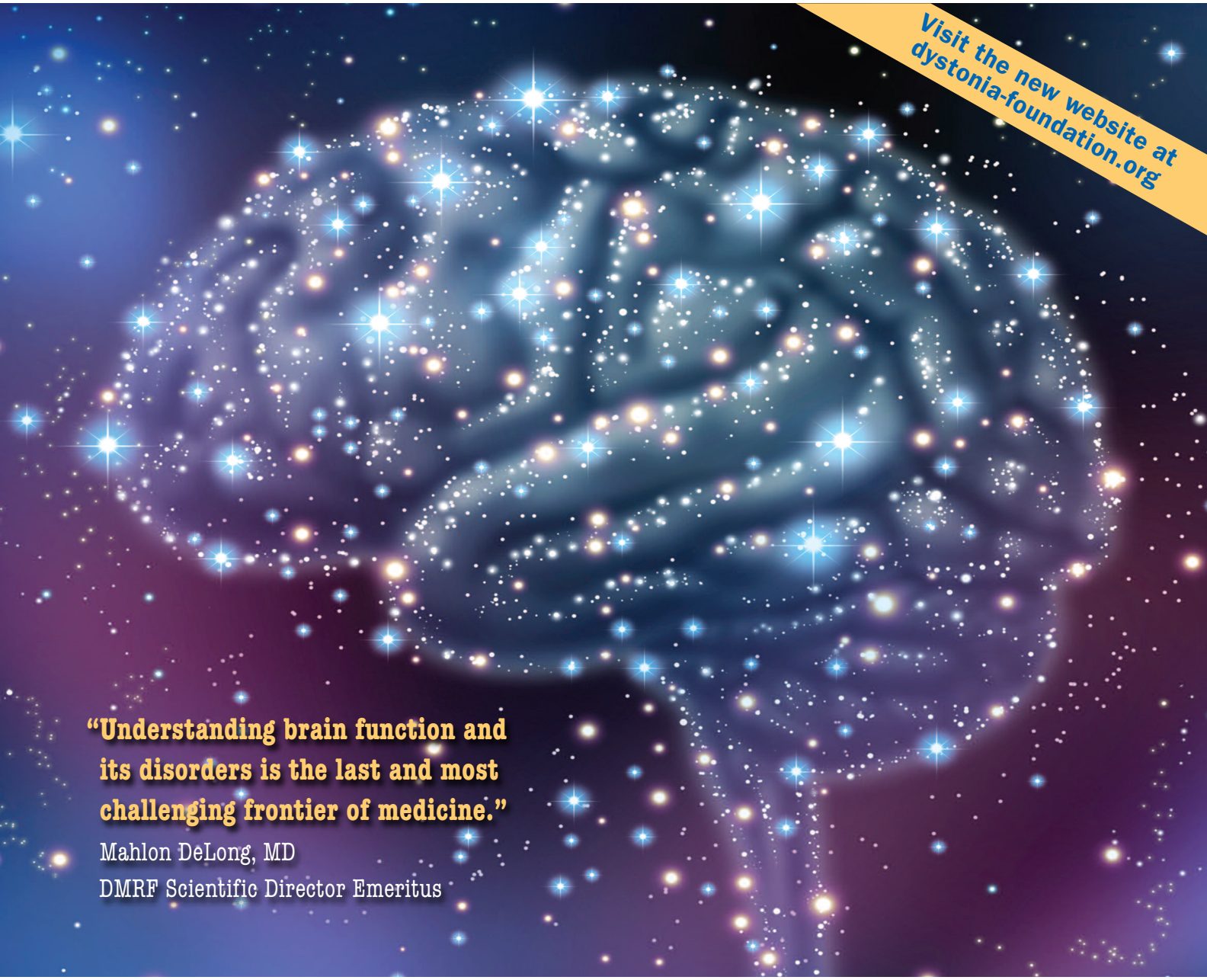
DYSTONIA MEDICAL RESEARCH FOUNDATION

Dystonia Dialogue

NEWSLETTER OF THE DYSTONIA MEDICAL RESEARCH FOUNDATION

Spring 2019 | Volume 42 • No. 1



"Understanding brain function and its disorders is the last and most challenging frontier of medicine."

Mahlon DeLong, MD
DMRF Scientific Director Emeritus

Inside this Issue

On the Cover:

The DMRF's mission to cure dystonia is a boundary-pushing exploration into medicine's final frontier: the brain. The human brain contains 100 billion neurons, and at least 1,000 different types. These neurons create a network of 100 trillion connections. The discoveries needed to find a cure for dystonia are waiting to be found within the brain's complex maze.

The DMRF is committed to expanding the field of dystonia research so that every opportunity to develop new therapies is pursued, not only to benefit families with dystonia today but also for generations to come.

The *Dystonia Dialogue* is the magazine of the Dystonia Medical Research Foundation (DMRF). It is published three times a year to provide information to individuals affected by dystonia, family members, and supporters of the DMRF.

The Dystonia Medical Research Foundation (DMRF) is a non-profit, 501c(3) organization founded in 1976. The mission is to advance research for more effective treatments and a cure, to promote awareness and education, and to support the well being of affected individuals and families.

The *Dystonia Dialogue* reports on developments in dystonia research and treatments but does not endorse or recommend any of the therapies discussed. Individuals are urged to consult a physician with questions and concerns about their symptoms and care.

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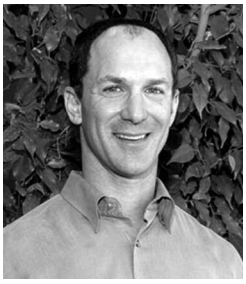
Foundation Update



Art Kessler
President

Janet L. Hieshetter
Executive Director

As a supporter of the Dystonia Medical Research Foundation (DMRF), you deserve an organization that is committed to the community, and this has been our priority from the beginning. You matter. You are the reason the DMRF exists. Our Founders, Samuel and Frances Belzberg, did not establish the DMRF only to make life better for their own daughter, who was diagnosed with dystonia as a young woman. The Belzbergs insisted that the mission of the DMRF embrace every person affected by this disorder.

You can depend on the DMRF to stand up for all affected families, providing hope and the promise of a cure.

Research funded by DMRF supporters has dramatically advanced our understanding of the brain structures and networks implicated in dystonia and the underlying neurological problems that ultimately lead to symptoms. The path toward a cure is becoming clearer. While much work remains to be done, we are energized by the ongoing progress. On pages 12–14 you can learn how recent research discoveries are important in the pursuit of dystonia drug targets. We share information about our latest research fellowships on page 8.

We understand the realities of life with dystonia. DMRF is committed to providing support resources to help affected individuals and families navigate life with a chronic, often daunting, disorder. For example, on page 18, we offer simple tips for self-care to help get through stressful times. If we can help provide even a few extra moments of comfort and encouragement, it is important for you to know you are not alone in your dystonia journey.

Your membership is extremely important to the DMRF because it makes an immediate positive impact on the dystonia community. You can help DMRF rise to the challenge of our mission, on behalf of every family impacted by this life-changing disorder.

Please consider starting or renewing your membership today. Thank you for joining the DMRF.

