Emerging Research on Orofacial Pain


In 2011, the Institute of Medicine published a report documenting that at least 100 million U.S. adults—more than the number afflicted by heart disease, diabetes, and cancer combined—suffer from common chronic pain conditions that persist for ≥3 mo ("Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research,"). The national annual costs for this burden was estimated to be in the range of $600 billion in treatment costs and lost work productivity. The report stated that this enormous burden would require a "cultural transformation in the way pain is understood, assessed and treated."

Acute pain is a sensory and emotional experience that is protective by providing a warning signal that there is a threat to our health. It usually can be managed successfully. Chronic pain is more complex. It often persists even after the cause of the pain is identified and remedied. In some cases, it becomes a disease in itself, reflecting dysfunction in the nervous system.

Today, pain is a health problem that requires a broader perspective than in the past. Millions of Americans suffer from overlapping chronic pain conditions that share comorbid behavioral, physiologic, and psychological characteristics as well as genetic determinants. Many of these conditions affect the orofacial region uniquely or have accompanied widespread systemic manifestations. This includes temporomandibular disorders (TMD), headache, arthritis, and fibromyalgia, to name just a few. The majority of patients diagnosed with TMD are women, indicating that there is an important need to provide better understanding and treatment for a major population.

The recognition of the above issues and their importance to students, dental scientists, and practitioners led the Journal of Dental Research to announce the publication of a special issue in 2016 highlighting the latest developments in the field of chronic orofacial pain. This issue interfaced with the November 2015 Eighth AADR Fall Focused Symposium in Washington, DC, titled "Advances in the Biology and Management of Chronic
TMDs are the major orofacial chronic pain condition and received considerable interest in manuscript submissions. The advances in this field can be found in review articles and original reports in this issue. They reveal important transformations in our understanding of these conditions that revolve around pain traits rather than localized inflammatory and pathologic changes in the temporomandibular joint or masticatory musculature. TMD is now considered a multidimensional biopsychosocial disorder that shares common features not only with other musculoskeletal conditions, such as fibromyalgia, low back pain, and headache, but with idiopathic inflammatory conditions, such as joint pain, irritable bowel syndrome, vulvodynia, and other somatic and visceral deep tissue injuries. Of interest is the common finding of widespread pain manifested outside the orofacial region and the presence of multiple comorbid persistent disorders in many patients. TMD is a complex systemic disease that has a genetic and immunologic basis. Furthermore, the pain involves changes in the nervous system, resulting in a mismatch between what is perceived and what pathology is actually observed at the peripheral target site. Proper diagnosis and treatment require collaborative efforts by dental and medical specialists. The Orofacial Pain: Prospective Evaluation and Risk Assessment (OPPERA) prospective study (Slade et al. 2016) identified risk factors in TMD-free adults by assessing genotypic and phenotypic measures of biological, psychosocial, clinical, and health status traits. The OPPERA model shown in the Figure displays 2 principal intermediate phenotypes (psychological distress and pain amplification) that contribute to the onset and persistence of TMD. Each phenotype represents a group of more specific risk factors that are subject to genetic regulation that take place in the presence of environmental contributions. As stated by the OPPERA group, "it is a misnomer and no longer appropriate to regard TMD as a localized orofacial pain condition." The Harper et al. (2016) review focuses on 1) TMD pain that is generated and maintained by mechanisms of sensitization in the central nervous system and 2) the need for personalized medicine to provide relief. The Ohrbach and Dworkin (2016) paper reviews the important development of a reliable and valid diagnostic system that has been critical in fostering TMD research over the past 2 decades.

Read complete article at: [http://jdr.sagepub.com/content/95/10/1081.full.pdf+html](http://jdr.sagepub.com/content/95/10/1081.full.pdf+html)

