THEOHARIS C. THEOHARIDES, PHD, MD, is the director of the Molecular Immunopharmacology and Drug Discovery Laboratory as well as a professor of pharmacology, biochemistry, and internal medicine at Tufts University. He received his degrees from Yale University. He has published over 300 research papers and three textbooks. Dr. Theoharides was the first to show that mast cells can be stimulated by non-allergic triggers, such as stress hormones, to secrete inflammatory mediators selectively leading to disruption of the gut-blood-brain barriers. Based on his discoveries, Dr. Theoharides proposed the novel concept that mast cells play a critical role in brain inflammation and autism. www.mastcellmaster.com.

SHAHRZAD ASADI, PHARMD, performs investigations in the Molecular Immunopharmacology and Drug Discovery Laboratory, Department of Pharmacology and Experimental Therapeutics, at Tufts University. She is currently working on the role of mast cells in stress-induced neuroinflammatory diseases. She has been investigating the effect of corticotropin-releasing hormone (CRH) and of mercury on human mast cell release of molecules that could disrupt the blood-brain barrier and contribute to the pathogenesis of autism. Of particular interest is the interaction of environmental, immune, and stress triggers of mast cell activation.

UNWANTED INTERACTIONS AMONG MOST COMMON TREATMENT REGIMENS IN AUTISM

BY THEOHARIS C. THEOHARIDES, MS, PHD, MD,[a,b,c,d] AND SHAHRZAD ASADI, PHARMD[a,e]

Affiliations:
a Molecular Immunopharmacology and Drug Discovery Laboratory, Department of Molecular Physiology and Pharmacology, and Departments of **b** Biochemistry, **c** Internal Medicine, and **d** Psychiatry, **e** Department of Pharmacy, Tufts University School of Medicine and Tufts Medical Center, Boston, MA 02111, USA

INTRODUCTION

Autism spectrum disorders (ASDs) are pervasive neurodevelopmental disorders affecting 0.5-1% of children and characterized by varying degrees of deficiencies in social interactions, concentration, language, and learning.[1,2,3] Such symptoms may become apparent as early as 6 months old and are often established by age 3 years. This is also the age at which many children who develop an ASD do so by regression, often after a specific event such as vaccination, even though they were developing normally.[4]

Behavioral interventions alone are insufficient to address the disruptive nature of ASD symptoms and their persistence throughout life, which instead necessitate the development of effective biomedical treatments. Drug therapy is typically used to treat irritability, hyperactivity, inattention, obsessive-compulsive symptoms, aggression, and self-injury because all of these symptoms can negatively interfere with the success of educational interventions and quality of family life.[5,6] Many children with ASDs also develop seizures with no apparent underlying pathology,[7,8,9] but traditional anti-seizure medications appear to worsen some ASD symptoms.[10] Overall, 70% of children with ASDs take at least 10 different drugs, dietary supplements, vitamins, or intravenous treatments,[6,11,12,13] including intravenous immunoglobulin (IVIG),[14] with little attention to unwanted drug-drug or drug-supplement interactions. Moreover, in many cases, as in the use of IVIG, there is a lack of well-designed double-blind studies,[15] so there should be continued vigilance for the possible development of inflammatory complications.[16]

Taking multiple drugs increases the risk of adverse reactions. In a recent study of spontaneous reporting of adverse drug-drug interactions in Italy, the incidence was 9.8% for two drugs but increased to 88.3% for 8 drugs or more.[17] There is less information on drug-supplement interactions. However, another study reported that 33.4% of patients using antipsychotics took traditional Chinese medicine concurrently; patients using both treatments had worse outcomes (7.2%) than those using antipsychotics alone (4.4%).[18] This short review attempts to provide information regarding the most obvious adverse interactions among treatment regimens in children with ASDs. Clinicians and parents ought to carefully weigh risks of pharmacologic and non-pharmacologic interactions when deciding on a treatment plan. They should also include healthy lifestyle instructions and regular side effect monitoring in their routine clinical care. Awareness of efficacy, safety, and unwanted interactions could increase the benefits of treatment and prevent adverse effects.

Behavioral interventions alone are insufficient to address the disruptive nature of ASD symptoms and their persistence throughout life, which instead necessitate the development of effective biomedical treatments.

Table 1: Unwanted interactions among popular treatment regimens for autism*

Tx#1	Tx#2	Interaction(s): Effect of Tx#1 on Tx#2	Clinical condition(s) affected
SUPPLEMENTS/VITAMINS			
Aloe vera juice	Herbs and supplements that might lower blood sugar Licorice/ laxative herbs	↓ Blood sugar ↑ Risk of lowering potassium levels	↑ Apraxia ↑ GI problems Muscle weakness, aches, cramps
Apple cider vinegar	Digoxin	Hypokalemia	↑ CHF/atrial fibrillation Muscle weakness, aches, cramps
Calcium Magnesium Potassium	Ciprofloxacin, doxycycline, minocycline, moxifloxacin, nitrofurantoin, tetracycline Levothyroxine Digoxin	↓ Effectiveness of antibiotics Affect thyroid hormone ↑ Arrhythmias	↑ Infection ↓ Effect of thyroid hormone Atrial fibrillation
Carnitine	Thyroid hormone drugs	Affect thyroid hormone (Carnitine antagonizes thyroid hormones by T3, T4 entrance inhibition)	↓ Effect of thyroid hormone Thyroid storm
Curcumin	Coumarins Epigallocatechin Naringin Pine bark Rutin	↓ Liver metabolism	↑ Levels Liver toxicity
Epigallocatechin	Acetaminophen	↑ Levels	Liver toxicity
Folinic acid	MTX, 5-FU	Affect autoimmune system	↓ Effectiveness Mask B12 deficiency Leukemia
Glutamate	NMDA receptor antagonist (e.g., Amantadine, dextromethorphan)	↓ CNS activation	↑ Sedation
Grapefruit juice	Dextroamphetamine Erythromycin Omeprazole Terfenadine	↑ Levels of drug	↓ Absorption of Tx#2 ↑ Allergies
L-tryptophan	BDZ Phenothiazines TCAs	↑ Serotonin	↑ Sleepiness
Oxy-Powder® (Intestinal cleansing supplement containing ozonated magnesium oxides, organic Germanium-132, and citric acid)	Many drugs/vitamins/minerals that cause diarrhea such as antibiotics	↓ Drug/vitamin/mineral absorption	↓ Drug/vitamin/mineral effect
Pycnogenol	Anticonvulsants Curcumin Quercetin	↓ Metabolism Polyphenolic overload	Blood or platelet count problems ↑ Hyperactivity
Rutin	Grape seed extract	↓ Liver metabolism	↑ Risk of allergies
Taurine	Dextroamphetamine (Adderall) SSRIs	↑ Neuronal activation	↑ Hyperactivity, anxiety There is some concern that taking too much taurine might worsen bipolar disorder inducing mania
Vitamin B12	Folic acid H2 blockers (cimetidine, ranitidine, famotidine) PPIs (lansoprazole, omeperazole)	Folic acid can mask a vitamin B12 deficiency ↓ Production of stomach acid ↓ Levels of vitamin B12 absorbed from foods	Anemia Anemia

