



MSUD NEWSLETTER



SYMPOSIUM NEWS

MSUD SYMPOSIUM 2018 REVIEW

The 2018 MSUD Symposium was held on June 28th-30th at the DoubleTree Green Tree outside of Pittsburgh, PA. Approximately 230 people from the US and 8 other countries attended the event. There were speakers, vendors and researchers in attendance in addition to MSUD families.

The agenda consisted of a variety of topics including medical management, dietary management, psychosocial issues, research, fundraising, advocacy and a low protein cooking demo. Many of the presentations were videotaped and are available on the MSUD website (www.msud-support.org).

We were fortunate to have staff from Children’s Hospital of Pittsburgh of UPMC host a liver transplant

breakout on Friday afternoon of the symposium. They also hosted a riverboat cruise on the three rivers in downtown Pittsburgh on Friday evening. The cruise was well attended by families and speakers. It was a beautiful evening on the boat and provided an opportunity to relax and socialize.

Based on the evaluation forms that symposium attendees completed, many felt that the research presentations, especially, were very informative and offered hope for better treatments and eventually a cure for MSUD. Also, families appreciated the social time to renew old friendships and meet new families.

The event would not be possible without the generous donations of our sponsors. Special thanks to our Gold Sponsors (\$5,000 or more), United Service Foundation, Children’s Hospital of Pittsburgh of UPMC and Acer Therapeutics.

Plans for the next symposium in June 2020 are underway. Save the date! Hope to see you there! ■

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MSUD SYMPOSIUM 2018 Comments from the evaluation forms

1. The river boat ride was great. We got to meet more people.
2. There is so much happening in research. I would like to be at the next symposium as well so that I can see the progress that has been made.
3. Really enjoyed the research speakers and the kid's panel.
4. The program was nicely broken up between speakers so it was easy to maintain focus.
5. There was a lot of new information at this symposium.
6. The topics and speakers gave us great hope that in the foreseeable future we may have a cure!
7. The most important role of the support group is keeping families informed and connected. I can't imagine navigating MSUD without this group.
8. The best part was catching up with friends who we haven't seen for awhile. ■

ADVOCACY UPDATE

MEDICAL NUTRITION EQUITY ACT

By Jordann Coleman, Advocacy Chairperson



Co-sponsors in the United States Congress and Senate are still needed for the Medical Nutrition Equity Act. Currently there are 27 co-sponsors on the House version of the bill (9 Republican & 18 Democrat) and 4 co-sponsors (1 Republican & 3 Democrat) for the Senate version of the bill. Several Democrats have expressed interest in co-sponsoring the bill but there is a need for more Republican co-sponsors as bi-partisan support is needed to help get this bill passed.

We are asking our US-based members to contact their members of Congress (especially if they are Republican) and ask them to co-sponsor this bill. You can go to <http://equity4.us/takeaction> to send an auto-generated email to your members of Congress. You can also visit medicalnutritionequityfor.us to share why having coverage for medical nutrition is important to you and your family.

We need as many voices as possible to help us pass this bill. Please share with your friends, family & social networks and ask them to contact their Congressional members. Together we can make coverage for medical nutrition a reality! ■



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MSUD FAMILY SUPPORT GROUP FUTURE DIRECTIONS SURVEY 2018

By Karen Dolins

This past June the Board sent out an electronic survey designed to understand your priorities as we move forward with current initiatives. We received responses from 95 members.

Respondents were provided with a list of initiatives and asked to rate how important each was to them. Most rated all of the specified initiatives as either important or very important. The results are listed in order from most important to least important.

1. Supporting research to develop treatment strategies and cures for MSUD
2. Public health policy advocacy (for example, coverage of medical foods, funding for rare disease research)
3. Providing updates in care for MSUD
4. Connecting families affected by MSUD
5. Communicating with Family Support Group members
6. Raising public awareness of MSUD
7. Identification of metabolic specialists

Supporting research to improve treatment and develop a cure for MSUD

As this was the most highly rated initiative, we asked about our efforts to mobilize our members to help fundraise in order to achieve this goal. Responses were as follows:

I agree with the need for research and agree that the MSUD FSG should appeal for needed donations from its members and others in order to support those goals.	72%
I agree with the need for research but feel that the MSUD FSG should rely only on voluntary donations that are made without any solicitation, even if it means that its goals cannot be met.	10%
I'm not sure I understand the need for research nor do I understand why fundraising is necessary.	0%

These goals are insufficient reason to fundraise. The MSUD FSG should NOT be fundraising from any sources, even if it means that we will be unable to support research directed at improved treatment and possible cure.	0%
I was not aware that the MSUD Family Support Group has been actively fundraising.	16%

We then asked about respondent's participation in our fundraising activities:

I have participated in fundraising efforts on behalf of our organization.	22%
I have not participated previously but am willing to fundraise on behalf of our organization.	22%
I can make a donation but will not solicit funds from others.	33%
I cannot or will not participate in fundraising.	9%

One person reported making a birthday donation through Facebook, and another reported remembering our group in their will.

Concern was raised that moneys used to promote research could detract from other important works of the organization. We want to emphasize that donations can be earmarked for research or other operating expenses. Money earmarked for research can be instrumental in getting small pilot projects off the ground. Favorable results from these small studies can then be used by researchers to apply for larger NIH grants.

Advocacy was rated 2nd highest in importance by respondents. However, while 48% indicated a willingness to advocate on behalf of our organization, only 22% stated that they have done so.

Finally, we asked respondents how effective our communication methods are in reaching them. Email blasts were rated as most effective, but we realize that the survey was delivered electronically therefore those who do not use this format would not have responded. The print newsletter and electronic newsletters were rated as equally effective.

The Board thanks all who participated in this survey as it allows us to make sure we are meeting your needs. We are always happy to hear from our members, so please feel free to contact us at any time with your concerns or suggestions. ■



VITAFLO HOSTS CHEF NEIL AT MSUD SYMPOSIUM



Vitaflo USA was happy to be able to support bringing Chef Neil Palliser-Bosomworth to the 19th Annual MSUD Symposium this past June in Pittsburgh.

Since December 2015, Chef Neil has been employed full time as a medical chef for Vitaflo International, part of Nestle Health Science.

Neil specializes in the field of inborn errors of metabolism in areas such as MSUD and PKU. He creates, develops and demonstrates his recipes in workshops around the world to both healthcare professionals and to patient groups and families with the aim of making managing a specialist diet a little easier.

Chef Neil was so excited to share the recipes he developed for Low Protein Diets and to cook with the MSUD community.

His recipes are created with the goal of being easy to

make and use ingredients that are readily available, mostly from your grocery store!

Vitaflo's formulas are generally designed to be lower in volume and calories with the hope that patients can obtain the majority of their calories from eating delicious and healthy foods.

Chef Neil and the Vitaflo team loved being able to meet the MSUD community in Pittsburgh and get to work with a few of you! ■

OBITUARY

It is with great sadness that we announce the death of Michael Woorman, age 43, of Rockville, MD. Michael had variant MSUD and passed away on November 30, 2017. Thanks to the Woorman family for honoring Michael by encouraging contributions to the MSUD Family Support Group.

MANAGEMENT**LIVING WELL
WITH A CHRONIC
CONDITION-
QUALITY OF LIFE**

By Kendra J. Bjoraker, Ph.D., L.P.
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Chronic illness or conditions presents a challenge to adjustment on both the individual and family level. Psychosocial adjustment plays a reciprocal role in the course, treatment effectiveness, and management of a chronic illness, which ultimately bear upon the patient's quality of life. My overall goal in speaking with children, adolescents and adults with a chronic condition is to share and provide them with information relating to the psychological and social (psychosocial) impact of their diagnosis. In learning about these issues, quality of life begins to improve as they begin to describe themselves not as "their illness," rather as who they are as a person. They begin to process and explore issues with the ultimate goal of acknowledging and becoming aware of the manifestations of the illness thus providing a normalizing and gratifying opportunity to be happier, feel better about themselves, and enjoy more success. One way to cultivate success is to find meaning in life or purpose in the context of your diagnosis.

Viktor E. Frankl, (1905-1997) was an Austrian neurologist and psychiatrist as well as a Holocaust survivor. He said, "For the meaning of life differs from man to man, from day to day and from hour to hour. What matters, therefore, is not the meaning of life in general, but rather the specific meaning of a person's life at a given moment." Liberated after several months in concentration camps, Frankl returned to Vienna, where he developed and lectured about his own approach to psychological healing. Frankl believed that people are primarily driven by a "striving to find meaning in one's life," and that it is this sense of meaning that enables people to overcome painful experiences.



