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Pharmacological Neuromodulation in Autism Spectrum Disorders

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1. Introduction

This chapter will examine pharmacological approaches to neuromodulation in Autism Spectrum Disorders (ASD), pharmacological clinical trials and pharmacological strategies on the horizon.

Drugs used in autism target neuromodulation at different neuronal sites. Those utilizing anti-convulsant, neuroleptic, anti-depressant, stimulant, cholinesterase inhibitors, anxiolytics, mood stabilizers and other pharmacological interventions in autism do so for a variety of purposes. Each of these classes of drugs will be examined relative to their proposed neuromodulatory actions as they relate to the Autism Spectrum Disorder population.

Children with ASD demonstrate deficits in 1) social interaction, 2) verbal and nonverbal communication, and 3) repetitive behaviors or interests. Many have unusual sensory responses. Symptoms range from mild to severe and present with individual uniqueness and complexity. Some aspects of learning may seem exceptional while others may lag. These children reflect a mix of communication, social, and behavioral patterns that are individual but fit into the overall diagnosis of ASD. Aggression, irritability and/or self-injury in children with autistic spectrum disorders often meet the threshold indicating pharmacological intervention.

Autism Spectrum Disorders have been shown to be related to complex combinations of environmental, neurological, immunological, and genetic factors. In addition to strong genetic links, environmental factors such as infection and drug exposure during pregnancy, perinatal hypoxia, postnatal infections and metabolic disorders have each been implicated in autistic populations. Summarizing an earlier Centers for Disease Control and Prevention Study (CDC) with subsequent major studies on autism prevalence, the CDC estimates 2-6 per 1,000 (from 1 in 500 to 1 in 150) children have an ASD. The risk is 3-4 times higher in males than females (Rice 2006)(CDC 2011).

The pathogenetic components and biological endophenotypes in autism spectrum disorders were described by Sacco and colleagues as: Circadian & Sensory Dysfunction; Immune Dysfunction; Neurodevelopmental Delay; and Stereotypic Behavior (Sacco R, et al 2010).

The heterogeneity of Autism Spectrum Disorders has resulted in many genes being studied that are thought to have an impact on the development of the pathological characteristics

associated with Autism Spectrum Disorder (Greer PL, et al 2010). The developmental neurobiology of ASD is incrementally illuminated at the cutting edges of science. The permutations of mutations and epigenetic effects in ASD are both daunting yet increasingly identifiable targets for pharmacologic intervention. Clinical necessity and clinical trials drive discoveries for therapeutic interventions until stem cell or genetic solutions arrive.

Some states or effects seen in ASD may be responsive to developmental interventions while others may not. As we know, prompt thyroid replacement in a hypothyroid infant will generally allow normative intellectual development and prevent developmental disability. An example of variation of developmental impact is a mutation in MECP2, which encodes the epigenetic regulator methyl-CpG-binding protein 2 and is associated with Rett Syndrome. A recent study asked the question whether providing MeCP2 function exclusively during early post-natal life might prevent or mitigate disease in adult animals. Re-expression of MeCP2 in symptomatic mice rescued several features of the disease. The investigators argue "...the temporal association of disease with the postnatal period of development may be unrelated to any 'developmental' or stage restricted function of MeCP2, at least in mouse models." They concluded that "...therapies for RTT, like MeCP2 function must be continuously maintained" (McGraw, et al 2011).

Genetic-environment interactions in ASD that continue to be investigated include: parental age; maternal genotype; maternal-fetal immunoreactivity; in vitro fertilization; maternal ingestion of drugs; toxic chemicals in the environment during pregnancy; and maternal illnesses during pregnancy such as maternal diabetes or infections (Hallmayer J, 2011). Recent studies are consistent with a fetal programming hypothesis of ASD that considers environmental risk factors that affect the fetal environment and interact with genetic variants (Szatmari 2011). The pathogenic potential of dysregulated states may further stress developmentally vulnerable neurodevelopment (Duke, B., 2008).

As these genes and interacting effects become better characterized therapeutic strategies can be developed (Buxbaum 2009) (Levy et al, 2011)(Sanders et al, 2011)(Gilman et al, 2011). These genes include those involved in the patterning of the central nervous system; those that govern biochemical pathways; those responsible for the development of dendrites and synapses; and, genes associated with the immune system and autoimmune disorders (Ashwood et al, 2006) (Careaga M et al, 2010).

Neuroimaging studies further enlighten our theoretical models and techniques such as diffusion tensor imaging (DTI) have gained prominence as a means of assessing brain development (Isaacson & Provenzale, 2011). Studies of emotional perception demonstrated that while listening to either happy or sad music, individuals with ASD activated cortical and subcortical brain regions known to be involved in emotion processing and reward. The investigators, using functional magnetic resonance imaging compared ASD participants with neurotypical individuals and found ASD individuals had decreased brain activity in the premotor area and in the left anterior insula, especially in response to happy music excerpts. Their findings illuminate our understanding of the neurobiological correlates of preserved and altered emotional processing in ASD (Caria A, et al 2011).

Other imaging studies have found: diminished gray matter within the hypothalamus in autism disorder and suggest this is a potential link to hormonal effects (Kurth F, et al 2011); elevated repetitive and stereotyped behavior (RSB) associated with decreased volumes in

several brain regions: left thalamus, right globus pallidus, left and right putamen, right striatum and a trend for left globus pallidus and left striatum within the ASD group (Estes A, et al 2011); alterations in frontal lobe tracts and corpus callosum in young children with autism spectrum disorder (Kumar A, et al 2010); and, revealed pervasive microstructural abnormalities (Groen WB, et al 2011).

As our theoretical constructs are tested and enriched clinical scientists are poised to learn exponentially as treatment response databases and measurement methods and systems are further developed. We are ready to experience an evolution and fusion of medical arts strengthened by scientific methods and information technology.

Psychopharmacological treatment guidelines for very young children suggest that children with persistent moderate to severe symptoms and impairment, despite psychotherapeutic interventions, may be better served by carefully monitored medication trials than by continuing ineffective treatments (Gleason MM, et al 2007).

The treatment of children with ASD has challenges that are also present in the treatment of many mood disorders and in schizophrenia. In Stephen Stahl's text, *Essential Psychopharmacology* (Stahl 2010), he deconstructs the syndrome of schizophrenia into five symptom dimensions: Positive and Negative symptoms, aggression, affect and cognition. These symptom dimensions are also relevant to children with ASD and many children with mood disorders. Individual presentations and variability of treatment response can be managed by enlisting the parents to be observers utilizing defined measurements.

Multiple medications have utility in ASD treatment and are sometimes used in combination. Thoughtful utilization and management of medications can offer children with autism spectrum disorders significant reductions of impairment. Each of the medications used, as true with any medication, has varying degrees and potential related to benefits, risk and limitations. Although the antipsychotic risperidone has been demonstrated as effective in reducing serious behavioral problems, it shares adverse neurological and metabolic risks with other typical and atypical antipsychotic agents. Nevertheless, risperidone has demonstrated efficacy at relatively low doses and treatment monitoring can assist in managing risks when substantial benefit is possible.

Antidepressants have been reported as helpful for some with ASD, particularly related to repetitive or obsessive compulsive behaviors, however, studies reviewing off-label uses of anti-depressants have also reported adverse effects of increased agitation, behavioral activation and sleep disturbance. If we consider these findings as evidence suggesting antidepressants, in some, perturb inhibitory- excitatory neuronal balance or, in a broad sense, contribute to central nervous system hyperarousal, it follows that such effects could contribute to pathogenesis rather than decrease the allostatic load. This does not suggest that anti-depressant medications can't be helpful. It is recognized that in many cases antidepressants are helpful; however, vigilance for signs of disinhibition or other dysregulation is prudent.

Known stimulant benefits include increased ability to sustain attention, reduced motoric hyperactivity and reduced impulsivity. Adverse effects associated with stimulants include dysphoric responses, sleep disturbances and appetite suppression.

Anticonvulsants have demonstrated their place in the treatment regimen of many children with ASD and approximately twenty percent of those with ASD are thought to have a

seizure disorder (Tuchman & Cuccaro, 2011). Benefits can include seizure control and mood stabilization while adverse effects can include cognitive dulling. When anticonvulsants are useful, cognitive dulling can often be managed by anticonvulsant selection and dosing.

Current pharmacological interventions in autism spectrum disorders are essentially directed at reducing cognitive and behavioral impairments. Treatment studies have demonstrated little observable benefit to core deficits of ASD, however, the argument is made that, in addition to the practical benefits of reducing behavioral and cognitive impairments, symptom reduction is a reflection of more efficient neural processing and development.

Effective impairment reduction often allows children to remain in a family home, function in a school setting, optimize responsiveness to behavioral and educational methods and, generally, function more normally than would otherwise be possible. Those of us who treat children who will otherwise be excluded from normal environments appreciate the importance and complexity of these interventions. The greater promise of pharmacological interventions is their potential, through early intervention, to inhibit or reduce the development of pathological and pathogenic endophenotypes.

