CHK MEDICAL FOODS

The Basis for Neurotransmitter Transporter Optimization In ADHD Patients

A long-time dream whose time has come

ADHD TREATMENT

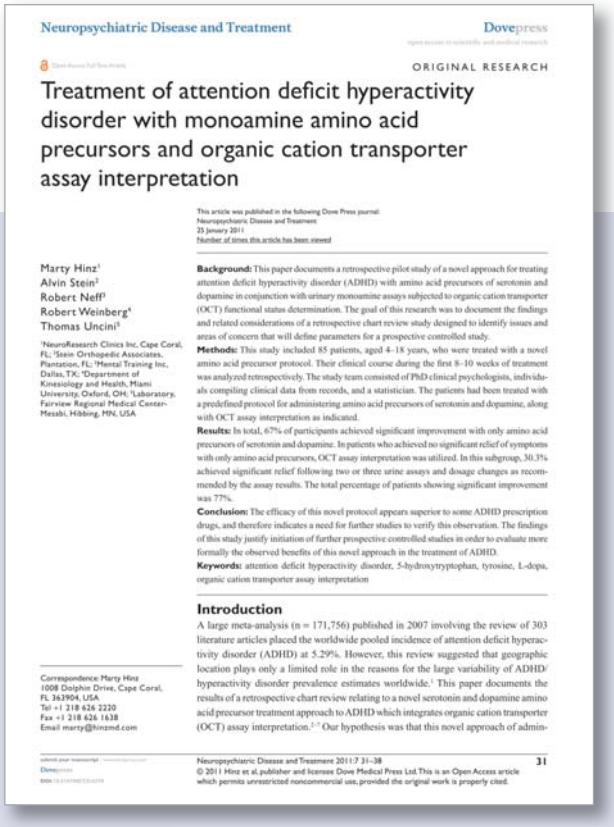
- **BETTER THAN DRUGS**
- **WITHOUT DRUG OR DRUG SIDE EFFECTS**

Medical foods for the dietary management of disease for which nutrient intake cannot be achieved by the modification of normal diet alone.

- **DEVELOPED BY MDs IN THEIR PRIVATE CLINICS**
- **NOW PUBLISHED IN PEER-REIVEWED SCIENCE**

ADHD is a neurotransmitter deficiency disease, not a drug deficiency disease. The only way to increase the total number of neurotransmitter molecules in the brain is with administration of properly balanced nutrients.

BASED ON PEER-REVIEWED SCIENCE



Neuropsychiatric Disease and Treatment — Dovepress

ORIGINAL RESEARCH

Treatment of attention deficit hyperactivity disorder with monoamine amino acid precursors and organic cation transporter assay interpretation

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Background: This paper documents a retrospective pilot study of a novel approach for treating attention deficit hyperactivity disorder (ADHD) with amino acid precursors of serotonin and dopamine in conjunction with urinary monoamine assays subjected to organic cation transporter (OCT) functional status determination. The goal of this research was to document the findings and related considerations of a retrospective chart review study designed to identify issues and areas of concern that will define parameters for a prospective controlled study.

Methods: This study included 85 patients, aged 4–18 years, who were treated with a novel amino acid precursor protocol. Their clinical course during the first 8–10 weeks of treatment was analyzed retrospectively. The study team consisted of PhD clinical psychologists, individuals compiling clinical data from records, and a statistician. The patients had been treated with a predefined protocol for administering amino acid precursors of serotonin and dopamine, along with OCT assay interpretation as indicated.

Results: In total, 67% of participants achieved significant improvement with only amino acid precursors of serotonin and dopamine. In patients who achieved no significant relief of symptoms with only amino acid precursors, OCT assay interpretation was utilized. In this subgroup, 30.3% achieved significant relief following two or three urine assays and dosage changes as recommended by the assay results. The total percentage of patients showing significant improvement was 77%.

Conclusion: The efficacy of this novel protocol appears superior to some ADHD prescription drugs, and therefore indicates a need for further studies to verify this observation. The findings of this study justify initiation of further prospective controlled studies in order to evaluate more formally the observed benefits of this novel approach in the treatment of ADHD.

Keywords: attention deficit hyperactivity disorder, 5-hydroxytryptophan, tyrosine, L-dopa, organic cation transporter assay interpretation

Introduction

A large meta-analysis (n = 171,756) published in 2007 involving the review of 303 literature articles placed the worldwide pooled incidence of attention deficit hyperactivity disorder (ADHD) at 5.29%. However, this review suggested that geographic location plays only a limited role in the reasons for the large variability of ADHD/hyperactivity disorder prevalence estimates worldwide.[1] This paper documents the results of a retrospective chart review relating to a novel serotonin and dopamine amino acid precursor treatment approach to ADHD which integrates organic cation transporter (OCT) assay interpretation.[2,3] Our hypothesis was that this novel approach of admin-

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Treating the real problem

"Transporters are the primary determinants of intracellular and extracellular neurotransmitter levels. Transport of the monoamines serotonin, dopamine, norepinephrine, and epinephrine needs to be in proper balance for symptoms to resolve. Drugs do nothing to increase the total number of neurotransmitter molecules in the brain. They inhibit transport leading to conditions that deplete neurotransmitters." (Hinz et al 2011a)

The first

CHK Medical Foods are based on the first peer-reviewed scientific study published on the use of monoamine amino acid precursors guided by transporter optimization in the treatment of ADHD. This study demonstrated effectiveness that is superior to the two leading ADHD prescription drugs with no drug side effects.

"Based on the FDA guidelines, the amino acid precursors of serotonin and dopamine, used in this study, are classified as 'generally recognized as safe' (GRAS), meaning no significant safety concerns exist regarding their use. The next question to ponder is whether the approach is effective. The FDA has not set the bar very high in demonstrating efficacy of prescription drugs. There are numerous examples of drugs being approved that are only 7%–13% more effective than placebo." (Hinz et al 2011a)

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Medical Foods

CHK NUTRITION

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SAFETY of ADHD Treatment

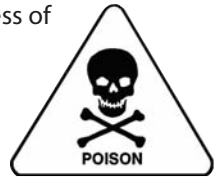
SIDE EFFECTS ASSOCIATED WITH ADHD DRUGS

Side effects and adverse reactions associated with ADHD prescription medications are significant, serious, and potentially life threatening. The following is a limited list of these events associated with the ADHD group of drugs as a whole, which includes, but is not limited to:

- Black boxes warning of increased risk of suicidal ideation.
- Severe liver injury.
- Sudden death in cases with pre-existing structural cardiac abnormalities or other serious heart problems.
- At risk for stroke and myocardial infarction.
- May exacerbate symptoms of behavior disturbance and thought disorder in patients with a pre-existing psychotic disorder.
- Induction of mixed/manic episodes.
- Treatment by stimulants at usual doses can cause emergent psychotic or manic symptoms, e.g., hallucinations, delusional thinking, or mania in children and adolescents without prior history of psychotic illness or mania.
- Amphetamines may impair the ability of the patient to engage in potentially hazardous activities such as operating machinery or vehicles.
- Higher incidence of infection, photosensitivity reaction, constipation, tooth disorders, emotional liability, decreased libido, somnolence, speech disorder, palpitation, twitching, dyspnea, sweating, dysmenorrhea, and impotence.
- Integument disorders include, but are not limited to, urticaria, rash, and hypersensitivity reactions including angioedema and anaphylaxis. Serious skin rashes, including Stevens Johnson Syndrome and toxic epidermal necrolysis.
- Lowering of seizure threshold.
- Increased aggression and hostility.
- Contraindicated in patients with marked anxiety, tension, and agitation, since the drugs may aggravate these symptoms.
- Risk of drug dependence.
- Development of leukopenia and/or anemia. (Hinz et al 2010a)

The central serotonin and catecholamine systems are completely intertwined in a manner similar to the sympathetic and parasympathetic nervous systems. In the competitive inhibition state it is impossible to effect change to one system without affecting the other system.