Finding meaning in life contributes greatly to improving quality of life. There are many determinants of quality of life that can improve or diminish how well you live day to day; however, finding your life's purpose creates a sense of meaning. If you love what you do, you gain connection with others and

your community, you help others and help yourself, and you develop confidence. A meaningful life connects people to a larger sense of purpose and value, making positive contributions, not only to our personal and spiritual growth, but also to society and the human civilization as a whole. As a result, meaningful life is one that guides wise actions, giving a sense of constructive direction.

Finally, we also cannot go through life alone, particularly when diagnosed with a rare genetic condition. Collective wisdom through consulting with experts is always going to give you better information. When working alone, it is oftentimes too easy to give up when things get hard. By surrounding yourself with others working toward a similar goal, you will get motivation and support to push yourself just a bit further than you would have done on your own. On those days when you most want to give up, you need to lean on your community the most. They believe in you. They inspire you.

Many authors have written that even in modern Western society, branded as individualistic to its core, the imperative of social connection is acknowledged in cultural works of all kinds: "People who need people," wrote lyricist Bob Merrill in 1964, "are the luckiest people in the world." The song went on to focus mainly on romantic relationships. But while romantic partners certainly qualify as "people who need people," they are not by any means the only people who do. We are all in the same boat, whether single, married, old, young, male, female; regardless of race, culture, or any other delineation, human social interaction is key to our survival. It would seem, then, that people who need people aren't just the luckiest people in the world, or even just the happiest

people. They're the only people. They are all of us.

Lessons from Geese provides a perfect example of the importance of needing each other or needing a community and how it can have a profound and powerful effect on any form of endeavor. When we use these five principles in our personal life it will help us to foster and encourage a level of passion and energy in ourselves, as well as those who are our friends, or medical team members.

Lesson 1: The Importance of Achieving Goals

As each goose flaps its wings it creates an uplift for the birds that follow. By flying in a 'V' formation the whole flock adds 71% extra to the flying range.

- When we have a sense of community and focus, we create trust and can help each other to achieve our goals. We can learn that people who share a common direction and goal can get where they are going quicker and with less effort because they benefit from the momentum of the group moving around them. Make sure your community is aligned towards a common goal.

Lesson 2: The Importance of Team Work

When a goose falls out of formation it suddenly feels the drag and resistance of flying alone. It quickly moves back into formation to take advantage of the lifting power of the birds in front.

- If we have as much sense as geese we would stay in formation with those headed where we want to go. We are willing to accept their help and give our help to others.

Lesson 3: The Importance of Sharing

When a goose tires of flying up front it drops back into formation and another goose flies to the point position. It pays to take turns doing the hard tasks.

- We should respect and protect each other's unique arrangement of skills, capabilities, talents and resources. People have unique skills, capabilities, and gifts to offer. Give them autonomy, trust and a chance to shine, and you will be surprised with the outcomes.

Lesson 4: The Importance of Encouragement

Geese flying in formation honk to encourage those up front to keep up with their speed.

- We need to make sure our honking is encouraging. In groups where there is encouragement, production is much greater. 'Individual empowerment results from quality honking.' Make sure we praise people and give them the recognition they deserve.

Lesson 5: The Importance of Empathy and Understanding

When a goose gets sick, two geese drop out of formation and follow it down to the ground to help and protect it. They stay with it until it dies or is able to fly again.

- If we have as much sense as geese we will stand by each other in difficult times, as well as when we are strong. It is easy to always be part of a winning team, but when things get difficult and people are faced with challenges that is when your community can provide you with support.

The original version of Lessons from Geese was written by Dr. Robert McNeish in 1972 ■



COMPILED RESOURCES FOR ANXIETY

WEBSITES:

- **Anxiety and Depression Association of America**
<https://www.adaa.org>
- **Anxiety.org**
<https://www.anxiety.org>
- **Anxiety Social Net**
<http://www.anxietysocialnet.com>
- **The Stress and Anxiety Research Society**
<http://www.star-society.org>
- **The Anxiety Network**
<http://anxietynetwork.com>
- **The Reality of Anxiety**
<http://anxiousnomore.blogspot.com>
- **The Child Anxiety Network**
<http://www.childanxiety.net>



APPS:

Anxiety Free

The Anxiety Free app uses self-hypnosis techniques to help lessen stress and quell feelings of anxiousness.



Relaxing Sounds of Nature

Free Relaxing Sounds of Nature app features 25 soothing nature sounds, plus another 35 sounds that you can use to craft your own relaxation soundtrack.

Headspace

Series of guided meditations is designed to train your brain in just 10 minutes a day, with the ability to track and reward yourself for progress along with a buddy system so that you can stay motivated and help others do the same.

HelloMind

HelloMind attempts to help users loosen these constraints. It does this with guided relaxation audios.

Relax and Rest Meditations

Relax and Rest Medications app is for brief meditations.

Self-Help for Anxiety Management

Learning how to relax can help you manage anxiety symptoms. In it, you'll find an anxiety tracking tool,

relaxation instruction, anxiety treatment guidance, and a community to interact with.

Acupressure: Heal Yourself

Acupressure: Heal Yourself guides you to the various pressure points that you can self-massage to get the relief you need from your anxiety, as well as from pain, addiction, and other common disorders.

Moods

Learning how to manage anxiety first requires you to know how to recognize it. With this mood tracking app, simply enter how you're feeling at any time of day, and use these inputs to track and identify patterns.

Sleep Time

Sleep Time lets you fall asleep to ambient, relaxing sounds and wake to the same.

Stop Panic & Anxiety Self Help

Made specifically for people suffering from panic disorders, Stop Panic & Anxiety Self Help has several features for folks who regularly face panic and anxiety attacks.

What's Up?

Cognitive behavioral therapy (CBT) involves learning more about how you think and how your thoughts affect your emotions.

The Worry Box

The Worry Box was designed to help people cope with worry and learn how to effectively manage the disruptive emotion.

Worry Watch

Worry Watch is an app that aims to help you manage worry and anxiety by delving into the thought processes that lead us down this path of unjustified stress.

MindShift

It teaches relaxation skills, develops new thinking, and suggests healthy activities.

BellyBio Interactive Breathing

Biofeedback device that monitors your breathing and plays sounds reminiscent of ocean waves when you relax.

Take a Break! Guided Meditations for Stress Relief

Listen to a seven-minute Work Break or 13-minute Stress Relief recording with or without music or nature sounds.

T2 Mood Tracker

Mood Tracker tracks symptoms of depression, anxiety, PTSD, traumatic brain injury, stress and general well-being.

BOOKS:***The Kissing Hand* by Audrey Penn**

It helps establish a routine that can get an anxious child through the day with a minimum of worry. In the book Mrs. Raccoon's kiss stays in Chester's hand all day long and reminds him of how much he is loved.

***Llama Llama Misses Mama* by Anna Dewdney**

This book does a great job of illustrating both in words and in pictures.

***I Love You All Day Long* by Francesca Rusackas and Priscilla Burris (ages baby-preschool)**

This book guide children through their first days at school.

***Your Anxious Child: How Parents and Teachers Can Relieve Anxiety in Children* by John S. Dacey, Ph.D. and Lisa B. Fiore, Ph.D**

It contains many activities that parents and teachers can use to teach children coping skills.

***Monkey Mind: A Memoir on Anxiety* by Daniel Smith**

A witty and insightful book that charts the landscape of what it is to have anxiety. It is a single person's story of dealing with severe anxiety.

***Feeling Good: The New Mood Therapy* by David D. Burns**

Just like the title says, Dr. Burn's book is all about "feeling good." He teaches us how to use cognitive therapy techniques to get rid of negative thoughts and decrease depression.

***The Anxiety and Phobia Workbook* by Edmund Bourne**

This is one of the classic books on the subject of anxiety. It shares many great ideas of many of the treatment options available.

***Furiously Happy: A Funny Book about Horrible Things* by Jenny Lawson**

This book is a journey with and lots of laughs for those who have only had sadness when dealing with anxiety.

***Anxiety as an Ally: How I Turned a Worried Mind into My Best Friend* by Dan Rykart**

This is another personal story about how one man went from having a panic attack during a roll call to

becoming a successful public speaker.