2. Conceptualization of clinical hypotheses, treatment strategies and measurement of treatment response

Physicians and clinician-scientists are humbled distinguishing among nosological categories in the context of the diverse and complex treatment circumstances presented by those significantly impaired within the spectrum of autism disorders.

Treatment decisions are based on symptom profiles, types and severity of impairment, risk-benefit calculations, potential treatments available and clinical hypotheses related to the nature of the disorder. Unlike elegantly designed experiments with exquisitely defined variables and thoughtful control of confounding variables, those suffering functional and qualitative impairment present with inherent experimental limitations. Despite these limitations, the application of scientific principles related to individual measurement and monitoring of treatment response provides a platform from which to assess treatment response and dynamically test clinical hypotheses.

The deconstruction of psychiatric syndromes into symptoms is described as a way to establish a diagnosis, deconstruct the condition into its symptoms, match the symptoms to a hypothetically malfunctioning circuit and consider the collection of neurotransmitters and neuromodulators known to regulate the circuit. "Next, one can match each symptom to a hypothetically malfunctioning circuit and – with knowledge of the neurotransmitters regulating that circuit and drugs acting on those neurotransmitters – choose a therapeutic agent to reduce that symptom. If such a strategy proves unsuccessful, it is possible that adding or switching to another agent acting on another neurotransmitter in that circuit can be effective. Repeating this strategy for each symptom can result in remission of all symptoms in many patients." (Stahl, 2010)

Knowledge gained in the study of abnormal circuitry in mood disorders, schizophrenia and other neuropsychiatric and neurological conditions provide models by which treatment responses and clinical hypotheses can be tested. Whether the symptoms are hyperkinetic

movement disorders or hyperactive mesolimbic systems, pharmacological strategies can inform and interact with the rapidly developing basic and translational sciences. Dysregulation of neuronal inhibition and excitability appears as a common theme among many disorders.

Consideration of the pathological developmental aspects of autism spectrum disorders provokes the possibility that altering disease progression may rescue or support improved functional neurodevelopmental outcomes. In a broad statement regarding psychiatric disorders that supports that potential, Stephen Stahl remarks, "It may also be possible to prevent disease recurrence and progression to treatment resistance by treating not only symptoms but also inefficient brain circuits that are asymptomatic. Failing to do so may allow 'diabolical learning' where circuits run amok, become more efficient in learning how to mediate symptoms, and are therefore more difficult to treat." (Stahl, 2010, p. 274)

The lessons and theoretical models related to pharmacological interventions in other neurological and psychiatric syndromes can be applied to treatment conceptualizations with the autistic spectrum disordered as well. For example, constructs investigated with antiepileptic drugs (AED) can also be considered within the neural circuitry issues involved in Autism Spectrum Disorders.

"Several pathophysiological mechanisms inducing a neuronal excitability seems to be involved in an imbalance of both GABAergic and glutamatergic neurotransmissions and therefore could be similar in epilepsy and hyperkinetic movement disorders. The main targets for the action of the AEDs include enhancement of GABAergic inhibition, decreased glutamatergic excitation, modulation of voltage-gated sodium and calcium channels, and effects on intracellular signaling pathways. All of these mechanisms are of importance in controlling neuronal excitability in different ways." (Siniscalchi, Gallelli & De Sarro, 2010)

When pharmacological interventions are applied, secondary to their clinical intent, they serve as probes of endophenotypic neural functioning and circuitry states revealing response to particular pharmacodynamic and pharmacokinetic profiles. The classes of antipsychotic drugs considered to be atypical are described by Schwartz with such considerations in mind.

"The second generation antipsychotics are clearly delineated in the treatment of psychosis and mania and share similar mechanisms of action to achieve these results: dopamine-2 receptor antagonism for efficacy and serotonin-2a receptor antagonism for EPS tolerability. From here, each agent has a unique pharmacodynamic and pharmacokinetic profile where some agents carry more, or less antidepressant, anxiolytic, or hypnotic profiles. Choosing an agent and dosing it in low, middle, or high ranges may result in differential effectiveness and tolerability" (Schwartz & Stahl, 2011).

We are further humbled by the incomplete pharmacodynamic and pharmacokinetic profiles of the drugs we employ. Many of the drugs and compounds used have poorly understood neuromodulatory effects in addition to known receptor specific actions. Nevertheless, contributions to our knowledge continue to further characterize and define drugs as well as continue to discover relationships of environmental effects and immunological response. Researchers, for example, have recently shown the inhibitory

effects of some antidepressants as well as some typical/atypical antipsychotics on the release of inflammatory cytokines and free radicals from activated microglia, which the investigators state have been discovered to cause synaptic pathology, a decrease in neurogenesis, and white matter abnormalities found in the brains of patients with psychiatric disorders. (Monji A, 2011). We operate with limited visibility that is increased by clinical experience and science.

Despite the complexity and challenges of ASD, potential for early interventions are supported by animal research. An example is the recent demonstration that autism risk genes differentially impact cortical development (Eagleson K, et al 2011). The demonstrations of these risk genes and their interaction with various states, illustrate animal models that may further elucidate pathogenic developmental processes. The role of glutamate (Hamberger A, et al 1992), serotonin (Levitt P, 2011) and sigma 1 ligands (Yagasaki Y, et al 2006) have each demonstrated potential importance in modulating glutamatergic and other developmentally critical signaling processes.

In autism spectrum disorders as well as in other neurological and neurodegenerative disorders, discoveries in developmental neurobiology and genetics will continue to provide increasingly sophisticated models in which interventions of developmentally specific neuropathogenic processes can be assessed and clinical hypotheses considered and tested. Coinciding are increasingly sophisticated objective measures that will allow greater definition of treatment response characteristics and endophenotypic response profiles. Applications related to treatment response measurement and management utilizing on-line observational and other measurements related to eye, facial, voice, reaction time consistency, sleep and activity are currently being studied and developed at the Child Psychopharmacology Institute.

3. Registered clinical trials (NIH- USA) in autism spectrum disorders

We can learn a great deal from the current foci of pharmacological interventions in ASD by reviewing clinical trials that have been conducted and those that are current.

	Frequency	Percent
Drug Studies	151	53.5
Behavioral Studies	43	15.2
Dietary Studies	18	6.4
Device or Procedure Studies	5	1.8
Obervational and Other Studies	65	23.0
Total	282	100.0

Table 1. ASD Study Types- NIH Registrations of Record July 2011

Drug Classes Used In Autism Spectrum Disorder Clinical Trials
Antidepressant
Stimulant
Anticonvulsant
Antipsychotic
NMDA Antagonists And Glutamatergic
Antibacterial Anti-Infective
Immunomodulator
Hyperbaric Oxygen
Hormone Or Enzyme Factors
Adrenergic
Anti-Hypertensive
Diuretic
Opioid Antagonist
Anti-Oxidants
Hypoglycemic Agents
Supplements
GABA B Receptor Agonist
Trichuris Suis Ova
Antidote Heavy Metal
Ampa Receptor Modulator
Anxiolytic