Table 1: Unwanted interactions among popular treatment regimens for autism* (cont.)

Tx#1	Tx#2	Interaction(s): Effect of Tx#1 on Tx#2	Clinical condition(s) affected
SUPPLEMENTS/VITAMINS			
Vitamin B12 (cont'd)	Metformin Anticonvulsants	↓ Absorption of vitamin B12 ↓ Absorption of vitamin B12	Anemia Anemia
Vitamin C (high levels)	Aluminum antacids Protease inhibitors (indinavir)	↑ Aluminum in the body ↓ Levels of indinavir	Diarrhea ↓ Effect of indinavir in HIV
Red yeast rice	Acetaminophen Carbamazepine Erythromycin Fluconazole Grapefruit juice HMG-CoA reductase inhibitors Isoniazid Itraconazole Phenytoin	Red yeast rice contains the statin drug lovastatin. Lovastatin might harm the liver. Taking red yeast along with other medications that might also harm the liver might increase the risk of liver damage.	Liver damage Muscle pain, tenderness, or weakness with fever, unusual tiredness, dark colored urine, or urinating less than usual
Zinc	Quinolones Tetracyclines Immunosuppressant medications (e.g. corticosteroids, cyclosporine) NSAIDs (e.g., ibuprofen)	↓ Effect of antibiotics Zinc may make the immune system stronger. ↓ Absorption of NSAIDs	↑ Infection ↑ Immune reactions ↑ Fever, pain, inflammation
PRESCRIPTION DRUGS			
Acetaminophen (paracetamol)	Antiviral Antibiotics Antifungal	↑ Blood levels	Liver toxicity
Antibiotics	Biotin	Long-term use of antibiotics (especially broad-spectrum antibiotics that kill a wide range of bacteria) could lead to biotin deficiency	Dermatitis
Antibiotics	Corticosteroids NSAIDs	↓ GI flora	↑ Diarrhea
Antibiotics	Probiotics	↓ Effect of probiotics	↑ GI problems (e.g., diarrhea)
Antibiotics: Clarithromycin/Erythromycin Isoniazide Antifungals: Itraconazole Ketoconazole	Carbamazepine (Tegretol)	↑ Levels of carbamazepine	↑ Risk of side effects: Anemia or other blood disorders Unusual bruising or bleeding Worsening of seizures Hallucinations Drowsiness Dizziness Nausea
Anticonvulsants: Carbamazepine Oxcarbazepine Phenobarbital Phenytoin Primidone	Biotin	Long-term use of anticonvulsants reduces blood levels of biotin	Hair loss Biotin deficient facies, a scaly red rash around the eyes, nose, and mouth Eczema in children
Anticonvulsants: Phenobarbital Phenytoin	Vitamin D (high levels)	Affects vitamin D metabolism/ calcium absorption	↑ Body's use of vitamin D
Antifungals: Fluconazole Ketokonazol Terbinafine	BDZ Acetaminophen Theophylline	↑ Levels of BDZ ↑ LFTs ↓ Theophylline clearance	↑ Sleepiness ↑ Liver toxicity ↑ Liver toxicity ↑ Asthma

Table 1: Unwanted interactions among popular treatment regimens for autism* (cont.)