***What to Say When You Talk to Your Self* by Dr. Shad Helmstetter**

Dr. Helmstetter's book is about the power of the mind. In fact, according to this book we can become what we think and tell ourselves.

***My Age of Anxiety: Fear, Hope, Dread, and the Search for Peace of Mind* by Scott Stossel**

Stossel discusses the social, neurological, and environmental causes of anxiety as well as many tools and tricks for decreasing the impact of these anxiety triggers.

***Dare: The New Way to End Anxiety and Stop Panic Attacks* by Barry McDonagh**

Based on science and Barry's personal experiences helping those who suffer from debilitating anxiety. Barry shares a comprehensive guide that draws from his extensive experience helping those who suffer from anxiety and panic attacks.

***The Anxiety Toolkit: Strategies for Fine-Tuning Your Mind and Moving Past Your Stuck Points* by Alice Boyes PhD**

This book gets right to the heart of the different ways anxiety affects the lives of its sufferers. It gives great detail on what causes people to feel anxiety as well as clear steps to decrease anxiety.

***Change your Brain Change your Life (Revised and Expanded): The Breakthrough Program for Conquering Anxiety, Depression, Obsessiveness, Lack of Focus, Anger, and Memory Problems* by Dr. Daniel G. Amen**

This is not "simply" a book about anxiety. It has sections dealing with all sorts of emotional issues: anger, focus, anxiety, depression, obsession, lack of focus and memory issues.

***Taking Control of Anxiety: Small Steps for Getting the Best of Worry, Stress, and Fear* by Bret A. Moore, PsyD**

This straightforward guide, filled with compelling case examples and easy to use techniques, will teach you to identify, reduce, eliminate, and prevent the negative effects of anxiety.

***My Anxious Mind: A Teen's Guide to Managing Anxiety and Panic* by Michael A. Tompkins, PhD and Katherine A. Martinez, PsyD**

My Anxious Mind outlines a simple and proven plan to help you understand and deal with your anxiety and panic. ■

IEPS AND 504 PLANS FOR SCHOOL-AGED KIDS

By Ashley Bricker, Mom of Johnny, Age 3



Sending a child with MSUD to school can be both a daunting and exciting task. How do you ensure that your child's MSUD is being managed properly at school? You create a 504 plan or an Individualized Education Plan (IEP)! Public schools are required to develop

and implement these plans by the Individuals with Disabilities Education Act (IDEA) and Section 504 of the Rehabilitation Act of 1973.

What is the difference between an IEP and a 504 Plan?

An IEP is a plan or program developed to ensure that a child who has a disability identified under the law and is attending a public elementary or secondary educational institution receives specialized instruction and/or related services. A 504 Plan is developed to ensure that a child who has a disability identified under the law and is attending an elementary or secondary educational institution receives accommodations that ensures their academic success and access to the learning environment. The difference between the two relates to the necessity of "specialized instruction". To simplify, does your child need speech therapy or occupational therapy in school (or any other service to assist in their academic success)? If the answer is "yes," then your child needs an IEP. If the answer is "no," then your child should have a 504 Plan. **It is important to note that private schools are exempt from this requirement unless they receive federal funds.**

Now, let's discuss preparing your child's 504 Plan.

First and foremost, make sure you are always a part of any 504 meeting your child's school has about his or her plan. Speak to whomever is in charge of this at their school and require that you are part of the 504 team at all times and that you are consulted prior to any changes being made to the plan. Get this in writing! MSUD is not a widely understood diagnosis and it's unlikely that your school has ever had a child with MSUD attend before. Some will compare MSUD to food allergies and fail to understand the severity of the disease. Without you, the 504 team will not know what your child needs or how to manage their care and diet while in school.

What should my child with MSUD have in their 504 Plan?

The long and short response to this is: everything you can think of! Even if you don't think it is important, add it! I work behind the scenes in Early Intervention and have been creating Johnny's 504 in my head for well over a year now (he is only 3 years old). Some things to consider including are:

- Your child's emergency room letter from their clinic
- Phone numbers for parents, medical teams and dietitians
- List of any allergies your child has to medications, medical tape, etc.
- List of any allergies your child has to food, drinks, etc.
- Access to pre-made medical formula at all times
- Storage of additional cans/packets of formula at school
- Access to Gatorade, water, formula and/or low protein snacks during and after gym classes and/or recess
- Unlimited access to a nurse (or nursing staff)
- Access to any prescribed medications at proper times throughout the day
- Permission to call their parent/guardian at any time should they feel unwell to describe their symptoms
- The ability to select teachers based on their ability to understand MSUD
- List of symptoms your child portrays which may

suggest elevated leucine levels

- Access to ketone test strips at school
- A nurse who knows how to properly read ketone test strips
- Unlimited access to the bathroom
- A cyber school/home bound plan if your child becomes ill
- The ability to pull your child from school and to be schooled remotely if need be during bad cold and flu seasons or outbreaks or any illness
- Mandatory and immediate notification if an outbreak of illness occurs at the school
- Mandatory and immediate notification if mold is found anywhere in the school
- Unlimited absences/no consequences for missing more days of school than “allowed”
- Promote good hand hygiene at all times for your child, classmates, teachers and all staff
- Child is to be seated 6 feet away from anyone in class who is ill
- More time to complete assignments if necessary
- Adding Cambrooke Cares to the lunch program (<https://www.cambrooke.com/blog/2018/01/metabolic-balance-during-school-lunch-its-the-law/>)
- Teaching the cafeteria to weigh food OR allowing your child (depending on age) to have a scale to weigh their own food before and after eating
- School staff and child are not to throw any uneaten food away whether they pack or buy
- Allowed snacks and drinks at all times
- Snacks MUST be sent in by parent or in approved snacks bins
- Child is not allowed any other snacks outside of what parent sends or is in snack bin unless parent is notified and gives permission
- Child is allowed to skip gym/recess and be given something else to do should they feel unwell
- In the case of an emergency evacuation from school, the child’s MSUD formula MUST be brought with him or her
- To be informed immediately if there is a substitute teacher in class
- Formula, food, emergency letter, etc. to be

brought in an appropriate cooler on field trips

If your child has a g-tube or port, you will want to add the following:

G-Tube

- Nurse and other staff must learn proper way to use g-tube
- Nurse and other staff must learn to replace g-tube should it come out
- Nurse and other staff must notify parents/guardians if g-tube becomes dislodged
- An appropriate schedule for enteral feedings will be created and maintained at all times
- All enteral feeds will be documented with date, time, what was fed, amount of what was fed and if the child had any issues with the feed (vomiting, nausea, discomfort, etc)
- Discuss WHO will supply the pump, bags, etc for feeds (school or you??)
- Nurse or other staff will perform a weekly inventory of feeding tube supplies. Should anything be needed, it will be ordered or a call made to parents
- Schoolwork can be sent with child to nurse’s office while child receives enteral feeding

Port

- Port is NEVER to be accessed by anyone other than an RN in a hospital setting where there is proper sanitization and standards followed
- Child is to be extremely cautious during contact sports because of port
- If child is not comfortable participating in an activity in gym or after school for fear their port may be harmed, child is allowed to sit out, no questions asked
- Child is allowed a protective port cover during gym or other such activities
- Child’s fever is to be checked anytime they are at the nurse; a fever of 101.4 requires an immediate call to parents as child may need to be admitted to hospital
- If port site is red, inflamed, or there are “lines” (that could look like blood vessels) around the port, parents are to be called immediately ■

WORKING WITH MSUD

By Laura Guthrie, 30 years old, atypical classic MSUD, UK



I would like to share an account of my transition from the world of study into the world of work, and what that has meant to me as an individual with MSUD. It is a journey by no means complete, with much to navigate along the way that is probably relevant to many adults with MSUD.

For 7 months I worked as a general assistant in a hotel, with an emphasis on reception duties. Although I made it clear that forty hours a week was the maximum I can manage (it is – I start feel progressively unwell if I try any more, and am more prone to colds), and my boss worked hard to try and accommodate my needs, she still frequently had to schedule me longer hours with later finish times. I was living a half hour's drive away, so it's easy to imagine the strain I incurred from this.

Unfortunately my schedule frequently changed at the last minute and I rarely had days off which I could plan in advance. On one occasion I had to do split shifts two days in a row. I had to constantly remind the person setting the schedule that eight hours a day five days a week was the maximum I could manage. After a couple of serious infections, general tiredness and a mental crash that had been in the making for several weeks, I finally decided I had no choice but to hand in my months' notice. That was not easy, but I believe it

was right and necessary. Since then my ex-boss has stated that she does not believe that MSUD was the reason I quit, though we are still on good terms. Yes, blood tests confirmed that my levels didn't actually go off during my time working at the hotel, even towards the end. However, a stable canoe is not an invitation to see how much rocking it can take.