The Drugs Can Do More Harm Than Good



"Previous writings suggest that the process of reuptake inhibition may deplete neurotransmitters throughout the body." (Hinz et al 2011a)

"The administration of amphetamine stimulants creates another potential area of concern relating to neurotoxicity." (Hinz et al 2011a)

PEER-REVIEWED LITERATURE indicates that:

- 60% to 80% of children taking Ritalin™ receive relief of symptoms no greater than a sugar pill.
- 60% to 85% of children taking Strattera™ receive relief of symptoms not greater than a sugar pill.

100% of these children are exposed to drug side effects.

Virtually all drugs used to treat ADHD can deplete the neurotransmitters. In addition, stimulant drugs are known to be neurotoxic (can cause permanent brain damage).

From Peer-reviewed Literature:

"The drugs prescribed for ADHD have potentially controversial concerns associated with them, including neurotransmitter depletion, neurotoxicity, drug side effects, and adverse reactions; this amino acid approach in comparison has none of these concerns associated with it. This gives a significant advantage to this amino acid approach if studies continue to bear out that it is similar or superior to prescription ADHD drugs in its efficacy." (Hinz et al 2011a)

AMINO ACID SAFETY

"There are no safety concerns with the amino acids used in this treatment approach. The FDA classifies them as "generally regarded as safe" (GRAS). All of the amino acids and components used in this treatment approach are sold in the US over the counter without a prescription." (Hinz et al 2011a)

Properly Balanced Transporters That Lead to Success

"Under the approach optimal results are dependent upon achieving a proper balance between the administered serotonin and dopamine precursors.

The administration of properly balanced amino acid precursors of serotonin and dopamine with OCT assay interpretation resulted in improvement that appears to be superior to methylphenidate and atomoxetine." (Hinz et al 2011a)

An ADHD medical foods dream whose time has come

Natural treatment that is more effective than drugs
Transporter optimization with the side effect profile of nutrients

"It is a generally accepted premise that a primary factor in development of ADHD is the status of the monoamine system to include serotonin, dopamine, norepinephrine, and epinephrine." (Hinz et al 2011a)

"ADHD drugs do not increase the total number of monoamine neurotransmitter molecules in the central nervous system. Their primary mechanism of action is thought to be reuptake inhibition which sets up conditions that move neurotransmitters from one place to another." (Hinz et al 2011a)

"This medical foods method of treating ADHD involves the use of monoamine amino acid precursors that do what drugs are unable to do. This novel approach has the ability to increase the total number of neurotransmitter molecules in the central nervous system with nutrients, leading to efficacy observations that appear greater than those of prescription drugs without the potential for neurotransmitter depletion, neurotoxicity issues, and severe potentially life-threatening drug side effects associated with prescription drugs." (Hinz et al 2011a)

The real cause of ADHD is serotonin and dopamine levels that are not high enough, i.e., there are not enough neurotransmitter molecules in the system. Drugs do nothing to increase the total number of neurotransmitter molecules. Drugs work by moving neurotransmitters from one place to another and in the process set up conditions that deplete neurotransmitters. The only way to increase the total number of neurotransmitter molecules in the brain is with administration of properly balanced amino acids.

DEPLETION

EFFECTIVENESS

PEER-REVIEWED ADHD TREATMENT (Hinz et al 2011a)

"Amino Acid Transporter Optimization" versus Methylphenidate (Ritalin®)

Percent of patients with significant improvement				
	Amino Acid Transporter Optimization	Methylphenidate (Ritalin®) double-blind studies		
		STUDY 1	STUDY 2	STUDY 3
N	85	154	97	18
Improved	77%	64%	52%	58%

Transporter optimization versus number one selling ADHD stimulant drug

"Amino Acid Transporter Optimization" versus Atomoxetine (Strattera®)

Percent of patients with significant improvement				
	Amino Acid Transporter Optimization	Atomoxetine (Strattera®) double-blind studies		
		STUDY 1	STUDY 2	STUDY 3
N	85	618	36	84
Improved	77%	71%	54%	59%

Transporter optimization versus number one selling ADHD reuptake inhibitor drug

"It would appear that the placebo effect is strong in ADHD studies, because 28%–40% of placebo patients achieved significant relief of symptoms in the atomoxetine studies reviewed, and 14%–31% had a placebo benefit in the methylphenidate study." (Hinz et al 2011a)

ADHD Medical Food Protocol

It takes 3 to 5 days for amino acids and neurotransmitters to equilibrate after a dosing change.

Pediatric Protocol
<17 yrs old

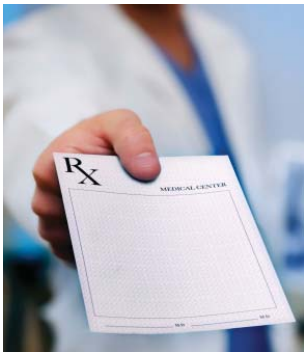
Week 1: Start 2 NeuroReplete twice a day (AM and 4 PM) with CysReplete 1 pill 3 times a day (noon, 4 PM, and bedtime).

Week 2: In one week, if symptoms persist, submit a urine sample to DBS Labs for "organic cation transporter functional status determination" (OCT assay). Then follow recommended changes when they are received.

Adult Protocol
>16 yrs old

Week 1: Start 4 NeuroReplete twice a day (AM and 4 PM) with CysReplete 2 pills 3 times a day (noon, 4 PM, and bedtime).

Week 2: In one week, if symptoms persist, submit a urine sample to DBS Labs for organic cation transporter functional status determination (OCT assay). Then follow recommended changes when they are received.



SUGGESTED TREATMENT:

- See patients weekly until stable.
- While many patients stabilize in one to six weeks, ensure all patients are able to participate in weekly visits for 2 to 4 months if needed at the start of treatment.
- Continue all drugs the patient is taking at the start of treatment.
- If a drug side effect develops, treat it as a drug side effect and do not decrease or stop the amino acids.
- Read pages 6 and 7 of the brochure for management of treatment problems.
- If the child has problems swallowing a capsule, twist it open and put the powder in juice or other water-soluble liquid.

NOT MERELY GOING TO THE HEALTH FOOD STORE

It is no secret that this documented scientific approach uses the nutrients 5-HTP, tyrosine, levodopa, and cysteine for treatment of ADHD patients. Proper use of these ingredients in medical treatment is not simple. Occasionally a patient will say, "Why do I want to take that, I can go to a health food store and buy it?" Attempting to achieve success by buying nutrients in a health food store is like going to an art store and buying a bunch of oil paints then going home and expecting to paint a masterpiece seen in an art gallery without any previous painting experience. These nutrients have tremendous potential due to their chemical properties. This potential is only fully realized in the hands of the trained professional using transporter optimization testing. It is not just giving a nutrient pill. It is the whole treatment approach trained physicians use to ensure that that treatment is on track to get symptoms under control.

MEDICAL FOODS STATEMENT: 1) These medical foods are specially formulated and processed products for partial feeding of the patient by means of oral intake. 2) These medical foods are intended for the dietary management of a patient who has other special medically determined nutrient requirements needing increased levels of monoamine neurotransmitters, the dietary management of which cannot be achieved by the modification of normal diet alone. 3) These medical foods are intended to be used under active and ongoing medical supervision wherein the patient requires medical care on a recurring basis for, among other things, instructions on the use of the medical food. 4) These medical foods provides nutritional support specifically modified for the management of the unique (distinctive) nutrient needs that result from the specific disease or condition, as determined by medical evaluation.