Table 2. Drug Classes Used in Autism Spectrum Disorder July 2011 NIH

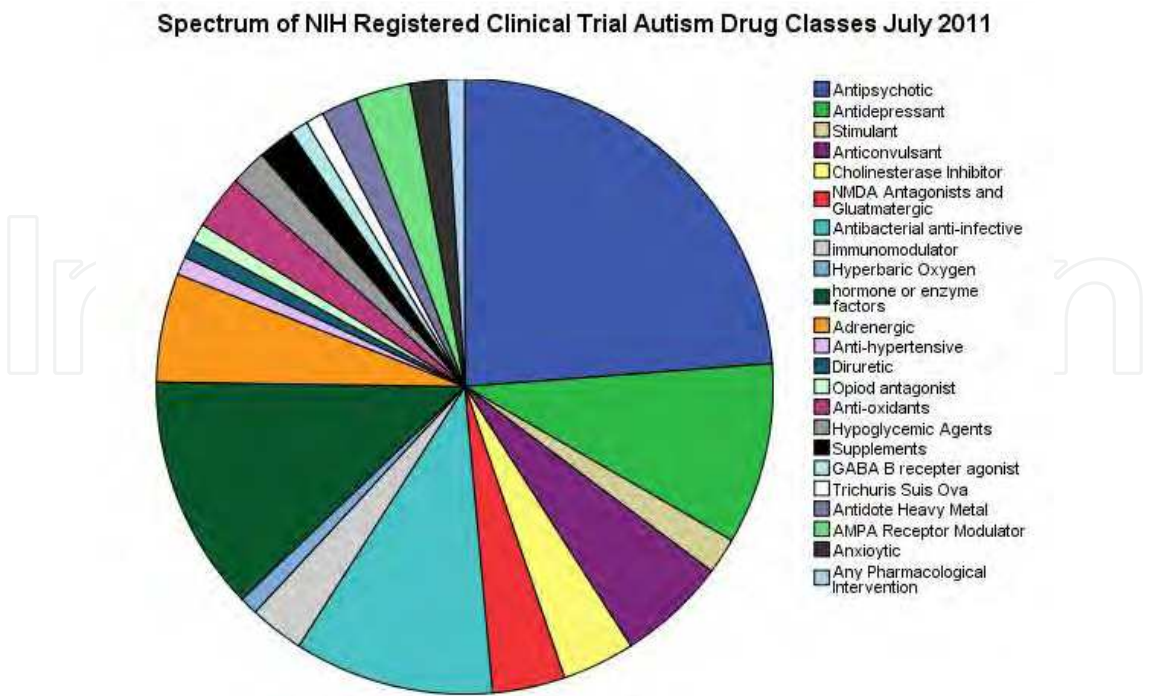


Fig. 1. Spectrum of Drug Classes in Autism Spectrum Disorders

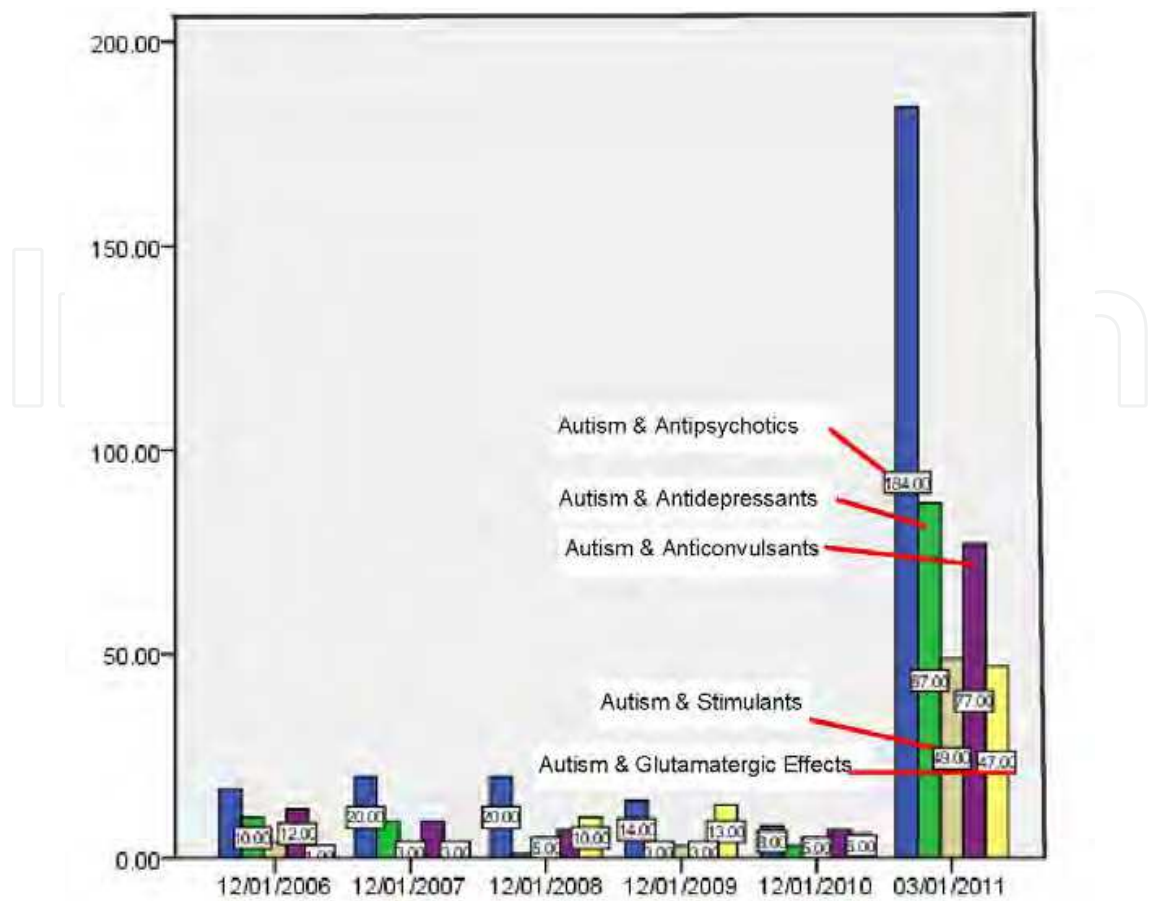


Fig. 2. NLM Clinical Trial Reviews 2006 to 2011

Table 3 displays a sampling of drugs in clinical trials and their generally proposed actions.

Antipsychotic Drugs
Risperidone is a selective blocker of dopamine d2 receptors and serotonin 5-ht2 receptors that acts as an atypical antipsychotic agent.
Aripiprazole has both presynaptic dopamine autoreceptor agonistic activity and postsynaptic D2 receptor antagonistic activity; use associated with hyperglycemia. It can also be described as a Dopamine Partial Agonist.
Ziprasidone -antipsychotic-A benzisothiazoylpiperazine derivative; has combined dopamine and serotonin receptor antagonist activity; structurally related to tiospirone.
Zyprexa (olanzapine) has combined dopamine and serotonin receptor antagonist activity.
Antidepressant Drugs
Fluoxetine: serotonin specific uptake inhibitor
Citalopram serotonin specific uptake inhibitor. The drug is also effective in reducing ethanol uptake in alcoholics and is used in depressed patients who also suffer from tardive dyskinesia
The SSRI fluvoxamine is not only an inhibitor of SERT, but also acts at sigma receptors, perhaps as a sigma-1 agonist, with some preclinical evidence that fluvoxamine can improve PCP-induced cognitive deficits
Atomoxetine: norepinephrine selective reuptake inhibitor.

Anticonvulsant Drugs
Divalproex sodium: A fatty acid with anticonvulsant properties used in the treatment of epilepsy. The mechanisms of its therapeutic actions are not well understood. It may act by increasing gamma-aminobutyric acid levels in the brain.
Riluzole: A glutamate antagonist (receptors, glutamate) used as an anticonvulsant (anticonvulsants) and to prolong the survival of patients with amyotrophic lateral sclerosis.
Lamotrigine,Sodium Valproate, or Carbamazepine: Anticonvulsants
Stimulant Drugs
Methylphenidate is a racemic mixture comprised of the d- and l-threo enantiomers. The d-threo enantiomer is more pharmacologically active than the l-threo enantiomer. Methylphenidate HCl is a central nervous system (CNS) stimulant.
Methylphenidate transdermal system: Methylphenidate HCl is a central nervous system (CNS) stimulant.
Choline and Cholinesterase Inhibitors
Choline: Precursor to Acetylcholine
Donepezil: Current theories on the pathogenesis attribute some symptoms to a deficiency of cholinergic neurotransmission. Donepezil hydrochloride is postulated to exert its therapeutic effect by inhibiting AChE boosting the availability of ACh.
Drugs with Glutaminergic Effects, AMPA Modulators and NMDA Antagonists
Acamprosate is a derivative of the amino acid taurine and, like alcohol, reduces excitatory glutamate neurotransmission and enhances inhibitory GABA neurotransmission
Memantine: a weak NMDA antagonist. Persistent activation of central nervous system N-methyl-D-aspartate (NMDA) receptors by the excitatory amino acid glutamate has been hypothesized to contribute to the symptomatology of Alzheimer's disease.
Dextromethorphan and quinidine sulfate (Nuedexta): NMDA antagonist; Sigma 1 agonist; binds to SERT; proposed neuromodulator.
Hormones
Oxytocin: A nonapeptide hormone released from the neurohypophysis (pituitary gland, posterior). it differs from vasopressin by two amino acids at residues 3 and 8.
Vasopressin
Anti-infective-Anti-bacterial-Immunomodulators
N Acetylcysteine N-acetyl derivative of cysteine. It is used as a mucolytic agent to reduce the viscosity of mucous secretions. It has also been shown to have antiviral effects in patients with HIV due to inhibition of viral stimulation by reactive oxygen.
Cycloserine Antibiotic substance produced by Streptomyces garyphalus.
Sapropterin: reduces blood phenylalanine (Phe) levels in patients with hyperphenylalaninemia (HPA) due to tetrahydrobiopterin- (BH4-) responsive Phenylketonuria (PKU). Proposed Neuroprotective and neurotransmitter effects.
Mecobalamin: a study (PMID: 20406575) demonstrated a progressive decrease of sciatic nerve IGF-1 mRNA and peptide contents, and peripheral nerve dysfunction in the saline-treated diabetics over 12 weeks in contrast to the normal control non-diabetics.