A mixture of things rendered this type of work unsuitable. It took some time for my boss to understand that MSUD isn't just a mild thing magnified in my mind by overprotective family constantly muscling in and mollycoddling me. How does one explain the implications of MSUD to employers and colleagues as necessary to safely work? I am faced with this question now as I search for the right type of job, the right workplace in which to perform that job, and the right role within that workplace. There's a brilliant essay by Christine Miserandino called *The Spoon Theory* that explains how this affects people with chronic conditions. You can find it on the website 'But You Don't Look Sick' (<https://butyoudontlooksick.com/articles/written-by-christine/the-spoon-theory/>).

MSUD doesn't 'look' like anything. I don't have brain damage that puts me in a wheelchair. An MRI done on me as a teenager didn't reveal anything out of the ordinary. My verbal skills are above average. My intellectual function has got me through three university degrees, and although I have Asperger's syndrome and some attention problems, in a social setting I don't stick out like a sore thumb.

In some ways trying to pare down an explanation of MSUD so that it's useful but doesn't dominate the focus of conversation or take up too much time is a bit like the poem 'The Blind Man and The Elephant' by John Godfrey Saxe (<https://www.poemhunter.com/best-poems/john-godfrey-saxe/the-blind-man-and-the-elephant/>). It's a brilliant commentary on skewed deductions from partial evidence. My point being, if I say 'I have high energy needs' people are liable to assume I just faint if I go too long without meals, which may be of some use, but wait until they try to offer me food I can't eat because it's too high in protein! MSUD is full of such intricacies and (on the face of it) contradictions. Then if I get ill, tired or

stressed I might have to explain that it isn't just food that's the issue – it's calories and muscle protein, especially when I'm ill.

It's hard to distinguish the extent to which certain learning difficulties common to MSUD, for reasons not fully known, affect me as a worker. I can't speak for anyone else with MSUD, but these are some things I am learning over time:

- I have trouble processing and applying a lot of new information and procedures that I am learning simultaneously at a fast pace. Doing so is incredibly stressful. To do it, I have to somehow find a way to 'revise' at home, at my own pace, to complement what I am learning in real-time.
- I am MUCH more prone to anxiety and depression than my peers, which can reduce the quality of my non-working time when employed, and impact my ability to take mental breaks from my work.
- I get 'mixed up' with numbers, statistics and intricate procedures requiring strategic thinking.
- I need things to be explained more times than most, in more detail than most and with more time taken than most.
- I need to check my understanding of things with people explaining them to me, more times and more thoroughly than most.
- Even then sometimes I make unusual mistakes that are hard for others to understand.
- My attention span seems to be shorter than most, and it seems to take more energy and discipline for me to stay focused in certain situations.
- My physical stamina seems to be lower than average, affecting how I 'budget' my energy.
- Though my biochemistry may be normal, some days I just feel 'off' and need more rest and calories, and though everyone gets days like this, I need to give them more respect than most.

How does one explain all this to busy people in the workplace who like simple and clear explanations/solutions, reliability and predictable, consistent results? To an employer I'm sure it can sound like I use MSUD as an excuse for everything when an issue

comes up. Who could blame a boss for running out of patience with such a bizarre medley of inexplicable invisible disability implications? Sometimes I just felt self-centered and demanding in stating my needs. Most likely every employed MSUDer has their own experiences and strategies in this respect.

Anyway, while earning a degree, you know you'll come out the other side and that it's a means to an ends. Full time work, however, takes up at least a third of your life, for most of your life, so you need to feel ok in it. For MSUDers there seem to be three dangerous periods: childhood, pregnancy/birth, and establishing a career. These are the times during which most reported sudden deaths or decompensations seem to occur. I reckon this is because those are times when people are really testing their limits and making compromises with their management for whatever reason. Non-MSUDers don't have to be nearly as regimented in their day to day routines, and that is reflected in workplace management, conventions and infrastructures, and the pressures and obligations placed on workers.

A popular disability rhetoric is to not let your diagnosis get in your way or limit your options. Well, MSUD may set boundaries for me, but it doesn't hold me hostage. It's like driving safely: 'the slowest route to your destination is via the cottage hospital'. Overcoming the dangers means sticking to the speed limit and wearing your seat belt.

One other important thing I have learned is that it is necessary to really know your limits yourself, in order to help other people respect them, and find a job that fits around them. The job aspect is not something I had ever really understood until I had a glimpse of the workplace that people without MSUD have to navigate. I am a much more typical MSUDer than I realised! From the MSUD community I draw hope and inspiration, counteract a sense of alienation, and know better how to use resources pertaining to MSUD to help me.

Love and thanks to all my MSUD family in the UK and US and beyond, for reading this, and for being my 'tribe' in a way I am feeling now more than ever before! ■

MEDICAL MANAGEMENT OF MSUD

By Dr. Nicholas Ah Mew

Dr. Ah Mew began his presentation with a review of the biochemical basis for the disease. MSUD results from a deficiency of branched-chain alpha-keto acid dehydrogenase complex (BCKDC) enzyme. The BCKDC enzyme has several components, each of which is coded for by a different gene. All forms of MSUD are inherited in an autosomal recessive manner.

Mutations may occur in different components of the branched-chain alpha-keto acid dehydrogenase complex (BCKDC) enzyme. Mutations of the E1 alpha component are responsible for 45% of MSUD cases, and a common mutation is found in the Mennonite population. E1 beta defects result in 35% of MSUD cases, and a common mutation is found in Ashkenazi Jews, while E2 defects result in 20% of MSUD cases and a common mutation is found in Central Americans.

Every state in the US currently screens for MSUD, in the majority of cases allowing treatment to start before symptoms or harmful effects occur.

Why is high blood leucine levels bad?

The effects of high blood leucine are not fully understood. A simplified view of our current understanding is that when elevated in the blood, leucine is preferentially transported into the brain. As a result, other amino acids which are needed to make neurotransmitters may be present in inadequate amounts, possibly causing neurological symptoms. The influx of amino acids into the brain may draw water along with it, causing a swelling of the brain, or edema.

Management:

Adequate amounts of BCAA are needed for normal

growth, while an excess is harmful. It is also essential to obtain the required number of calories along with vitamins and minerals to support normal growth and to prevent acute crises.



Infections are often the cause for metabolic instability. To reduce risk of infection it is important to practice good hand washing habits and stay on top of vaccinations, including an annual flu vaccine.

Sick day plan:

It is essential to contact the metabolic team when an illness occurs. If the patient is ill but acting normally, typical strategies include:

- Reduce dietary leucine
- Increase formula
- Increase calories
- Increase fluids
- Increase isoleucine and valine
- Treat the underlying cause of the infection (antibiotics if appropriate)

Go to hospital if experiencing:

- Change in mental status
- Inability to tolerate feeding by mouth
- Abundant urine ketones
- Caregiver is not comfortable with home management

Management of acute crises:

Leucine levels are reduced when the body uses it to make protein. In MSUD, the only other way to reduce elevated leucine levels is through dialysis, which is the quickest way to accomplish this. However, there are risks associated with dialysis, and the use of dialysis during acute crisis in MSUD is still debated among metabolic doctors.

To promote protein synthesis, all amino acids except leucine must be provided. This is usually accomplished through the metabolic formula or TPN. Isoleucine and valine should be supplemented. Extra calories are needed to stop the breakdown of body tissues. Dextrose (at least 10% at a high rate) and fat (intralipids) can be given through an IV. A small amount of insulin can also be added to promote protein synthesis.

The brain must be protected, and a CT or MRI should be conducted if edema is a concern. If edema is present, fluid intake should be reduced. A hypertonic saline, mannitol, and diuretics may also be useful.

Long-term considerations:

Developmental delays are a concern. All families should be referred to early intervention.

ADHD, anxiety or mood disorders are common and may require referral to a mental health professional.

Movement disorders (tremor, dystonia) may occur, requiring a referral to a neurologist or movement disorder specialist.

Liver transplantation:

This can be performed when the patient is clinically stable and can restore enough enzyme activity to allow for an unrestricted diet and prevent acute crisis BUT there is a considerable risk of complications and a need for immunosuppression therapy.