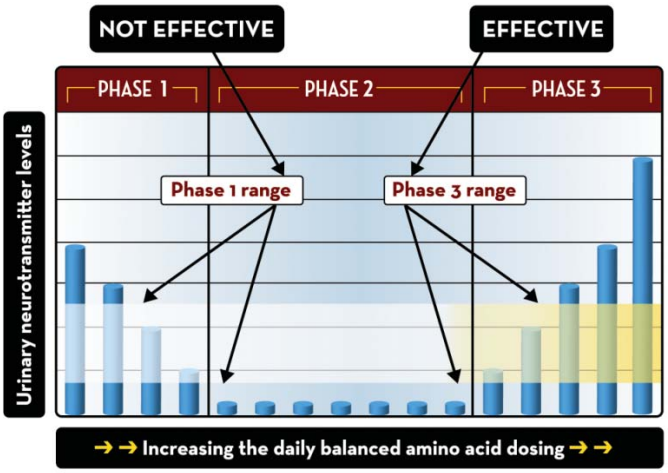
ORGANIC CATION TRANSPORTER ASSAY INTERPRETATION

(Continued on page 8)

DBS Labs
8723 Falcon Street
Duluth, MN 55808
877-476-7229
www.DBSlabs.com

The source of urinary monoamine neurotransmitters

"The serotonin and dopamine filtered at the glomerulous are metabolized by the kidneys, and significant amounts do not make it to the final urine. Serotonin and dopamine found in the urine are monoamines synthesized in the proximal convoluted renal tubule cells and have never been found in the central nervous system or peripheral system. Serotonin and dopamine that are newly synthesized by the kidneys meet one of two fates. Urinary serotonin and dopamine levels are primarily dependent on the interaction of the basolateral monoamine transporters (OCT2s) and the apical monoamine transporters (OCTN2s) of the proximal convoluted renal tubule cells of the kidneys. The OCTN2s of the proximal convoluted renal tubule cells transport serotonin and dopamine that is not transported by the OCT2. While in the competitive inhibition state, serotonin and dopamine not transported by the OCT2s are found in the final urine as waste. Although there are numerous other forces that interact with the newly synthesized renal monoamines, they are small compared with the effects of these transporters. Proper interpretation of urinary serotonin and dopamine levels in the competitive inhibition state determines the functional status of the OCT2s of the proximal convoluted renal tubule cells of the kidneys, known as OCT assay interpretation. The OCT2s exist in three different phases dependent on the status of the entrance gate and lumen saturation." (Hinz et al 2011)



ORGANIC CATION TRANSPORTER RESPONSE

The goal of this approach is to achieve the:

- urinary serotonin in the phase 3 therapeutic range of 80 to 240 µg serotonin/g of creatinine
- urinary dopamine in the phase 3 therapeutic range of 475 to 1,100 µg dopamine/g of creatinine (Hinz et al 2011)

The 3 phase response of the organic cation transporters

Serotonin and dopamine exist in two states. "The endogenous state" is found when no amino acid precursors are being administered. "The competitive inhibition state" is found when significant amounts of amino acid precursors of both serotonin and dopamine are administered simultaneously.

"The basis for OCT assay interpretation requires that the entire system be placed into the competitive inhibition state and then two or more urinary serotonin and dopamine assays performed while taking serotonin and dopamine amino acid precursors at significantly varied dosing values. The results are then compared in order to determine the change in urinary serotonin and dopamine levels in response to the change in amino acid precursor dosing values. Urinary serotonin and dopamine values found on assay were reported in micrograms of monoamine per gram of creatinine in order to compensate for fluctuations in urinary specific gravity. A urinary serotonin or dopamine value less than 80 or 475 µg of monoamine per 1 g of creatinine, respectively, is defined as a Phase 2 response. A urinary serotonin or dopamine value greater than 80 or 475 µg of monoamine per 1 g of creatinine, respectively, is interpreted as being in Phase 1 or Phase 3. Differentiation of Phase 1 from Phase 3 is a follows. If a direct relationship is found between amino acid dosing and urinary assay response, it is referred to as a Phase 3 response. An inverse relationship is referred to as a Phase 1 response. The Phase 3 therapeutic range for urinary serotonin is defined as 80–240 µg of serotonin per g of creatinine. The Phase 3 therapeutic range for urinary dopamine is defined as 475–1100 µg of dopamine per g of creatinine." (Hinz et al 2011)

RESPONSE is like a light switch

Some patients get relief of symptoms in one week while others may not get relief of symptoms until 2 or 3 months into treatment. Along the way most patients do not get better gradually with each amino acid dosing value adjustment. For most the response to amino acids is like a light switch, "on or off", with no relief of symptoms occurring until the proper amino acid dosing value is found secondary to several urinary transporter assays being performed.

PROPER MANAGEMENT OF AMINO ACIDS

PATIENT ORIENTATION:

At the first visit all patients need to be instructed as follows: **"If there are any problems in the first week of treatment, stop the amino acids until you get back to clinic and I will tell you what to do."** Failure to properly orient patients at the first visit will result in patients dropping out of care if problems are experienced in the first week of treatment.

GI UPSET → ON START UP

THE PROBLEM: Approximately 1% to 2% of patients (higher in some medical practices where patients have been exposed at a higher rate to drugs that deplete neurotransmitters) experience GI upset or nausea on starting the amino acids. Typically, this starts with the first dose and builds with every dose until the third day, at which point the patient can no longer tolerate the symptoms.

THE CAUSE: The patients who are most depleted of neurotransmitters experience GI upset or nausea on starting the amino acids. *These are the very patients who need the amino acids the most*.

MANAGEMENT: Restart the NeuroReplete taking only one pill at bedtime. Bedtime is when the patient is ready to get in bed and go to sleep, not when the patient gets in bed and reads a book for an hour. If the patient can fall asleep within 20 minutes after taking the one pill of NeuroReplete there should be no problems with GI upset. After 3 or 4 nights with no GI problems increase the NeuroReplete to 2 pills at bedtime. When the patient is able to take 2 pills at bedtime with no problems, start 1 pill in the AM then increase to two pills after 3 or 4 days of no problems. In adults, when the patient is taking 2 pills of NeuroReplete twice a day, submit a urine sample for transporter evaluation.

GI UPSET → CARBOHYDRATE INTOLERANCE

THE PROBLEM: Once the proper dosing values of the amino acids have been established, patients may experience transient nausea lasting 45 to 60 minutes periodically during the day. The etiology of this problem is distinctly different than "GI upset on start up" discussed above.

THE CAUSE: With optimization of neurotransmitter transporters, the way the body reacts to specific carbohydrates may change causing nausea.

MANAGEMENT: Usually only one food needs to be changed. Most of the time, it is a bread, cereal, or noodle that needs to be changed. Examples of effective management include 1) Changing from white to whole wheat bread. 2) Changing from one type of noodle to another. 3) Changing from one cereal to another, for example changing from Wheaties to Shredded Wheat. At times identification of the food can be difficult, one case of carbohydrate intolerance was tracked down to the breading on chicken eaten with most lunches.

HEARTBURN (PYROSIS)

THE PROBLEM: Intense substernal or epigastric burning or nausea after taking the pills.

THE CAUSE: When the veggie caps are simply gulped down with some water the surface does not liquefy properly causing the pills to stick in the esophagus and dissolve, at which time an intense substernal and/or epigastric burning is experienced.

MANAGEMENT: Hold the pills in the mouth with water for 10 to 15 seconds before swallowing so that the capsule surface starts to liquefy and slides down easily.

PRESCRIPTION DRUG SIDE EFFECTS

THE PROBLEM: The recommendation is to leave all drugs in place when starting the amino acids. Side effects not associated with the amino acids may occur in 3% to 5% of patients while starting or changing the amino acid dosing.

THE CAUSE: Drugs that work with neurotransmitters not only become more effective as neurotransmitter levels increase with amino acid administration; the side effects of these drugs may display as well.

MANAGEMENT: Proper management is to treat the event like a drug side effect. DO NOT stop the amino acids. Tapering or stopping the drug causing the side effect is proper management.

Amino acid only side effect profile

Dry mouth	2.1%
Insomnia	0.9%
Headache	0.7%
Nausea	0.6%
Dizziness	0.4%
Constipation	0.4%

All other side effects occur at a rate less than 1 in 500 visits

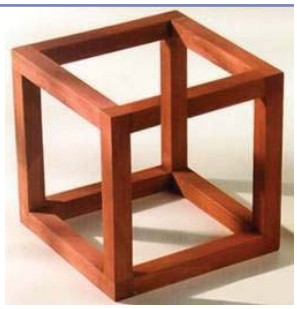
WHEN AMINO ACIDS STOP WORKING

THE PROBLEM: The patient's symptoms are under control, then it appears that the pills stopped working and symptoms of disease return.

THE CAUSE: Missing one or more doses of amino acids can cause symptoms of disease to return. It then may take three to five days for symptoms to get back under control once the pills are taken correctly. If the patient misses one pill dosing every three to four days multiple times, it may appear that the amino acids have quit working.

