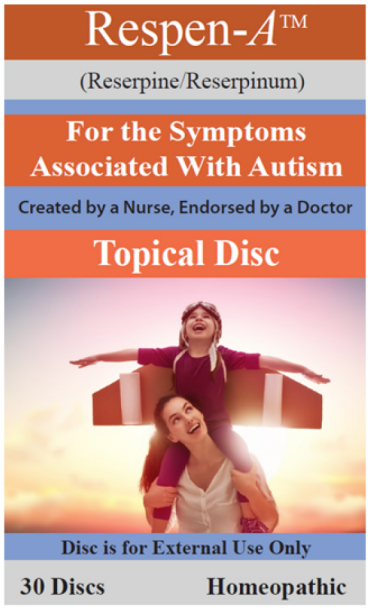


Homeopathic Topical Disc For Symptoms of Impaired Social Interaction, Impaired Communication, and Repetitive Behaviors

10 Palmer Ave,
P.O. Box 4,
Loomis WA 98827
Phone: 425-870-9366
Email: elaine.delack@gmail.com

US Patent 8,440,685

Table of Contents

Respen-A™ requires a prescription. Any doctor with prescription authority can prescribe Respen-A™. It is currently available as a compounded prescription medication from:

Hopewell Pharmacy
1 West Broad Street
Hopewell, NJ 08525
Toll Free: 1-800-792-6670

Pure Compounding Pharmacy
603 East Diehl Rd, #131
Naperville, IL 60563
Tel: 630-995-4300

Wellness Pharmacy
3401 Independence Dr Ste 231
Birmingham, AL 35209
Toll Free: 1-800-227-2627

INTRODUCTION

Autism Spectrum Disorder, also known as Pervasive Developmental Disorders (PDD) encompasses five disorders: Autism; Asperger Syndrome; Rett Syndrome; Childhood Disintegrative Disorder; and Pervasive Developmental Disorder Not Otherwise Specified (atypical autism). Childhood autism, also known as autistic disorder or infantile autism is a neuro-developmental condition that is characterized by impairment in social interaction, impairment in communication and restricted or stereotyped patterns of behavior and interest usually manifested before the age of 3 years. Common symptoms of ASD include: impaired social and communication skills (verbal and nonverbal); delayed or unusual speech patterns; hyper or hypo sensitivity to light, sound, crowd and other external stimulation; some degree of fine and gross motor difficulty; repetitive behaviors and ritualized activities; aloofness or disengagement with surrounding environment, inability to handle stress or change in routine or environment; some patients have a degree of mental retardation and one in four develop seizures. The severity of these symptoms is very individualized in persons diagnosed with ASD.

ASD has increased dramatically over the past 30 years and today 1 in 100 children are diagnosed as having ASD. It is four times more common in boys than girls. The cause of ASD still eludes the medical community, but several factors have been implicated such as hereditary, heavy metal toxicity, vaccinations, exposure to high amounts of Pitocin (oxytocin) and/or opioids during birth, food allergies, and vitamin and mineral deficiencies.

Many people have claimed an association of vaccinations containing thimerosal, a mercury preservative in many vaccines. Although thimerosal has been present in many vaccines for decades, it is hypothesized that the amount of mercury that a child is exposed to has greatly increased over the past twenty years due to the increased number of vaccines that children are now given today at a very early age. But the prevalence of autism continues to increase despite the reduction or removal of the thimerosal in the vaccines. So what other factors may be contributing to this escalating trend in ASD?

HYPOTHESIS

MedDEV began researching oxytocin and arginine vasopressin (AVP) as a possible piece of the puzzle since oxytocin is involved in social behaviors, bonding and language development. Research has shown that low doses of oxytocin have resolved the repetitive behaviors in adults with autism. (Hollander et al, 2003).