Table 3. Sampling of Drugs in ASD Clinical Trials and Their Generally Proposed Actions

Study of Aripiprazole to Treat Children and Adolescents With Autism	Phase II	The Clinical Global impression (CGI) Improvement Scale.; The Irritability subscale of the Aberrant Behavior Checklist (ABC); The Clinical Global Impression Severity Scale.
A Study of Aripiprazole in Children and Adolescents With Aspergers and Pervasive Developmental Disorder.	Phase II	The Clinical Global impression(CGI) Improvement Scale.; The Irritability subscale of the Aberrant Behavior Checklist (ABC); The Clinical Global Impression Severity Scale.;CY-BOCS (Children's Yale-Brown Obsessive Compulsive Scale)
Study of Aripiprazole in the Treatment of Serious Behavioral Problems in Children and Adolescents With Autistic Disorder (AD)	Phase III	Number of Participants With Serious Adverse Events (SAEs), Treatment-Emergent Adverse Events (AEs), Deaths, AEs Leading to Discontinuation, Extra Pyramidal Syndrome (EPS)-Related AEs; Mean Change From Baseline in Total Simpson-Angus Scale (SAS)
Aripiprazole in Children With Autism: A Pilot Study	Phase II	Clinical Global Impressions; Children's Psychiatric Rating Scale
An Open-Label Trial of Aripiprazole in Autism Spectrum Disorders	Phase II	Clinical Global Impressions-Improvement; Aberrant Behavior Checklist-Irritability subscale
Pilot Study of the Effect of Aripiprazole Treatment in Autism Spectrum Disorders on Functional Magnetic Resonance Imaging (fMRI) Activation Patterns and Symptoms	Phase IV	RBS-R (Repetitive Behavior Scale - Revised); CY-BOCS (Children's Yale-Brown Obsessive Compulsive Scale)
OPT - Phase IV Long Term Maintenance Study of Aripiprazole for the Treatment of Irritability Associated With Autistic Disorder	Phase IV	Time from randomization to relapse; Mean change from end of Phase 1 to Week 16 endpoint (LOCF) on the Aberrant Behavior Checklist - Irritability Subscale; Mean Clinical Global Impression - Improvement scale score at Week 16 endpoint (LOCF)
Study of Aripiprazole in the Treatment of Children and Adolescents With Autistic Disorder (AD)	Phase III	Mean Change (Week 8 - Baseline) in the Autistic Behavior Checklist (ABC) Irritability Subscale Score; Mean Clinical Global Impressions Improvement Scale (CGI-I) Score; Number of Participants With Response at Week 8; Mean Change (Week 8 - Baseline)
Study of Aripiprazole in the Treatment of Children and Adolescents With Autistic Disorder (AD)	Phase III	Mean Change (Week 8 - Baseline) in the Autistic Behavior Checklist (ABC) Irritability Subscale Score; Mean Clinical Global Impressions Improvement Scale (CGI-I) Score; Number of Participants With Response at Week 8; Mean Change (Week 8 - Baseline)

Evaluating the Effectiveness of Aripiprazole and D-Cycloserine to Treat Symptoms Associated With Autism	Phase III	Aberrant Behavior Checklist (ABC) Irritability Subscale; Clinical Global Impression (CGI) Scale; ABC Subscales; Vineland Maladaptive Behavior Subscales; A modified version of the Compulsion Subscale of the Children's Yale-Brown Obsessive Compulsive Scale.
Efficacy of Aripiprazole Versus Placebo in the Reduction of Aggressive and Aberrant Behavior in Autistic Children	Phase I	Clinical Global Impression Improvement (CGI-AD); Aberrant Behavior Checklist; Abnormal Involuntary Movement Scale (AIMS)
Long-Term Olanzapine Treatment in Children With Autism	Phase II Phase III	Children's Psychiatric Rating Scale; Aberrant Behavior Checklist; Clinical Global Impressions; Treatment Emergent Symptoms Scale; Olanzapine Untoward Effects Checklist; Abnormal Involuntary Movement Scale; Neurological Rating Scale

Table 4. Antipsychotic Clinical Trials, Trial Phase and Outcome Measures (Continued on table 5)

A Controlled Study of Olanzapine in Children With Autism	Phase II	Children's Psychiatric Rating Scale; Clinical Global Impressions; Abberant Behavior Checklist; Treatment Emergent Symptoms Scale; Olanzapine Untoward Effects Checklist; Abnormal Involuntary Movement Scale; Neurological Rating Scale
Study of Paliperidone ER in Adolescents and Young Adults With Autism	Phase III	The IrritabIrritability subscale of the Aberrant Behavior Checklist (ABC) will be used as the caregiver-rated primary outcome measure. The Clinical Global Impression- Improvement(CGI-I) will be included as a primary outcome measure
A Study of the Effectiveness and Safety of Two Doses of Risperidone in the Treatment of Children and Adolescents With Autistic Disorder	Phase IV	Allocation: Randomized; Endpoint Classification: Safety/Efficacy Study; Intervention Model: Parallel Assignment; Masking: Double Blind (Subject, Caregiver, Investigator); Primary Purpose: Treatment
A Study of the Effectiveness and Safety of Risperidone Versus Placebo in the Treatment of Children With Autistic Disorder and Other Pervasive Developmental Disorders (PDD)	Phase III	Change in the Irritability Subscale of the Aberrant Behavior Checklist (ABC) and other ABC subscales at end of treatment compared with baseline; Change from baseline to end of treatment in Nisonger Child Behavior Rating Form (N-CBRF), Visual Analogue Scale

Pharmacogenomics in Autism Treatment	Phase II Phase III	ABC and CGI; ABC
Treatment of Autism in Children and Adolescents	Phase III	
Risperidone Pharmacokinetics in Children With Pervasive Developmental Disorder (PDD)	Phase I	Quantify tVariability of clearance and volume of distribution among AE rating, weight gain and ABC responder status; Exploratory analysis will be performed to examine the relationship of other factors to risperidone and metabolite concentrations.
Pharmacogenetics of Risperidone in Children With Pervasive Developmental Disorder (PDD)	Phase I	
Comparison of Applied Behavioral Analysis (ABA) Versus ABA and Risperidone		
RUPP PI PDD: Drug and Behavioral Therapy for Children With Pervasive Developmental Disorders		Home Situations Questionnaire; Vineland Daily Living Skills Scale; Irritability subscale- Aberrant Behavioral Checklist; Clinical Global Impressions-Improvement (CGI-I)
Risperidone Treatment In Children With Autism Spectrum Disorder And High Levels Of Repetitive Behavior	Phase II	Aberrant Behavior Checklist
Ziprasidone in Children With Autism: A Pilot Study	Phase II	Clinical Global Impressions; Children's Psychiatric Rating Scale
An Observational Study to Evaluate the Safety and the Effects of Risperidone Compared With Other Atypical Antipsychotic Drugs on the Growth and Sexual Maturation in Children		To comparZ-scores for height, age at current Tanner stage, and prolactin-related adverse events between patients exposed to risperidone and patients exposed to other atypical antipsychotic drugs.; Assess the prolactin value and risk of hyperprolactine

Table 5. Antipsychotic Clinical Trials, Trial Phase and Outcome Measures (Continued)

Citalopram for Children With Autism and Repetitive Behavior (STAART Study 1)	Phase II	Clinical Global Improvement; Safety Monitoring Uniform Research Form (SMURF); Children's Yale-Brown Obsessive-Compulsive Scale (CYBOCS); Repetitive Behavior Scale-Revised (RBS-R); Parent Chief Complaint; Aberrant Behavior Checklist;
Functional MRI Evaluation of the Effect of Citalopram in Autism Spectrum Disorders	Phase I	Functional Magnetic Resonance Imaging; Clinicians Global Improvement Scale; Childrens Yale- Brown Obsessive Compulsive Scale
Randomized Study of Fluoxetine in Children and Adolescents With Autism	Phase I	
Study of Fluoxetine in Adults With Autistic Disorder	Phase I	
Extended Management and Measurement of Autism	Phase III	Safety Outcomes: Laboratory determinations, Urine drugs of abuse tests,Vital Signs,Physical Examinations, Adverse Events/Serious Adverse Events, Clinical Global Impression of Severity (CGI-S AD)
Fluoxetine Essay in Children With Autism	Phase II	Subscores of Autism Diagnostic Interview (ADI-R)at each visit of the protocol (LECOUTER et RUTTER, 1989); Sides effect scale (FSEC); Aberrant Behavior Checklist (Aman et al., 1985); Clinical Global Impressions (CGI) severity and improvement.
Study of Fluoxetine in Autism	Phase III	The percentage change from baseline to the endpoint visit for the CYBOCS-PDD score; The time and dose related course of therapeutic effects; The inter-relationship between these effects in the context of global clinical changes; The indirect effect.
Effectiveness of Early Intervention With Fluoxetine in Enhancing Developmental Processes in Children With Autism (STAART Study 2)	Phase III	Feasibility and safety of conducting placebo control trial of fluoxetine; Side effect and drop out evaluation
Fluvoxamine and Sertraline in Childhood Autism - Does SSRI Therapy Improve Behaviour and/or Mood?	Phase III	The severity of the autistic child's behaviour or condition (assessed by parents); Weight and vital signs; Blood count and liver function studies
Mirtazapine Treatment of Anxiety in Children and Adolescents With Pervasive Developmental Disorders	Phase III	Pediatric Anxiety Rating Scale (PARS); Clinical Global Impressions (CGI)