MANAGEMENT: In 99% of patients for whom the pills stop working it is a compliance issue relating to taking the pills properly. Have the patient journal (write down) all pills taken for 7 to 10 days. After journaling if the patient's symptoms are not under control, submit a urine sample for transporter assay. Only 1% of patients experience a change in dosing needs during treatment and retesting can manage this problem.

PARADOXICAL REACTIONS



THE PROBLEM: A specific amino acid dosing value is started or changed and the patient complains of an exacerbation of symptoms related to one or more monoamine neurotransmitter related diseases (see page 8). For example, depression may get worse, sleep may get worse, the patient may get more agitated, anxiety may get worse, migraines may get worse, etc.

THE CAUSE: The exact cause of paradoxical reactions is unknown, but it is known that there is a dosing range within which they do occur.

MANAGEMENT: When a paradoxical reaction is identified, it is an indication that the amino acid dosing value needs to be increased, at which point the paradoxical symptoms will resolve in one to two days. If the dose is lowered in hopes of increasing the dosing values slowly, the patient's suffering will be unnecessarily prolonged as the patient is subjected to the dosing value range where symptoms occur for a prolonged period of time.

DIZZINESS

THE PROBLEM: Dizziness (vertigo) may be caused by many different things when taking amino acids. As with paradoxical reactions, in many cases it is an indication to increase the amino acid dosing.

THE CAUSE: While complaints of dizziness may have many etiologies, dizziness associated with inadequate amino acid dosing is responsive to food intake. If the patient complains of dizziness and which resolves after eating a small amount of carbohydrate such as a candy, cookie, pastry, etc. it is a carbohydrate-dependent vertigo which can develop during amino acid treatment.

MANAGEMENT: Management of "carbohydrate-dependent vertigo" involves increasing the amino acid dosing to the level where symptoms will resolve in one to two days. Any patient taking amino acids with complaints of dizziness needs to be properly evaluated for "carbohydrate-dependent vertigo".

HYPERSOMNOLENCE

THE PROBLEM: The patient recently started on amino acids may present at the clinic complaining of excess sleepiness to the point of having problems staying awake at work or during other daily activities.

THE CAUSE: In general, these patients were suffering from poor sleep prior to treatment and have a "sleep debt" that needs to be repaid prior to feeling optimal again.

MANAGEMENT: The first thing to do when complaints of excessive tiredness are encountered is to take a medical history to determine whether the cause is an imbalance in the amino acids or if the patient is suffering from a sleep debt that needs to be repaid. In patients with very poor sleep prior to treatment (3 to 4 hours per night), stop the amino acids and restart them on a Friday if the patient has the weekend off, telling the patient to sleep all weekend. If sleep was not a problem prior to treatment, cut the amino acid dosing in half, then obtain a urinary transporter analysis in order to determine the proper level of amino acids needed.

Two heads are better than one, and experience trumps all. There are no problems that should require long-term stoppage of the amino acids other than the patient quitting treatment.

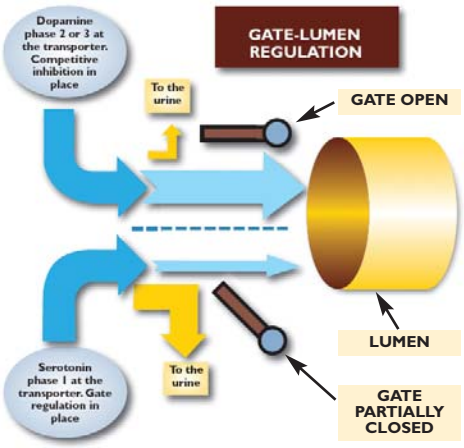
TRANSPORTER FUNCTIONAL STATUS DETERMINATION

(Continued from page 5)

Neurotransmitter levels for all systems are primarily dependent on the functional status of the organic cation transporters.

GATE-LUMEN TRANSPORTER STATUS FOR EACH PHASE

	Gate	Lumen
Phase 1	Partially closed	Unsaturated
Phase 2	Open	Unsaturated
Phase 3	Open	Saturated



**Dual-gate lumen organic cation transporter model developed by Hinz et al 2010.*

As noted in numerous peer-reviewed scientific writings, determination of transporter functional status can only be done in the "competitive inhibition state" found when significant amounts of serotonin and dopamine amino acid precursors are being taken simultaneously. Assays in the endogenous state performed while taking no amino acids are meaningless.

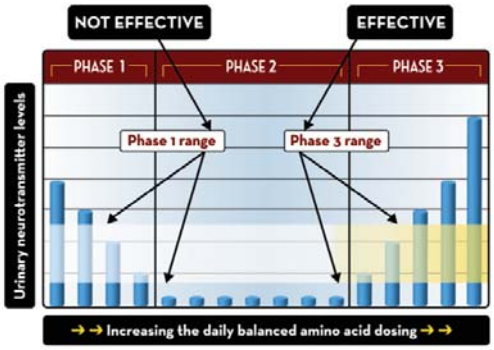
The goal of treatment is to get both the serotonin and dopamine into the phase 3 responses with urinary levels just over the phase 2 threshold (80 to 240 µ of serotonin per g of creatinine and 475 to 1,100 µ of dopamine per g of creatinine).

Interpretation of urinary data for phase determination rests on some simple concepts, but actual interpretation can become quite complex.

With each urine sample submitted to DBS Labs, a formal lab report is generated, followed the next day by a phase interpretation with suggested recommendations for moving serotonin and dopamine closer to the desired phase 3 ranges.

The phases of serotonin and dopamine occurs independent of each other. Serotonin and dopamine can be in any of the three phases independent of each other.

Relief of symptoms is like shooting at a target, where urinary serotonin and dopamine in the phase 3 therapeutic ranges is the bull's eye. Some patients are symptom free by merely hitting the edge of the target; others need to be fully into the phase 3 therapeutic ranges before relief of symptoms is seen.



The organic cation transporters of the kidneys, brain, liver, and bowels are "identical and homologous". Once the amino acids and neurotransmitters are at equilibrium, determining the functional status of one set of transporters will give insight into other sets of transporters.

Monoamine Neurotransmitter Diseases

(Partial listing)

- Parkinsonism
- Obesity
- Bulimia
- Anorexia
- Depression
- Anxiety
- Panic Attacks
- Migraine Headaches
- Tension Headaches
- Premenstrual Syndrome (PMS)
- Menopause Symptoms
- Obsessive Compulsive Disorder (OCD)
- Compulsivity
- Insomnia
- Impulsivity
- Obsessionality
- Inappropriate Aggression
- Inappropriate Anger
- Psychotic Illness
- Fibromyalgia
- Chronic Fatigue Syndrome
- Adrenal Fatigue/Burnout
- Hyperactivity
- ADHD/ADD
- Hormone Dysfunction
- Adrenal Dysfunction
- Dementia
- Alzheimer's Disease
- Traumatic Brain Injury
- Phobias
- Chronic Pain
- Nocturnal Myoclonus
- Irritable Bowel Syndrome
- Crohn's Disease
- Ulcerative Colitis
- Cognitive Deterioration
- Functional Deterioration
- Increased Mortality Rate
- Organ System Dysfunction
- Chronic Stress
- Cortisol Dysfunction
- Hormone Dysfunction
- Restless Leg Syndrome

TECH SUPPORT:
877-626-2220
www.HinzMD.com

MEDICAL FOODS based on scientific writings found in the following peer-reviewed scientific research:

Hinz, M. 2009 Depression, In: Kohlstadt I. editor. Food and Nutrients in Disease Management CRC Press; 465-481.