Tx#1	Tx#2	Interaction(s): Effect of Tx#1 on Tx#2	Clinical condition(s) affected
PRESCRIPTION DRUGS			
Antiviral: Valacyclovir (Valtrex)	Aminoglycosides Amphotericin B Cyclosporine NSAIDs Cimetidine Probenecid Tacrolimus Vancomycin	↑ Blood levels	Kidney damage Liver toxicity
Benztropine mesylate (Cogentin) Belladonna	Antihistamines Antipsychotics TCAs	↑ Anticholinergic effects	Urine retention Blurred vision Confusion ("brain fog")
Betaine	Antacids (e.g., cimetidine, omeperazole)	↓ Benefits	Possibly worsen GERD
Buspirone (Buspar)	Haloperidol	↑ Levels of haloperidol	↑ Dyskinesia
Clomipramine (Anafranil)	Haloperidol Phenobarbital Dextroamphetamine (Adderall)	↑ Risk of ventricular arrhythmias ↓ Seizure threshold ↑ NE	↑ Clomipramine toxicity Myocardial infarction and stroke ↑ Seizures ↑ ADHD ↑ Anxiety
Clozapine (Clozaril)	BDZ/other psychotropic drugs Phenytoin Caffeine, cimetidine, ciprofloxacin, citalopram, erythromycin, paroxetine	↓ Respiratory drive ↑ Metabolism ↑ Extrapyramidal symptoms	Orthostatic hypotension Respiratory collapse Loss of speech, amentia, tics, poor coordination, delusions, hallucinations, involuntary movement, dysarthria, amnesia, memory loss, histrionic movements
Dextroamphetamine (Adderall)	TCAs Diphenhydramine Chlorpromazine/ haloperidol	↑ Activity ↑ Concentration Rapid heart beat Rhabdomyolysis, kidney damage ↓ Metabolism of amphetamines Weight gain Psychotic symptoms	Serotonin syndrome (including ↑ ADHD and ↑ aggression) can develop when TCAs and Adderall are given together and could be fatal ↑ Risk of side effects ↑ Psychotic disorders
Donepezil (Aricept) (cholinesterase inhibitor)	Anticholinergics: Antihistamines, TCAs Antiemetics (prochlorperazine, promethazine) Antipsychotics (chlorpromazine, clozapine, olanzapine, thioridazine) Antivertigo (meclizine, scopolamine) GI drugs (belladonna, chlordiazepoxide, cimetidine, clidinium, dicyclomine, diphenoxylate atropine, hyoscyamine, propantheline, ranitidine) Muscle relaxants (cyclobenzaprine, dantrolene) Anti-parkinsonism (amantadine, benztropine, biperiden, trihexyphenidyl)	Competitive inhibition	Variable effects on: Urine retention Blurred vision ↑ Asthma Confusion ("brain fog")

Table 1: Unwanted interactions among popular treatment regimens for autism* (cont.)

Tx#1	Tx#2	Interaction(s): Effect of Tx#1 on Tx#2	Clinical condition(s) affected
PRESCRIPTION DRUGS			
Donepezil (cont'd)	Urinary incontinence (oxybutynin, propantheline, solifenacin, tolterodine)		
Ethosuximide (Zarontin)	Phenytoin Valproic acid	↑ Levels of phenytoin, valproic acid	↑ Side effects Dizziness, drowsiness, headache
Felbamate (Felbatol)	Anticonvulsants: Carbamazepine Phenobarbital Phenytoin Valproate	Change in levels of anticonvulsants	↑ Levels of phenobarbital, phenytoin, and valproic acid ↓ Levels of carbamazepine but ↑ levels of carbamazepine epoxide (a carbamazepine metabolite)
Gabapentin (Neurontin)	Felbamate Hydrocodone Naproxen	↓ Clearance ↑ Levels of gabapentin ↑ Levels of gabapentin	Prolong the half-life ↑ Levels of felbamate ↑ Side effects, such as dizziness, drowsiness
Hydroxyzine (Atarax)	BDZ Chlorpromazine TCAs	Additive CNS, respiratory-depressant effects	↑ Sleepiness
Intravenous immunoglobulin (IVIG)	Live virus vaccines Oligoprocyanthocyanidins (OPC-3) and other immune-enhancing substances	High doses of IVIG inhibits the response to vaccine when given shortly afterwards ↑ Immune system	↓ Vaccine response Possible development of inflammatory complications
Lamotrigine (Lamictal)	Carbamazepine Methsuximide Oxcarbazepine Phenobarbital Primidone Rifampin Risperidone Ritonavir Rufinamide Sertraline Valproate	↑ Levels of lamotrigine	↑ Sleepiness Nausea Dizziness Headaches
Lithium	SSRIs Haloperidol	Additive effects Additive effects	Diarrhea, confusion, tremor, dizziness, agitation Extremely serious rigidity, very high fever
Memantine (Namenda)	NMDA antagonists: Amantadine Dextromethorphan Ketamine Drugs with renal elimination, including cimetidine, hydrochlorothiazide, metformin, ranitidine	↑ Additive effects	Confusion Hallucinations Lack of coordination Fainting Seizures ↑ Blood pressure Severe headache Blurred vision Trouble concentrating Chest pain Numbness Seizures
Montelukast (Singular)	Anticonvulsants	↓ Levels of Singulair	↑ Asthma

Table 1: Unwanted interactions among popular treatment regimens for autism*

Tx#1	Tx#2	Interaction(s): Effect of Tx#1 on Tx#2	Clinical condition(s) affected
PRESCRIPTION DRUGS			
Naltrexone (Revia)	Codeine Diphenoxylate Hydrocodone Propoxyphene	↓ Effectiveness of Tx#2	↑ Diarrhea ↑ Pain
	Thioridazine	Severe drowsiness, lethargy, somnolence	
Nortriptyline (Aventil, Pamelor)	Fluphenazine Prochlorperazine Promazine Thioridazine Trifluoperazine Triflupromazine	↑ Levels of nortriptyline	↑ TCAs side effects: Dry mouth, constipation, urinary retention, ↑ heart rate, sedation, irritability, dizziness, ↓ coordination
	Other TCAs	Block acetylcholine	Constipation, paralysis of the intestine (paralytic ileus)
	Barbiturates, BDZ, narcotics	↑ Effectiveness of the medications that slow brain activity	↑ Risk of side effects
Paroxetine (Paxil)	TCAs: Desipramine Imipramine	TCAs toxicity	Serotonin syndrome: ↑ Heart rate, shivering, sweating, dilated pupils
	Oxazepam	Additive effects	Drowsiness, sedation, ↓ alertness, impaired psychomotor function
	Phenytoin	↓ Levels of phenytoin	Seizures
	Risperidone	Serious adverse effects	↑ Levels of risperidone Extrapyramidal signs: Akinesia, akathisia Extreme restlessness, involuntary movements, uncontrollable speech
	Donepezil	↑ Levels of donepezil	↑ Risk of donepezil side effects: Bradycardia, nausea, diarrhea, anorexia, abdominal pain
Pemoline (Cylert)	Anticonvulsants	↓ Seizure threshold	↑ Seizures
Phenytoin (Dilantin)	Chloramphenicol Cimetidine Diazepam Ethosuximide Fluoxetine H2 blockers Methylphenidate Phenothiazines Salicylates Sulfonamides Trazodone	↑ Levels of phenytoin	↑ Side effects
	Corticosteroids Digitoxin Doxycycline Paroxetine Quinidine Rifampin Theophylline Vitamin D	↓ Efficacy by phenytoin	↑ Seizures
Primidone (Mysoline)	Antidepressants, barbiturates, BDZ	↑ Risk of side effects	Drowsiness Confusion Memory loss Difficulty breathing