Table 6. Antidepressant Clinical Trials, Trial Phase and Outcome Measures

Methylphenidate for Attention Deficit Hyperactivity Disorder and Autism in Children	Phase III	Conners' Teacher Rating Scale-Revised (CTRS-R); Continuous Performance Test (CPT); Matching Familiar Figures Test (MFFT); Speeded Classification Task (SCT); Delay of Gratification Task (DOG); Conners' Parent Rating Scale (CPRS)-Short Form;
A Pilot Study of Daytrana TM in Children With Autism Co-Morbid for Attention Deficit Hyperactivity Disorder (ADHD) Symptoms	Phase III	Determine if Daytrana is safe and well-tolerated by children with Autism co-morbid for ADHD; Determine if Daytrana is effective in both school and home

Table 7. Stimulant Clinical Trials, Trial Phase and Outcome Measures

Divalproex Sodium ER vs Placebo in Childhood/ Adolescent Autism	Phase II	Clinical Global Impression-Improvement; Aberrant Behavior Checklist Clinical Global Impression-Improvement; Aberrant Behavior Checklist; Clinical Global Impression-Improvement; Aberrant Behavior Checklist
Divalproex Sodium ER in Adult Autism	Phase IV	
A Study of Divalproex Sodium in Children With ASD and Epileptiform EEG	Phase II	epileptiform EEG discharges; Improvement in behavior
Oxcarbazepine Versus Placebo in Childhood Autism	1	Vineland Adaptive Behavior Scales; Aberrant Behavior Checklist; Clinical Global Impression Improvement Scale; Autism Diagnostic Observation Schedule
Riluzole to Treat Child and Adolescent Obsessive-Compulsive Disorder With or Without Autism Spectrum Disorders	Phase II	Reduction of 30% or more in Children's Yale-Brown Obsessive-Compulsive Scale (CY-BOCS) and Repetitive Behavior Scale; Much/Very much improved on Clinical Global Impressions - Improvement score (CGI-I)
Valproate Response in Aggressive Autistic Adolescents	Phase III	

Table 8. Anticonvulsant Clinical Trials, Trial Phase and Outcome Measures

Treatment With Acetyl-Choline Esterase Inhibitors in Children With Autism Spectrum Disorders	Phase IV	Core autistic symptoms (ATEC); Side effects and adverse events questionnaire; Linguistic performance (CELF-4); Adaptive functioning (Vineland-II); Co-morbid behaviors (CSI-4 questionnaire); Executive functions (BRIEF) questionnaire
Drug Treatment for Autism	Phase II	Cognitive Assessment
The Effect of Donepezil on REM Sleep in Children With Autism	Phase II	The primary outcome measure of this protocol is to determine if donepezil can increase the percentage of time that subjects with autism spend in REM sleep.; A secondary aim of this protocol is to examine changes in functional outcome, including cognitive.
Galantamine Versus Placebo in Childhood Autism	Phase III	Autism Diagnostic Observation Schedule- Generic (ADOS-G)- Change from Baseline to Final Visit; Clinical Global Impression Improvement (CGI)- Change from Baseline to Final Visit; Aberrant Behavior Checklist (ABC) (hyperactivity/irritability sections).

Table 9. AcetylCholine Esterase Inhibitors Clinical Trials, Trial Phase and Outcome Measures

An Open Label Extension Study of STX209 in Subjects With Autism Spectrum Disorders	Phase II	Irritability subscale of the Aberrant Behavior Checklist
Study of Arbaclofen for the Treatment of Social Withdrawal in Subjects With Autism Spectrum Disorders	Phase II	Aberrant Behavior Checklist-Social Withdrawal Subscale
Open-Label Study of the Safety and Tolerability of STX209 in Subjects With Autism Spectrum Disorders	Phase II	Adverse events; Irritability Subscale of the Aberrant Behavior Checklist, Community Version

Table 10. Immunomodulator Clinical Trials, Trial Phase and Outcome Measures

Open-Label Extension Study of Kuvan for Autism	Phase II Phase III	Clinical Global Impressions Scale; Vineland Adaptive Behavior Scale; Clinical Global Impression: Severity; Children's Yale Brown Obsessive Compulsive Scale; Parental Global Assessment; Preschool Language Scale; Connor's Preschool ADHD question
Intranasal Oxytocin for the Treatment of Autism Spectrum Disorders	Phase II	Change from Baseline to week 12 on the Diagnostic Analysis of Nonverbal Accuracy (DANVA2); Change from Baseline to week 12 on the Social Responsivity Scale (SRS); Change from Baseline to week 12 on the Clinical Global Impressions Scale - Improvement
Intranasal Oxytocin in the Treatment of Autism	Phase II	Clinical Global Impressions Scale (CGI); Diagnostic Analysis of Nonverbal Accuracy, Adult Paralanguage Test (DANVA2-AP); Repetitive Behavior Scale (RBS); Event Contingent Reporting; Yale-Brown Obsessive-Compulsive Scale (YBOCS); Social Responsiveness.
An fMRI Study of the Effect of Intravenous Oxytocin vs. Placebo on Response Inhibition and Face Processing in Autism	Phase I	
A Study of Oxytocin in Children and Adolescents With Autistic Disorder	Phase II	Tolerability of Oxytocin Nasal Spray; Biomarkers; Feasibility; Acceptability of Oxytocin Nasal Spray
Brain Imaging Study of Adults With Autism Spectrum Disorders	Phase I	Changes in brain activations; Performance scores and reaction time on behavioral tasks.
Study of Glutathione, Vitamin C and Cysteine in Children With Autism and Severe Behavior Problems	Phase I	Improvement in both developmental skills and behavior with either glutathione or glutathione, Vitamin C and N-acetylcysteine therapy as compared to placebo therapy. Subjects will also be monitored using clinical and laboratory safety parameters.
Synthetic Human Secretin in Children With Autism	Phase III	
Synthetic Human Secretin in Children With Autism and Gastrointestinal Dysfunction	Phase III	

Sapropterin as a Treatment for Autistic Disorder	Phase II	Clinical Global Impression -- Improvement (CGI-I) Scale; Preschool Language Scale (PLS); Vineland Adaptive Behavior Scale-II; Children's Yale Brown Obsessive Compulsive Scale (C-YBOCS); Connor's Preschool ADHD questionnaire; Adverse Events Scale
Secretin for the Treatment of Autism	Phase III	
The Effects of Oxytocin on Complex Social Cognition in Autism Spectrum Disorders	Phase I	Empathic accuracy performance; fmri BOLD response during empathic accuracy task
Cholesterol in ASD: Characterization and Treatment	Phase I Phase II	Behavioral Changes

Table 11. Hormone or Related Clinical Trials, Trial Phase and Outcome Measures

A Study of Atomoxetine for Attention Deficit and Hyperactive/Impulsive Behaviour Problems in Children With ASD
Atomoxetine and Parent Management Training in Treating Children With Autism and Symptoms of Attention Deficit Disorder With Hyperactivity
Effectiveness of Atomoxetine in Treating ADHD Symptoms in Children and Adolescents With Autism
Atomoxetine Versus Placebo for Symptoms of Attention-Deficit/Hyperactivity Disorder (ADHD) in Children and Adolescents With Autism Spectrum Disorder
Atomoxetine, Placebo and Parent Management Training in Autism
Efficiency of Bumetanide in Autistic Children
Early Pharmacotherapy Aimed at Neuroplasticity in Autism : Safety and Efficacy
Buspirone in the Treatment of 2-6 Year Old Children With Autistic Disorder
A Trial of CM-AT in Children With Autism- Open Label Extension Study
A Trial of CM-AT in Children With Autism
Effects of CX516 on Functioning in Fragile X Syndrome and Autism
Mercury Chelation to Treat Autism
Dimercaptosuccinic Acid (DMSA) Treatment of Children With Autism and Heavy Metal Toxicity
Trial of Low-Dose Naltrexone for Children With Pervasive Developmental Disorder (PDD)
A Pilot Trial of Mecamylamine for the Treatment of Autism
Treatment of Sleep Problems in Children With Autism Spectrum Disorder With Melatonin

An Open-label Trial of Metformin for Weight Control of Pediatric Patients on Antipsychotic Medications.
Efficacy Study of Subcutaneous Methyl-B12 in Children With Autism
Methylphenidate in Children and Adolescents With Pervasive Developmental Disorders
Omega-3 Fatty Acids Monotherapy in Children and Adolescents With Autism Spectrum Disorders
Evaluation and Treatment of Copper/ Zinc Imbalance in Children With Autism
Dose Finding Study of Pioglitazone in Children With Autism Spectrum Disorders (ASD)
Transcranial Magnetic Stimulation (TMS) Measures of Plasticity and Excitatory/Inhibitory Ratio as Biomarkers: R-baclofen Effects in Normal Volunteers
Melatonin for Sleep in Children With Autism
Trichuris Suis Ova Adult Autism Symptom Domains
Multidimensional Measurement of Psychopharmacological Treatment Response * CPI

Table 12. Other Clinical Trials

4. Pharmacological strategies in autism spectrum disorders

Treatment monitoring and treatment response measurement provide methods by which treatment strategies may be assessed, tested and dynamically applied to the treatment process. Two examples are presented. The first illustrates the longitudinal measurement of risperidone response and the second illustrates a treatment review and re-conceptualization of treatment strategy.