**Painful Temporomandibular Disorder: Decade of Discovery from OPPERA Studies**


In 2006, the OPPERA project (Orofacial Pain: Prospective Evaluation and Risk Assessment) set out to identify risk factors for development of painful temporomandibular disorder (TMD). A decade later, this review summarizes its key findings. At 4 US study sites, OPPERA recruited and examined 3,258 community-based TMD-free adults assessing genetic and phenotypic measures of biological, psychosocial, clinical, and health status characteristics. During follow-up, 4% of participants per annum developed clinically verified TMD, although that was a "symptom iceberg" when compared with the 19% annual rate of facial pain symptoms. The
The most influential predictors of clinical TMD were simple checklists of comorbid health conditions and nonpainful orofacial symptoms. Self-reports of jaw parafunction were markedly stronger predictors than corresponding examiner assessments. The strongest psychosocial predictor was frequency of somatic symptoms, although not somatic reactivity. Pressure pain thresholds measured at cranial sites only weakly predicted incident TMD yet were strongly associated with chronic TMD, cross-sectionally, in OPPERA’s separate case-control study. The puzzle was resolved in OPPERA’s nested case-control study where repeated measures of pressure pain thresholds revealed fluctuation that coincided with TMD’s onset, persistence, and recovery but did not predict its incidence. The nested case-control study likewise furnished novel evidence that deteriorating sleep quality predicted TMD incidence. Three hundred genes were investigated, implicating 6 single-nucleotide polymorphisms (SNPs) as risk factors for chronic TMD, while another 6 SNPs were associated with intermediate phenotypes for TMD. One study identified a serotonergic pathway in which multiple SNPs influenced risk of chronic TMD. Two other studies investigating gene-environment interactions found that effects of stress on pain were modified by variation in the gene encoding catechol O-methyltransferase. Lessons learned from OPPERA have verified some implicated risk factors for TMD and refuted others, redirecting our thinking. Now it is time to apply those lessons to studies investigating treatment and prevention of TMD.

The full article is available at: http://jdr.sagepub.com/content/95/10/1084.full.pdf+html.

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**Should FDA Rush Approvals When Patients Demand It?**

The following article is by Art Caplan, Ph.D., Division of Medical Ethics at the New York University Langone Medical Center. Posted May 13, 2016 on Medscape.com.

If a child is being treated with a drug that they and their family believes to be beneficial, who should decide whether they can continue to receive it? This issue was recently raised regarding eteplirsen, a drug for treating Duchenne muscular dystrophy. A huge hearing took place at the US Food and Drug Administration (FDA) in Hyattsville, Maryland, attended by parents, their wheelchair-bound children with this condition, and scientific experts. The tremendous interest in the drug and the questions surrounding its use required the FDA to use a larger meeting hall than usual.

The advisory committee recommended against approving this drug or allowing accelerated access to it. That led to quite a backlash from upset and outraged parents as well as young patients suffering from this condition, who believe that this drug helps them with improved mobility. They wondered why the FDA didn't listen to them, instead of just looking at the data. The data consisted of a report on 12 patients. The drug is for a relatively rare condition and comes from a small company that didn't produce it in substantial amounts.

Doctors often get requests from patients for drugs they've seen on the Internet or heard about them from a neighbor, which they think might help them. They want to know how they can access something that isn't yet approved. It is true that the FDA should not be modifying its standards of evidence even in the presence of testimonials from parents or, in this case, young children, saying that a drug helps. The FDA's job is to get drugs out on the market that are proven safe and effective. In this case, there simply were not enough data in place from the corporate sponsor to make that possible.

At the same time, companies shouldn't be deluding patients and families into thinking that they have enough data to go to the FDA. They shouldn't approach the FDA unless they truly have the available data to get
approved. Relying on patient testimonials and lobbying is not the path to drug approval.

Should children who believe that they have been helped by the drug have continued access to it? I would say yes. Companies should form compassionate use programs to make particular drugs available while the studies continue. Some might ask who will participate in the study if they can get a drug through a compassionate use program. Companies have to establish limits as to who can be in the compassionate use program, clearly state who is going to be in the randomized trial, and ensure that they can do both as best as possible. Companies may also say that they can't afford such programs, as it's too expensive to make the drug. Compassionate use programs should therefore be factored into the cost of drug development to ensure that a drug is available for people when it appears to be safe and helping patients.

We have to listen to patients and their families. They sometimes detect improvements that would perhaps be harder to observe in a clinical trial. At the same time, we can't have public policy made solely on the basis of patients saying that a drug worked for them or helped them. There's too much history of bad experiences with ultimately failed treatments to trust only patient testimonials. The balance has to be there. The FDA must take the long view by not approving treatments unless the evidence is truly there and supported by a sound study design in order to convince experts. Patients should have some access in situations where a treatment represents their last shot for help when they're losing their life or mobility. I think that we can do both, but I don't think asking the FDA to bend its rules will do the public or future generations any favors.

Genes Associated with Risk for Fibromyalgia Found

One of the overlapping chronic pain conditions associated with TMD is fibromyalgia, a condition characterized by multiple musculoskeletal pains and dysfunction. Please note that the finding of a couple of gene variants (polymorphisms) more common in fibromyalgia patients is no guarantee that if you have those variants you are bound to develop the condition. Such findings do aid research however, because they help investigators understand the pathology and suggest possible treatments.