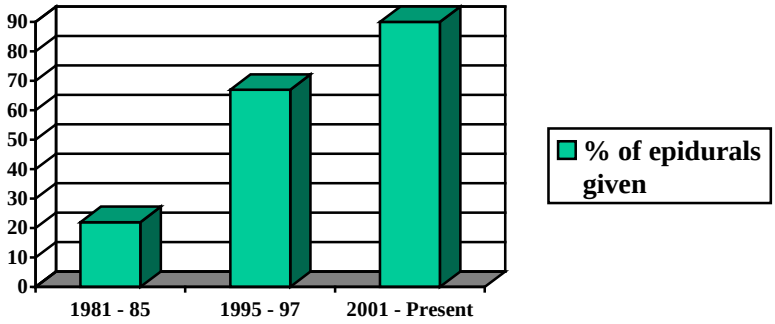
The hypothalamic neurohypophysial system (HNS), which is involved in autism, is responsible for the synthesis of oxytocin. As the HNS grows, arginine-vasopression is produced and travels down the axons of this system, much of it being converted to oxytocin as the HNS grows. When the oxytocin reaches a certain level it tells the HNS to quit growing. Oxytocin is not supposed to reach the concentration level to trigger the HNS to stop growing until 7-10 days postpartum. It has been postulated that high doses of Pitocin (synthetic oxytocin) administered during childbirth could trigger the HNS to stop growing resulting in inadequate oxytocin receptors and production in the infant/child (Wahl, 2004). Although a study by Gale et al in 2003, studied the birth histories of 41

boys meeting the criteria of ASD compared to 25 age and IQ matched controls and no association was determined between exogenous oxytocin administration and neurodevelopmental abnormalities.

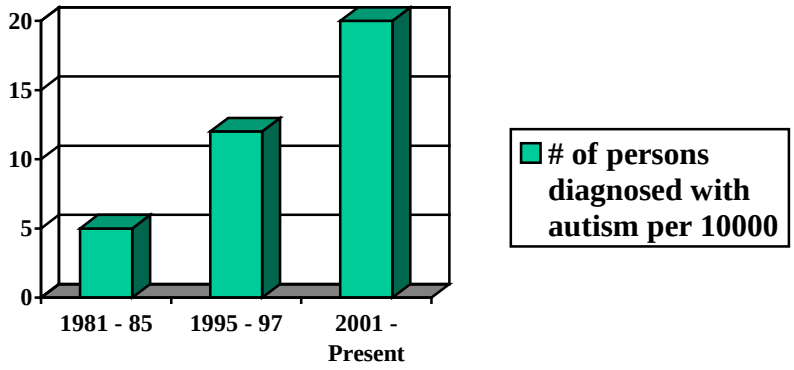
The Gale et al study reviewed birth records of Pitocin induction of labor, but not if women had received Pitocin augmentation following the administration of epidural anesthesia/analgesia. It is common that contraction augmentation with Pitocin is often needed with epidurals. Also the Pitocin is continued often through the partuition stage because the mother often does not push effectively with epidural anesthesia/analgesia and this is where the risk may lay. The cytochrome P-450 enzyme, cyp3A4, is increased during pregnancy and it is the enzyme that metabolizes Pitocin in the liver. This increased activitiy of the cyp3A4 during the pregnancy prevents contractions that could easily be triggered from the growing fetus. This enzyme is also in the placenta. The initiation of labor begins with a decrease in the cyp3A4 resulting in an increase in the oxytocin levels and contractions begin. The medications used in epidurals, bupivacaine and more recently ropivacaine, are metabolized by cyp3A4. These compete with Pitocin for the cyp3A4 enzyme and this can result in high levels of oxytocin, possibly high enough to trigger the negative feedback on the growth of the neurohypophysial system in the newborn. Ropivacaine has shown to be about 40% less potent than bupivacaine, but it has been promoted in the more recent years because it is the newer product to the market (1996). This can result in larger doses of the ropivacaine being needed, which can result in more competition for the cyp3A4 enzyme and higher Pitocin levels. If bupivacaine or ropivacaine are given with the analgesic, Fentanyl, then their effect is equal, but Fentanyl also is metabolized in the liver by cyp3A4. Another interesting fact is that females have more cyp3A4 than males do. This may also contribute to the increased rate of autism in boys.

So these children that have been exposed to higher levels of oxytocin due to the epidural with Pitocin augmentation of contractions may have decreased oxytocin synthesis due to the premature growth cessation of the neurohypophysial system. Thus the infant/child may be at more risk for further insult on the endogenous oxytocin system by mercury exposure that inhibits oxytocin. Resulting in increased risk of autism in the child. See Graph 1a and 1b illustrating similar prevalence trends in the number of women receiving epidurals and the number of ASD cases respectively.