The first case is an actigraphic, psychometric and observational study of risperidone response in a six year old autism spectrum disordered child with Kabuki Syndrome. It provides an illustration of circadian and behavioral disturbances in a child, and the utility of single subject repeated actigraphic, psychometric and observational measurements of treatment response (Duke, 2010).

Actigraphic measurements, such as those used in the following case, are not necessary to obtain meaningful treatment response data, although additional measurements, such as actigraphic data, are helpful.

The non-invasive nature of watch-like actigraphy devices (Rispironics Actiwatch) is particularly attractive for use in pediatric populations. Meaningful treatment response measurements are obtained when actigraphic data is combined with psychometric and observational repeated measurements.

This case study includes baseline and repeated psychological, observational and actigraphic measurements that were initiated prior to treatment with risperidone and repeated throughout the treatment process.

Actigraphic measurements provide a basis by which to measure sleep and sleep onset latency as well as periods of mobility and immobility. In this case the actigraphic device was programmed to record activity every thirty seconds.

Actigraphic measurements were made utilizing a watch-like actigraphic device with an 11 day baseline actigraphic measurement period and continued measurements that included the initiation of a pharmacological intervention for 6 days, followed by a planned adjustment to b.i.d. dosing that was measured for an additional 4 days. This initial actigraphic study resulted in over 65,000 measurements of activity. Repeated observations continued throughout the treatment period and actigraphic studies were repeated after 23 months of risperidone treatment.

The measurement methods included the Personality Inventory for Children (PIC) an objective multidimensional measurement of affect, behavior, ability and family function. The PIC was administered prior to treatment with risperidone and repeated after 23 months of treatment. The PIC serves as both an actuarial pre-treatment diagnostic tool as well as a post-treatment repeated measurement indicating treatment and developmentally associated change (Duke, B., 1991).

Observational methods were employed throughout the treatment process. A primary observer (The Child's Mother) was trained to report symptom percentages present since previous observations utilizing the operationally defined and observer defined items of the Systematic Observation Scale™ (Duke, B., 1990) throughout the treatment process. The Systematic Observation Scale™ utilizes single-subject repeated measurements. Symptoms and issues of interest are defined and a variety of frequency and sampling methods can be applied. The Systematic Observation Scale was designed so Primary Observers (parents, guardians, self observers or others) can make pre-treatment and subsequent observations to track, document and evaluate symptom variation over the course of an illness. The measurement utilized is the percentage of time the symptom is observed by the primary observer since the previous observation.



Fig. 3. The child's parents kindly consented to the use of this photograph.

The actigraphic study was designed to select a child anticipating a psychopharmacological intervention.

The study was reviewed and approved by the Child Psychopharmacology Institute Institutional Review Board and was registered with the National Institutes of Health Protocol Registration System (NCT00723580) as a non-randomized, single subject, case study clinical trial.

The Study Investigator's DSM-IV diagnoses were:

- Axis I
- 299.80 Pervasive Developmental Disorder Not Otherwise Specified
- 314.01 Attention-Deficit Hyperactivity Disorder
- 327.30 Circadian Rhythm Sleep Disorder (unspecified type)
- Axis II
- 317 Mild Mental Retardation
- Axis III
- Kabuki Syndrome*
- Hearing Impairment

The child's impulsivity and inability to sleep represented a significant symptom and risk factors. She frequently moved about restlessly until 5:00 AM and would often sleep (or partially sleep) with her eyes open. She had frequent infections and had been previously stimulated by diphenylhydramine, over-sedated on clonidine and had mood destabilization when tried on mirtazapine. The child's diagnosis of Kabuki Syndrome had been previously established by a geneticist at the Mayo Clinic. The child presented with severe impulsivity, psychomotor acceleration, severe insomnia and obsessive compulsive behaviors that included touching objects to the whites of her eyes (these behaviors occurred multiple times an hour). An MLL2 mutation has been verified in this child. It has recently been reported that Kabuki Syndrome is caused by mutations in MLL2, a gene that encodes a Trithorax-group histone methyltransferase, a protein important in the epigenetic control of active chromatin states (Hannibal et al, 2011).

Dr. Niikawa and Dr. Kuroki described Kabuki Syndrome in 1981. The term was used because of the affected children's facial resemblance to the famous Kabuki actors that perform in traditional Japanese theater.

Kabuki Syndrome is rare and diagnosis is complicated by the diverse spectrum of characteristics. Arched eyebrows, thick eyelashes, eversion of the lateral lower lid and long palpebral fissures contribute to the resemblance. Skeletal and dermatological abnormalities are common along with short stature, behavioral and pervasive developmental disorders and mild to moderate intellectual disability. Congenital heart defects and hearing impairment are often associated with the syndrome. The proportion of male to female occurrence is equal and no correlation with birth order has been found (Adam & Hudgins, 2005).

The assessment and treatment plan included a baseline biopsychosocial history, a baseline cognitive and personality assessment and the initiation of actigraphy measurements. The initial 21 day study of actigraphic measurements included an eleven day baseline prior to pharmacological interventions. The pharmacological Intervention following the medication free baseline utilized risperidone .25 mg q.h.s. initiated for seven days and then increased to twice daily dosing. Subsequent actigraphic measurements reflected the subsequent risperdal dose of .5 mg three times daily. Systematic observations continued throughout the treatment period and the personality assessment was repeated at the study end point. The established treatment goals were to: improve sleep; reduce general impairment; reduce hyperactivity; reduce impulsivity; reduce irritability and improve social functioning.

Hypotheses and Outcome Measures:

H1: Reduced percentages of primary symptoms will be associated with increased sleep during sleep periods (activity and sleep measurements). Actiwatch Communication and Sleep Analysis Instruction Manual (Respironics).

H2: Sleep quality will be reflected by reduced standard deviations of activity during sleep periods.

H3: Positive treatment response as reflected by reduced percentages of primary symptoms will be associated with decreased activity during activity periods.

H4: Reduced impulsivity will be associated with reduced standard deviations of activity during activity periods.

Outcome Measures

- a. Actigraphic Measurement of Treatment Conditions:
- b. Baseline May 12, 2008 and two additional 21 day periods between May 12, 2008 to July 14, 2010
- c. Systematic Observation Scale™ Measurements: May 7, 2008 to July 14th, 2010
- d. Personality Inventory for Children-Revised: pre-test May 2008 and post-test April 2010

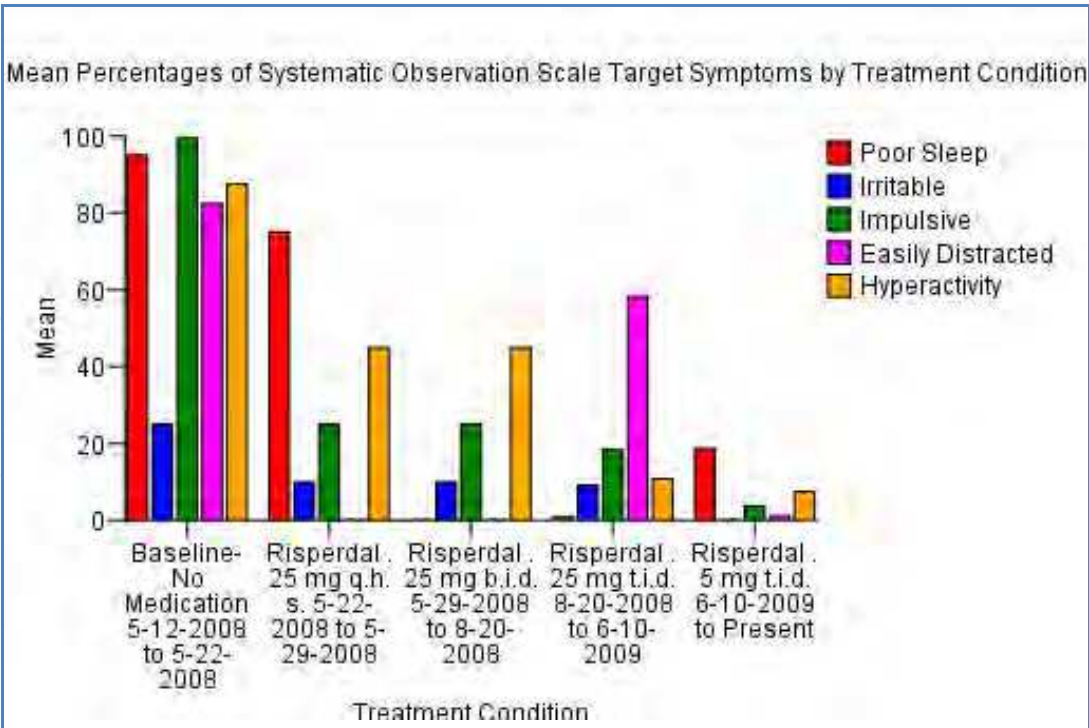


Fig. 4. Target Symptoms by Treatment Condition (BL- .25 mg - .5 mg t.i.d)