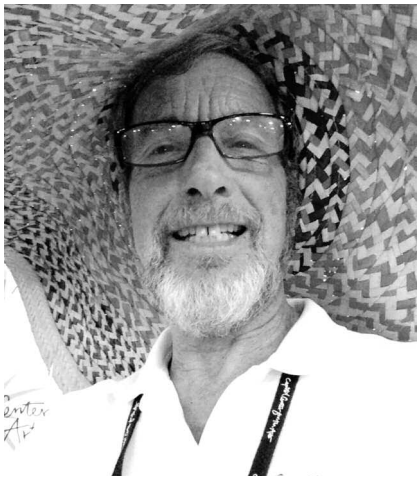
Art Kessler
President

Janet L. Hieshetter
Executive Director

RENEW YOUR MEMBERSHIP OR JOIN TODAY
dystonia-foundation.org/membership

Thank you for your support!

IN MEMORIAM: Richard (Dick) Stuart, MC, DMin

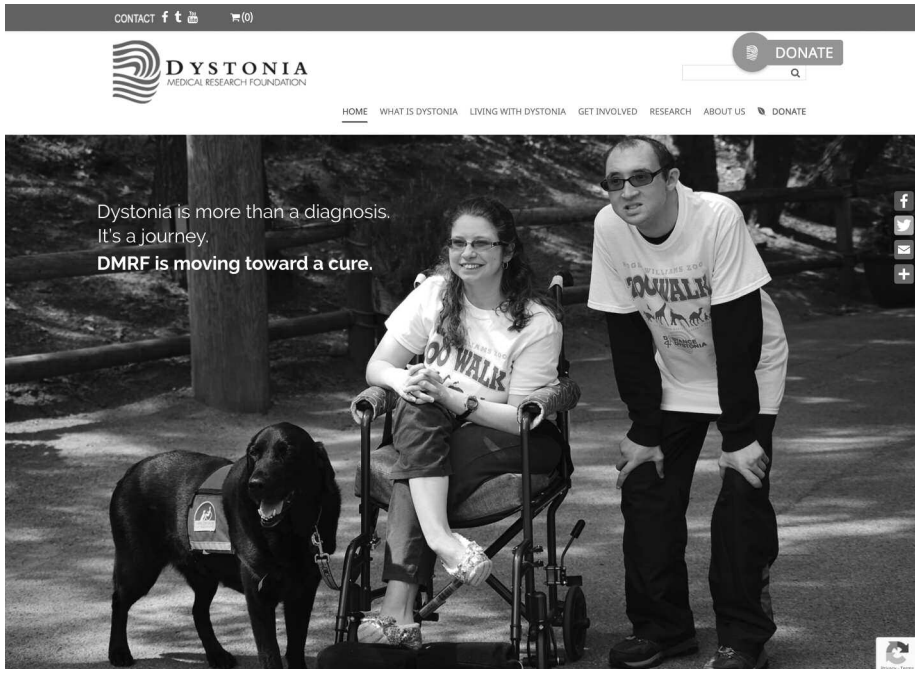


The DMRF is heartbroken to share that Dick Stuart, a beloved member of the dystonia community, passed away in November of last year. He died following complications from a medical procedure. Dick was a retired clergyman and psychotherapist, former member of the New Hampshire House of Representatives, and active public servant. He served as a DMRF Regional Coordinator and participated in dystonia and spasmodic dysphonia support groups since the 1970s. An extensive interview with Dick appeared in the *Dystonia Dialogue* in 2015. He was a devoted legislative advocate for dystonia, rare disease communities, and a host of humanitarian causes. Dick's wife Ruth and daughter Elizabeth were also dedicated supporters of the dystonia community.

"Dick was one of a kind. His devotion to helping others in the dystonia community touched countless lives. His kindness, enthusiasm, and joy of life made the world a better place."

Janet Hieshetter, DMRF Executive Director

New DMRF Website is Go-To Resource for Dystonia Community



The DMRF is proud to announce the launch of a new website at dystonia-foundation.org.

The website was designed to better serve the dystonia patient community as well as the research community. Some of the new-and-improved features include:

☑ **A home page that makes it easier to find what you need** – More intuitive links and an improved search function get you where you want to go with the fewest clicks and minimal scrolling.

☑ **Resources for researchers** – Dystonia investigators have easy access to information describing all aspects of the DMRF's research activities and funding programs.

☑ **Resources to help you connect** – It is easier than ever to find a community event, locate a support group, or discover online forums to connect with others in the dystonia community.

☑ **A map to locate physicians** – A searchable voluntary directory of doctors who treat dystonia helps you identify movement disorder centers and specialists near you.

☑ **Social Sharing** – The website makes it easy to share information with family and friends via email or social media.

Bookmark the site and visit often for continued improvements and additions. Connect with the DMRF on Facebook and Twitter for announcements as updates and new content are added.

NINDS Holds Meeting to Advance Dystonia Research Priorities

DMRF participated in "Defining Emergent Opportunities in Dystonia Research," a meeting organized by the National Institute of Neurological Disorders & Stroke (NINDS), October 29–30, 2018, in Bethesda, Maryland to determine research opportunities to continue advancing dystonia science. NINDS is the primary federal agency to fund research on brain and nervous system disorders. The meeting convened world renowned dystonia experts and brought increased visibility of dystonia to a critical federal medical research agency. Director of NINDS, Walter J. Koroshetz, MD, opened the meeting which was Co-Chaired by Laurie Ozelius, PhD of Harvard Medical School and David G. Standaert, MD, PhD of University of Alabama at Birmingham. DMRF Chief Scientific Advisor Jan Teller, MA, PhD was among the presenters.

The program agenda included a detailed review of advancements in dystonia research and discussion of future research priorities. A section of the meeting was dedicated to applying the National Institutes of Health BRAIN Initiative efforts to dystonia research. The Brain Research through Advancing Innovative Neurotechnologies® (BRAIN) Initiative is a collaborative, public-private research program announced under President Barack Obama in 2013, with the goal of supporting the development and application of innovative technologies that improve understanding of brain function. The workshop also highlighted resources available to dystonia investigators such as patient registries, research databases, tissue samples, animal models, and more. A paper summarizing the meeting is under development.

Save the Date: 6th International Dystonia Symposium

The DMRF, in partnership with Dystonia Europe, is proud to announce the Samuel Belzberg 6th International Dystonia Symposium, a research conference to take place June 4–6, 2020 in Dublin, Ireland. The meeting is named for DMRF Co-Founder Samuel Belzberg who passed away in 2018. Co-Chairs are H. A. "Buz" Jinnah, MD, PhD of Emory University School of Medicine and Antonio Pisani, MD, PhD of University of Rome Tor Vergata. The program is designed for clinicians and investigators to provide a comprehensive overview of important scientific advances in the field and stimulate discussion within and across disciplines. The International Dystonia Symposium is the seminal international dystonia meeting for investigators and clinicians, dating back to 1975.