Table 1: Unwanted interactions among popular treatment regimens for autism* (cont.)

Tx#1	Tx#2	Interaction(s): Effect of Tx#1 on Tx#2	Clinical condition(s) affected
PRESCRIPTION DRUGS			
Primidone (cont'd)	Certain antifungal medications: Fluconazole Itraconazole Ketoconazole Voriconazole	↓ Levels of the antifungal	↑ Fungal infection
SSRIs (e.g., fluxetine, paroxetine)	NSAIDs	GI problems	↑ GI discomfort Bleeding
Thioridazine (Mellaril)	Barbiturates (e.g., phenobarbital)	Additive effects	↑ Risk of sedation and other problems
	Anticonvulsants: Divalproex sodium Fosphenytoin Phenytoin Valproic acid		↑ Risk of drowsiness and seizures
	SSRIs, TCAs	↑ Levels of thorazine in blood	↑ Risk of thorazine side effects
Triazolam (Halcion)	Psychotropic medications Anticonvulsants Antihistamines	↑ CNS depressant effects	↑ Sleepiness
	Ranitidine Cimetidine	↑ Levels of triazolam	↑ Sleepiness
Valproic acid (Depakene)	Phenytoin	↑ Clearance of valproate	↑ Side effects ↓ Efficacy
	Felebamate, chlorpromazine	↑ Levels of valproic acid	
	Clonazepam, diazepam	↑ Levels of diazepam	
	Ethosuximide	↓ Metabolism of ethosuximide	
	Lamotrigine	Serious skin reactions	Stevens-Johnson syndrome and toxic epidermal necrolysis
	Phenobarbital	↓ Metabolism of phenobarbital	↑ Seizures
	Phenytoin	↑ Phenytoin clearance	↓ Efficacy
	Topiramate	Urea cycle disorders, hypothermia	Hyperammonemia without encephalopathy
Zolpidem (Ambien)	BDZ	↑ Additive effect	Slow/shallow breathing, severe drowsiness, dizziness

***ABBREVIATIONS:**

ADHD (attention-deficit/hyperactivity disorder)
BDZ (benzodiazepines)
CHF (congestive heart failure)
CNS (central nervous system)
GERD (gastroesophageal reflux disease)
GI (gastrointestinal)
HIV (human immunodeficiency virus)
HMG-CoA (3-hydroxy-3-methylglutaryl-coenzyme A)
IVIG (intravenous immunoglobulin)
LFT (liver function tests)
MTX (methotraxate)
NE (norepinephrine)
NMDA (N-methyl-D-aspartate)
NSAIDs (nonsteroidal anti-inflammatory drugs)
PPI (proton-pump inhibitor)
SSRIs (selective serotonin reuptake inhibitors)
TCAs (tricyclic antidepressants)
5-FU (5-fluorouracil)

All antipsychotic drugs have considerable adverse effects, while their long-term safety in children remains unknown.

