo. Six studies reported that the nighttime administration of exogenous melatonin was associated with better daytime behaviors. Four studies reported improvements with exogenous melatonin supplementation when other sleep medications had previously failed. Adverse effects of melatonin were minimal to none in the twenty treatment studies. These studies indicate that the administration of exogenous melatonin for abnormal sleep parameters in ASD is evidence-based. Further studies examining optimal effective dosing and timing of dosing are warranted.

Rutter, M., A. LeCouteur and C. Lord (2003). Adi-r: The autism diagnostic interview-revised. Los Angeles, CA, Western Psychological Services.

Sahu, J. K., S. Gulati, S. Sapra, R. Arya, S. Chauhan, M. R. Chowdhury, N. Gupta, M. Kabra, Y. K. Gupta, S. N. Dwivedi and V. Kalra (2013). "Effectiveness and safety of donepezil in boys with fragile x syndrome: A double-blind, randomized, controlled pilot study." Journal of Child Neurology **28**(5): 570-575.

The present study was designed as a 12-week, randomized, double-blind, placebo-controlled pilot study to evaluate the effectiveness and safety of donepezil in boys with fragile X syndrome. Twenty boys with fragile X syndrome were randomized to receive 12 weeks of treatment with either placebo or donepezil (2.5 mg daily for initial 4 weeks followed by 5 mg daily for next 8 weeks). The outcome measures included change in intelligence quotient scores on Stanford-Binet Intelligence Scale (Hindi adaptation by Kulshrestha), change in behavioral scores by Conners 3 Parent Rating Scale (Short) and Childhood Autism Rating Scale, safety, and tolerability of donepezil. The study failed to show significant difference in intelligence quotient and behavioral scales with donepezil therapy over 12 weeks. However, donepezil appeared to be safe and well tolerated.

Sahu, J. K., S. Gulati, S. Sapra, R. Arya, S. Chauhan, M. R. Chowdhury, N. Gupta, M. Kabra, Y. K. Gupta, S. N. Dwivedi and V. Kalra (2012). "Effectiveness and safety of donepezil in boys with fragile x syndrome: A double-blind, randomized, controlled pilot study." Journal of Child Neurology.

Scahill, L., V. Hallett, M. G. Aman, C. J. McDougle, L. Eugene Arnold, J. T. McCracken, E. Tierney, Y. Deng, J. Dziura, B. Vitiello and N. Research Units on Pediatric Psychopharmacology Autism (2013). "Brief report: Social disability in autism spectrum disorder: Results from research units on pediatric psychopharmacology (rupp) autism network trials." Journal of Autism and Developmental Disorders **43**(3): 739-746.

There is growing interest in measuring social disability as a core element of autism spectrum disorders in medication trials. We conducted a secondary analysis on the Aberrant Behavior Checklist Social Withdrawal subscale using data from two federally-funded, multi-site, randomized trials with risperidone. Study 1 included 52 subjects assigned to placebo and 49 subjects to risperidone under double-blind conditions. Study 2 included 49 subjects assigned to risperidone only and 75 subjects assigned to risperidone plus parent training. After 8 weeks of treatment, all active treatments were superior to placebo (effect sizes ranging from 0.42 to 0.65). The findings suggest that the Social Withdrawal subscale may be a useful measure of social disability in acute treatment trials.

Srivastava, R. K., M. Agarwal and A. Pundhir (2011). "Role of donepezil in autism: Its conduciveness in psychopharmacotherapy." Case Rep Psychiatry **2011**: 563204.

A woman consulted psychiatric Out-Patient Department (OPD) for her 5-year and 2-month-old son presenting with typical autistic symptoms like social, behavioural, and communicational ineptitudeness. Subsequent treatment with Donepezil resulted in marked improvement in the aforementioned symptomatology. Recent studies in autistic child have shown diminished acetylcholine and nicotinic receptor activity, thus an acetylcholinergic enhancer, Donepezil, likely accounts for improvement in autistic symptoms. Evidently, the case report consolidates Donepezil role as a potentially useful agent in the treatment of cognitive and behavioural symptoms observed in this disorder.