Dr. Ah Mew emphasizes that all treatment strategies must be discussed with one's treatment team. ■

NEW OPTION FOR CUSTOM AMINO ACID INFUSION BLENDS: INTEGRITY COMPOUNDING PHARMACY

By Casey Gaetano

Integrity Compounding Pharmacy has recently begun providing custom amino acid infusion blends for patients with inborn errors of metabolism, including MSUD. Integrity, located just outside of Atlanta, Georgia, has been conducting high-risk sterile compounding since 2013 for a variety of other medical disciplines. However, upon learning about the lack of providers and the critical need for these particular therapies, we have developed a new division to ensure that a source remains located in the United States to service these patients.

Currently, we are contracting with many of the hospitals that may need custom amino acid infusion blends in the future. As we undertake this process, we implore you to reach out to us directly in the event of an emergency in which a supplier cannot be located. Our website is www.MixWithIntegrity.com, and our phone number is 404.815.1610.

We intend to connect with all of the key stakeholders – patients, families, providers, researchers, and more – over the next few years. Hopefully we will have the opportunity to meet many of you at symposiums, camps, and conferences in the years to come. Integrity Compounding Pharmacy is grateful and excited for the opportunity to serve the MSUD community.

Editor's note:

Total parenteral nutrition (TPN) is sometimes used as a way of delivering nutrition to patients in metabolic crisis when it is not possible to obtain adequate nutrition orally or through tube feeding. These IV solutions have been provided in the past by Coram, but this company is no longer making them. We are thankful that Integrity will step in as a provider of this vital product. ■

NUTRITION MANAGEMENT OF MSUD

By Dr. Rani Singh

The goals of nutrition management of MSUD are to:

- Reduce toxic metabolites by limiting branched-chain amino acids (BCAAs)
- Prevent BCAA deficiencies
- Minimize catabolism (breakdown) of the body's proteins
- Promote adequate protein synthesis
- Monitor clinical, biochemical and nutritional status, and individualize intake to promote growth, development, and health

It is important for an individual with MSUD to know their entire nutrition prescription, not just the amount of leucine allowed. This includes:

- Protein from medical foods and intact protein
- Energy
- Vitamins and minerals
- Essential fatty acids (these should be checked as levels are often low with MSUD)

Parents should start children on fruits and vegetables early to ensure adequate amounts since they are generally low in protein and are nutrient dense. This is important for long term control of blood leucine levels and will potentially enhance nutrition status of the individual.

Formulas vary in nutrient content. Some provide complete nutrition while others do not. It is important to understand the differences between these formulas. While those with MSUD are reliant on medical formulas for most of their protein requirement and other nutrients, it is important to select the optimal formula. Modified low protein foods can make the diet more palatable and provide a source of calories. As an alternative, blenderized foods and breast milk can be provided as a source of intact protein when using a G- tube.

Treating MSUD is more than just giving formula. Clinicians must understand the art and science of treatment. A group of experts led by Dianne Frazier RD have developed Nutrition Management Guidelines for MSUD. This is available to metabolic dietitians along with a toolkit on the GMDI (Genetic Metabolic Dietitians International) website. One page summary sheets will also be made available for parents.

Nutrition goals during acute illness:

The following is recommended to prevent catabolism and minimize elevation of leucine levels during illness:

- 150% of energy requirement
- 120-150% recommended BCAA-free amino acids
- Fluids and electrolytes
- ~20-70mg/kg/day isoleucine and valine for those under 4 years of age, 250-500mg/day for those older than 4 years of age.
- Insulin to prevent hyperglycemia

Nutrition considerations during pregnancy and lactation:

Leucine requirements increase during the 3rd trimester of pregnancy. Blood levels should be monitored with greater frequency. For some, home monitoring using filter paper is available. It is important to prevent catabolism during delivery by providing adequate calories.

Lessons learned through years of experience:

- Higher doses of isoleucine and valine, up to 100 mg/kg/day, can help reduce leucine levels quickly. Formula should be introduced as early as possible during illness. The energy (calories) provided in BCAA free mixtures will promote anabolism (tissue building).
- Proper attention must be paid to the quality of protein in the diet. The most healthful food options should be selected within the limitations of the diet.
- Frequent (monthly) monitoring is encouraged to avoid nutrient deficiencies, and it is

valuable to see the dietitian at regular intervals for diet adjustments, especially during rapid periods of growth.

- Use of a G tube should be considered in cases where feeding issues make it difficult to consume adequate nutrition.
- Use of BCAA- free TPN is recommended during acute illness if the gut cannot be used to provide nutrition.
- Access to low protein modified foods is necessary to add variety to the diet and to meet energy needs.
- To evaluate responsiveness to thiamine, a starting dose of at least 100 mg B1 (thiamine) daily should be used. ■

RESEARCH



GENETIC THERAPIES FOR MSUD

By Dr. James Wilson

Orphan diseases, including MSUD, are caused by a mutation in a gene. This mutated gene is unable to produce messenger RNA (mRNA), which carries the information from the gene needed to produce a protein.

In **gene therapy**, a normal version of the gene is introduced into the cell. This is very difficult to do, and is usually accomplished by using a virus which will infect the cell and deliver the new gene. The virus is modified so that it cannot cause disease. The adeno-associated virus inserts its DNA into the nucleus of the cell where it can then make the healthy mRNA and the necessary protein. As it reproduces prolifically, the hope is that it will continue to make the required protein. This technique is now being used successfully in retinal disease, where the genes can easily be introduced into the appropriate cells in the eye.

Gene therapy for MSUD would require an introduction of the normal version of the BCKH gene into the liver. The blood vessels of the liver have

large pores, and anything introduced into the blood will enter the liver.

Hemophilia, characterized by an absence of the gene which causes blood to clot, has been successfully treated by injecting the missing protein into the blood. This treatment must be repeated weekly as proteins don't last. With gene therapy, the gene will be injected into the blood and taken up by the liver. In this way, adequate protein can be made for a long period of time.

A clinical trial for gene therapy is now under way for a urea cycle disorder called ornithine transcarbamylase deficiency (OTC). This is another metabolic liver disease controlled by diet and drugs.

Dr. Wilson's lab is currently involved in a pilot gene therapy study using mice with intermediate MSUD (iMSUD mice). While reduced levels of BCAA have been observed, it is not yet known whether this will allow the mice to live (they currently die after a few weeks of life).

Messenger RNA (mRNA) therapy: This is an alternative technique to gene therapy in which mRNA is packaged and delivered to the liver using IV infusion. mRNA will make healthy protein, but will not be retained by the cell and will need to be reintroduced approximately every 2-4 weeks. However, this may be safer than gene therapy. As it bypasses the gene step, it provides activity within hours.

Genome editing: This technique aims to fix the mutation rather than adding a normal version of the gene. While this would be a permanent fix, it would require a different drug for each mutation. Dr. Wilson does not feel that this is viable for MSUD in the near future.

Future of Molecular Therapies for MSUD

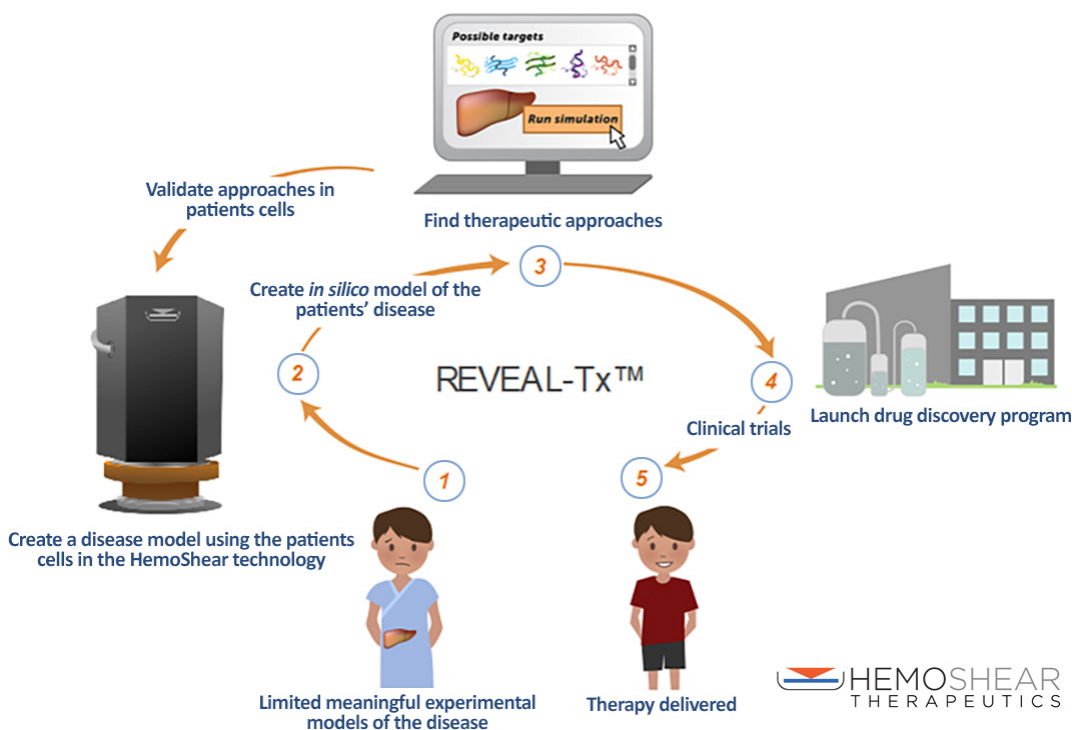
UPenn is now evaluating the feasibility of gene therapy vs mRNA therapy for MSUD. Clinical trials are planned for July 2020. ■