Graph 1a:



Graph 1b:



As stated earlier, low doses of oxytocin have decreased the repetitive behaviors in autistic adults, but that has been the extent of the benefits. Could it be that the effects of exogenous oxytocin are limited due to deficient oxytocin neuron growth and receptors?

Hyperserotonemia has been shown to inhibit oxytocin neuron growth in the offspring of the Sprague-Dawley rat model of autism (McNamara et al, 2008). Most ASD patients have elevated blood levels of serotonin, norepinephrine, and elevated dopamine metabolism resulting in elevated levels of homovanillic acid (HVA) Launay et al, 1988; Lake et al, 1977; Hranilovic et al, 2007; Gillberg & Svennerholm, 1987). The cause of these neurotransmitter imbalances is unknown, but are indicative of decreased monoamine oxidase-A (MAO-A) activity and increased monoamine oxidase-B (MAO-B) activity. MAO-A metabolizes serotonin, norepinephrine and histamine into the active aldehyde metabolite. MAO-B metabolizes dopamine.

Ropivacaine has been shown to be associated with the risk of serotonin syndrome manifestation if given with a Selective Serotonin Reuptake Inhibitor (SSRI). Thus, it appears that ropivacaine may have a MAO-A inhibitory effect. This coupled with the research that shows that maternal depression and personality disorders (but not the father) increases the risk of autism in the offspring, may show a genetic MAO-A deficiency. MAO-A is genetically expressed on the X chromosome. MAO-A is expressed as low activity and high activity alleles. High MAO-A activity genotype is less likely to develop antisocial problems (Craig, 2005). Low activity alleles within the gene promoter region of the MAO-A gene were correlated in the autistic patients tested (Cohen et al, 2003; Davis et al, 2008). There was a consistent association between the “low activity” allele and larger brain volumes for regions of the cortex in children with autism. (Davis et al, 2008). Autistic infants have a smaller head circumference at birth and then undergo two phases of sudden excessive increase in head size between 1 to 2 months and 6 to 14 months. This increase in head size was related to greater cerebral cortex volume at 2 to 5 years of age (Courchesne et al, 2003). Individuals with the low activity allele MAO-A gene polymorphism display behaviors of alcoholism, antisocial personality, and impulsivity (Contini et al, 2006). A male has a 50% chance of having the low activity allele whereas the female has only about a 25% risk of having the expression of the low activity allele if it is recessive to the high activity allele. But if the mother has suffered from depression, it confirms that her MAO-A activity has been decreased whether by toxins, stress, high estrogen, or having a low activity allele. (Mercury, aluminum, high

copper, high cadmium, stress, lipid peroxidation, high estrogen all inhibit MAO-A). Thus, the mother can have elevated serotonin levels, which have been shown in research to decrease the growth of the oxytocin neurons in the offspring if the mother is given serotonin during pregnancy (McNamara et al, 2008). Interestingly, most autism isn't diagnosed until after 3 years of age and the infant has higher levels of MAO-A, which begin to decrease slowly with age.

Many parents are reporting improvement in their autistic children with a gluten free casein free (GFCF) diet. Gluten has been shown to increase the serotonin production in the gut. The resulting increased serotonin levels due to gluten ingestion will be amplified in a child who has decreased MAO-A activity. Hyperserotonemia in the blood but low levels of serotonin in the brain have been correlated with autism. A possible explanation for this phenomenon may be that the serotonin secreted in the peripheral system i.e. the gastrointestinal tract, may result in high levels of serotonin in the blood. The high levels of serotonin in the blood may cross the blood-brain-barrier into the central nervous system resulting in elevated levels of serotonin in the nerve synapses. The excess serotonin is picked up by serotonin reuptake transporters and delivered to the 5-HT1A receptors which when stimulated shutdown the release of serotonin into the nerve synapses and decreases MAO-A activity. This would result in low levels of serotonin in the brain and decreased production of the active aldehyde metabolite that is produced by the metabolism of serotonin by MAO-A.