A retrospective analysis has found two genetic polymorphisms with a statistically significant association with fibromyalgia: C-reactive protein (CRP; rs1205) and protein tyrosine phosphatase, nonreceptor type 11 (PTPN11; rs2301756). According to the researchers, these findings could contribute to the discovery of better diagnostic and treatment modalities for the disease.

"Collectively, our results show that genetic testing for CRP and PTPN11 may help determine the risk of fibromyalgia," said Zoie Badura, MS, the primary author of the study, and a researcher at Proove Biosciences. "These findings need to be validated but suggest genetic testing may aid in diagnosis and, potentially, treatment intervention based on biomarker expression."

Despite advances in research and better understanding of the disorder, as Ms. Badura reported at the 2016 annual meeting of the American Academy of Pain Medicine, fibromyalgia remains undiagnosed in as many as three of four people with the condition.

Meet Carolyn...

Hello, my name is Carolyn and I am 59 years old. I found out that I had TMJ when I was 23 years old. I could no longer close my mouth to bite and chew food. I was in a car accident when I was 18 and was told I probably had whiplash. I also had an over and open bite which only made things worse.

I have worked for 30 plus years and finally had to "retire" due to my health. I cannot describe the pain, but the closest I can come is what I would imagine is bone on bone pain. An example I use is to imagine a tennis player having his/her shoulder dislocated and still having to play the game of tennis. With TMD I still have to talk, smile, laugh, kiss, and eat; most often this is done with pain. Another issue is that I cannot take pain medication without taking a nausea pill. If I take both a nausea and a pain pill it completely knocks me out, so I have to choose between living in pain or going to sleep without pain. When I was 23 years old I didn't have pain, but in the last 10 years the pain has been horrible. I was taking 8 to 12 Advil a day because it seemed to help the pain; however I was told to stop because of its effect on my kidney function. At this point I have to decide whether to take Advil to help the pain or lose my kidneys.

I have a great dentist. He has made me several splints, because I have worn several out. He has tried equilibration, but as I get older he says I probably have arthritis and some nerve damage. I am sure I have both. I have seen a TMJ specialist who told me to save my money because he would be doing the same treatments my dentist had already done. I feel hopeless and helpless and a complete failure as a wife, mother, and grandmother, because I never "want" to do anything. I have a wonderful, supportive family, but my husband is the only one who really knows and sees how bad the pain is, and he feels so helpless because he can't fix it for me that I try not to let him see me at this point. I can usually hang in there until noon, but after that it all does downhill, and by five or six I am ready to knock myself out.

I wish I could find a pain management doctor who could help. Again, I can't take pain pills. I would like to try a muscle relaxer to relax my jaw muscles which are spasming by the end of the day, but no one wants to give me a prescription for fear I would become addicted to the medication. At this point I just don't care; I just need someone to listen, to help, and work with me, instead of just telling me medicine can't help. I try not to complain in public. I'm sure there are people with cancer who are in a lot of pain, but when you are in a lot of pain and cannot get relief, it is the most miserable situation anyone can be in. This is my story. If anyone has any suggestions, I'm open to hearing them.

Opioid Pain or Cough Medicines Combined With Benzodiazepines: Drug Safety Communication - FDA Requiring Boxed Warning About Serious Risks and Death

A U.S. Food and Drug Administration (FDA) review has found that the growing combined use of opioid medicines with benzodiazepines or other drugs that depress the central nervous system (CNS) has resulted in serious side effects, including slowed or difficult breathing and deaths. Opioids are used to treat pain and cough; benzodiazepines are used to treat anxiety, insomnia, and seizures. In an effort to decrease the use of opioids and benzodiazepines, or opioids and other CNS depressants, together, we are adding Boxed Warnings,
our strongest warnings, to the drug labeling of prescription opioid pain and prescription opioid cough medicines, and benzodiazepines.

**Health care professionals** should limit prescribing opioid pain medicines with benzodiazepines or other CNS depressants only to patients for whom alternative treatment options are inadequate. If these medicines are prescribed together, limit the dosages and duration of each drug to the minimum possible while achieving the desired clinical effect. Warn patients and caregivers about the risks of slowed or difficult breathing and/or sedation, and the associated signs and symptoms. Avoid prescribing prescription opioid cough medicines for patients taking benzodiazepines or other CNS depressants, including alcohol.