Abstract submissions will open in November. More information is available at internationaldystoniasymposium.org

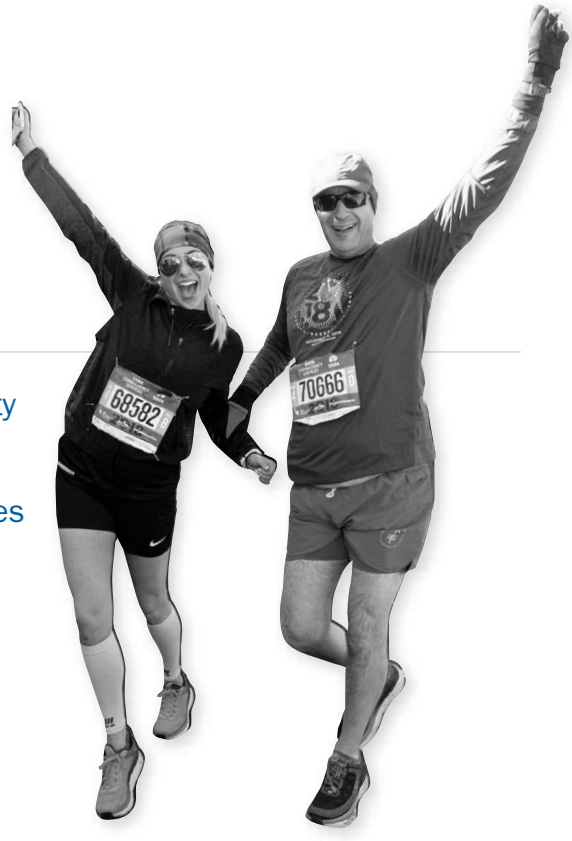
Matching Grant Boosts Facebook Fundraising

Thanks to a very generous donor, all donations raised for DMRF through Facebook's fundraiser tool in 2019 will be matched dollar for dollar. In 2018, Facebook fundraisers raised $65,000 to support critical research and programs—enough to fund a research grant. This generous challenge will help us continue to cultivate support for dystonia research toward a cure.

Facebook does not notify DMRF of fundraisers created on our behalf, so we are not always able to thank donors appropriately. If you or a family member are raising donations for DMRF via Facebook, please notify us to be included in the match. You can notify DMRF of your fundraiser by sending us a message on Facebook or posting to our page.

The DMRF Facebook page can be found by logging into Facebook and searching "Dystonia Medical Research Foundation." Thank you to our Facebook friends for participating in this exciting challenge.

Runners with Dystonia Compete at TCS NYC Marathon



Several members of Team DMRF at the 2018 TCS New York City Marathon on November 4 once struggled to walk a single step. Disabled by dystonia as children, and after years of misdiagnoses and failed treatment, they reclaimed their mobility and ran on behalf of the greater dystonia community.

"I would never run for any organization except for the DMRF. The research they fund changes lives, including mine and my sister's. This organization changed my life!"

~ Carrie Siu Butt, Team DMRF

Team DMRF included 10 runners, all with a personal connection to dystonia, who participated to raise research funds and public awareness.

Carrie Siu Butt was diagnosed with dystonia at age 12. By her 30s, the simple act of walking was a painful, frustrating ordeal. As a last resort against losing the ability to walk completely, she underwent deep brain stimulation (DBS) surgery, an invasive neurosurgical procedure. The results were so dramatic that within six weeks she was walking unassisted. She took her new found mobility and literally ran with it, since completing multiple 10Ks, half-marathons, and now two marathons.

For 30+ years, Ginny Bryan lived in a body with a 'mind of its own.' She was born with myoclonus-dystonia, a rare movement disorder that causes uncontrollable jerking muscle contractions (myoclonus) and twisting, repetitive movements and awkward postures (dystonia). Two years ago she underwent DBS which has drastically reduced her symptoms. This was her first marathon. Ginny is a member of the DMRF Community Leadership Council. Running to support Ginny were Heather Barskaya and Amy Amendola.

"The TCS NYC Marathon gave me an incredible opportunity," said Ginny, "to raise funds for the mission of the DMRF and to raise awareness about dystonia. For each step I took during the marathon, with a smile that just kept getting bigger, it was with gratitude in my heart for every helper, my family and friends, and everyone who supported and loved me so that I was able to run a marathon after 37 years with myoclonus-dystonia, and a few years after bilateral DBS."

Beginning at age 14, Larry Dubill experienced uncontrollable attacks of involuntary jerking and shaking movements up to 100 times a day. As a performing musician, music teacher, and athlete, he learned over the years to anticipate triggers for the attacks and avoid them as much as possible. He was ultimately diagnosed with dystonia after noticing a dystonia awareness advertisement on the milk carton

"Josh finds the strength every day to live with dystonia. His determination to raise awareness and funds for a cure prompted my decision to join the NYC Marathon team for DMRF."

~ Carole Tordi, Team DMRF, on behalf of Josh Gebeloff

in his refrigerator and consulting a movement disorder neurologist. Larry was ultimately unable to participate in the marathon for health reasons, but trained and fundraised to support DMRF.

Additional members of Team DMRF include Jim Metherell and Jaime Dimitri who ran on behalf of Jim's teenage son who has dystonia. Jim is a member of the DMRF Community Leadership Council. Marissa Rozenfeld ran in honor of her brother who has dystonia along with Stephen Gebeloff and Carole Tordi.

Support Resources to Help Feel Connected

Feeling connected to other people affected by dystonia can have a profound impact on your health, physically and emotionally.

DMRF connects you to people who understand life with dystonia:

- **Support Groups** – DMRF offers peer support groups in communities across the USA. Search support groups at *dystonia-foundation.org/support_groups*
- **Online Forums** – Online groups are available for specific types of dystonias, parents, loved ones, young adults, and individuals who have had deep brain stimulation. Find links for online forums at *dystonia-foundation.org/online*
- **Individual Support** – DMRF is available by phone, email, web, and social media to those seeking information and support.

Benefits of Peer Support:

- ☑ New friendships
- ☑ Advice for daily living
- ☑ Reduced stress
- ☑ Greater acceptance of life with dystonia

Support resources also provide opportunities to volunteer for dystonia awareness, legislative advocacy, and fundraising.

Don't have a dystonia support group in your community? Consider starting one. Contact the DMRF at *dystonia-foundation.org/contact or 800-377-3978*.

Groundbreaking Investigations Seek Cure for Disabling Childhood Dystonia

The DMRF announced its latest fellowship awards to advance research toward improved dystonia treatments and a cure. The post-doctoral research fellows reflect the recent swell of groundbreaking new findings about dystonia including discoveries into the underlying pathophysiology. Advances in research technology, combined with decades of investing in basic science in dystonia, are creating opportunities for novel investigations not previously possible. The funded investigators are focusing on one of the field's greatest puzzles: how changes in a mysterious protein in the brain leads to a disabling inherited type of dystonia that targets children. Many thanks to Ron Oliver and family for their generous support.

THE DMRF POST-DOCTORAL RESEARCH FELLOWSHIP AWARDEES ARE AS FOLLOWS:

Barbara Oliver Memorial Dystonia Research Award
Investigator: Gabriela Huelgas-Morales, PhD, University of Minnesota
Mentor: David Greenstein, PhD
Project: Using the Nematode Caenorhabditis elegans to Identify Candidate Substrates for OOC-5/TorsinA

In 1997 researchers funded by DMRF discovered that a tiny error in the DYT1 gene was responsible for a severe type of childhood dystonia. The genetic error interferes with the ability of a protein in the brain called TorsinA to function correctly. Dystonia investigators around the world have been working to understand how TorsinA operates normally and what cellular functions go wrong when the protein is dysfunctional. Dr. Morales is using a worm model to identify TorsinA substrates, i.e. proteins that TorsinA acts upon. This is critical to understanding the basic cellular functions of TorsinA and origins of DYT1 dystonia.