Hinz, M. Stein, A, Uncini T. 2010a The dual-gate lumen model of renal monoamine transport Neuropsychiatric Disease and Treatment 6 387–392

Hinz, M. Stein, A, Trachte, G, Uncini T. 2010b Neurotransmitter testing of the urine; a comprehensive analysis. Open Access Journal of Urology 2010:2 177–183

Hinz, M. Stein, A. Uncini T. 2010c A pilot study differentiating recurrent major depression from bipolar disorder cycling on the depressive pole, NeuroPsychiatric Disease and Treatment Neuropsychiatric Disease and Treatment:6 741–747

Hinz, M. Stein A. Uncini T. 2011a Treatment of attention deficit hyperactivity disorder with monoamine amino acid precursors and organic cation transporter assay interpretation Neuropsychiatric Disease and Treatment 2011:7 31–38

Hinz, M. Stein, A. Uncini T. 2011b Urinary neurotransmitter testing: considerations of spot baseline norepinephrine and epinephrine Open Access Journal of Urology 2011:3 19–24

Hinz, M. Stein, A. Uncini T. 2011c Amino acid management of Parkinson's disease: A case study International Journal of General Medicine 2011:4 1–10

Stein, A. Hinz, M. Uncini T. Amino acid responsive Crohn's disease, a case study. Clinical and Experimental Gastroenterology 2010:3 171–177

Trachte, G. Uncini, T. Hinz, M, 2009 Both stimulatory and inhibitory effects of dietary 5-hydroxytryptophan and tyrosine are found on urinary excretion of serotonin and dopamine in a large human population Neuropsychiatric Disease and Treatment:5 227–235

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ORIGINAL RESEARCH

Treatment of attention deficit hyperactivity disorder with monoamine amino acid precursors and organic cation transporter assay interpretation

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Background: This paper documents a retrospective pilot study of a novel approach for treating attention deficit hyperactivity disorder (ADHD) with amino acid precursors of serotonin and dopamine in conjunction with urinary monoamine assays subjected to organic cation transporter (OCT) functional status determination. The goal of this research was to document the findings and related considerations of a retrospective chart review study designed to identify issues and areas of concern that will define parameters for a prospective controlled study.

Methods: This study included 85 patients, aged 4–18 years, who were treated with a novel amino acid precursor protocol. Their clinical course during the first 8–10 weeks of treatment was analyzed retrospectively. The study team consisted of PhD clinical psychologists, individuals compiling clinical data from records, and a statistician. The patients had been treated with a predefined protocol for administering amino acid precursors of serotonin and dopamine, along with OCT assay interpretation as indicated.

Results: In total, 67% of participants achieved significant improvement with only amino acid precursors of serotonin and dopamine. In patients who achieved no significant relief of symptoms with only amino acid precursors, OCT assay interpretation was utilized. In this subgroup, 30.3% achieved significant relief following two or three urine assays and dosage changes as recommended by the assay results. The total percentage of patients showing significant improvement was 77%.

Conclusion: The efficacy of this novel protocol appears superior to some ADHD prescription drugs, and therefore indicates a need for further studies to verify this observation. The findings of this study justify initiation of further prospective controlled studies in order to evaluate more formally the observed benefits of this novel approach in the treatment of ADHD.

Keywords: attention deficit hyperactivity disorder, 5-hydroxytryptophan, tyrosine, L-dopa, organic cation transporter assay interpretation

Introduction

A large meta-analysis (n = 171,756) published in 2007 involving the review of 303 literature articles placed the worldwide pooled incidence of attention deficit hyperactivity disorder (ADHD) at 5.29%. However, this review suggested that geographic location plays only a limited role in the reasons for the large variability of ADHD/hyperactivity disorder prevalence estimates worldwide.[1] This paper documents the results of a retrospective chart review relating to a novel serotonin and dopamine amino acid precursor treatment approach to ADHD which integrates organic cation transporter (OCT) assay interpretation.[2–7] Our hypothesis was that this novel approach of admin-

istering amino acid precursors of serotonin and dopamine with OCT assay interpretation when indicated may have efficacy that is superior to some of the prescription drugs currently used in the treatment of ADHD.

The diagnosis of ADHD is dependent upon meeting the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria in the areas of inattention, hyperactivity, and impulsivity which negatively affect performance in school and work, as well as in relationships with others.[8] It is a generally accepted premise that a primary factor in development of ADHD is the status of the monoamine system to include serotonin, dopamine, norepinephrine, and epinephrine. In response, the pharmaceutical industry has demonstrated, to the satisfaction of the US Food and Drug Administration (FDA), that certain drugs that impact the monoamine systems meet FDA efficacy standards. Examples of these drugs include neutral sulfate salts of dextroamphetamine and amphetamine,[9] methylphenidate,[10] dexmethylphenidate,[11] atomextine,[12] and lisdexamfetamine dimesylate.[13]

Side effects and adverse reactions associated with ADHD prescription medications are significant, serious, and potentially life-threatening. The following is a limited list of these events associated with the ADHD group of drugs as a whole, which include, but are not limited to:[9–13]

- Black box warning of increased risk of suicidal ideation
- Severe liver injury
- Sudden death in cases with pre-existing structural cardiac abnormalities or other serious heart problems
- Risk of stroke and myocardial infarction
- Exacerbation of symptoms of behavior disturbance and thought disorder in patients with a pre-existing psychotic disorder
- Induction of mixed/manic episodes
- Treatment by stimulants at usual doses can cause emergent psychotic or manic symptoms, eg, hallucinations, delusional thinking, or mania in children and adolescents without prior history of psychotic illness or mania
- Amphetamines may impair the ability of the patient to engage in potentially hazardous activities such as operating machinery or vehicles
- Higher incidence of infection, photosensitivity reaction, constipation, tooth disorders, emotional liability, decreased libido, somnolence, speech disorder, palpitation, twitching, dyspnea, sweating, dysmenorrhea, and impotence
- Integument disorders including, but not limited to, urticaria, rash, and hypersensitivity reactions, including angioedema and anaphylaxis; serious skin rashes, including Stevens Johnson syndrome and toxic epidermal necrolysis
- Lowering of seizure threshold
- Increased aggression and hostility
- Contraindicated in patients with marked anxiety, tension, and agitation, because the drugs may aggravate these symptoms
- Risk of drug dependence
- Development of leukopenia and/or anemia.

These drugs do not increase the total number of neurotransmitter molecules in the central nervous system. Their primary mechanism of action is thought to be reuptake inhibition which sets up conditions that move neurotransmitters from one place to another.[4–8] However, previous writings suggest that the process of reuptake inhibition may deplete neurotransmitters throughout the body.[4,14–19] The administration of amphetamine stimulants creates another potential area of concern relating to neurotoxicity.[20–22]

There has been no previous peer-reviewed literature published addressing the efficacy of amino acid precursors of serotonin and dopamine simultaneously administered in the treatment of ADHD. The immediate amino acid precursors of serotonin and dopamine are 5-hydroxytryptophan (5-HTP) and L-3,4-dihydroxyphenylalanine (L-dopa), respectively. They freely cross the blood-brain barrier and are then synthesized into serotonin and dopamine without biochemical feedback inhibition. L-tryptophan and L-tyrosine are immediate precursors of 5-HTP and L-dopa, respectively. L-tryptophan and L-tyrosine have the ability to be synthesized into serotonin and dopamine, respectively. They are actively transported across the blood–brain barrier in competition with other amino acids. Synthesis of serotonin and dopamine from L-tryptophan and L-tyrosine, respectively, is regulated by biochemical feedback. Under the approach of this pilot study, optimal results are dependent upon achieving a proper balance between the administered serotonin and dopamine precursors. [2–7]

This study reviews the effects of a novel method of treatment involving the use of monoamine amino acid precursors that do what drugs are unable to do. This novel approach has the ability to increase the total number of neurotransmitter molecules in the central nervous system,[3–7] leading to efficacy observations that appear greater than those of prescription drugs without the potential for neurotransmitter depletion, neurotoxicity issues, and severe potentially life-threatening drug side effects associated with prescription drugs.

Material and methods

The study included 85 children aged 4–18 years who had been diagnosed as having ADHD under the DSM-IV criteria by a licensed PhD clinical psychologist. The patients were then treated by a clinical psychologist. The medical charts and treatment results were reviewed retrospectively. Patients were evaluated twice during treatment with the ADHD Rating Scale (ADHD-RS).[17] Other variables assessed via a questionnaire included: taking/not taking ADHD medicine; previous history of taking stimulant drugs; gender; age; perceived amount of improvement as noted by a conversation between the parent (or patient alone if an adult over 18 years) and the psychologist; and number of comorbid factors (eg, depression, cerebral palsy, chronic indigestion, hair pulling, seizures, autism, obsessive compulsive behavior).