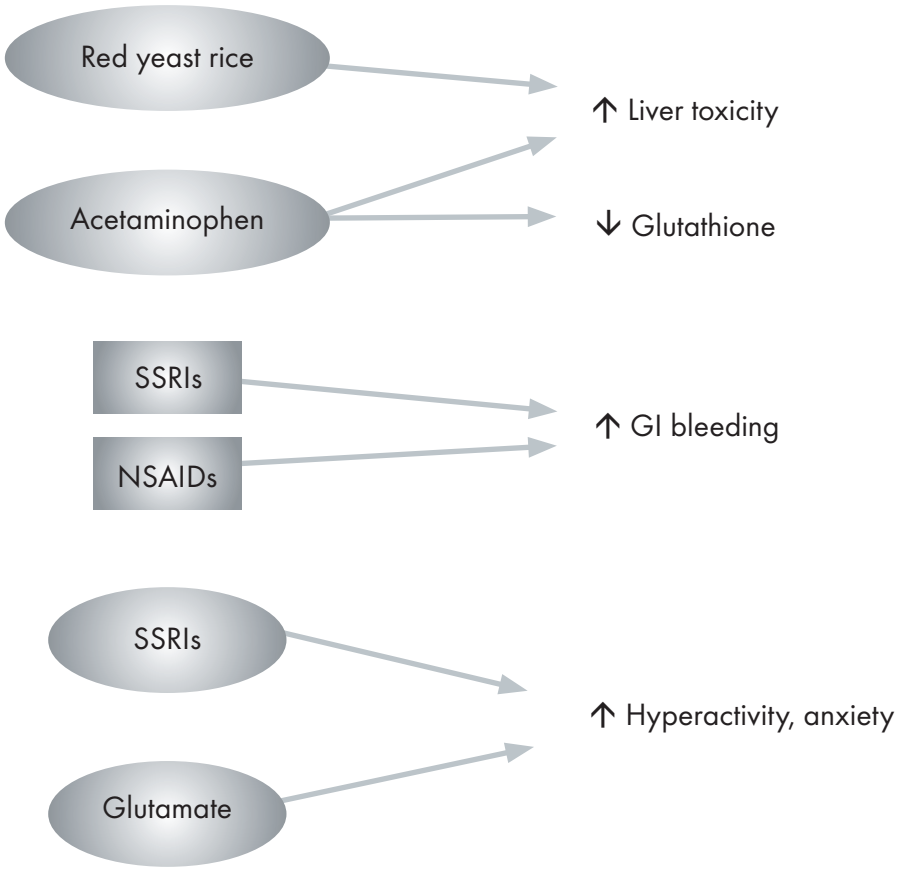
USE OF ANTIPSYCHOTIC MEDICATIONS AND ANTIDEPRESSANTS IN ASD

A cross-sectional study in Denmark found that the prevalence of treatment with antipsychotic medications in a nationwide child and adolescent psychiatric sample was 6.4%.[19] Some pediatric patients were prescribed additional medications, with 24% receiving antidepressants, 8% sedative medications, and 4% psychostimulants.[19] Many children with ASDs also take antipsychotic medications.[20] In a national sample of children and adolescents with ASDs, the percentage of outpatients being treated with antipsychotic medications was almost 30%.[21]

Among ASD children, risperidone[22] is the most common antipsychotic medication taken. This class of drugs also includes haloperidol as well as the newer "atypical" compounds.[23,24] Risperidone is the only drug with FDA approval for ASD, approved for treating aggressiveness, stereotypic behaviors, and self-injurious behaviors. A recent review of 21 randomized, placebo-controlled trials using psychopharmacologic agents[25] showed that only risperidone for hyperactivity[26,27] and methylphenidate for aggressive behavior[28] produced significant improvement in more than one

Figure 1

Most common and serious interactions



Two recent reviews concluded that there is insufficient evidence for any benefit of SSRIs or other psychotropic drugs in ASD.

study.[25] However, all antipsychotic drugs have considerable adverse effects,[20] while their long-term safety in children remains unknown. For instance, risperidone leads to significant weight gain, while haloperidol is limited by tardive dyskinesia. Long-term effectiveness, as already suggested, is also a concern; in another study of ASD children from a national registry, 35% of children received psychotropic medications, but adding a second-generation antipsychotic to the stimulant did not have any significant additional benefit on any of the parameters studied.[29]

Many children with ASDs are also prescribed antidepressants, especially selective serotonin reuptake inhibitors (SSRIs). However, two recent reviews concluded that there is insufficient evidence for any benefit of SSRIs or other psychotropic drugs in ASD.[30,31] In fact, the results of a recent trial indicate that one SSRI, citalopram, not only was not effective for children with ASDs but may actually be detrimental.[32] Another recent study indicates that the combined use of nonsteroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen, with SSRIs reduces the antidepressant effect of the latter.[33] This problem is in addition to the GI bleeding caused by SSRIs and the increased risk of GI bleeding when administered together with NSAIDs (Figure 1).[34]

POLYPHENOLS AND LIVER METABOLISM

Most psychotropic agents are metabolized in the liver. They should, therefore, be used with caution when administered with other drugs or supplements that affect liver metabolism (Table 1). For instance, a study reported that autistic children have decreased capacity to sulphoconjugate acetaminophen and, therefore, are unable to effectively metabolize particularly phenolic amines such as dopamine, tyramine, and serotonin.[35] Some authors even hypothesize that the increased rate of ASD may be at least partly due to acetaminophen's ability to decrease glutathione levels (Figure 1).[36]

Polyphenols include many natural and synthetic compounds, such as anthocyanidins, coumarins, and flavonoids present in plants, fruits, vegetables, and tea.[37,38] The broad category of flavonoids includes the subgroups of flavonols (for example, quercetin) and flavones (including luteolin). Increasingly, ASD treatment approaches have featured the use of quercetin and other polyphenolic compounds such as curcumin, pycnogenols (extracted from pine bark), green tea, and ginseng extract. These substances have varying antioxidant and anti-inflammatory properties, mostly due to the degree of hydroxylation of their phenolic rings.[37] The main metabolism of a flavonol such as quercetin is by glucoronidation (quercetin-3´-glucuronide) and sulphation (quercetin-3´-sulphate).[39,40]

A few anecdotal reports have suggested that quercetin or its glycoside rutin may increase hyperactivity in some ASD children. This may possibly happen when combined with other foods, supplements, or drugs containing high quantities of polyphenolic compounds that may overburden the liver in susceptible ASD children. For instance, it was recently reported that the major green tea ingredient, epigallocatechin, can cause liver damage.[41] In addition, the main polyphenolic ingredients of grapefruit juice, the coumarins, can inhibit the liver enzyme CYP3A, affecting both the metabolism and/or activation of numerous drugs and natural substances, while the main polyphenolic flavonoid naringin can inhibit the organic anion-transporting polypeptide (OATP) family responsible for the transport of many hormones and drugs.[42] Not all phenolic compounds carry the same potential risk. For instance, pycnogenol has 15 hydroxyl groups and naringin has eight hydroxyl groups as compared with quercetin's five and luteolin's four. Any adverse effect of quercetin or rutin is, therefore, more likely due to interactions. Unwarranted generalizations can lead to a great deal of confusion, especially when they are contrary to published reports.