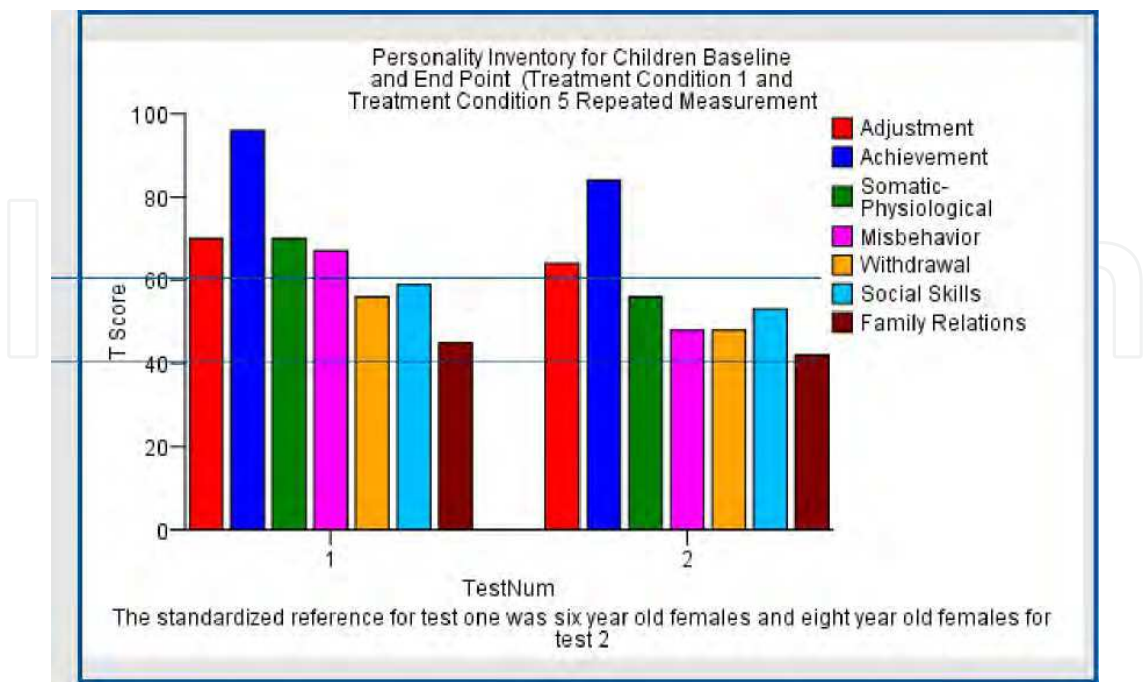


Fig. 5. Personality Inventory Pre-Test and Post-Test

Study conclusions: Sleep quantity was increased; Sleep quality was improved; Hyperactivity was reduced; Impulsivity was reduced; Significance between treatment conditions, activity and target symptoms was demonstrated.

The second case is a ten year old male who had received numerous medications over the past several years. Despite these treatments, and optimal family environment and commitment, the primary symptoms of mood instability and cognitive impairment continued. The child was receiving aripiprazole 5 mg q.a.m. and Concerta 36 mg q.a.m. Prior to the treatment review, the child had become disinhibited and severely impulsive in response to treatment with an SSRI, which was discontinued. He had also demonstrated a dose related worsening when tried on quetiapine. The quetiapine was discontinued due to associated insomnia and worsened mood and behavioral states.

At the time of the review the child presented with neurological immaturity, delayed fine motor integration, jerky saccadic eye movements and possible symptoms of partial complex seizures. The child's episodic emotional dyscontrol, attention and cognitive functioning did not appear to be, pharmacologically, optimally addressed.

DSM IV Diagnoses: Axis I:

299.80 Pervasive Developmental Disorder NOS

296.90 Mood Disorder NOS

314.01 Attention Deficit/Hyperactivity Disorder, Combined Type

307.7 Encopresis

		Sum of Squares	df	Mean Square	F	Sig.
Activity	Between Groups	4.476E8	3	1.492E8	1057.569	.000
	Within Groups	2.698E10	191235	141065.613		
	Total	2.742E10	191238			
Poor Sleep	Between Groups	16583.631	4	4145.908	10.542	.002
	Within Groups	3539.583	9	393.287		
	Total	20123.214	13			
Impulsive	Between Groups	13278.274	4	3319.568	15.707	.000
	Within Groups	1902.083	9	211.343		
	Total	15180.357	13			
Hyperactivity	Between Groups	11034.524	4	2758.631	10.994	.002
	Within Groups	2258.333	9	250.926		
	Total	13292.857	13			
Irritable	Between Groups	838.095	4	209.524	4.481	.029
	Within Groups	420.833	9	46.759		
	Total	1258.929	13			
Easily Distracted	Between Groups	14721.131	4	3680.283	4.379	.031
	Within Groups	7564.583	9	840.509		
	Total	22285.714	13			

Fig. 6. Treatment Response: Analysis of Variance

Following the treatment review the initial strategy was to add carbamazepine 200 mg ER q.p.m. x 7 days then b.i.d. Subsequent to improved emotional stability and broadly reduced symptoms the contribution of aripiprazole was assessed by a dose reduction to 2.5 mg q.a.m. for four days and subsequently replaced with risperidone .5 mg b.i.d. Plans were made to subsequently assess his stimulant treatment response as the monitoring continued. Figure 7 displays symptom percentage averages over the treatment transition.

Printable observation forms and item definitions are available and free for non-commercial use on the Child Psychopharmacology Institute website (www.ChildPsychopharmacologyInstitute.org).

5. Pharmacological protection and prevention strategies on the horizon:
Glutamatergic modulation and neuroprotection

Although pharmacological interventions utilized in Autistic Spectrum Disorders are generally associated with targeting behavioral or emotional impairments, little attention has been given to the important potential of glutamatergic regulation and neuroprotection in this vulnerable population.

While a single drug has not triumphed in the treatment of autism spectrum disorders, many drugs have proven helpful to varying degrees and for various purposes. The dearth of children’s pharmacological studies stand in stark contrast to wide use of pharmacological interventions in ASD children.

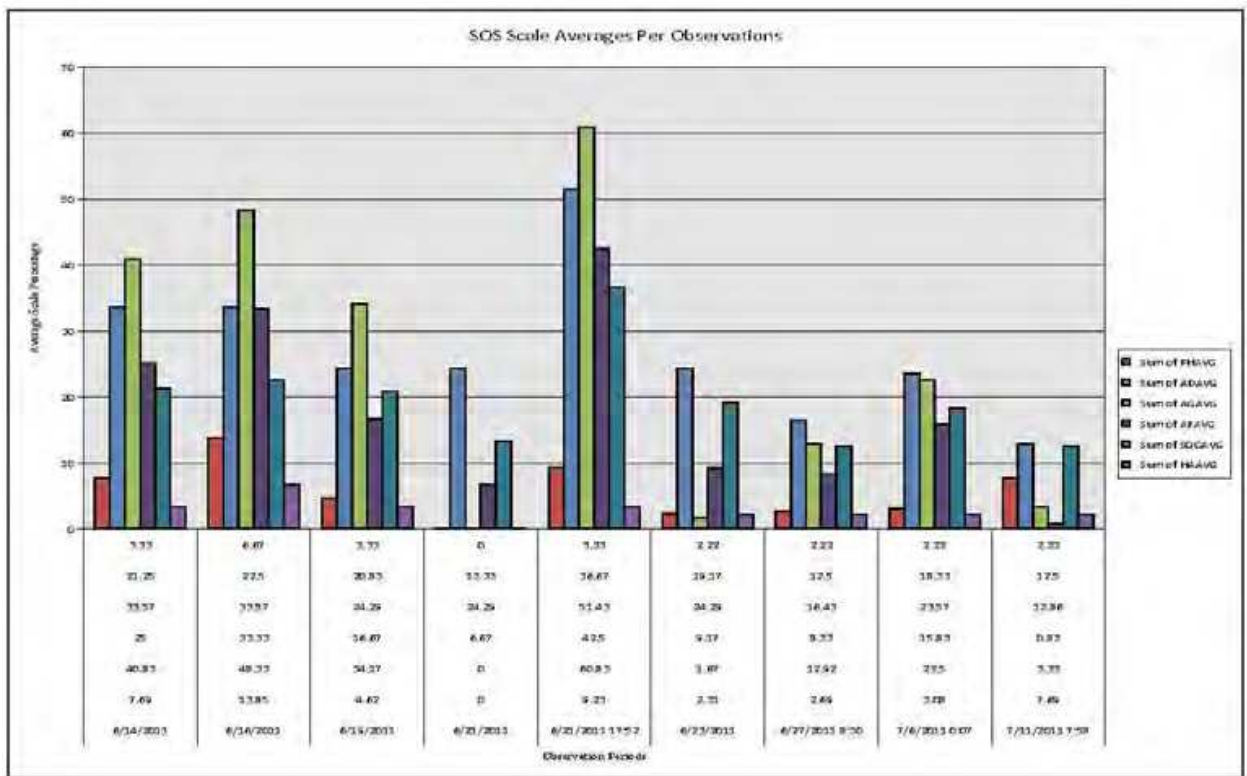


Fig. 7. Symptom Percentage Observation Scale Averages

Alternative pathways of ASD pathology being explored include the study of tetrahydrobiopterin (BH₄) as a novel therapeutic intervention and point to ASD children as having low levels of BH₄. Early studies suggest low BH₄ levels during development have devastating consequences on the central nervous system leading to or potentiating the neuropathology of ASD (Frye, et al, 2010). These studies are promising and may suggest a role for BH₄ treatment or treatment augmentation in the ASD population.