The time period covered in the review was 18 months. The individual patients were treated for a period of 8–10 weeks with staggered starting of treatment. If no relief of symptoms was observed in the first 3–4 weeks of treatment, while administering the amino acid dosing protocol values of Tables 1 and 2, a urine sample was collected. Urinary serotonin and dopamine assay results were then subjected to OCT assay interpretation in order to define the needed change in amino acid dosing values. The goal of treatment was resolution of symptoms or achieving urinary serotonin and dopamine in the phase 3 therapeutic ranges, whichever came first.[3–7] The amino acid dosing values of the protocol were developed by NeuroResearch Clinics Inc, Duluth, MN.[3–7]

The statistician performing data analysis had no exposure to any aspects of active patient treatment, prior hypotheses, treatment expectations, and anticipated results in the data relating to the study. The researchers performing the charting were also blind to any hypotheses being evaluated. A P value ≤ 0.05 was considered statistically significant. JMP (SAS Institute, Cary, NC) software was used to perform the statistical analysis.

For the purposes of the study, participants 16 years of age and younger were placed on the pediatric dosing protocol (Table 1). Participants 17 years of age and older were placed on the adult dosing protocol (Table 2).

Table 1 Pediatric protocol for patients aged 16 years of age and younger

mg 5-HTP/mg L-tyrosine			
	Morning	**4 pm**	**7 pm**
Level 1	75/750	75/750	–
Level 2	112.5/1125	112.5/1125	–
Level 3	112.5/1125	112.5/1125	112.5/1125

Table 2 Adult protocol for patients 17 years of age and older

mg 5-HTP/mg L-tyrosine			
	Morning	**Noon**	**4 pm**
Level 1	150/1500	–	150/1500
Level 2	225/2250	–	225/2250
Level 3	150/1500	150/1500	225/750

In addition to the basic amino acid dosing values, other daily cofactors generally required for synthesis of the monoamine and maximum benefit from the protocol were administered. These included vitamin C 1000 mg, calcium citrate 220 mg, vitamin B6 75 mg, folate 400 µg, L-lysine 500 mg, L-cysteine 4500 mg for adults and 2250 mg for children, and selenium 400 µg for adults and 200 µg for children. In general, L-dopa in the form of standardized mucuna pruriens 40% was added when the recommendation of the first urinary OCT assay interpretation demonstrated its need, which was a frequent occurrence.[4]

Patients were seen weekly. The initiation of a treatment prescription with amino acid precursors of serotonin and dopamine was at the level 1 dosing values of Tables 1 and 2. If the symptoms persisted after one week of treatment, the dosing was advanced week to week to level 2, then level 3. Patients who did not achieve relief of symptoms on level 3 dosing values had a urine sample collected after one week on that dosage; serotonin and dopamine levels were determined and reported in µg of monoamine per g of creatinine. Reported values were then subjected to OCT assay interpretation. Reporting of urinary monoamine levels as µg of monoamine per g of creatinine compensated for the specific gravity of the urine.[3–7]

OCT assay interpretation

Peer-reviewed publications from 2009 and 2010 outlined a novel urinary "three-phase model" of urinary serotonin and dopamine response to simultaneous administration of serotonin and dopamine amino acid precursors in significant amounts. This three-phase model is the basis for OCT assay interpretation.[2–7] A 2010 paper proposed a novel renal organic cation transporter model which potentially describes the etiology of the "three-phase response" of serotonin and dopamine during simultaneous administration of their amino acid precursors in varied daily dosing values.[3]

The urinary neurotransmitter testing model should with the OCT assay interpretation model used in this study. The urinary neurotransmitter testing model merely attempts to determine if urinary neurotransmitter levels are high or low, making no provision for phase determination or OCT

functional status interpretation. The flawed science behind the urinary neurotransmitter testing model was discussed in a 2010 paper.[6]

The serotonin and dopamine filtered at the glomerulus are metabolized by the kidneys, and significant amounts do not reach the final urine. Serotonin and dopamine found in the urine, in patients not suffering from a monoamine-secreting tumor, primarily represent monoamines that are newly synthesized in the proximal convoluted renal tubule cells of the kidneys and have never been in the central nervous system or peripheral system. The fate of the newly synthesized serotonin and dopamine inside the proximal convoluted renal tubule cells is primarily dependent upon the interaction of the basolateral monoamine transporters and the apical monoamine transporters of these proximal tubule cells. The basolateral monoamine transporter transports both serotonin and dopamine to the renal interstitium where they ultimately end up in the peripheral system via the renal vein. The apical monoamine transporters transport the newly synthesized serotonin and dopamine not transported by the basolateral monoamine transporter to the proximal nephrons and, from there, ultimately end up in the final urine as waste.[3,24]

Serotonin and dopamine are found in two states. The endogenous state is found when no amino acid precursors are administered. The competitive inhibition state is found when significant amounts of both serotonin and dopamine precursors are simultaneously administered. Proper OCT assay interpretation requires that the serotonin and dopamine systems be simultaneously placed in the competitive inhibition state prior to OCT assay interpretation.[3–7,24]

The basis for OCT assay interpretation requires that two or more urinary serotonin and dopamine assays be performed while taking serotonin and dopamine amino acid precursors at significantly varied dosing values. The results are then compared to determine the change in urinary serotonin and dopamine levels in response to the change in amino acid precursor dosing values.[2–7]

A urinary serotonin or dopamine value less than 80 µg or 475 µg of monoamine per g of creatinine, respectively, is defined as a phase 2 response. A urinary serotonin or dopamine value greater than 80 µg or 475 µg of monoamine per g of creatinine, respectively, is interpreted as being in phase 1 or phase 3. Differentiation of phase 1 from phase 3 is a follows. If a direct relationship is found between amino acid dosing and urinary assay response, it is referred to as a phase 3 response. An inverse relationship is referred to as a phase 1 response. The phase 3 therapeutic range for urinary serotonin is defined as 80–240 µg of serotonin per g of creatinine. The phase 3 therapeutic range for urinary dopamine is defined as 475–1100 µg of dopamine per g of creatinine.[2–7]

Processing, management, and assay of the urine samples collected for this study were as follows. Urine samples were collected about six hours prior to bedtime, with 4 pm being the most frequent collection time point. The samples were stabilized in 6 N HCl to preserve the dopamine and serotonin. The urine samples were collected after a minimum of one week during which time the patient was taking a specific daily dosing of amino acid precursors of serotonin and dopamine where no doses were missed. Samples were shipped to DBS Laboratories (Duluth, MN) which is operated under the direction of one of the authors (TU, hospital-based pathologist, dual board-certified in laboratory medicine and forensic pathology). Urinary dopamine and serotonin were assayed utilizing commercially available radioimmunoassay kits (3 CAT RIA IB88501 and IB89527, both from Immuno Biological Laboratories Inc, Minneapolis, MN). The DBS laboratory is accredited as a high complexity laboratory by CLIA to perform these assays. OCT assay interpretation was performed by one of the authors (MH, NeuroResearch Clinics Inc).

Results

The retrospective chart review of this pilot study covered the treatment of 85 children aged 4–18 years diagnosed under DSM-IV criteria to have ADHD. The age distribution of the study group was 4–8 years (n = 7), 9–12 years (n = 36), and 13–18 years (n = 22). The mean age of the subjects was 12.2 years. There were 51 boys and 34 girls evenly distributed across the three age ranges.

Of the 85 patients, 62 (72.9%) had previously taken a stimulant drug for ADHD, and 23 (27.1%) had no history of treatment with an ADHD stimulant drug. There were 28 patients (30.0%) currently taking an ADHD drug while 57 (70.0%) were not. The breakdown of drugs taken at the start of treatment was as follows: 14 were taking amphetamine enantiomers; five were taking methylphenidate; five were taking atomoxetine; three were taking other drugs not specifically defined; and one was taking a combination of amphetamine enantiomers with atomoxetine. Parents sought treatment under this novel approach primarily due to concerns over lack of drug efficacy and/or drug side effects.