Taylor, M. A., K. A. Schreck and J. A. Mulick (2012). "Sleep disruption as a correlate to cognitive and adaptive behavior problems in autism spectrum disorders." Research in Developmental Disabilities **33**(5): 1408-1417.

Sleep problems associated with autism spectrum disorders (ASD) have been well documented, but less is known about the effects of sleep problems on day-time cognitive and adaptive performance in this population. Children

diagnosed with autism or pervasive developmental disorder-not otherwise specified (PDD-NOS) (N = 335) from 1 to 10 years of age (M = 5.5 years) were evaluated for the relationships of Behavioral Evaluation of Disorders of Sleep (BEDS; Schreck, 1998) scores to measures of intelligence and adaptive behavior. Results suggested that children who slept fewer hours per night had lower overall intelligence, verbal skills, overall adaptive functioning, daily living skills, socialization skills, and motor development. Children who slept fewer hours at night with waking during the night had more communication problems. Breathing related sleep problems and fewer hours of sleep related most often to problems with perceptual tasks. The results indicate that quality of sleep--especially sleep duration--may be related to problems with day-time cognitive and adaptive functioning in children with autism and PDD-NOS. However, future research must be conducted to further understand these relationships.

Teh, L. K. and L. Bertilsson (2012). "Pharmacogenomics of cyp2d6: Molecular genetics, interethnic differences and clinical importance." Drug Metabolism and Pharmacokinetics **27**(1): 55-67.

CYP2D6 has received intense attention since the beginning of the pharmacogenetic era in the 1970s. This is because of its involvement in the metabolism of more than 25% of the marketed drugs, the large geographical and inter-ethnic differences in the genetic polymorphism and possible drug-induced toxicity. Many interesting reviews have been published on CYP2D6 and this review aims to reinstate the importance of the genetic polymorphism of CYP2D6 in different populations as well as some clinical implications and important drug interactions.

Tordjman, S., I. Najjar, E. Bellissant, G. M. Anderson, M. Barburoth, D. Cohen, N. Jaafari, O. Schischmanoff, R. Fagard, E. Lagdas, S. Kermarrec, S. Ribardiere, M. Botbol, C. Fougerou, G. Bronsard and J. Vernay-Leconte (2013). "Advances in the research of melatonin in autism spectrum disorders: Literature review and new perspectives." Int J Mol Sci **14**(10): 20508-20542.

Abnormalities in melatonin physiology may be involved or closely linked to the pathophysiology and behavioral expression of autistic disorder, given its role in neurodevelopment and reports of sleep-wake rhythm disturbances, decreased nocturnal melatonin production, and beneficial therapeutic effects of melatonin in individuals with autism. In addition, melatonin, as a pineal gland hormone produced from serotonin, is of special interest in autistic disorder given reported alterations in central and peripheral serotonin neurobiology. More specifically, the role of melatonin in the ontogenetic establishment of circadian rhythms and the synchronization of peripheral oscillators opens interesting perspectives to ascertain better the mechanisms underlying the significant relationship found between lower nocturnal melatonin excretion and increased severity of autistic social communication impairments, especially for verbal communication and social imitative play. In this article, first we review the studies on melatonin levels and the treatment studies of melatonin in autistic disorder. Then, we discuss the relationships between melatonin and autistic behavioral impairments with regard to social communication (verbal and non-verbal communication, social interaction), and repetitive behaviors or interests with difficulties adapting to change. In conclusion, we emphasize that randomized clinical trials in autism spectrum disorders are warranted to establish potential therapeutic efficacy of melatonin for social communication impairments and stereotyped behaviors or interests.

Wasdell, M. B., J. E. Jan, M. M. Bomben, R. D. Freeman, W. J. Rietveld, J. Tai, D. Hamilton and M. D. Weiss (2008). "A randomized, placebo-controlled trial of controlled release melatonin treatment of delayed sleep phase syndrome and impaired sleep maintenance in children with neurodevelopmental disabilities." Journal of Pineal Research **44**(1): 57-64.