**Patients** taking opioids with benzodiazepines, other CNS depressant medicines, or alcohol, and caregivers of these patients, should seek medical attention immediately if they or someone they are caring for are experiencing symptoms of unusual dizziness or lightheadedness, extreme sleepiness, slowed or difficult breathing, or unresponsiveness. Unresponsiveness means that the person doesn't answer or react normally or you can't wake them up. Talk with your health care professional if you have questions or concerns about taking opioids or benzodiazepines.


### Acetaminophen Safety Awareness

The priority of the Acetaminophen Awareness Coalition (AAC), a group of 10 leading healthcare provider and consumer organizations, is to ensure that patients know how to safely use medicines containing acetaminophen. The AAC's 'Know Your Dose' campaign has collaborated with the U.S. Food and Drug Administration (FDA) and over 25 organizational partners to reach more than 400 million healthcare providers and patients with awareness messages over the last five years.

Acetaminophen education is working. New research evaluating data from the National Poison Data System (NPDS) shows a steady decline in unintentional exposures of acetaminophen, including therapeutic errors and accidental misuse, since a peak in 2009. Consumer knowledge about how to use acetaminophen safely and awareness of the risks are at record highs.

We encourage patients to participate by educating themselves about acetaminophen safety by visiting KnowYourDose.org. Additionally, health care providers are encouraged to join in the effort by ordering complimentary educational materials to display in their offices and talking to patients about safe acetaminophen use.

### Antidepressants: Rise in Off-label Prescriptions

*We have included the article that follows because we are aware that many TMD patients may concurrently experience depression and/or anxiety. They may also have other systemic conditions for which antidepressants have been prescribed off-label. This is not necessarily reckless or unethical behavior on the part of the provider, because many drugs prescribed for brain disorders are not specific. They may target neurotransmitters or brain centers active in emotional experience, but may also affect other parts of the brain, including centers responsive to pain or motor activity. Of course we heartily agree that appropriate clinical studies are needed to...*
Antidepressant use in North America has increased over the last 2 decades. A suspected reason for this trend is that primary care physicians are increasingly prescribing antidepressants for nondepressive indications, including unapproved (off-label) indications that have not been evaluated by regulatory agencies.

In a study appearing in the May 24 issue of JAMA, Jenna Wong, a Ph.D student in the department of Epidemiology, Biostatistics and Occupational Health, and colleagues analyzed treatment indications for antidepressants and assessed trends in antidepressant prescribing for depression.

The researchers used data from an electronic medical record and prescribing system that has been used by primary care physicians in community-based, fee-for-service practices around 2 major urban centers in Quebec, Canada. The study included prescriptions written for adults between January 2006 and September 2015 for all antidepressants except monoamine oxidase inhibitors. Physicians participating in the study had to document at least 1 treatment indication per prescription using a drop-down menu containing a list of indications or by typing the indication(s).

During the study period, 101,759 antidepressant prescriptions (6 percent of all prescriptions) were written by 158 physicians for 19,734 patients. Only 55 percent of antidepressant prescriptions were indicated for depression. Physicians also prescribed antidepressants for anxiety disorders (18.5 percent), insomnia (10 percent), pain (6 percent) and panic disorders (4 percent). For 29 percent of all antidepressant prescriptions (66 percent of prescriptions not for depression), physicians prescribed a drug for an off-label indication, especially insomnia and pain. Physicians also prescribed antidepressants for several indications that were off-label for all antidepressants, including migraine, vasomotor symptoms of menopause, attention-deficit/hyperactivity disorder, and digestive system disorders.

"The findings indicate that the mere presence of an antidepressant prescription is a poor proxy for depression treatment, and they highlight the need to evaluate the evidence supporting off-label antidepressant use," the authors write.

Treatment Indications for Antidepressants Prescribed in Primary Care in Quebec, Canada, 2006-2015, Jenna Wong; Aude Motulsky; Tewodros Eguale; David L Buckeridge; Michal Abrahamowicz; and Robyn Tamblyn is published in JAMADOI:10.1001/jama.2016.4447

Musculoskeletal Inflammation and Natural Products

Many natural products have purported anti-inflammatory properties, and some have a long history of use for treating inflammation and the pain that is associated with musculoskeletal inflammatory conditions such as osteoarthritis, rheumatoid arthritis, and tendinitis. Although there is some limited evidence that a few natural products may provide modest benefits, in general, there is insufficient evidence to support the use of many of these natural products for inflammatory conditions. This issue of the digest provides a current summary of the evidence of several natural products marketed for improving these conditions. Click here to read more.