The ADHD-RS inventory was administered at the start and end of treatment. Results indicated that group

Table 3 Changes in Attention Deficit Hyperactivity Disorder Rating Scale scores at initiation and end of treatment

Group ADHD-RS changes				
	Pre-Rx	End-Rx	t-test	*P*
2s	4.6	1.2	8.42	<0.001
3s	8.3	2.3	12.26	<0.001

Abbreviations: Rx, treatment; ADHD-RS, Attention-Deficit-Hyperactivity Disorder Rating Scale.

scores (2 and 3) on the ADHD-RS scale (behavioral symptoms of ADHD) decreased significantly ($P < 0.001$) from the first to the second testing. ADHD-RS results are shown in Table 3.

The decrease in 2 and 3 scores shown in Table 3 occurred regardless of the variable being investigated, including age and gender. This reduction in symptoms is noteworthy. Prior to treatment, the number of significant ADHD behavioral indicators that were displayed as "often" or "very often" were in the 5–9 range. Only two post-treatment behavioral indicators were noted. The only variable that approached significance ($P < 0.08$) was gender. More males experienced a decrease in symptoms in the ADHD-RS (3) from 8.9 to 2.3 versus females in whom this score decreased from 7.1 to 2.2.

In addition to the statistical analysis parameters that were identified on the DSM-IV, the following observations were calculated relating to other issues. Some of the more compelling findings are included in the tables.

The results shown in Table 4 revealed that 67% of the participants achieved significant improvement with only amino acid precursors of serotonin and dopamine. Patients who achieved no significant relief of symptoms with only amino acid precursors represent a subgroup in whom urine samples were collected and OCT assay interpretation was utilized. In this subgroup, 30.3% achieved significant relief of symptoms following two or three urine assays. The total percentage of patients showing significant improvement was 77%.

Referring to Table 6, a further 10% of patients who had taken stimulant drugs in the past reported complete symptom relief. There seems to be some advantage for the effectiveness of the amino acid supplement treatment when there is a history of having taken stimulant drugs in the past.

Table 4 Percentage of the entire group (n = 85) achieving significant relief of symptoms by weeks 3 and 8 ($P < 0.05$)

	Week 3	Week 8
Significant relief	67%	77%

Table 5 Percentage of the entire group (n = 85) achieving complete relief of symptoms by weeks 5 and 8

	Week 5	Week 8
Complete relief	30%	33%

As noted in Table 7, a potential advantage was identified with the administration of amino acid precursors relating to taking ADHD drugs.

Urine tests did not typically occur until visit 4, and were indicated if the patient did not show significant improvement with relief of the majority of major ADHD symptoms after one week taking level 3 dosing values of Table 1 or Table 2. Those who experienced control of symptoms prior to or at visit 4 were excluded from urine testing. Results of the patients who had an OCT assay are shown in Table 8.

Therefore, it appears that urine testing with OCT assay interpretation was beneficial because urinary serotonin and dopamine assay interpretation defined the proper dosing values. To establish urinary serotonin and dopamine phases firmly requires two assays performed with varied amino acid precursor dosing values. The significant relief values of 64% prior to testing and 70% after two assays noted in Table 7 and Table 8 represent only one amino acid dosing change, with the confidence of knowing the serotonin and dopamine phases.

Discussion

The data generated in the study were compared with data generated in double-blind, placebo-controlled studies. Tables 9 and 10 summarize the results of this literature search. It would appear that the placebo effect is strong in ADHD studies, because 28%–40% of placebo patients achieved significant relief of symptoms in the atomoxetine studies reviewed (Table 10), and 14%–31% had a placebo benefit in the methylphenidate study (Table 9).

To meet the criteria for approval under FDA guidelines, a drug has to demonstrate efficacy and safety.[32] The amino acids and cofactors used in this retrospective study are classified by the FDA as generally recognized and accepted as

Table 6 The percentage of patients with and without a history of taking a stimulant for treatment of ADHD who experienced complete relief of symptoms at weeks 5 and 8

	Week 5	Week 8
No stimulant drug in past	22%	28%
Stimulant drug in past	32%	35%

Table 7 Effect of taking and not taking a prescription ADHD drug on the endpoint of the study

	Week 5	Week 8
	Significant relief	Complete relief
Not taking a drug	64%	28%

Table 8 Approximately 59% of patients in the group achieved relief of symptoms with administration of amino acids and no testing

	Urine test group
Two tests	70%
Three tests	78%

Notes: If no response was observed after treatment with the three amino acid dosing levels of Table 1 or Table 2, organic cation transporte assay interpretation was initiated leading to an increase in the number of patients in the study who experienced significant relief of symptoms.

safe (GRAS), in the same category as supplemental vitamins and minerals.[33] There are no safety concerns with the amino acids based on this FDA position. All of the amino acids and components used in the study are sold in the US over the counter without a prescription.

The drugs prescribed for ADHD have potentially controversial concerns associated with them, including neurotransmitter depletion, neurotoxicity, drug side effects, and adverse reactions; this amino acid approach in comparison has none of these concerns associated with it. This gives a significant advantage to this amino acid approach if studies continue to bear out that it is similar or superior to prescription ADHD drugs in its efficacy.

This retrospective study was performed in order to focus on the structure needed for a formal prospective study. In the course of this study, the following observations and considerations came to light. The administration of properly balanced amino acid precursors of serotonin and dopamine with OCT assay interpretation resulted in improvement that appears to be superior to methylphenidate and atomoxetine (Tables 9 and 10). This certainly provides encouragement to undertake further studies.

Even if the finding was that use of serotonin and dopamine amino acid precursors with OCT assay interpretation was equal to reported efficacy values found with atomoxetine and methylphenidate, it is asserted that this approach would be superior because it does not share the adverse reactions, potential depletion of neurotransmitters, and neurotoxicity concerns reported with the group of drugs prescribed for ADHD treatment.

There is variance identified and reported in children who were and were not taking drugs during this study. Future studies need to be designed to address the impact of amino acids on subgroups such as this. A further identified issue in this study that needs to be corrected in future studies is the timeline of the study. In response to the lack of amino acid efficacy at visit 4 (taking level 3 dosing values for one week from Tables 1 and 2), OCT assay interpretation was started. For children in the study for 10 weeks, three urinary tests were obtained. Experience leading up to this study suggested that a significant number of patients with ADHD do not achieve relief of symptoms until both urinary serotonin and dopamine are in the phase 3 therapeutic ranges. Data analysis revealed that it typically takes 2–8 urine tests with OCT assay interpretation to achieve this goal. Provisions need to be made in future studies to move away from rigid time guidelines and position the studies as a process independent of time where the endpoint is urinary serotonin and dopamine in the phase 3 therapeutic ranges or relief of symptoms, whichever comes first.

Table 9 Retrospective study results, significant improvement in patients (Table 4) versus reported results in double-blind, placebo-controlled studies taking methylphenidate

	Pilot study results	Methylphenidate studies		
	AA with OCT assay interpretation	Study 1[26]	Study 2[27]	Study 3[28]
n	85	154	97	18
% improved	77% (Table 4)	64%	52%	58%
% placebo improved	N/A	27%	31%	14%
% drug improvement over placebo	N/A	37%	21%	44%

Notes: The "% placebo improved" row represents percentage of subjects taking placebo who experienced significant remission of symptoms to the defined threshold of the study or greater. The bottom row is the advantage of the drug over placebo in the study cited.
Abbreviations: AA, amino acid; OCT, organic cation transporter.

Table 10 Retrospective study results, significant improvement in patients (see Table 4) versus reported results in double-blind, placebo-controlled studies of patients taking atomoxetine

	Pilot study results	Atomoxetine studies		
	AA with OCT assay interpretation	Study 1[29]	Study 2[30]	Study 3[31]
n	85	618	36	84
% improved	77% (Table 4)	71%	54%	59%
% placebo improved	N/A	28%	40%	31%
% drug improvement over placebo	N/A	43%	14%	28%

Notes: The "% placebo improved" row represents percentage of subjects taking placebo who experienced significant remission of symptoms to the defined threshold of the study or greater. The bottom row is the advantage of the drug over placebo in the study cited.
Abbreviations: AA, amino acid; OCT, organic cation transporter.

It is also suggested that the scrutiny of this retrospective study be expanded to identify more phenotype traits. Incorporation of expanded data fields such as this into further studies would facilitate more indepth comparison with other studies and statistical evaluation of subgroups.

