



# TMJA

*The TMJ Association, Ltd.*

Issue 2 - February 2016

In this month's issue, we feature a summary article on a systematic review of randomized controlled trials on Botox therapy for TMD, an article on new drugs for migraine headaches, NIH research opportunities, and the personal story of one of our readers, Ashley, as she shares her TMD experience with you.

## Painful Truth about Opioid Abuse

Currently, bills addressing opioid misuse, overdose and addiction are quickly moving through Congress. However, legislation proposed to date has failed to include a critical component - **funding for vital pain research to elucidate the causes and mechanisms of chronic pain and to develop safe, effective, non-addictive therapies to replace the need for addictive medications in the treatment of chronic pain.**

[We authored a blog post published in the Capitol Hill newspaper, \*The Hill\*, on February 23rd.](#) We hope this publication helps to stimulate a long overdue national discussion on the crucial need for a robust basic, translational and clinical research effort on chronic pain; a discussion that spans across federal agencies and is commensurate with its human and economic toll. Further, it is our hope that funding for such an effort be allocated through regular channels and that the resulting bills address opioid misuse, so that both of these interrelated public health crises are adequately and appropriately addressed.

## CGRP Antibodies for Migraine? Four Drug Companies Think So

*We know that many TMD patients also experience migraines and other headaches as overlapping pain conditions. The following is a summary of a news [article from the January 8, 2016 edition of Science magazine by Emily Underwood.](#) We found it*

*informative and hopeful for patients.*

Readers of *TMJ News Bites* are aware that pain pathways are among the most complex in the nervous system, involving a variety of neurotransmitters that can excite or inhibit the signals that nerves send from the body to the spinal cord and brain and back. One of the latest molecules to figure in the pain story is called calcitonin-gene-related-peptide, CGRP for short. The reason for that name is because the gene that codes for it also codes for calcitonin, a hormone produced in the thyroid gland that regulates sodium and calcium levels in the body. It is an example of how the DNA of a gene can be sliced and diced in different ways to code for different proteins.

CGRP turns out to be a small protein that can dilate brain blood vessels but also figures prominently in pain pathways. As early as 1990 investigators analyzing samples of blood drawn from the jugular veins of migraine patients seeking emergency room treatment found significant levels of CGRP during and after their headache attacks. At first the thinking was that CGRP triggered migraines by expanding blood vessels, the most prominent theory of the cause of migraines at the time. But further studies showed CGRP was a potent neurotransmitter in pain pathways. That discovery led to early trials of several drugs that could prevent CGRP from locking on to its receptor on nerve cells and exciting them. The blocking agents helped some migraine patients but toxic side effects precluded further development.

Nevertheless, CGRP continued to spark interest, eventually leading to an approach using CGRP antibodies. The use of antibodies is attractive because they are very specific and can persist in the body for some time, and thus avoid the need for frequent injections. But because antibody molecules are relatively large there has been concern they would not be able cross the blood-brain barrier to target CGRP in the brain. Now it seems that may not matter. Blocking CGRP outside the brain (in the peripheral nervous system) appears to work, although some researchers think that the blood-brain barrier can be breached by antibodies in some places. Currently four different drug companies are conducting Phase 2 clinical trials (for efficacy) for CGRP-antibody-based formulations and are enthusiastic, citing findings that some diehard life-long migraine sufferers have found complete relief.

There remain many unanswered questions on how exactly CGRP functions in migraines. Some researchers think that increases in CGRP at the start of an attack sensitize the trigeminal system so that normal levels of light, sound, or smell become overwhelming and intolerable. The trigeminal nerves supply pain and other sensory qualities to the head and face. Others conjecture that migraineurs may have some genetic disposition to an abnormal form of brain activity called cortical spreading depression (csd), which has also been associated with the migraine "aura," and causes increases in CGRP in animal studies. Still others suggest that stress may play an important role, noting that the stress hormone corticotropin-releasing hormone also increases CGRP production.

In any case it is clear that the race is on for new migraine drugs. The hope is that the current CGRP antibody clinical trials will yield relief for the roughly 12 percent of the world's population who have at least one attack of migraine a year, a number in which

women outnumber men by three to one.

## Blocking a Stress-Related Gene Relieves Chronic Pain

*M. Maiarù et al., "The stress regulator FKBP51 drives chronic pain by modulating spinal glucocorticoid signaling," Science Translational Medicine, doi:10.1126/scitranslmed.aab3376, 2016.*