An exhaustive search of the literature does not uncover any documented adverse effects for flavonoids, especially quercetin or its structural analogue luteolin.[44,44] On the contrary, a number of papers report protective effects of quercetin and luteolin both in the brain and liver.[45,46] For example, quercetin prevented liver toxicity induced by acetaminophen (paracetamol)[47] and reduced haloperidol-induced dyskinesia.[48] In addition, quercetin prevented methylmercury-induced DNA damage,[49] while luteolin prevented mercury and thimerosal-induced inflammatory mediator release from immune cells.[50] Luteolin was recently shown to inhibit microglial activation while also being neuroprotective.[51-57]

In fact, a luteolin analogue was shown to mimic the activity of brain-derived neurotrophic factor (BDNF).[58,59] A recent report also indicated that olive leaf extract can prevent blood-brain barrier disruption.[60] Disruption of the blood-brain barrier has been proposed as a key pathogenetic factor in ASD.[13,61] Formulations containing luteolin in olive kernel extract (OKE) are, therefore, likely not only to permit higher absorption of luteolin in the brain but also provide the additional benefit of OKE itself.

OVERVIEW OF TREATMENT INTERACTIONS IN ASD

In Table 1 we summarize the adverse effects and interactions most likely to arise with treatment regimens commonly used in children with ASD. We consider supplements and vitamins as well as a wide range of prescription medications (including antibiotics, antifungals, antivirals, anticonvulsants, antipsychotics, and SSRIs). As the table shows, careful consideration and caution are warranted to select treatment strategies that will be beneficial while minimizing the likelihood of adverse effects.

Although comprehensive, the information in Table 1 is not designed to be all-inclusive. More detailed information on interactions in general can be found elsewhere.[42,62] Moreover, there are patients who may still have idiosyncratic reactions. Such reactions typically involve activation of a unique immune cell, the mast cell, found in all tissues and responsible for allergic and inflammatory reactions.[63] The likelihood of idiosyncratic reactions would, therefore, be increased in the subgroup of ASD patients who appear to have "allergic-like symptoms"[64] that involve mast cell activation by non-allergic triggers.[65]

CONCLUSION

Given the high percentage of children with ASD being treated with multiple pharmacologic and non-pharmacologic interventions, attention to interactions is a vital but often overlooked aspect of clinical supervision. As this brief article shows, a wide variety of interactions are possible.

Some authors even hypothesize that the increased rate of ASD may be at least partly due to acetaminophen's ability to decrease glutathione levels.

REFERENCES

1. Fombonne E. Epidemiology of pervasive developmental disorders. *Pediatr Res.* 2009 Jun;65(6):591-8.

2. Johnson CP, Myers SM. Identification and evaluation of children with autism spectrum disorders. *Pediatrics.* 2007 Nov;120(5):1183-215.

3. Kogan MD, Blumberg SJ, Schieve LA, Boyle CA, Perrin JM, Ghandour RM et al. Prevale nce of parent-reported diagnosis of autism spectrum disorder among children in the US, 2007. *Pediatrics.* 2009 Nov;124(5):1395-403.

4. Rapin I, Tuchman RF. What is new in autism? *Curr Opin Neurol.* 2008 Apr;21(2):143-9.

5. Campello S, Scorrano L. Mitochondrial shape changes: orchestrating cell pathophysiology. *EMBO Rep.* 2010 Sep;11(9):678-84.

6. Francis K. Autism interventions: a critical update. *Dev Med Child Neurol.* 2005 Jul;47(7):493-9.

7. Hughes JR. A review of recent reports on autism: 1000 studies published in 2007. *Epilepsy Behav.* 2008 Oct;13(3):425-37.

8. Trevathan E. Seizures and epilepsy among children with language regression and autistic spectrum disorders. *J Child Neurol.* 2004 Aug;19(Suppl 1):S49-S57.

9. Tuchman R, Rapin I. Epilepsy in autism. *Lancet Neurol.* 2002 Oct;1(6):352-8.

10. Frye RE, Sreenivasula S, Adams JB. Traditional and non-traditional treatments for autism spectrum disorder with seizures: an on-line survey. *BMC Pediatr.* 2011 May;11:37.

11. Adams JB. Summary of biomedical treatments for autism. Autism Research Institute, ARI Publication 40, April 2007.

12. Bradstreet JJ, Smith S, Baral M, Rossignol DA. Biomarker-guided interventions of clinically relevant conditions associated with autism spectrum disorders and attention deficit hyperactivity disorder. *Altern Med Rev.* 2010 Apr;15(1):15-32.

13. Theoharides TC, Doyle R, Francis K, Conti P, Kalogeromitros D. Novel therapeutic targets for autism. *Trends Pharmacol Sci.* 2008 Aug;29(8):375-82.

14. Feasby T, Banwell B, Benstead T, Bril V, Brouwers M, Freedman M et al. Guidelines on the use of intravenous immune globulin for neurologic conditions. *Transfus Med Rev.* 2007 Apr;21(2 Suppl 1):S57-S107.

15. Gupta S. Antibodies: basic mechanisms and emerging concepts. *J Clin Immunol.* 2010 May;30(Suppl 1):S1-S3.

16. Cunningham-Rundles C. Key aspects for successful immunoglobulin therapy of primary immunodeficiencies. *Clin Exp Immunol.* 2011 Jun;164(Suppl 2):16-9.

17. Leone R, Magro L, Moretti U, Cutroneo P, Moschini M, Motola D, Tuccori M, Conforti A. Identifying adverse drug reactions associated with drug-drug interactions: data mining of a spontaneous reporting database in Italy. *Drug Saf.* 2010 Aug 1;33(8):667-75.

18. Zhang ZJ, Tan QR, Tong Y, Wang XY, Wang HH, Ho LM, Wong HK, Feng YB, Wang D, Ng R, McAlonan GM, Wang CY, Wong VT. An epidemiological study of concomitant use of Chinese medicine and antipsychotics in schizophrenic patients: implication for herb-drug interaction. *PLoS One.* 2011 Feb;6(2):e17239.

19. Deurell M, Weischer M, Pagsberg AK, Labianca J. The use of antipsychotic medication in child and adolescent psychiatric treatment in Denmark. A cross-sectional survey. *Nord J Psychiatry.* 2008;62(6):472-80.