It is proposed that pharmacological approaches with neuroprotective characteristics have potential to reduce the dynamic pathogenic states that are likely occurring in highly symptomatic young children who are in developmentally critical stages of neural patterning and maturation. In a manner similar to the example provided regarding atypical antipsychotics, drugs will increasingly be chosen based on their particular characteristics or used together for separate or synergistic effects.

Arriving at a full understanding of these approaches will take further studies that consider the potential for unwanted effects. The Frye study, for example, noted that based on seven studies in which 451 patients with autism were treated with sapropterin (synthetic BH₄) that ninety-seven (21.5%) experienced adverse effects for which a causal relationship with the study drug could not be ruled out. The most frequently reported adverse effects were sleep disorders, excitement, hyperkinesia, enuresis and diarrhea. It will be important to learn if sapropterin's benefits are primarily from developmentally critical neuroprotective effects and/or effects on neurotransmitters. It will also be important to determine if indiscriminate neurotransmitter potentiation in dysregulated neurons and circuits are being reflected in the adverse effect profile that some demonstrate.

Synaptic molecules are important targets for protective treatments, to slow disease progression and preserve cognitive and functional abilities by preserving synaptic structure and function. Glutamate receptors and post synaptic density proteins play a central role in excitatory synaptic plasticity. Synaptic dysregulation may contribute to brain disorders present in those with Autism Spectrum Disorders by preventing appropriate synaptic signaling and plasticity.

The NMDA receptor is fundamental to excitatory synaptic plasticity and neurological diseases. Synaptic loss is a pathologic correlate of cognitive decline. Synaptic dysfunction is evident long before synapses and neurons are lost. The synapse constitutes an important target for treatments to slow progression and preserve cognitive and functional abilities in these diseases. (van Spronsen & Hoogenraad, 2010)

5.1 Excitotoxicity and glutamatergic activity

Current hypotheses propose excessive glutamate activity can lead to excitotoxicity interfering with normal neurodevelopment in schizophrenia. Similarly, these effects may be involved in the neurodevelopment in ASD. The excitotoxicity is hypothesized to continue and is linked to disease progression in schizophrenia ultimately resulting in pathologically functioning NMDA glutamate receptors. These hypotheses are consistent with those that identify the final common pathway of many neuropsychiatric diseases as synaptic pathology.

While the future promises biomarkers, RNAi strategies, stem cell transplantation and other genetic treatments, arresting and/or reducing developmental pathogenic potential by discovering and developing methods of effecting glutamatergic regulation by NMDA antagonism or other methods is a worthy, if not urgent, treatment goal for Autism Spectrum Disordered children. Blocking or moderating excessive glutamate neurotransmission with NMDA antagonists may prevent or mitigate damage, maladaptive neurodevelopment or neurodegenerative processes.

Some NMDA antagonists appear to be neuromodulators that reduce the excitotoxicity effects of dysregulated circuits and support dendritic health, long term potentiation and neural plasticity. Such treatments may one day provide preventative pharmacological interventions as well as those that can reduce impairment and improve functioning.

Two NMDA antagonists are particularly interesting candidates for therapeutic potential in the ASD population, memantine and dextromethorphan/quinidine (Duke & Kaye, 2010).

Memantine, as an augmenting agent, demonstrated significant improvements in open-label use for language function, social behavior, and self-stimulatory behaviors, although self-stimulatory behaviors comparatively improved to a lesser degree. Chronic use so far appears to have no serious side effects (Chez MG, et al 2007).

Dextromethorphan/quinidine (DM/Q) shares the attributes of being an uncompetitive NMDA antagonist with memantine, however, importantly; DM/Q is a sigma 1 agonist and binds to SERT. Binding data comparing memantine with DM/Q demonstrate the presence of Sigma 1 and SERT binding in DM/Q but not in memantine (Werling, et al 2007).

One of the characteristics that suggests DM/Q might have therapeutic potential in ASD is its efficacy in pseudobulbar affect (PBA). The efficacy and safety of dextromethorphan and quinidine was demonstrated in clinical trials of late stage neurological conditions (amyotrophic lateral Sclerosis and Multiple Sclerosis) demonstrating reductions of emotional lability and improvements in sleep. These findings suggest that the pharmacological characteristics of DM/Q may, at some level rescue synaptic signaling and may have the potential to affect neurodevelopmental trajectory in dysregulated developing nervous systems such as those with Autism Spectrum Disorders.

AVP-923 was approved by the FDA in 2010 as Nuedexta™ the first and only treatment for Pseudobulbar Affect (PBA). This is an important therapeutic for those suffering the debilitating effects of pseudobulbar affect. The efficacy in reducing dysregulated and involuntary congruent and incongruent emotional expressions is a significant achievement. Why is DM/Q (Nuedexta) effective in PBA? That, of course, is unknown, but PBA is often considered the result of connectivity and neural circuitry failures and ASD is known to have signaling and connectivity pathologies. Emotional lability is often associated with behavioral dyscontrol, irritability, assaultive and raging behaviors that prompt pharmacological intervention in children with ASD.

NMDA antagonists may offer a therapeutic pathway through modulation or regulation of dysregulated glutamatergic processes. The potential of DM/Q (Nuedexta) in ASD, particularly in the early developmental stages of the illness, to rescue and support synaptic function is worthy of further study.

Although the mechanism of action of DM/Q is not fully characterized, its unique properties as an NMDA receptor antagonist and as a Sigma 1 receptor agonist appear to convey effects of both neuroprotection and neuromodulation. Future studies will help us determine if these unique characteristics will lead to improved outcomes for those with autism spectrum disorders.

6. Conclusion

The distress, irritability and emotional lability often seen in Autism Spectrum Disorders may be a reflection of pathological glutamatergic functioning or otherwise dysregulated circuits relative to inhibitory-excitatory balance. When sustained, these symptoms demonstrate potential for pathological development of abnormal neural circuits capable of dysregulation through neural synchronicity and state dependent effects on genetic expression. Within the framework of this hypothesis the neural plasticity and critical periods, present in developing brains, place them at particular risk.

We currently have drugs and compounds that have the ability to reduce impairment and improve functioning in many with ASD when used, monitored and managed thoughtfully. Early pharmacological intervention related to severe emotional lability, irritability and dysregulated circuits may also reduce the pathogenic potential and reduce or prevent the development or maintenance of pathological processes.

7. Acknowledgement

As a faculty member of the Child Psychopharmacology Institute and as a consultant for Avanir Pharmaceuticals I wish to express my gratitude to my colleagues Randall Kaye, M.D., MPH, R. Dennis Staton, Ph.D., M.D. and Scott Siegert, Pharm.D. for their collegial support and expertise.

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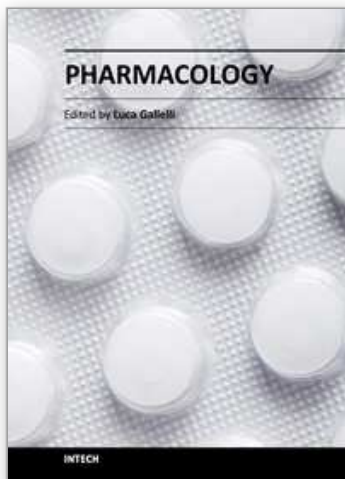
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Pharmacology

Edited by Dr. Luca Gallelli

ISBN 978-953-51-0222-9

Hard cover, 720 pages

Publisher InTech

Published online 14, March, 2012

Published in print edition March, 2012

The history of pharmacology travels together to history of scientific method and the latest frontiers of pharmacology open a new world in the search of drugs. New technologies and continuing progress in the field of pharmacology has also changed radically the way of designing a new drug. In fact, modern drug discovery is based on deep knowledge of the disease and of both cellular and molecular mechanisms involved in its development. The purpose of this book was to give a new idea from the beginning of the pharmacology, starting from pharmacodynamic and reaching the new field of pharmacogenetic and ethnopharmacology.

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Bill J. Duke (2012). Pharmacological Neuromodulation in Autism Spectrum Disorders, Pharmacology, Dr. Luca Gallelli (Ed.), ISBN: 978-953-51-0222-9, InTech, Available from:
<http://www.intechopen.com/books/pharmacology/pharmacological-neuromodulation-in-autism-spectrum-disorders>

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