"A group of drugs being developed to treat mood disorders could also relieve chronic pain, finds new University College London (UCL) research funded by the Medical Research Council. The study, published in *Science Translational Medicine*, reveals how a protein that shapes the body's response to stress also drives chronic pain and so offers new targets for future pain treatments. The researchers studied genetically modified mice that lacked a protein called FKBP51. This protein is very important for regulating stress. Variations in the human FKBP5 gene are linked to the risk of developing stress-related psychiatric disorders, such as major depression and post-traumatic stress disorder (PTSD). Previous studies have shown that people with specific FKBP5 variations feel greater physical pain after serious trauma, and the UCL team has now discovered that mice without FKBP51 experience reduced chronic pain from nerve damage and arthritic joints. 'Inhibiting FKBP51 has a very powerful effect in mice with chronic pain,' says lead author Dr Maria Maiaru (UCL Cell & Developmental Biology). 'Not only does it block the pain from their injury without affecting their normal pain response, it also makes them more mobile. We did not find any negative side-effects.' The team then tested an FKBP51-blocking compound called SAFit2, developed by Dr Felix Hausch at the Max Planck Institute of Psychiatry to treat mood disorders by acting in the brain to reduce anxiety. By selectively blocking FKBP51 in the spinal cord, the UCL researchers were able to test its effects on chronic pain independently of its known effects on the brain. They found that SAFit2 substantially alleviated chronic pain in mice, making it a promising candidate for drug development."

[Click here to read more in depth about this study.](#)

[Source: http://www.mdlinx.com/rheumatology/medical-news-article/2016/02/16/6539087/](http://www.mdlinx.com/rheumatology/medical-news-article/2016/02/16/6539087/)

## Unclear Results of Botulinum Toxin Therapy for TMD Pain

*Summary by Karen Raphael, Ph.D., Professor, New York University College of Dentistry*  
*This review was also summarized most recently by [James Keenan at NYU College of Dentistry in the publication Evidence Based Dentistry, \(2015\)](#) again concluding that benefits and risks of Botox® for treatment of TMJ-related muscle pain remain unclear.*

Increasingly, clinicians, research scientists like myself, and advocates at The TMJ Association are asked, "What about Botox® therapy for treatment of my painful muscles? Does it help?" As *TMJ News Bites* has noted in the past, **use of Botox® for treatment of TMJ disorders is not approved by the FDA**, yet a growing group of dentists and some physicians--especially those who also offer Botox for cosmetic

reasons--offer it to TMJ patients "off label," injecting the chewing muscles approximately once every three months.

In the past decade, several published clinical position papers have advocated its use for patients suffering from facial pain. In contrast to these general review papers, a recent systematic review focusing on studies presenting only the highest quality of evidence was conducted by Chen and colleagues and published in the *International Journal of Oral and Maxillofacial Surgery* (2015). Although well over 100 published articles addressed some aspect of the use of Botox® in TMJ disorders, surprisingly, only 5 studies published through 2014 met the highest scientific standards for research with human subjects. These were randomized, controlled clinical trials, involving a total of 123 patients treated with Botox®. All participants had chronic, muscle-based TMJ pain.

These five studies reached different conclusions, with two reporting that Botox® reduced pain, one reporting that its improvement was similar to improvement among patients treated with a muscle manipulation technique, and two reporting that it did not reduce pain at a level that was statistically different than a "placebo" injection consisting of salt water. Thus, given the increasingly broad use of Botox® for multiple clinical problems, it is frustrating that studies are still unable to answer the question, "What about Botox® therapy for treatment of my painful muscles? Does it help?" Unfortunately, in 2016, we still have no answer. We do not even know enough about potential side effects of Botox® when used to treat muscle-based TMJ pain, particularly when used over long periods, with repeated injection cycles. None of the five studies examined long-term beneficial effects or side effects over multiple treatment sessions.

Source: [Chen YW, Chiu YW, Chen CY, Chuang SK. Botulinum toxin therapy for temporomandibular joint disorders: a systematic review of randomized controlled trials. Int J Oral Maxillofac Surg 2015; 44: 1018-1026.](#)

*Editor's note: TMJ News Bites has reported on Botox treatments for TMD a number of times over the decade, always recommending caution. As Dr. Raphael points out, human studies have been inconclusive with regard to risks or benefits, and provide no long-term follow-up. In contrast, animal studies (rabbits, rats) show loss of bone density over time and some muscle atrophy from disuse. So there is every reason to continue to urge caution in trying Botox treatments, especially if injections are to be repeated multiple times. As TMJA President Terrie Cowley notes, "The history of treatments for TMD is noteworthy for sensational claims of the efficacy, even cures, with this or that treatment, which all too often has resulted in more harm than good."*

## Meet Ashley



Hi, my name is Ashley. I am 24 years old turning 25 in February. I grew up in Pittsburgh, Pennsylvania. I have been known to excel and do what my heart desires. I was about 9 years young when all of a sudden I opened my mouth and heard a slightly loud pop. I was young, so I simply ignored it, and thought it was nothing but growing pains.

At about age 18, my jaw began getting worse just as I was graduating from high school. I was referred to see an oral surgeon. He made me a hard splint. The splint helped for about 2 years. At age 23 my pain really started to kick in, and my teeth kept shifting.

My boyfriend at the time was unsupportive. To make things worse, neither was his family, and some of my friends were even quite rude. I've been dealing with this since I was 9 years old all the way until now. I have had 3 splints made, including a special one called an "NTI" splint. Splints are not made for long-term use! Nobody ever told me this, and my teeth were moving everywhere especially when I am so young. I have a few health problems such as chronic migraines, a bad heart, and a past history of epilepsy, but I doubt that would contribute to the TMD.