Investigator: Anthony Rampello, PhD, Yale University
Mentor: Christian Schlieker, PhD
Project: A Genetic Approach towards Identifying Torsin Function in Relation to DYT1 Dystonia

CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats) represents a profound advancement in genome editing technology. CRISPR is used to edit genetic material in living organisms easier, faster, and with greater precision than previous methods. Dr. Rampello is using CRISPR to establish a TorsinA interaction map by systemically tracking down genes and proteins that have a functional relationship to TorsinA. Mapping the network of cellular processes in which TorsinA is involved is critical to understanding how TorsinA causes dystonia when made dysfunctional by errors in the DYT1 gene. This project is supported by the family of Ron and Barbara Oliver and the Barbara Oliver Memorial Research Fund.

Learn more about DMRF's research efforts at dystonia-foundation.org/research

New Congress Provides Opportunity for Dystonia Advocacy

Dystonia Advocacy Network

- Benign Essential Blepharospasm Research Foundation (BEBRF)
- Dystonia Medical Research Foundation (DMRF)
- National Spasmodic Dysphonia Association (NSDA)
- National Spasmodic Torticollis Association (NSTA)

In January, 100 new US Representatives and 10 new US Senators took office. The DMRF is working hard to ensure that all new Members of Congress understand the basic facts about dystonia and unique healthcare needs of the community. At the beginning of each new Congressional term, informational packets are hand-delivered to all new Members in the House and Senate so they are aware of what dystonia is and how it changes lives.

To follow up, dystonia advocates from across the country will receive legislative training and attend meetings in Congressional offices as part of Dystonia Advocacy Day, March 26–27, 2019 in Washington, DC. Dystonia Advocacy Day is organized by the Dystonia Advocacy Network (DAN), a grassroots organization that brings people together to speak out with a unified, powerful voice on legislative and public policy issues relevant to dystonia. The DAN continuously works to develop and advance a legislative agenda that raises awareness, educates policymakers, addresses patient care issues, and moves research forward. Dystonia Advocacy Day is held each spring on Capitol Hill. DMRF is proud to provide staff support for the DAN.

How You Can Help

DAN advocates work year round to develop relationships with legislative leaders and enlist their help to address the challenges faced by those living with dystonia and their families.

By becoming a dystonia advocate, you can have a powerful effect on the laws and policies that affect your life and the lives of countless others in the dystonia community. To get started:

- Visit dystonia-advocacy.org/agenda to read a summary of the most urgent issues facing the dystonia community.
- Sign up to receive DAN legislative alerts via email at: dystonia-advocacy.org/contact
- When you receive a DAN legislative alert, respond promptly by calling or sending an email to your legislators. The DAN makes it easy. Every legislative alert includes simple instructions to take action.

For more information on the DAN and becoming a dystonia advocate, visit dystonia-foundation.org/advocacy or contact the DMRF at dystonia@dystonia-foundation.org or 312-755-0198.

How Does Advocacy Impact Dystonia Research?

Legislative advocacy can be a powerful catalyst to stimulate medical research. DAN advocates first convinced Congress to include dystonia on the list of diseases eligible for study through the Department of Defense's (DOD) Peer-Reviewed Medical Research Program in the FY 2010 Defense Appropriations Bill. DAN volunteer advocates have successfully kept dystonia in the research program every year since, resulting in $14 million awarded to dystonia investigators.

On page 12, read about cutting-edge research investigations that are currently funded through the DOD Peer-Reviewed Medical Research Program, thanks to the DAN. This groundbreaking research would not be possible without years of legislative advocacy to protect and grow federal research funding for investigators. Numerous dystonia investigators previously funded by DMRF have successfully applied for DOD funding.

Interviews with dystonia investigators funded through the DOD Peer-Reviewed Medical Research Program are available for viewing at dystonia-foundation.org/get-involved/advocacy-network/

Adult Onset Focal Dystonia

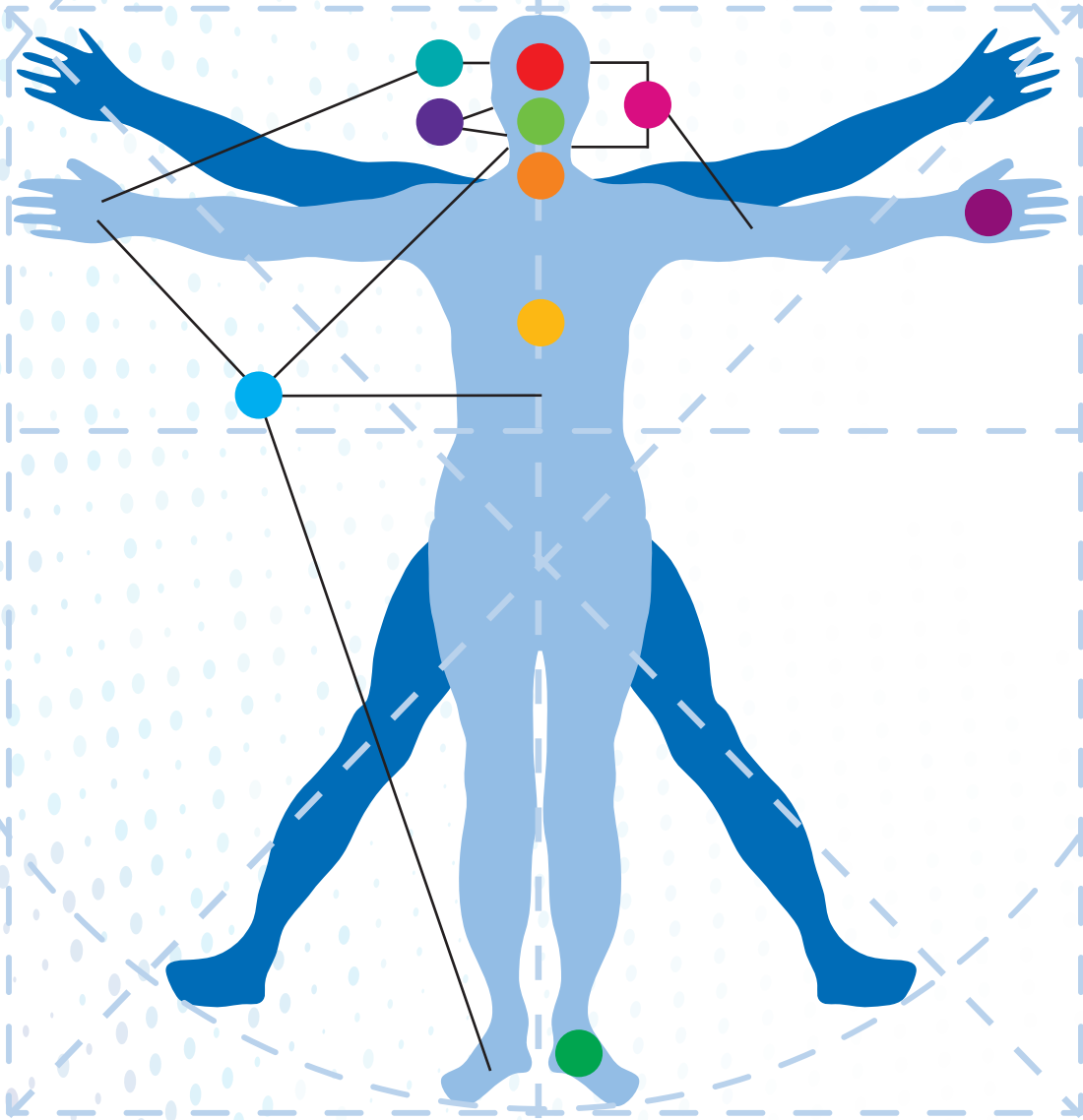
Dystonia that begins in adulthood usually affects a specific part of the body. It typically occurs without additional neurological symptoms, with the exception of tremor.