MODELING MSUD TO ADVANCE PROGRESS TOWARDS NEW TREATMENTS

By Brian Wamhoff, PhD, Head of Innovation at HemoShear Therapeutics

New treatments are greatly needed to improve the quality of life for people with maple syrup urine disease (MSUD). In order for progress to be made, however, we need to really understand how the disease works and identify opportunities to disrupt and correct the faulty metabolic process of MSUD.

HemoShear Therapeutics' Drug Discovery Process - REVEAL-Tx™



I am head of innovation at HemoShear Therapeutics, a biotechnology company dedicated to generating the important insights that may lead to new therapies for MSUD and other rare inborn errors of metabolism.

As I shared at the MSUD Family Support Symposium in June, our company is recreating the human disease biology of MSUD. We are working beyond the traditional approach of examining static cells in a petri dish. Our innovative platform, called REVEAL-Tx,™ combines the power of dynamic human biology and computational science to discover new pathways for treating MSUD. We have established a global network to collect the

donated livers of MSUD patients who have undergone liver transplants. We have harvested the cells from these diseased livers and used our proprietary technology to build a dynamic bioreactor that recreates MSUD in our laboratories. This enables us to understand MSUD better than ever before.

We model MSUD in a computer, turning genes on and off to see if they fix the disease. We then use our bioreactor that mimics the human biology of MSUD to validate the approach.

We are making good and steady progress. Through the insights generated from our bioreactor, we have identified a novel therapeutic target for MSUD. We are now building molecules that address this target and are validating them in our system, with the goal of developing a drug to treat this disease.

This process can be painstaking and expensive. We work with a great sense of urgency as we focus on building partnerships and raising money to move a drug forward. The drug development field learns through failure. Our goal is to fail fast, so we can learn faster and maintain momentum toward developing a safe and effective treatment for MSUD.

We could not have gotten to where we are now without the support of the patients and their families who donated their livers to our research. They inspire us to continue our important work.

We will continue to keep the MSUD community aware of our progress and hope to one day move into the clinic with a promising new treatment.

See my presentation at the 2018 MSUD Family Support Meeting (<https://www.msud-support.org/featured/news/718-2018-msud-symposium-presentations>) ■

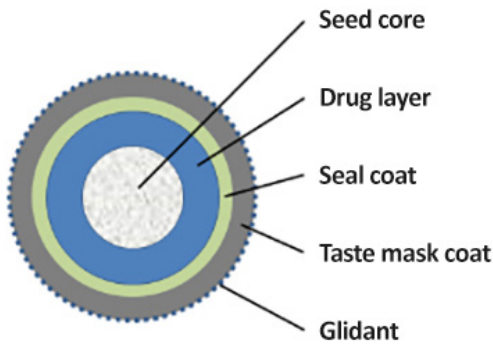
UPDATE ON DRUG DEVELOPMENT

By Bob Steiner, MD - Consultant to Acer Therapeutics

Acer is working closely with key opinion leaders and patient advocacy groups to provide a compelling treatment option for patients with MSUD and urea cycle defects (UCD). ACER-001 is a new formulation of phenylbutyrate being developed for MSUD that provides significant differentiation from other approved formulations of phenylbutyrate. It is a taste-masked, immediate release formulation of sodium phenylbutyrate, provided as an oral powder for reconstitution in liquid. Phenylbutyrate has been shown to reduce leucine levels in some individuals with MSUD, and may prove to be an effective adjunct to diet in the treatment of this disease. The goal of ACER-001 development is to improve palatability of sodium phenylbutyrate with a new formulation and show bioequivalence to the current drug, Buphenyl, in a clinical trial.

The product design is shown below.

Multi Layer Coated Particle:

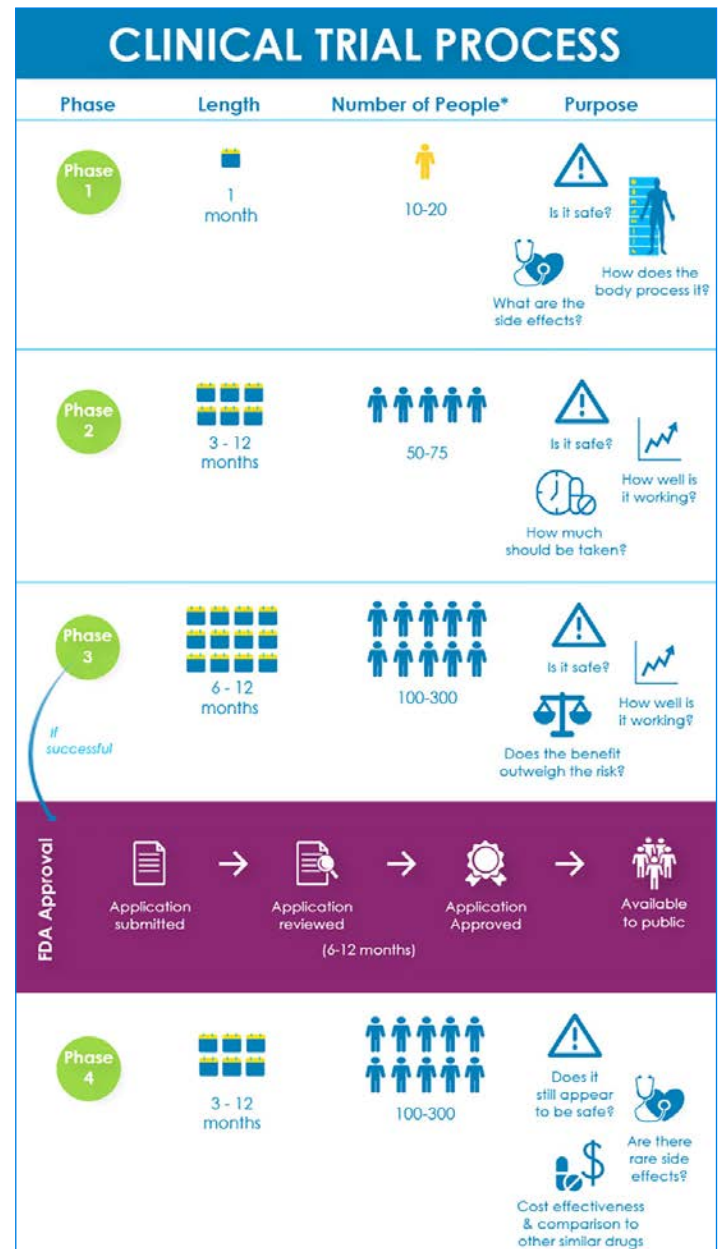


Characteristics of current forms of phenylbutyrate compared with ACER-001:

Phenylbutyrate Formulations			
	ACER-001	RAVICTI	BUPHENYL
Efficacy/Safety in UCD	✓	✓	✓
Efficacy/Safety in MSUD	✓	✗	✓
Palatability / Compliance	✓	✓	✗
Relatively Reasonable Orphan Pricing	✓	✗	✓

The first clinical trial of ACER-001 will be a study to show bioequivalence to Buphenyl, which is currently planned for 2019. The development plan for ACER-001 has been delayed because manufacturing ACER-001 has been difficult and has taken a lot of time to develop, resulting in this new timeline. Nevertheless, Acer intends to submit a new drug application (NDA) for UCD in end of Q4 2019 with anticipated sNDA submission for MSUD about a year later. Acer holds orphan drug designation in MSUD, and plans for advantageous orphan pricing with a robust program to support reimbursement and patient access.