The purpose of this study was to determine the efficacy of controlled-release (CR) melatonin in the treatment of delayed sleep phase syndrome and impaired sleep maintenance of children with neurodevelopmental disabilities including autistic spectrum disorders. A randomized double-blind, placebo-controlled crossover trial of CR melatonin (5 mg) followed by a 3-month open-label study was conducted during which the dose was gradually increased until the therapy showed optimal beneficial effects. Sleep characteristics were measured by caregiver who completed somnologs and wrist actigraphs. Clinician rating of severity of the sleep disorder and

improvement from baseline, along with caregiver ratings of global functioning and family stress were also obtained. Fifty-one children (age range 2-18 years) who did not respond to sleep hygiene intervention were enrolled. Fifty patients completed the crossover trial and 47 completed the open-label phase. Recordings of total night-time sleep and sleep latency showed significant improvement of approximately 30 min. Similarly, significant improvement was observed in clinician and parent ratings. There was additional improvement in the open-label somnolog measures of sleep efficiency and the longest sleep episode in the open-label phase. Overall, the therapy improved the sleep of 47 children and was effective in reducing family stress. Children with neurodevelopmental disabilities, who had treatment resistant chronic delayed sleep phase syndrome and impaired sleep maintenance, showed improvement in melatonin therapy.

Wirojanan, J., S. Jacquemont, R. Diaz, S. Bacalman, T. F. Anders, R. J. Hagerman and B. L. Goodlin-Jones (2009). "The efficacy of melatonin for sleep problems in children with autism, fragile x syndrome, or autism and fragile x syndrome." Journal of Clinical Sleep Medicine **5**(2): 145-150.

STUDY OBJECTIVE: To determine the efficacy of melatonin on sleep problems in children with autistic spectrum disorder (ASD) and fragile X syndrome (FXS). METHODS: A 4-week, randomized, double blind, placebo-controlled, crossover design was conducted following a 1-week baseline period. Either melatonin, 3 mg, or placebo was given to participants for 2 weeks and then alternated for another 2 weeks. Sleep variables, including sleep duration, sleep-onset time, sleep-onset latency time, and the number of night awakenings, were recorded using an Actiwatch and from sleep diaries completed by parents. All participants had been thoroughly assessed for ASD and also had DNA testing for the diagnosis of FXS. RESULTS: Data were successfully obtained from the 12 of 18 subjects who completed the study (11 males, age range 2 to 15.25 years, mean 5.47, SD 3.6). Five participants met diagnostic criteria for ASD, 3 for FXS alone, 3 for FXS and ASD, and 1 for fragile X premutation. Eight out of 12 had melatonin first. The conclusions from a nonparametric repeated-measures technique indicate that mean night sleep duration was longer on melatonin than placebo by 21 minutes ($p = .02$), mean sleep-onset latency was shorter by 28 minutes ($p = .0001$), and mean sleep-onset time was earlier by 42 minutes ($p = .02$). CONCLUSION: The results of this study support the efficacy and tolerability of melatonin treatment for sleep problems in children with ASD and FXS.

Wright, B., D. Sims, S. Smart, A. Alwazeer, B. Alderson-Day, V. Allgar, C. Whitton, H. Tomlinson, S. Bennett, J. Jardine, N. McCaffrey, C. Leyland, C. Jakeman and J. Miles (2011). "Melatonin versus placebo in children with autism spectrum conditions and severe sleep problems not amenable to behaviour management strategies: A randomised controlled crossover trial." Journal of Autism and Developmental Disorders **41**(2): 175-184.

Twenty-two children with autism spectrum disorders who had not responded to supported behaviour management strategies for severe dysomnias entered a double blind, randomised, controlled crossover trial involving 3 months of placebo versus 3 months of melatonin to a maximum dose of 10 mg. 17 children completed the study. There were no significant differences between sleep variables at baseline. Melatonin significantly improved sleep latency (by an average of 47 min) and total sleep (by an average of 52 min) compared to placebo, but not number of night wakenings. The side effect profile was low and not significantly different between the two arms.

Yamreudeewong, W., E. K. Dolence and D. Pahl (2006). "Stability of donepezil in an extemporaneously prepared oral liquid." Journal of Pharmacy Practice **19**(5): 282-285.

Yoo, J. H., M. G. Valdovinos and D. C. Williams (2007). "Relevance of donepezil in enhancing learning and memory in special populations: A review of the literature." Journal of Autism and Developmental Disorders **37**(10): 1883-1901.

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.