135,000 adult onset focal dystonia cases in the USA

1.3+ million global cases of adult onset focal dystonia

These figures are taken from a recent study published by investigators in Finland, who used national health care records to study dystonia epidemiology.

Ortiz R, Scheperjans F, Mertsalmi T, Pekkonen E (2018) The prevalence of adult-onset isolated dystonia in Finland 2007–2016.PLoS One. 13(11):e0207729.



Most Common Isolated Adult Onset Dystonias

FOCAL CERVICAL DYSTONIA (neck)
300 per million = 100,000+ in USA

FOCAL BLEPHAROSPASM (eyes)
25 per million = 9,000 in USA

FOCAL UPPER LIMB
15 per million = 5,000 in USA

FOCAL SPASMODIC DYSPHONIA (voice)
12 per million = 4,000 in USA

FOCAL OROMANDIBULAR DYSTONIA (jaw, lower face)
5 per million = 2,000 in USA

FOCAL LOWER LIMB
1 per million = 350 in USA

FOCAL AXIAL (spine)
1 per million = 350 in USA

SEGMENTAL
30 per million = 10,000 in USA

MULTIFOCAL
6 per million = 2,000 in USA

GENERALIZED
2 per million = Less than 1,000 in USA

These figures do not include focal dystonia acquired by a known cause, for example injury or drug reaction. The figures also do not include inherited childhood onset dystonia or paroxysmal dystonia.

Focal dystonia appears to be more common in women than men.

One of the challenges of studying how many people have dystonia is that dystonia often goes undiagnosed or misdiagnosed.

Common Signs of Dystonia

- A body part is flexed or twisted into an abnormal position.
- Repetitive and patterned body movements, which may resemble tremor.
- Dystonic symptoms may worsen or occur only with specific tasks.
- Attempting a movement task on one side of the body may activate dystonia symptoms on the opposite side.
- Dystonic movements and postures may be temporarily relieved by a gentle touch or specific action called a sensory trick.

Task- Specific Focal Dystonia

Task-specific focal dystonia affects a specific body part and is triggered by a specific action. Professional musicians, for example, may develop dystonia symptoms that occur only when playing their instrument. Task-specific focal dystonia has been reported in golfers, baseball players, pistol shooters, surgeons, seamstresses, and other occupations that require skilled, repetitive fine motor movements. It usually affects the hands, arm, facial muscles, or vocal cords.

Task-specific focal dystonia typically begins between 30-60 years of age. Unlike other adult onset focal dystonias, task-specific focal dystonia appears more common in men.

Vocabulary

Focal: Dystonia that affects a single body part, for example, the neck.

Segmental: Dystonia that affects two or more connected body parts, for example, the face, neck, and arm.

Generalized: Dystonia that affects the torso and at least two other body areas, frequently the limbs.

Isolated: Dystonia is the only neurological symptom a person has.

Acquired: Dystonia that appears to have a specific cause such as drug reaction or brain injury.

ON TARGET

DMRF's Drug Discovery Efforts Pursue New & Improved Treatment

Drug discovery and development efforts are an important part of DMRF's multi-faceted science strategy. "The dystonia community cannot wait for pharmaceutical and biotech companies to necessarily get interested in dystonia on their own," explains Jan Teller, MA, PhD, DMRF's Chief Scientific Advisor. "DMRF has a responsibility to encourage and support drug discovery efforts while we work constantly to engage pharma and industry partners."

In late 2018, DMRF organized a workshop entitled "Targeted Drug Discovery for Dystonia" in Chicago. Meeting participants included seasoned dystonia investigators and non-dystonia experts experienced in protein-based drug discovery. The workshop was co-chaired by Christian Schlieker, PhD of Yale School of Medicine and Thomas Schwartz, PhD of Massachusetts Institute of Technology, whose recent work is discussed later in this article. The goal of the meeting was to summarize and discuss recent efforts to identify drug targets for dystonia, with special emphasis on DYT1 dystonia because it is among the best understood dystonias at this time.

A drug target is a molecule in the body, often a protein, that is essential in a disease process and that can be manipulated by a drug to correct or interrupt this process. Identifying drug targets for dystonia is critical to developing new medications and/or identifying existing drugs that may be effective.

"A clear take away from the drug discovery meeting," says Dr. Teller, "was that we need extensive mechanistic studies in order to understand the biology of dystonia if we are to approach drug development in a thoughtful and responsible way."

Pushing Aside the Side Effects

Anticholinergic drugs, such as trihexyphenidyl (Artane®), can be effective at controlling dystonia symptoms but are not a viable treatment for many patients because the side effects can be unbearable: memory difficulties, sedation, even hallucinations. These unwanted effects occur because anticholinergic drugs act on many receptors in the brain, not only the receptors associated with dystonia symptoms. If the drugs acted more precisely, and targeted only the receptors associated with dystonia, this would avoid the unwanted side effects.

Dr. Teller explains: "There is a lot of interest in making existing drugs 'cleaner' and less prone to producing side effects. This has significant advantages over designing new drugs, in terms of time and cost. DMRF has supported numerous research teams pursing this."

Ellen Hess, PhD of Emory University is a past DMRF grant recipient. She is leading an investigation funded through the Department of Defense (DOD) Peer Reviewed Medical Research Program to better understand how medications to treat dystonia work in the brain and how to improve them. She and her team found that trihexyphenidyl corrects an imbalance of dopamine, a neurotransmitter in the brain critical for normal movement. This restoration of normal dopamine processing reduces dystonia symptoms. The discovery provides clues about which receptors are important for treating dystonia. The scope of the DOD grant includes outreach to pharmaceutical companies and academic institutions that possess compounds not yet on the market that target the helpful receptors for possible development into commercially available medications.

Dr. Hess recently received a grant from the DMRF to detect abnormal patterns of brain activity associated with dystonia, and that work is ongoing.

Additional investigators who are making important discoveries related to anticholinergic drugs and receptors include DMRF grant recipients Antonio Pisani, MD, PhD of University of Rome Tor Vergata (whose work is discussed below), and P. Jeffrey Conn, PhD of Vanderbilt Center for Neuroscience Drug Discovery. A member of Dr. Conn's team, Mark Moehle, PhD, recipient of the DMRF's Mahlon DeLong Young Investigator Award, presented on their work at the recent DMRF drug discovery workshop.