20. Posey DJ, Stigler KA, Erickson CA, McDougle CJ. Antipsychotics in the treatment of autism. *J Clin Invest.* 2008 Jan;118(1):6-14.

21. Gerhard T, Chavez B, Olfson M, Crystal S. National patterns in the outpatient pharmacological management of children and adolescents with autism spectrum disorder. *J Clin Psychopharmacol.* 2009 Jun;29(3):307-10.

22. McDougle CJ, Holmes JP, Carlson DC, Pelton GH, Cohen DJ, Price LH. A double-blind, placebo-controlled study of risperidone in adults with autistic disorder and other pervasive developmental disorders. *Arch Gen Psychiatry.* 1998 Jul;55(7):633-41.

23. Chavez B, Chavez-Brown M, Sopko MA Jr, Rey JA. Atypical antipsychotics in children with pervasive developmental disorders. *Paediatr Drugs.* 2007;9(4):249-66.

24. McDougle CJ, Stigler KA, Erickson CA, Posey DJ. Atypical antipsychotics in children and adolescents with autistic and other pervasive developmental disorders. *J Clin Psychiatry.* 2008;69(Suppl 4):15-20.

25. Parikh MS, Kolevzon A, Hollander E. Psychopharmacology of aggression in children and adolescents with autism: a critical review of efficacy and tolerability. *J Child Adolesc Psychopharmacol.* 2008 Apr;18(2):157-78.

26. McCracken JT, McGough J, Shah B, Cronin P, Hong D, Aman MG et al. Risperidone in children with autism and serious behavioral problems. *N Engl J Med.* 2002 Aug;347(5):314-21.

27. Scott LJ, Dhillon S. Risperidone: a review of its use in the treatment of irritability associated with autistic disorder in children and adolescents. *Paediatr Drugs.* 2007;9(5):343-54.

28. Research Units on Pediatric Psychopharmacology Autism Network. Randomized, controlled, crossover trial of methylphenidate in pervasive developmental disorders with hyperactivity. *Arch Gen Psychiatry.* 2005 Nov;62(11):1266-74.

29. Rosenberg RE, Mandell DS, Farmer JE, Law JK, Marvin AR, Law PA. Psychotropic medication use among children with autism spectrum disorders enrolled in a national registry, 2007-2008. *J Autism Dev Disord.* 2010 Mar;40(3):342-51.

30. Williams K, Wheeler DM, Silove N, Hazell P. Selective serotonin reuptake inhibitors (SSRIs) for autism spectrum disorders (ASD). *Cochrane Database Syst Rev.* 2010 Aug 4;8:CD004677.

31. McPheeters ML, Warren Z, Sathe N, Bruzek JL, Krishnaswami S, Jerome RN, Veenstra-Vanderweele J. A systematic review of medical treatments for children with autism spectrum disorders. *Pediatrics.* 2011 May;127(5):e1312-e1321.

32. King BH, Hollander E, Sikich L, McCracken JT, Scahill L, Bregman JD et al. Lack of efficacy of citalopram in children with autism spectrum disorders and high levels of repetitive behavior: citalopram ineffective in children with autism. *Arch Gen Psychiatry.* 2009 Jun;66(6):583-90.

33. Warner-Schmidt JL, Vanover KE, Chen EY, Marshall JJ, Greengard P. Antidepressant effects of selective serotonin reuptake inhibitors (SSRIs) are attenuated by antiinflammatory drugs in mice and humans. *Proc Natl Acad Sci USA.* 2011 May 31;108(22):9262-7.

34. Theoharides TC, Asadi S, Weng Z, Zhang B. Serotonin-selective reuptake inhibitors and nonsteroidal anti-inflammatory drugs-important considerations of adverse interactions especially for the treatment of myalgic encephalomyelitis/chronic fatigue syndrome. *J Clin Psychopharmacol.* 2011 Aug;31(4):403-5.

35. Alberti A, Pirrone P, Elia M, Waring RH, Romano C. Sulphation deficit in "low-functioning" autistic children: a pilot study. *Biol Psychiatry.* 1999 Aug1;46(3):420-4.

36. Becker KG, Schultz ST. Similarities in features of autism and asthma and a possible link to acetaminophen use. *Med Hypotheses.* 2010 Jan;74(1):7-11.

37. Middleton E, Jr., Kandaswami C, Theoharides TC. The effects of plant flavonoids on mammalian cells: implications for inflammation, heart disease and cancer. *Pharmacol Rev.* 2000 Dec;52(4):673-751.

38. Erlund I, Kosonen T, Alfthan G, Maenpaa J, Perttunen K, Kenraali J et al. Pharmacokinetics of quercetin from quercetin aglycone and rutin in healthy volunteers. *Eur.J Clin Pharmacol.* 2000 Nov;56(8):545-53.

39. Manach C, Donovan JL. Pharmacokinetics and metabolism of dietary flavonoids in humans. *Free Radic Res.* 2004 Aug;38(8):771-85.

40. Walle T. Absorption and metabolism of flavonoids. *Free Radic Biol Med.* 2004 Apr 1;36(7):829-37.

41. Mazzanti G, Menniti-Ippolito F, Moro PA, Cassetti F, Raschetti R, Santuccio C et al. Hepatotoxicity from green tea: a review of the literature and two unpublished cases. *Eur J Clin Pharmacol.* 2009 Apr;65(4):331-41.

42. Hanley MJ, Cancalon P, Widmer WW, Greenblatt DJ. The effect of grapefruit juice on drug disposition. *Expert Opin Drug Metab Toxicol.* 2011 Mar;7(3):267-86.

43. Formica JV, Regelson W. Review of the biology of quercetin and related bioflavonoids. *Food Chem Toxicol.* 1995 Dec;33(12):1061-80.