The typical drug development/clinical trial process was briefly discussed at the MSUD Symposium, and is outlined below:



NEWBORN SCREENING CONNECT PATIENT REGISTRY

By Aileen Kenneson-Adams, PhD, MS
Emory University School of Medicine



Newborn Screening Connect (NBS Connect) is a web-based self-reported patient registry and resource for individuals and families affected by inherited metabolic disorders included in the newborn screening panel. NBS Connect was launched in 2012 by Emory University, as a part of the Southeastern Regional Genetics Network Initiative funded through HRSA with years of planning and grassroots work by professionals, consumers, and industry. The purpose of NBS Connect is to collect and analyze data on diagnosis, treatment, symptoms, outcomes, and barriers to care. NBS Connect also provides resources for patients and families including educational materials, low protein recipes analyzed by registered dietitians, interactive health tracking tools, information about the latest research and clinical trials, opportunities to connect with experts and a forum for patients and their parents to connect with each other.

At the time of the MSUD Symposium in June 2018, about 80 individuals with MSUD were registered with NBS Connect, and 47 of them had completed the survey about their experiences with MSUD. Here we provide an overview of what we've learned from the MSUD participants in NBS Connect.

MSUD participants ranged in age from four months to 41 years. Almost half (42%) had been hospitalized in the previous year. Those that had been hospitalized were younger (average=10 years) than those who had not been hospitalized in the prior year (average=17 years). Three of the participants had received a liver transplant. Most participants (61%) had received genetic testing, and most were willing to share the results of the test with the registry, but only one person did so. An NBS Connect genetic counselor is available to assist patients and families with adding their genetic test results into the registry. Children under the age of five years were more likely to have leucine levels in the target range (87%) than were individuals over the age of five years (45%).

Thirty-one of the participants were diagnosed through newborn screening. Most of the individuals (56%) had a height that was below the normal range for their age. However, individuals who were diagnosed through newborn screening were more likely to reach the normal height range for their age.

Most participants (95%) reported that they currently had a prescribed diet with protein restriction. The exceptions were three individuals who had received a liver transplant, and one other person. Three-quarters of the people follow their prescribed diet at all times. The most commonly-reported barriers to care were getting reimbursement for specially modified low protein foods (30%) and medical food (formula) (17.5%). Other items for which people struggled to receive reimbursement included free amino acids, blood leucine testing, lab work, MSUD specialist visits and genetic testing.

The most common symptoms at the time of diagnosis included lethargy/weakness, poor feeding, maple syrup odor, nausea/vomiting, and coma. Symptoms were more common in individuals who were diagnosed later than in those who were diagnosed by newborn screening. Despite dietary management, many individuals reported ongoing symptoms, including poor concentration, lethargy/weakness, and maple syrup odor. Just over half (55%) had experienced a skin condition, including rashes, eczema, psoriasis, acne and dry scalp. Mental health symptoms were reported by 39% of participants, including ADD/ADHD, anxiety and depression. Those who started their diet earlier were less likely to report such symptoms.

In conclusion, despite dietary treatment, leucine levels were above the target range in about half of the survey respondents. There were high rates of hospitalizations, mental health symptoms, and skin conditions. Diagnosis through newborn screening and early treatment may help improve outcomes.

Help yourself and the MSUD community by joining the registry, if you have not already done so, and completing the survey to tell us about your experiences with MSUD. The registry is online at NBSconnect.org, or you can contact the NBS Connect Registry Project Coordinator, Yetsa Osara, by email at coordinator@nbsconnect.org or by phone at (404) 778-0553. ■

FROM THE PROFESSIONAL JOURNALS

Summarized by Karen Dolins

Long-term metabolic follow-up and clinical outcome of 35 patients with maple syrup urine disease.

Abi-Wardé MT1, Roda C1, Arnoux JB1, et al. *J Inherit Metab Dis.* 2017 Nov;40(6):783-792

This study investigated psychosocial outcomes in individuals with MSUD and how they related to metabolic control. Information was collected from medical records for a period of 49 years. Of the 35 patients studied, 61% were independent as adults, with 56% requiring some level of psychological or psychiatric treatment. The need for this treatment was associated with the number of metabolic decompensations which occurred.

The authors note that a high level of depression and anxiety has been observed in those who experienced a coma in the neonatal period. ■

Incidence of maple syrup urine disease, propionic acidemia, and methylmalonic aciduria from newborn screening data.

Chapman KA1, Gramer G2, Viall S1, Summar ML. *Mol Genet Metab Rep.* 2018 Apr 5;15:106-109.

Incidence for maple syrup urine disease varies by population. This paper reported on newborn screening results from the United States, a region in Germany, and Kuwait. The incidence of MSUD in the United States was calculated to be 1: 220,219, in South-West Germany 1: 119,573, Germany nationwide 1:177,978, and in Kuwait 1: 59,426. Incidence for propionic acidemia and methylmalonic aciduria, other inborn errors of metabolism, were also reported. ■

Successful pregnancy in maple syrup urine disease: a case report and review of the literature.

Grünert SC1, Rosenbaum-Fabian S2, Schumann A2, et al *Nutr J.* 2018 May 12;17(1):51.

This paper describes the pregnancy of a 26 year old woman with classical MSUD. Blood branched-chain amino acid levels were monitored weekly from the 7th week of gestation. Leucine levels were frequently elevated during the first trimester while consuming 700 mg leucine daily, but her tolerance to leucine increased dramatically in the second and third trimesters to 2400 mg leucine daily. She was started on TPN several hours prior to a scheduled Caesarean section in week 38 of gestation, when she delivered a healthy girl. Dietary leucine was reduced to 200 mg daily immediately after birth as levels can spike at that time, but was gradually increased to 1700 mg daily while she breastfed. Leucine levels remained stable throughout the postpartum period. The authors showed that with careful monitoring and collaboration between treatment teams, an individual with MSUD can remain healthy throughout pregnancy, birth, and the postpartum period. ■

Fourteen new mutations of *BCKDHA*, *BCKDHB* and *DBT* genes associated with maple syrup urine disease (MSUD) in Malaysian population.

Ali EZ, Ngu LH *Mol Genet Metab Rep.* 2018 Sep 13;17:22-30.

A number of genetic mutations can cause the enzymatic defects responsible for MSUD. This study identified the specific mutations found in 31 MSUD patients in Malaysia, and found 21 different mutations including 14 which had not been previously identified. The authors concluded that Malaysian MSUD patients have a variety of mutations, but that 1 may be specific to this population. ■

GENE EDITING AND CELL TRANSPLANTATION FOR THE TREATMENT OF LIVER DISEASE

By Stephen Strom PhD, Karolinska Institute

The Strom laboratory at the Karolinska Institute in Sweden has pioneered the use of cellular therapy to treat liver disease, first with the transplantation of human liver cells to correct liver disease and later in the development of a stem cell from human placenta that functions as a liver cell when transplanted. Both of those endeavours continue in the laboratory.

We are now working in specially-designed clean rooms and isolating and freezing the stem cells with European Medical Products Agency approved technique and procedures which will allow us to apply for full approval to treat patients with these promising stem cells. We anticipate that we will submit a full application to the medical product agency in Sweden by mid to late 2019.

A third rail of activity has begun in the laboratory. Using the newly discovered gene editing technology, we are attempting to correct the mutations in the cellular DNA that cause liver disease. We are initially focusing mainly on urea cycle defects because the disease is severe enough that the patients are frequently referred for liver transplantation. Thus, the mutation in the liver cell results in a metabolic problem that is severe and life threatening.

Also, at transplant the liver is removed and we have access to the mutant liver tissue, allowing us to isolate liver cells, analyse the genetic defect, model the disease, and attempt to correct it. Urea cycle defects, like MSUD, frequently arise from single base mutations in DNA, so investigations of gene editing for urea cycle defects would be directly relevant to MSUD and other genetic-based liver diseases. In one series of investigations, we made stem cells from the cells isolated from the mutant liver cells,

identified the mutation in the patient's cells and with gene editing technology, corrected the mutation in the DNA.