The Dopamine Enigma

Individuals with dystonia vary in their response to oral medications. And it is not clear why. For example, dopa-responsive dystonia is an inherited movement disorder in which the body cannot properly process dopamine, a neurotransmitter critical for coordinating normal movement. Levodopa, an oral medication that boosts dopamine, can dramatically reduce dystonia symptoms. However, levodopa produces inconsistent results in other types of dystonia, for example, DYT1 and other inherited dystonias. Furthermore, some dystonia patients respond to dopamine-blocking drugs, such as tetrabenazine, rather than dopamine-boosting drugs.

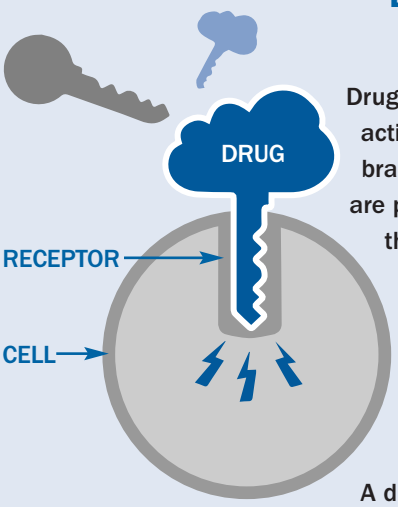
A newly published study led by DMRF grant recipient and former member of the Medical & Scientific Advisory Council Antonio Pisani, MD, PhD of University of Rome Tor Vergata offers new insights into the role of dopamine in DYT1 dystonia. It may explain why DYT1 dystonia patients vary in their response to dopamine-boosting medications such as levodopa. The work of Dr. Pisani and his group highlight the role of RGS9-2, a protein that regulates dopamine signaling in the striatum, part of the basal ganglia in the brain. The researchers have shown that activating RGS9-2 may potentially correct the dopamine imbalance in the brain associated with dystonia and other movement disorders.

Dr. Pisani's work is revealing important information about dopamine receptors. The dopamine receptor DRD2 regulates the synthesis, storage, and release of dopamine. Lower levels of DRD2 can slow down dopamine production and activity, leading to neurologic effects. DRD2 receptor levels are lower in DYT1 dystonia as well as in animal models of the disorder. Notably, the majority of current antipsychotic drugs, which can trigger movement disorders, also target the DRD2 receptor.

RGS9-2 belongs to specific molecular machinery associated with the DRD2 receptor. Dr. Pisani and his group discovered that lower levels of the DRD2 receptor correspond with reduction in RGS9-2 protein. These changes have direct negative consequences for neurophysiological function of striatal neurons and control of movement. The researchers were able to reverse these negative consequences by

Continued on page 14

DRUGS & RECEPTORS: HOW DRUGS WORK



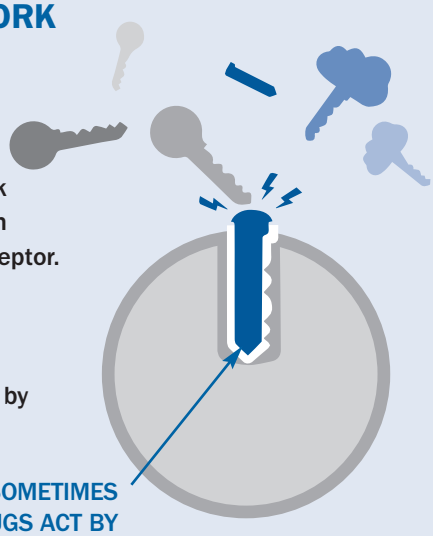
Drugs most often work by acting on receptors in the brain and body. Receptors are protein molecules in cells that can receive information from outside the cell.

Receptors are like locks that are activated by a matching key.

A drug activates the receptor by binding to it. The activated receptor then sends signals to the cell in response to the drug.

Sometimes a drug fits into a receptor but only acts to block other molecules from binding with that receptor.

Neurotransmitters, hormones, and other molecules also work by binding to receptors.



SOMETIMES DRUGS ACT BY BLOCKING A RECEPTOR.

experimentally increasing the level of RGS9-2, which restored the levels of DRD2 and its normal function. The dopamine imbalance was corrected by influencing the DRD2 receptors, by increasing RGS9-2 levels.

The results from this study shed new light on the role of dopamine signaling in DYT1 dystonia, and suggest the RGS9-2 protein could be an important therapeutic target for dystonia.

Starting from Scratch

Oral medications currently available to treat dystonia are used off-label, which means they are not specifically approved by the US Food & Drug Administration for dystonia. Doctors are permitted to prescribe them based on clinical experience. At the moment, there are no oral medications intentionally designed or developed to treat dystonia. However, work by Thomas Schwartz, PhD of Massachusetts Institute of Technology could ultimately help pave the way toward custom-made dystonia medications.

Dr. Schwartz received a DMRF research grant several years ago to take on one of dystonia research's most pressing challenges: solving the structure of TorsinA, the protein responsible for causing DYT1 dystonia when it becomes dysfunctional due to genetic changes. The function of a protein is determined by its shape, so solving TorsinA's structure is critical to understanding its role in cells and the processes that fail when the protein does not function properly. Using sophisticated X-ray crystallography techniques, Dr. Schwartz successfully solved the structures of both normal and mutated TorsinA—a critical, fundamental step toward therapies that correct dystonia at the source of the problem. Dr. Schwartz revealed that the disease mutation causes subtle surface changes on the protein that could potentially be repaired by an appropriate drug. Dr. Schwartz previously established that TorsinA can only function when activated by associated proteins, LAP1 and LULL1, which opens up additional potential opportunities to manipulate TorsinA for therapeutic purposes.

Dr. Schwartz recently received a large grant from the Department of Defense (DOD) to build upon the work funded by DMRF and screen for drugs that may act on TorsinA. This work represents the latest steps toward truly novel therapeutic approaches to dystonia.

Next Steps

"These projects are true drug discovery attempts but also, inevitably, expand our fundamental knowledge about dystonia, something companies rarely, if at all, do," says Dr. Teller. Continuing to understand the fundamental causes of dystonia is essential to identifying dystonia drug targets and the future of treatment.

Dr. Teller continues: "Something we can do right away is to encourage and intensify information exchange and collaboration among investigators. Sharing information and organizing more frequent meetings will undoubtedly speed up the process of acquiring knowledge and conscientiously proceeding to drug development. DMRF can play a significant role in this area."

See page 9 to learn about the role of the Dystonia Advocacy Network in activating Department of Defense funding for dystonia investigators.

Neurotransmitters

Dystonia symptoms result from an imbalance in the delicate system of neurotransmitters at work in the brain and nervous system. Medications used to treat dystonia work by acting on specific neurotransmitters in the brain, attempting to correct the imbalance.

Acetylcholine is an excitatory neurotransmitter found throughout the nervous system. Acetylcholine has several functions, acting on neurons and muscles. It is the chemical that motor neurons in the nervous system release to activate muscles.

Dopamine is involved in the control of movement, cognition, affect, and other critical biological functions. In the basal ganglia, dopamine performs two functions: it acts to help execute voluntary movements as well as to prevent unwanted muscle contractions from interfering with voluntary movement. The dual role of dopamine allows for fine-tuning of movement.

Gamma-aminobutyric acid (GABA) is an inhibitory neurotransmitter, which means it blocks impulses between neurons. GABA acts as a counter balance to the excitatory neurotransmitters.