Patients in Los Angeles or New York City Needed for Clinical Study - Comparative Study of Women Considering or Currently Receiving Botox©
Injections for TMJ Pain

Are you a woman with TMJ pain in facial muscles, who has either:
   a. recently had Botox© injections for your pain or
   b. not had Botox© for your pain but has thought about such treatment?

If either is true for you, you may qualify for an observational research study centrally administered by the New York University College of Dentistry. It is funded by the National Institutes of Health (NIH). The purpose of this study is to understand potential health risks that may be caused by treating "TMJ pain" with Botox© injections. Potentially eligible women must first complete a brief interview via telephone to confirm eligibility. Click here for further study information and details.

Patients Needed for Research Study in Baltimore MD

Researchers at Johns Hopkins School of Medicine and the University of Maryland Dental School are looking for volunteers with widespread pain that includes jaw pain (TMD) to participate in a research study to investigate the effect of three different non-drug treatments on pain and sleep symptoms. If you live in the in the Baltimore, MD area and are interested in further information, please read through the study information brochure and patient consent form for further details.

NIH Funding Opportunities

Basic and Clinical Research

In an effort to promote greater understanding of TMD, and to develop safe and effective evidence-based diagnostics and treatments, The TMJ Association promotes and encourages basic and clinical research on Temporomandibular Disorders. We invite you to view a listing of the latest National Institutes of Health (NIH) funding opportunities for scientists interested in advancing TMJ research. The following are the newest NIH requests for information and funding announcements:

- **Request for Information: Increasing the Varieties of Marijuana and Marijuana products for Research (NOT-DA-16-034)**

  The National Institute on Drug Abuse (NIDA) supports the production of research grade marijuana and marijuana products (i.e. extracts, purified cannabinoids, etc.) for research.

- **Factors Underlying Differences in Female and Male Presentation for Dental, Oral, and Craniofacial Diseases and Conditions (R01)**

- **Factors Underlying Differences in Female and Male Presentation for Dental, Oral, and Craniofacial Diseases and Conditions (R21)**

The purpose of this funding opportunity announcement is to encourage exploratory/developmental research on mechanisms underlying the manifestations of sex-based differences in Dental, Oral, and Craniofacial (DOC)-related diseases and conditions. Specifically, this initiative encourages studies aimed at understanding immune reactivity, genetic variation, environmental triggers, aging, and
hormonal changes as they affect sex-based differences in DOC-related diseases and conditions including, but not limited to, Sjögren’s Syndrome (SS), orofacial pain, temporomandibular joint (TMJ) disorder (TMD), salivary gland tumors, and human papillomavirus (HPV)-associated oropharyngeal cancers.

- **NIDCR Small Research Grants for Secondary Analysis of FaceBase Data (R03)**

The FaceBase Consortium is developing a variety of comprehensive datasets on craniofacial development that are available to the wider scientific community at [www.facebase.org](http://www.facebase.org). This funding opportunity announcement (FOA) will support meritorious research projects that conduct secondary data analyses of these FaceBase datasets relevant to craniofacial development, human craniofacial conditions or traits, and animal models of those craniofacial conditions. Informatics projects that integrate data from multiple FaceBase datasets are especially encouraged.

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### TMD Nutritional Guide

**TMD Nutrition and You**

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

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### Research E-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. These conditions 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.

The most current issues are 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.](#)

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### Educational Brochure on TMD

**A Resource Guide for Temporomandibular Disorders**

This brochure is a straightforward, easy-to-read booklet that guides patients in how to make health care
decisions. It is available by mail or as a PDF on our website and we encourage you to share it with your friends, health care professionals and family members.

**Dental Care Guide**

*Temporomandibular Disorders, Dental Care and You*

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

**Do You Clip Coupons?**

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Support The TMJ Association by using Coupons.com's 1-800-Flowers coupons, Barnes & Noble coupons, Target coupons or any of the thousands of coupon codes available for your favorite online retailers.

**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, as well as safe and effective treatments. We cannot change the face of TMJ without YOU.

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

"My daughter lost some of her childhood to TMD. She went undiagnosed for so long. The doctors judged her and us. It seems that most doctors don't understand how debilitating this syndrome can be. They need to be educated. This contribution is in honor of our little girl who had no voice" - Michelle, New York

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

- 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.