44. Li L, Gu L, Chen Z, Wang R, Ye J, Jiang H. Toxicity study of ethanolic extract of Chrysanthemum morifolium in rats. *J Food Sci.* 2010 Aug 1;75(6):T105-T109.

45. Domitrovic R, Jakovac H, Milin C, Radosevic-Stasic B. Dose- and time-dependent effects of luteolin on carbon tetrachloride-induced hepatotoxicity in mice. *Exp Toxicol Pathol.* 2009 Nov;61(6):581-9.

46. Janbaz KH, Saeed SA, Gilani AH. Protective effect of rutin on paracetamol- and CCl4-induced hepatotoxicity in rodents. *Fitoterapia.* 2002 Dec;73(7-8):557-63.

47. Yousef MI, Omar SA, El-Guendi MI, Abdelmegid LA. Potential protective effects of quercetin and curcumin on paracetamol-induced histological changes, oxidative stress, impaired liver and kidney functions and haematotoxicity in rat. *Food Chem Toxicol.* 2010 Nov;48(11):3246-61.

48. Naidu PS, Singh A, Kulkarni SK. Quercetin, a bioflavonoid, attenuates haloperidol-induced orofacial dyskinesia. *Neuropharmacology.* 2003 Jun;44(8):1100-6.

49. Barcelos GR, Grotto D, Serpeloni JM, Angeli JP, Rocha BA, de Oliveira Souza VC et al. Protective properties of quercetin against DNA damage and oxidative stress induced by methylmercury in rats. *Arch Toxicol.* 2011 Sep;85(9):1151-7.

50. Asadi S, Zhang B, Weng Z, Angelidou A, Kempuraj D, Alysandratos KD, Theoharides TC. Luteolin and thiosalicylate inhibit mercury and thimerosal-induced VEGF release from human mast cells. *Int J Immunopathol Pharmacol.* 2010 Oct-Dec;23(4):1015-20.

51. Chen HQ, Jin ZY, Wang XJ, Xu XM, Deng L, Zhao JW. Luteolin protects dopaminergic neurons from inflammation-induced injury through inhibition of microglial activation. *Neurosci Lett.* 2008 Dec 26;448(2):175-9.

52. Dirscherl K, Karlstetter M, Ebert S, Kraus D, Hlawatsch J, Walczak Y et al. Luteolin triggers global changes in the microglial transcriptome leading to a unique anti-inflammatory and neuroprotective phenotype. *J Neuroinflammation.* 2010 Jan 14;7:3.

53. Jang S, Dilger RN, Johnson RW. Luteolin inhibits microglia and alters hippocampal-dependent spatial working memory in aged mice. *J Nutr.* 2010 Oct;140(10):1892-8.

54. Jang S, Kelley KW, Johnson RW. Luteolin reduces IL-6 production in microglia by inhibiting JNK phosphorylation and activation of AP-1. *Proc Natl Acad Sci USA.* 2008 May 27;105(21):7534-9.

55. Kao TK, Ou YC, Lin SY, Pan HC, Song PJ, Raung SL et al. Luteolin inhibits cytokine expression in endotoxin/cytokine-stimulated microglia. *J Nutr Biochem.* 2011 Jul;22(7):612-24.

56. Kempuraj D, Tagen M, Iliopoulou BP, Clemons A, Vasiadi M, Boucher W et al. Luteolin inhibits myelin basic protein-induced human mast cell activation and mast cell dependent stimulation of Jurkat T cells. *Br J Pharmacol.* 2008 Dec;155(7):1076-84.

57. Verbeek R, Plomp AC, van Tol EA, van Noort JM. The flavones luteolin and apigenin inhibit in vitro antigen-specific proliferation and interferon-gamma production by murine and human autoimmune T cells. *Biochem Pharmacol.* 2004 Aug 15;68(4):621-9.

58. Coleta M, Campos MG, Cotrim MD, Lima TC, Cunha AC. Assessment of luteolin (3,4,5,7-tetrahydroxyflavone) neuropharmacological activity. *Behav Brain Res.* 2008 May 16;189(1):75-82.

59. Jang SW, Liu X, Yepes M, Shepherd KR, Miller GW, Liu Y et al. A selective TrkB agonist with potent neurotrophic activities by 7,8-dihydroxyflavone. *Proc Natl Acad Sci USA.* 2010 Feb 9;107(6):2687-92.

60. Mohagheghi F, Bigdeli MR, Rasoulian B, Hashemi P, Pour MR. The neuroprotective effect of olive leaf extract is related to improved blood-brain barrier permeability and brain edema in rat with experimental focal cerebral ischemia. *Phytomedicine.* 2011 Jan 15;18(2-3):170-5.

61. Theoharides TC, Asadi S. Neurotensin and extracellular mitochondrial DNA: potential biomarkers and novel treatment targets. *Autism Science Digest.* 2011 Apr;1:36-41.

62. Theoharides TC. Essentials of pharmacology. In TC Theoharides (Ed.), *Essentials of Pharmacology.* Boston, MA: Little, Brown & Co, 1986.

63. Theoharides TC, Alysandratos KD, Angelidou A, Delivanis DA, Sismanopoulos N, Zhang B et al. Mast cells and inflammation. *Biochim Biophys Acta.* 2010 Dec 23.

64. Angelidou A, Alysandratos KD, Asadi S, Zhang B, Francis K, Vasiadi M et al. Brief report: "Allergic symptoms" in children with autism spectrum disorders. More than meets the eye? *J Autism Dev Disord.* 2011 Jan 6.

65. Theoharides TC, Angelidou A, Alysandratos KD, Zhang B, Asadi S, Francis K et al. Mast cell activation and autism. *Biochim Biophys Acta.* 2011 Dec 28.