As a chronic pain sufferer I became so desperate I spent over \$600 alone on splints! I have tried chiropractic treatment, physical therapy, and ice on my jaw. I have been to at least 3 pain clinics that have been unable to help me. I have even let the doctors inject my face with shots several times, and the pain got worse for almost a whole month! The pain was supposed to go away for at least 6 hours, but the relief lasted for only about 3-4 hours. I am undergoing orthodontic treatment because I have been evaluated many times by physicians, my oral surgeon, dentists, orthodontists, holistic doctors, etc. They all told me to get braces to alleviate the pain.

I am still under A LOT of pain on a daily basis. I barely get any sleep every day; I can barely talk on the phone sometimes. I love singing and cannot sing due to pain. I limit excessive talking and struggle to even take medicine since swallowing is difficult, etc. I am very leery of considering surgery because I have heard nothing but terrible things, and a good outcome is now guaranteed. From my experience and knowledge about living with TMD I urge everyone to make copies of TMD diagrams, educate people, telling them as much as you know based on research and more importantly how YOU live with pain each and EVERYDAY.

I am only 24 years old, and I have to give up so many foods because of how I chew or how difficult it is for me; I don't even like to go out anymore. I feel as if this is taking over my life. The doctors need to step in and really learn how deadly this illness is.

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Please consider sharing your TMD experience with the larger community. The voice of the patients and loved ones is very important for all of us to hear. The TMJA values receiving this information as it impacts the work that we do. Please send submissions to [info@tmj.org](mailto:info@tmj.org).

## New Electronic Newsletter

*Cutting Edge - COPCs Research Advances*

Cutting Edge - COPCs Research Advances, is a new electronic newsletter published by the Chronic Pain Research Alliance, an initiative of The TMJ Association.

Developed to keep the medical-scientific community abreast of recent research

advances, this publication contains abstracts of recently published studies on the epidemiology, pathophysiology and clinical management of Chronic Overlapping Pain Conditions, which include **temporomandibular disorders**, chronic low back pain, chronic migraine and tension-type headache, endometriosis, myalgic encephalomyelitis/chronic fatigue syndrome, fibromyalgia, vulvodynia, irritable bowel syndrome and interstitial cystitis/painful bladder syndrome.



Our first issue, January 2016 is now available for your review at:

[http://www.cpralliance.org/New\\_Findings](http://www.cpralliance.org/New_Findings). If you would like to receive future issues of *COPCs Research Advances*, [click here to register](#).

## NIH Funding Opportunities

Basic and Clinical Research

The TMJ Association encourages basic and clinical research on Temporomandibular Disorders in order to provide a greater understanding of the conditions and develop safe and effective diagnostics and treatments based on scientific evidence. [We invite you to view a listing of the latest National Institutes of Health \(NIH\) funding opportunities for scientists interested in advancing TMJ research.](#)

## Educational Brochure on TMD

A Resource Guide for Temporomandibular Disorders

This brochure is a straightforward, easy-to-read guide for patients making health care decisions. Available [by mail](#) or as a [PDF on our website](#), we encourage you to share this brochure with your friends, health care professionals and family.

## TMD Nutritional Guide

### *TMD Nutrition and You*

*TMD Nutrition and You*, was specifically developed for those with compromised oral function to help them maintain a diet of good nutrition in spite of their oral disability as well as making their dental appointments as comfortable as possible. [Click here to download a free copy of our booklet.](#)

## Dental Care Guide

### *Temporomandibular Disorders, Dental Care and You*

The TMJ Association developed this guide to provide you with oral hygiene self-care tips you can do at home as well as suggestions for future dental appointments. Maintaining your teeth and gums on a routine basis should reduce the risk of dental disease and the need for invasive dental treatments. [Click here to view on our website.](#)

## Support Our Work

The TMJ Association (TMJA) is the only patient advocacy organization fighting for the best science that will lead to a greater understanding of Temporomandibular and related disorders and safe and effective treatments. We cannot change the face of TMJ without YOU.

[Click HERE to make a tax-deductible online contribution today!](#)



*"I am glad your organization exists. I could not find a similar one here in Canada. I appreciate your informative website...I would like my contribution to go toward promoting scientific research so probably the 2016 TMJA science meeting is the best way to use my donation. Since TMD affects so many people it's surprising that not more research has been done. Diseases that affect quality of life just do not get adequate funding in my opinion." John, Canada*

*"The TMJA is a great organization. I am impressed by your objectivity and transparency. Thank you for your hard work." - Lisa, Hummelstown, PA*

## About The TMJ Association

### *Changing the Face of TMJ*

The TMJ Association, Ltd. is a nonprofit, patient advocacy organization whose mission is to improve the quality of health care and lives of

everyone affected by Temporomandibular Disorders (TMD). For over 25 years we have shared reliable information on TMD with people like you. We invite you to visit our website, [www.tmj.org](http://www.tmj.org).

- If you're not currently receiving *TMJ News Bites* and would like to be on our mailing list, [sign up here](#).
- [Past issues of \*TMJ News Bites\*](#) are also available on our website.

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