While this is exciting, in order to move this to the clinic we would need to make hepatocytes (liver cells) in culture dishes from the corrected stem cells and transplant the patient's own, but now genetically-corrected, liver cells back into the patient. Approval from the FDA for this type of study will likely take another 3-5 years because of the possibility of tumor formation from any stem cells that do not fully become hepatocytes.



A second line of gene editing attempts to correct the mutation in the actual liver cells (not stem cells made from the liver cells like the previously described studies). With certain mutations in the urea cycle genes that we have identified, we are now able to correct 50% or more of the hepatocytes we expose to these gene editing procedures. It is expected that gene editing of the hepatocytes themselves would make it to the clinic much faster than working through the stem cell intermediate.

All of this early work with stem cells and liver cells outside of the body are directed at establishing the safety and efficacy of the gene editing procedures.

Once these are established, we will progress to a 3rd approach, where we will investigate ways to correct the genetic defect in the liver of the patient. This final approach will be designed to correct the mutation in the person's liver by delivering gene editing tools into the blood stream where they will be delivered to the liver and correct the mutation without surgery or transplant procedures. We are working with a major Pharma company to try to move gene editing for liver diseases to the clinic within 2 years. ■

FOOD AND NUTRITION

PICKLED CHERRY TOMATOES

By Dana White, RD

When sauce and salsa recipes have been exhausted and there's still copious amounts of tomatoes from the garden. Pickled. Cherry. Tomatoes. Makes 1 quart



- 2 pints cherry tomatoes
- 1 small jalapeno pepper, stem removed
- 1 large clove garlic, peeled
- 2 springs fresh thyme
- 1/2 cup white wine vinegar
- 1 tablespoon granulated sugar
- 1 cup water
- 2 teaspoons kosher salt
- 1 teaspoon peppercorns
- 1 tablespoon mustard seeds

Using a toothpick or skewer poke a small hole in each tomato and cut the top off of jalapeno (cut in half and remove seeds if you want less heat).

Place tomatoes, jalapeno, garlic clove and thyme in a large jar (a 4-cup Ball jar works perfectly for this).

In a medium saucepan combine vinegar, sugar, water, salt, peppercorns and mustard seeds. Bring to a boil and simmer for 2 to 3 minutes until sugar and salt are dissolved.

Pour or ladle vinegar mixture into jar over tomatoes; allow to cool completely before covering. Store in the refrigerator for up to 2 weeks.

Entire recipe has **5.2 grams protein 184 mg leucine**

<http://danawhitennutrition.com/2017/08/pickled-cherry-tomatoes/> ■

BACK TO SCHOOL WITH CAMBROOKE

It is back to school time, and Cambrooke



Therapeutics has many convenient low protein foods for the active child and busy Mom and Dad.

A few easy items for those mornings when you are rushing to catch the bus are Apple Breakfast Bars, Bagel Bars, French Toast or Cinnamon Raisin Bread.

Take time to sleep in late every so often, knowing that you have these simple items in your panty for those lazy mornings.

We know how hard lunchtimes can be, and most kids want their lunch to look like everyone else's. Tweekz (i.e. nuggets), Mini Pockets PB&J, Instant Noodle Soup-Chicken, and Go! Pockets-Burrito are just a few of the kid's favorites and are easy to prepare. And for those afternoon snacks to add to the lunch box, try tortilla chips-sea salt, wise onion rings, or savory cracker thins.

For the sweet tooth, gourmet chocolate chip cookie or raspberry gems will delight kids at the end of their school day before homework begins. Cambrooke offers more than 100 delicious and nutritious low protein food items to please any child's appetite.

And for the Mom or Dad with MSUD, work life balance can be even more difficult. Try Lynn's Enchiladas, Medley Meal- Thai or Yuca-Tater Home Fries to spice up the night. Try many of our recipes at <http://www.cambrooke.com/recipes> that pair well with Vilactin AA Plus.

Request a sample at <http://samples.cambrookefoods.com> ■

PERSONAL/EVENT

GALEN CARRINGTON

Galen Carrington Jr, 29 year old resident of Hidden Valley returned from Salt Lake City, Utah with 5 Gold Medals after competing in the Transplant Games of America!



The Games had participants from 43 states including international competitors from Brazil, Australia and India.

Galen participated in 5 swimming events in the 18-29 year old age group and swept each event!

Team Indiana placed 3rd overall and the Games set a Guinness Book of World Records for the largest gathering of organ transplant recipients - more than 540 in total!

Please look for Galen to compete again in the World Transplant Games in New Castle, England 2019 and then stateside in Meadowlands, New Jersey 2020.

He dedicated his Medals to his donor family and to his grandfather who passed away a few days before his competition. ORGAN DONATION SAVES LIVES! Galen is thankful for his life-saving liver transplant 6 years ago which cured him of a metabolic disorder. ■

MSUD RESEARCH AND THE MILLION DOLLAR BIKE UPDATE

By Ed Fischler, VP MSUD Family Support Group



Following our success with the 2018 Million Dollar Bike Ride, we are excited that The MSUD Family Support Group has been invited by the Orphan Disease Center (ODC) in Philadelphia to participate in the 2019 Million Dollar Bike Ride. This event will be held on Saturday, June 8, 2019.

The MSUD Family Support Group received over 400 donations totaling in excess of \$74,000 through our participation in the 2018 fundraising event. The ODC provided matching funds of \$50,000 from sponsors of the Million Dollar Bike Ride, making the total amount of funds raised for MSUD research nearly \$125,000!

As a result of the 2018 success, the ODC is funding two research grants for work towards improved treatment and/or a cure of MSUD. Our intent is to award one grant for a gene therapy project and one grant for a non-gene therapy approach to treatment. Proposals for the research have been received by the ODC and will be reviewed by their staff and the Family Support Group's Medical Advisory Panel to select those having the best scientific merit. Research is scheduled to begin in January, 2019.

The Million Dollar Bike Ride provides an opportunity for the MSUD Family Support Group to engage in an activity to support MSUD research along with other rare disease teams facing similar issues. Also, the Orphan Disease Center, which sponsors the event provides much of the management support needed for the event and manages the research process, making our participation easy.

Early in 2019, we will follow up with the member families of the MSUD Family Support Group and ask you to help us repeat the success we enjoyed earlier this year so we can continue with our research program.

Not a bike rider? No worries! YOU DO NOT NEED TO RIDE A BIKE TO PARTICIPATE IN THIS EVENT! ■

JEFF FREDERICKS, 43 YEARS CLASSIC MSUD

By Anne Fredericks, Mom

The Fredericks family from Pa. is so glad to be part of the MSUD family support group and to receive this newsletter. We have learned so much about medical advances, recipes, family issues, and so much more. Thanks to all who contribute to this newsletter especially Karen Dolins. Every couple of years, we like to update you on successes accomplished by our son, Jeff. We think that it helps others who have adults with MSUD. Our son was diagnosed late so he has cognitive issues and dietary problems especially since he has hit his 40's. While he lives with us now, we contacted the ARC to find ways to help him with skills he needs so he can live in a supported way in the future. He has a mentor who comes twice a week. On Tuesday, he goes grocery shopping for his own needs. He then comes home and prepares something. Sometimes it is dessert for all of us, sometimes it is a meal with



meat just for us, and he is now cooking things that we can all eat. The pictures for this article show him cooking a meatless shepherd's pie.



His mom has compiled a kit of cooking utensils just for him.

One interesting item is a red silicone device that helps him pull out the rack in the oven since he has always been afraid of the heat. He also has 2 shiny gloves he wears that will not allow a knife to cut through when he is making a salad. We just purchased an air fryer so he can make fries without the fear of hot oil.

On Thursday, he works on many skills. He cleans his bedroom and bathroom. The mentor has helped him with organizing his space. He is still working on that bottom fitted sheet. He continues to work on money and other things he needs for daily living. Having a mentor has helped Jeff tremendously since he really did not want to do them for his mom. ■

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Thanks for your help with the symposium:

- Sarah Dworcan - travel arrangements
- Karen & Hannah Dolins - travel arrangements
- Camille Libunao-Erpelo & Eric Erpelo - children's activities
- Ed Fischler - videography
- Michelle Flanagan - low protein menu
- Denise Langosch - donors/exhibitors
- Jennifer McIntosh - low protein food, toys for children's room
- Susan Needleman - children's activities
- Susan Mays - symposium planning/assistance with details
- Eddy Wang - MSUD website

GALLERY FROM MSUD SYMPOSIUM 2018



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