People on the Move

The DMRF is grateful for the grassroots volunteers across the country working to improve dystonia awareness in their communities. Every volunteer makes a difference!

Area Cooperative Educational Services (ACES) in southern Connecticut organized a dress down day in honor of longtime DMRF supporter **Tim Insogna**, raising over $420 in support of DMRF.

After learning about the growing number of businesses and municipalities phasing out disposable drinking straws, **Marti Lambert** was concerned because she knows firsthand how essential straws are for many individuals with dystonia. She created "Utensils to Go," which packages stainless steel straws and bamboo eating utensils to be portable and convenient. She donates a portion of proceeds to support DMRF.

Rogers Middle School Student Council in St Louis, Missouri held a hike to raise money and awareness for dystonia thanks to Student Council Sponsor **Erica Meyer**.

The Buffalo Bills are champions for dystonia awareness. In December the Bills hosted a cornhole tournament to bring visibility to dystonia and raise funds to support the DMRF. Special thanks to DMRF Community Leadership Council Member **Jim Metherell** for making this special event possible.

The first-ever Dystonia Day at Phoenix Zoo in November was a terrific success. The event raised dystonia awareness and an estimated $25,000 for medical research toward a cure. Congratulations and thanks to organizers **Bob and Virginia Spencer, Mary Stone, Steve Swarr,** and **Lisa Troub**. Guest speakers included neurologist **Dr. Guillermo Moguel-Cobos** from Barrow Neurological Institute.

Metal heads in Charleston, West Virginia supported The Big D.A.M.N. Metal Show (**D**ystonia **A**wareness **M**atters **N**ow) in November. Many thanks to DMRF supporters **Will Lares** and **WTSQ radio host Mya Ross** for organizing this special event to benefit $5Cure4Dystonia. Iron Maiden tribute band Up In Irons and Dirt Stack performed.

Congratulations and many thanks to **Martha Murphy** and members of the Dystonia Support & Advocacy Group of San Diego County for a successful first-ever Dystonia Day at San Diego Zoo in November. Special guests included **Marcus Bush** on behalf of San Diego **City Councilmember Georgette Gomez**.

Artist **Josh Anderson** is once again generously donating his talent for a unique dystonia awareness t-shirt you won't find anywhere else. Shirts are $15 and available for pre-order until April 15, 2019. Shirts will ship in May. Proceeds support DMRF. For information and to order visit: dystonia-foundation.org/awareness-tee

FOCUS ON

Drug-Induced Dyskinesia & Dystonia

Drug-induced movement disorders come in different forms and can be caused by a number of medications that alter brain chemistry.

The movement symptoms may be focal to a specific body part, affect one side of the body, or be generalized throughout the body. Drug-induced movement disorders can sometimes, but not always, be relieved by stopping the offending drug.

What Drugs Can Cause Movement Disorders?

The types of drugs most commonly associated with causing movement disorders are dopamine blocking medications (i.e. dopamine antagonist or anti-dopaminergic medications), which suppress a neurotransmitter in the brain called dopamine. This category of drugs includes:

- First generation antipsychotics (neuroleptics)
- Second generation (atypical) antipsychotics
- Anti-nausea drugs (antiemetics)
- Lithium
- Stimulants (amphetamines, cocaine)
- Antidepressants (selective serotonin reuptake inhibitors and tricyclic antidepressants)

Tardive Dyskinesia

Tardive dyskinesia is involuntary twitching or writhing movements, often affecting the face, mouth, and tongue. The symptoms can include lip-smacking, chewing movements, and tongue movements. The limbs and trunk are less commonly affected. Tardive dyskinesia can be accompanied by feelings of inner restlessness (akathisia).

Tardive dyskinesia is typically associated with at least three months use of dopamine blocking medications.

Symptoms are initially mild and progress over time. Symptoms may decrease with a sensory trick or during sleep. Symptoms may occur while the individual is taking the medication or after stopping the medication.

Treatment may include discontinuing the offending drug, though there may be individuals for whom discontinuing antipsychotics or antiemetics is not appropriate. Medications approved by the US Food & Drug Administration to suppress tardive dyskinesia symptoms include valbenazine or deutetrabenazine. Additional therapeutic agents may include tetrabenazine, clonazepam, amantadine, propranolol, and Ginkgo biloba.

Deep brain stimulation may be a treatment option for severe cases that do not respond to medications.

Treating co-occurring anxiety is an important part of the treatment strategy given its tendency to worsen overall symptoms.

Acute Dystonia

Acute dystonia, sometimes called an acute dystonic reaction, can occur within hours or days of exposure to a dopamine blocking drug or, less commonly, after an increased dose of a dopamine blocking drug or decreased dose of a concurrent anticholinergic drug (e.g. benztropine).

Acute dystonia often includes involuntary movements of the face, eyes, jaw, tongue, neck, trunk, and sometimes limbs.

Treatment for acute dystonia includes discontinuing the offending drug and treatment with anticholinergics or antihistamines (i.e. diphenhydramine), often by injection or intravenously. Even without medical treatment, most cases resolve within 12 to 48 hours.

Tardive Dystonia

Tardive dystonia affects different patient populations and responds differently to treatment compared to classic tardive dyskinesia.

Tardive dystonia occurs after prolonged use (more than three months) of dopamine blocking drugs. Many of the same medications that cause tardive dyskinesia can cause tardive dystonia.

Tardive dystonia tends to progress but more so in children who develop dystonia. Dystonia in adults tends to stay focal to a specific body area rather than involve multiple body parts.

Focal tardive dystonia often affects the facial muscles, often with akathisia (feelings of inner restlessness). Symptoms of focal dystonia can occur days or years after drug exposure.

Common presentations of tardive dystonia, as compared to dystonia due to other causes, include:

- Head tipping back
- Trunk arching back
- Internal rotation of arms, elbow extension, wrist flexing
- Jerking movements in addition to dystonia
- Movement symptoms decrease with voluntary motion, such as walking

Treatment for tardive dystonia can include dopamine blocking drugs, anticholinergic drugs, benzodiazepines, botulinum neurotoxin injections, and deep brain stimulation.

For more information on drug-induced movement disorders, visit dystonia-foundation.org

Special thanks to past DMRF Clinical Fellow Christopher L. Groth, MD for reviewing the content of this article.

Have You Considered… Registering as a Brain Donor?

Registering in advance as a brain donor is a way to contribute to the field of dystonia research that assists researchers working today and in the future.

The DMRF works in partnership with the Harvard Brain Tissue Resource Center (HBTRC) at McLean Hospital in Belmont, Massachusetts to assist people interested in registering as brain donors. The HBTRC maintains a private collection of brain tissue from individuals with all forms of dystonia. The DMRF also serves as the administrative center for the Dystonia Brain Collective, a partnership among several dystonia patient groups to facilitate brain donation for research purposes. Donated tissue is available to investigators for dystonia-related studies.

For more information or to begin the registration process, visit dystonia-foundation.org/brain or contact the DMRF at 800-377-3978 or brainbank@dystonia-foundation.org.

Did You Know…?