Increased levels of serotonin resulting in 5-HT1A receptor stimulation stimulates the release of hypothalamic corticotropin-releasing hormone (CRH), increases ACTH secretion 3-5 fold and increases secretion of proopiomelanocortin hormone (POMC) 15-27%, all of which have been shown to be elevated in ASD (Jergensen et al, 2002). POMC stimulates the production of Beta-endorphins, which has been shown to be high in many autistic patients especially those who display self-injurious behavior (Sandman et al, 2002). Gluten intake has been shown to increase opiate production, whether it is by the metabolism of the gluten or by the POMC stimulation from the high serotonin levels produced from gluten's effect on the gut.

ASD patients have a slowed response to stress despite elevated levels of ACTH (Marinovic`, 2008). MAO-A knockout mice have demonstrated a diminished response to stress (Popova). Chronic stress in persons with MAO-A alleles associated with less transcriptional activity display a pattern of cortisol excretion--a decrease from overnight to daytime—that is suggestive of HPA axis blunting as compared to those persons with more active MAO-A alleles (Brummett et al, 2008). Children with infantile autism have shown an abnormal diurnal rhythm for cortisol production (Hoshino et al, 1987).

DHEA-S is low in adult ASD patients (Strous et al, 2005). DHEA is synthesized in the zona reticularis of the adrenal cortex and MAO-A is widespread throughout the adrenal cortex and adrenal capsule (Dharia & Parker, 2004; Harper et al, 1999).

ASD patients such as those with Asperger Syndrome have elevated total cholesterol and low-density lipoprotein (LDL) levels (Dziobek et al, 2007). Higher total cholesterol, LDL/HDL ratios, and triglycerides were associated with low activity MAO-A alleles (Brummett et al, 2008).

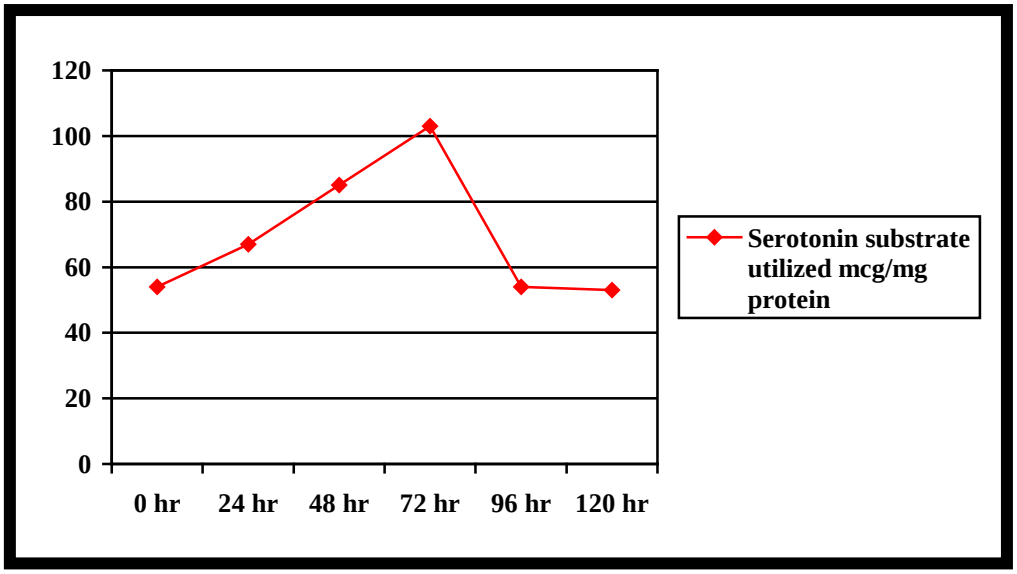
A decrease in the MAO-A activity can decrease the mitochondrial complex II activity (reduced flavin adenine dinucleotide (FADH)) as it is dependent on the MAO-A activity (Heron et al, 2001). Inhibition of mitochondrial complex II results in an accumulation of dopamine's metabolite HVA (Cakala et al, 2006). HVA is elevated in ASD patients (Gillberg & Svennerholm, 1987).

Bufontenine (N-N-dimethyl-5-idroxytryptamine) is produced in the pineal gland and is a known hallucinogenic. Bufontenine is metabolized by MAO-A (Jiang, 2013). Bufontenine is elevated in the urine of ASD patients and is positively correlated with hyperactivity scores (Emanuele et al, 2010).