This analysis does provide some initial evidence of the efficacy of amino acids in significantly reducing symptoms associated with ADHD. Tables 9 and 10 reveal the efficacy of this treatment protocol to be potentially superior to results seen with prescription drugs. Future studies are needed to investigate the reliability of these observed effects. If these results can be replicated in controlled studies, then such important issues as cause and effect for the changes in ADHD symptoms, potential mediating variables, and long-term uses can be further investigated and clarified.

Conclusion

Based on the FDA guidelines, the amino acid precursors of serotonin and dopamine, used in this study, are classified as GRAS, meaning no significant safety concerns exist about their use. The next question to ponder is whether the approach is effective. The FDA has not set the bar very high in demonstrating efficacy of prescription drugs. There are numerous examples of drugs being approved that are only 7%–13% more effective than placebo.[4] Under these conditions, it would appear that the findings of this study have the potential to demonstrate at least that level of efficacy in a prospective study based on Tables 9 and 10.

The purpose of this paper was to document formally the results and findings generated during the course of this retrospective pilot study involving 85 children, and define parameters that allow focus on a future prospective study. It is the goal of this paper to spark interest, research, awareness, and scrutiny of these findings, and to raise awareness of potential neurotransmitter depletion and neurotoxicity issues relating to ADHD drugs.

Disclosure

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References

1. Michelson D, Buitelaar JK, Danckaerts M, et al. Relapse prevention in pediatric patients with ADHD treated with atomoxetine: A randomized, double blind, placebo controlled study. *J Am Acad Child Adolesc Psychiatry*. 2004;4:896–904.
2. Trachte G, Uncini T, Hinz M. Both stimulatory and inhibitory effects of dietary 5-hydroxytryptophan and tyrosine are found on urinary excretion of serotonin and dopamine in a large human population. *Neuropsychiatr Dis Treat*. 2009;5:227–235.
3. Hinz M, Stein A, Uncini T. The dual-gate lumen model of renal monoamine transport. *Neuropsychiatr Dis Treat*. 2010;6:387–392.
4. Hinz M. Depression. In: Kohlstadt I, editor. *Food and Nutrients in Disease Management*. Boca Raton, FL: CRC Press; 2009.
5. Hinz M, Stein A, Uncini T. A pilot study differentiating recurrent major depression from bipolar disorder cycling on the depressive pole. *Neuropsychiatr Dis Treat*. 2010;6:741–747.
6. Hinz M, Stein A, Trachte G, Uncini T. Neurotransmitter testing of the urine: A comprehensive analysis. *Open Access Journal of Urology*. 2010;2:177–183.
7. Stein A, Hinz M. Uncini Amino acid responsive Crohn's disease, a case study. *Clin Exp Gastroenterol*. 2010;3:171–177.
8. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorder IV, Fourth Edition. Text Revised*. Washington, DC: American Psychiatric Association; 1994.
9. Shire US Inc. FDA approved prescribing information for neutral sulfate salts of dextroamphetamine and amphetamine. Available from: http://pi.shirecontent.com/PI/PDFs/AdderallXR_USA_ENG.PDF. Accessed Oct 14 2010.
10. Concerta®. FDA approved prescribing information for methylphenidate. Available from: http://www.concerta.net/sites/default/files/pdf/Prescribing_Info-short.pdf. Accessed Oct 14, 2010.

11. Novartis. FDA approved prescribing information for dexmethylphenidate. Available from: http://www.pharma.us.novartis.com/product/pi/pdf/focalin.pdf. Accessed Oct 14 2010.
12. Lilly. FDA approved prescribing information for atomoxetine. Available from: http://pi.lilly.com/us/strattera-pi.pdf. Accessed Oct 14 2010.
13. ADHD & ADD Information Centre. FDA approved prescribing information for lisdexamfetamine dimesylate. Available from: http://www.adhdinfocentre.com/vyvanse/Vyvanse%20Prescribing%20Information.PDF. Accessed Oct 14 2010.
14. National Institute on Drug Abuse. The neurobiology of ecstasy (MDMA). 2010. Available from: http://www.nida.nih.gov/pubs/teaching/Teaching4/Teaching.html. Accessed Sep 2010.
15. Stenfors C, Yu H, Ross S. Pharmacological characterization of the decrease in 5-HT synthesis in the mouse brain evoked by the selective serotonin re-uptake inhibitor citalopram. *Naunyn Schmiedebergs Arch Pharmacol*. 2001;363:222–232.
16. De Abajo F, Jick H, Derby L. Intracranial haemorrhage and use of selective serotonin reuptake inhibitors. *Br J Clin Pharmacol*. 2000;50: 43–47.
17. Meier R, Schlienger R, Jick H. Use of selective serotonin reuptake inhibitors and risk of developing first-time acute myocardial infarction. *Br J Clin Pharmacol*. 2001;52:179–184.
18. Dalton S, Johansen C, Mellemkjær L, et al. Use of selective serotonin reuptake inhibitors and risk of upper gastrointestinal tract bleeding. *Arch Intern Med*. 2003;163:59–64.
19. Trouvin J, Gardier A, Chanut E. Time course of brain serotonin metabolism after cessation of long-term fluoxetine treatment in the rat. *Life Sci*. 1993;52:187–192.
20. Advokat C. Literature review: Update on amphetamine neurotoxicity and its relevance to the treatment of ADHD. *J Atten Disord*. 2007;11: 8–16.
21. Ricaurte G, Mechan A, Yuan J, et al. Amphetamine treatment similar to that used in the treatment of adult attention-deficit/hyperactivity disorder damages dopaminergic nerve endings in the striatum of adult nonhuman primates. *J Pharmacol Exp Ther*. 2005;315:91–98.
22. Berggin P. Psychostimulants in the treatment of children diagnosed with ADHD: Risks and mechanism of action. *International Journal of Risk and Safety in Medicine*. 1999;12:3–35.
23. Bright Futures. Vanderbilt ADHD Diagnostic Teacher Rating Scale. Available from: http://www.brightfutures.org/mentalhealth/pdf/professionals/bridges/adhd.pdf. Accessed Oct 14 2010.
24. Koepsell H, Schmitt B, Gorboulev V. Organic cation transporters. *Physiol Biochem Pharmacol*. 2003;150:36–90.
25. Delgado P, Moreno F. Role of norepinephrine in depression. *J Clin Psychiatry*. 2000;61 Suppl 1:5–12.
26. Greenhill L, Findling R, Swanson J. A double-blind, placebo-controlled study of modified-release methylphenidate in children with attention-deficit/hyperactivity disorder. *Pediatrics*. 2002;109:E39.
27. Wilens T, McBurnett K, Bukstein O, et al. Multisite controlled study of OROS methylphenidate in the treatment of adolescents with attention-deficit/hyperactivity disorder. *Arch Pediatr Adolesc Med*. 2006;160:82–90.
28. Stein M, Sarampote CS, Waldman ID, et al. A dose-response study of OROS methylphenidate in children with attention-deficit/hyperactivity disorder. *Pediatrics*. 2003;112:404–413.
29. Svanborg P, Thernlund G, Gustafsson P, et al. Atomoxetine improves patient and family coping in attention deficit/hyperactivity disorder: A randomized, double-blind, placebo-controlled study in Swedish children and adolescents. *Eur Child Adolesc Psychiatry*. 2009;18: 725–735.
30. Faraone S, Biederman J, Spencer T, et al. Efficacy of atomoxetine in adult attention-deficit/hyperactivity disorder: A drug-placebo response curve analysis. *Behav Brain Funct*. 2005;1:16.
31. Michelson D, Allen AJ, Busner J, et al. Once-daily atomoxetine treatment for children and adolescents with attention deficit hyperactivity disorder: A randomized, placebo-controlled study. *Am J Psychiatry*. 2002;159:1896–1901.
32. US Food and Drug Administration. About Science & Research at FDA. 2010. Available from: http://www.fda.gov/ScienceResearch/AboutScienceResearchatFDA/default.htm. Accessed Nov 9 2010.
33. US Food and Drug Administration. Generally recognized as safe. 2010. Available from: http://www.fda.gov/Food/FoodIngredientsPackaging/GenerallyRecognizedasSafeGRAS/default.htm. Accessed Nov 9 2010.