- Brain tissue samples are a rare and valuable resource for dystonia investigators.
- Certain types of research studies can only be done with post-mortem brain tissue samples. Brain donors are essential to future scientific progress.
- Brain donation does not alter the appearance of the donor or interfere with memorial services or remembrance practices.
- There is no cost to the donor or family.
- Brain donation does not violate the tenets of most religious or spiritual organizations.
- Donor information remains confidential. However donors must inform next of kin that they are registered to donate their brain.
- Donated brain tissue must arrive at the HBTRC within 24 hours of death. HBTRC staff are available 24 hours a day.
- Individuals can withdraw from the program at any time.
- By combining brain donation with financial support, you multiply your assistance to the progress of dystonia research.

Tips for Self-Care in Stressful Times

Stress is notorious for making dystonia symptoms worse. The following gentle reminders may help ease stress before it becomes overwhelming.

- **Acknowledge loss and change.** This may include the loss of being able to do everything you once did. Changes in daily living impact our lives, even if they are happy changes. Acknowledging the change helps ease tension.
- **Assess and prioritize.** Look at your calendar and mark the activities and responsibilities that are important to you. This will help you make positive choices about how you spend your time and energy.
- **Good sleep** is the number one self-care activity that can boost your coping and physical wellness in times of stress. Have a sleep routine and watch your caffeine intake. If you need help sleeping better, talk to your doctor or mental health professional.
- **Alter routines and traditions.** Don't be afraid to talk with friends and family members about choices you are making. Help them understand your limitations. Embrace new ways of doing things.
- **Stay connected.** Connecting with friends, family, and community builds a sense of security and pride.
- **Look for hope and joy, and savor them.** A stranger's smile, hearing your favorite song on the radio, spending time with family and friends. Recognize the small moments that give you joy and remember them with gratitude.
- **Take deep breaths.** Even just two slow, deep breaths can help you relax and stay focused. Use this method when you start to feel tense or stressed.
- **Don't be afraid to reach out.** If you are struggling with depression or have feelings of despair talk to your doctor, talk to those safe people in your life, or seek help from a mental health professional. Resources are available if you don't know where to turn. Additional information is available at: dystonia-foundation.org/living-dystonia/mental-health/

Adapted from the webinar "Self-Care for the Holidays" with Margie Frazier, PhD, LISW-S, presented by Dystonia Medical Research Foundation and available for viewing on YouTube at https://www.youtube.com/FacesofDystonia

Get Social

Join DMRF Online Groups

If you do not have access to a local support group, you can still connect with others in the dystonia community. Check out the following online social forums.

Cervical Dystonia Support Forum
facebook.com/groups/dmrf.cervical/
Moderators: Denise Gaskell & Tom Seaman

Oromandibular, Blepharospasm & Cranial Dystonia Support Forum
facebook.com/groups/OMDBleph/

Generalized Dystonia Support Forum
facebook.com/groups/dmrf.gen/
Moderator: Paula Schneider

20/30 Dystonia Group - A Forum for People in Their 20s and 30s
facebook.com/groups/2030dmrf/
Moderators: Chelsi Christman & Marcie Povitsky

Support4Parents of Children with Dystonia
facebook.com/groups/support4parents.dmrf/
Moderators: Carol-Ann Peralta & Dena Sherry

Parenting with Dystonia Support Forum
facebook.com/groups/dmrf.parenting/
Moderator: Jenelle Dorner

Dystonia Spouses & Loved Ones
facebook.com/groups/dmrf.lovedones/

DBSforDystonia Yahoo Group
health.groups.yahoo.com/group/DBSforDystonia/
Moderator: Dee Linde

Online Dystonia Bulletin Boards
dystonia-bb.org/
Moderators: Bob Campbell, Jeff Harris & Linda Walking Woman

For a complete list of DMRF's online social forums, visit: dystonia-foundation.org/online

PERSONAL PROFILE

Brad Schmitt

Brad and Shanna Schmitt lead the Minnesota Dystonia Support Group and organize the Twin Cities Dystonia Zoo Walk. They are dedicated awareness advocates and have participated in Dystonia Advocacy Day in Washington, DC.

How did your symptoms start and how were you diagnosed?

My symptoms started in 2007 as back pain near my shoulder blade. Gradually it increased to the point where I would go to bed in the evening and within two or three hours I would wake up because the muscles in my back and chest and shoulders had seized up so much that it was difficult and painful to breathe. I saw a neurologist in 2008 who took one look at me and said you have dystonia. I flippantly made a comment about isn't that a Baltic republic that used to be part of the Soviet Union? I've since learned that is not remotely an original joke, but that was exactly what I was thinking.

What was the impact on your daily life? Your career?

I was a technical field service representative and drove all over the metro area working on television and computer systems in hotels. There were days I would call my boss and tell him I've just slept so poorly I don't feel safe driving. I would nap a little bit and go into work later. I was also schlepping around bags with 25 pounds of equipment or a 50 pound computer, and as the muscle pain and tightness got worse, it became much more difficult for me to do the physical aspects of my job. I was probably the last person to accept that I was not going to be able to work. I discovered the Minnesota Vocational Rehab Services about the same time that my employer decided I had to go on short term disability. Vocational Rehab Services work with people who have become physically unable to do the job they've been trained to do and assess what their skills and aptitudes might be, and make recommendations to move them into another profession. They put me through tests to assess my mental aptitudes, my interests, my ability to learn new skills, but they observed how unpredictable my symptoms were. I might be fine one minute and need to sit down with an ice pack to calm the spasms the next. Ultimately they told me my symptoms are too unpredictable for anyone to give me a job. They recommended applying for Social Security disability benefits. That was not something I wanted to hear at 38 years of age. I always joked that I wanted to retire by the time I was 40, but that wasn't what I had in mind. It took a long time to mentally come to terms with that.

What treatment works best for you?

Botulinum toxin injections are the primary treatment. The other stuff is my way of coping in between the injections. My regimen involves medication for the spasms, massage therapy and physical therapy, and I have a TENS unit. I have a variety of heating pads and ice packs. I still have good days and bad days. One of the tricks I use is when I'm doing something around the house, like laundry, I'll set a timer for 30 minutes and after the time is up I stop whatever I'm doing. If I wait until my body tells me I've done enough, then it's too late and it may knock me down for a week or even two weeks if I have pushed too far. So I may work for 30 minutes and then need a two or three hour break because my muscles are twitching so badly and my tremors are going.

What has kept you going? Any advice for others?

Having a support network is vital and in my case that starts with my wife. There's no way I could do this without Shanna. If you don't have that spouse or partner who can provide that support then you need to find it somewhere—a relative or support group, even Facebook. I also try to keep a sense humor. I'm home all day by myself and having a cat that's my constant companion is definitely something that's improved my situation, having a pet in my life. The temptation, when you have pain or you have anything chronic going on, is to want to crawl into a shell. But you need to go out and live your life as best you can. If you need a support group or a psychologist for help, you need to make that happen so you can be out in the world.

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Renew Your DMRF Membership Today

As a member of the DMRF, you will continue to receive the latest news and information.

- **Go to dystonia-foundation.org/membership,**
- **Use the enclosed donation envelope,**
- **Complete and return the form on the back of this newsletter, OR**
- **Call the DMRF headquarters at 312-755-0198.**

Stay in Touch

Request to join DMRF's monthly e-newsletter for the latest updates and announcements: dystonia-foundation.org/contact