Based on this hypothesis, MedDEV has a patent for the use of reserpine and/or Rauwolfia analogues that increase the activity of MAO-A. Research has shown that reserpine increases the activity of MAO-A two-fold within 72 hours of the first dose. See Graph 2.

Graph 2:

MAO-A activity in rat brain after reserpine injection
(28 February, 1978, Biochemical Pharmacology 27(15) pp. 1895-1896)



Reserpine is the active ingredient in Respen-*A*™. Reserpine's FDA approved indication is hypertension. Central to all homeopathy is the determination of the effect of substances on healthy volunteers according to the homeopathic principle of similia similibus curentur - Let Likes be cured by Likes. High doses of oral or parenteral reserpine can worsen the symptoms of autism such as hyperactivity, irritability, inattentiveness, and depression. Therefore, very low homeopathic doses are used to treat the same symptoms caused by higher allopathic doses of the same drug.

Respen-*A*™ Drug Summary Sheet

MedDEV has a patent for the method of administering a low dose of reserpine or an MAO-A agonist to lessen or alleviate the symptoms associated with Autism Spectrum Disorder. Respen-*A*™ is the trademark for the homeopathic topical disc described in the patent application. Respen-*A*™ requires a prescription and is currently only available as a compounded presciption medication from:

Hopewell Pharmacy
1West Broad Street
Hopewell, NJ 08525
toll free 1-800-792-6670

Key Pharmacy
530 South 336th Street
Federal Way, WA 98003
toll free 1-800-878-1322

Wellness Pharmacy
3401 Independence Dr Ste 231
Birmingham AL 35209
toll free 1-800-227-2627

Table 1a

Respen-*A*™ [Reserpinum (Reserpine)]	
HPUS Monograph Number	7623
NDA Number for Reserpine	9838, filed 6/20/1955
Route of Administration	Topical
Dosage Form	Topical Disc

Table 1b

INGREDIENTS		
Name (Active Moiety)	Type	Strength
Reserpinum (Reserpine)	Active	12C in ethanol in 1 disc

Reserpine is FDA approved for use as an antihypertensive and for the treatment of agitated psychotic states such as associated with schizophrenia. The usual dosage range for the approved indications is 0.1-0.5 mg per day.

Dosage and Usage: Respen-*A*™ is a homeopathic topical disc containing the active ingredient, reserpine in a 12C dilution of ethanol. Respen-*A*™ is administered via a disc that is applied to the skin in the morning and removed at bedtime daily.

Potential Adverse Reactions: The only side effect that has been reported with the use of Respen-*A*™ in children with ASD has been increased motor activity, such as hyperactivity particularly if used in conjunction with some antidepressants, which has been resolved by discontinuing or decreasing the antidepressants or reducing the dose of Respen-*A*™.

The following adverse reactions have been observed with rauwolfia preparations. These adverse effects have been reported in oral and parenteral administration of reserpine in dosages of 0.1 mg and higher, with the increased risk of occurrence of such adverse effects being positively correlated with the higher dosage range. **(Respen-*A*™ contains a trillion times less reserpine than the dosages that have been correlated with these adverse effects.)** There has not been enough systematic collection of data to support an estimate of their frequency. Consequently the reactions are categorized by organ system and are listed in decreasing order of severity and not frequency.

Digestive: Vomiting, diarrhea, nausea, anorexia, dryness of mouth, hypersecretion.

Cardiovascular: Arrhythmias (particularly when used concurrently with digitalis or quinidine), syncope, angina-like symptoms, bradycardia, edema.

Respiratory: Dyspnea, epistaxis, nasal congestion.

Neurologic: Rare Parkinsonian syndrome and other extrapyramidal tract symptoms; dizziness; headache; paradoxical anxiety; depression; nervousness; nightmares; dull sensorium; drowsiness.

Musculoskeletal: Muscular aches.

Genitourinary: Pseudolactation, impotence, dysuria, gynecomastia, decreased libido, breast engorgement.

Metabolic: Weight gain.

Special Senses: Deafness, optic atrophy, glaucoma, uveitis, conjunctival injection.

Hypersensitive Reactions: Purpura, rash, pruritus.

Reserpine Official FDA Information, Side Effects and Uses. http://www.drugs.com/pro/reserpine.html