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Antibiotics for Back Pain: Does a New Study Doom a Highly Publicized Treatment "Breakthrough"?

A recent randomized controlled trial (RCT) from Norway suggests that antibiotic therapy is *not* an effective treatment for chronic back pain in the presence of Modic changes—i.e. disruption of the vertebral endplates with accompanying inflammatory and structural findings.

The results of this replication study are shocking since they contradict one of the most widely publicized studies of the past decade: a 2013 RCT from Denmark by Hanne Albert, PhD, and colleagues showing an unprecedented improvement in pain and disability scores among patients treated with three months of antibiotics for Modic Type 1 changes and back pain that occurred in the wake of a disc herniation. (See Albert et al., 2013.)

The architects of major back pain guidelines have been reluctant to recommend this treatment approach based on the existing evidence—which comes largely from a single RCT with some methodologic issues. (See Schoene, 2013 for a discussion of those issues).

In light of the new study, their reluctance will certainly grow. This RCT could doom this treatment approach altogether. That low-grade infection could be a cause of chronic low back pain—and antibiotics a potential treatment—may still be a live hypothesis. However, it remains to be seen whether funders will be willing to underwrite further large, expensive, and meticulous RCTs given the contradictory results in this area.

There are at least two additional RCTs on this topic registered and apparently under way—one at Monash University in Australia and one at Tabriz University in Iran. If they are completed, they may shed further light on these issues. Readers can find details of these ongoing studies at the Australian New Zealand Trials Registry. (See https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=368913; see https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=365042)

A Ground-Breaking Replication Trial

In the newly published study, called the AIM trial, Lars Christian Haugli Bråten, MD, from Oslo University Hospital in Norway and colleagues performed a double-blind, randomized, placebo-controlled, multicenter trial involving 180 patients with chronic low back pain, a previous disc herniation, and type 1 or type 2 Modic changes.

The researchers found a small, statistically significant advantage in the antibiotic treatment group—with a stronger effect in patients with type I Modic changes. But patients in the antibiotic treatment groups did not achieve a *clinically important* advantage as defined in the new RCT. In other words, patients would have to risk weeks of antibiotic therapy to achieve, on average, a borderline advantage in symptoms and function.

"In conclusion, we were not able to replicate the findings of the previous randomized

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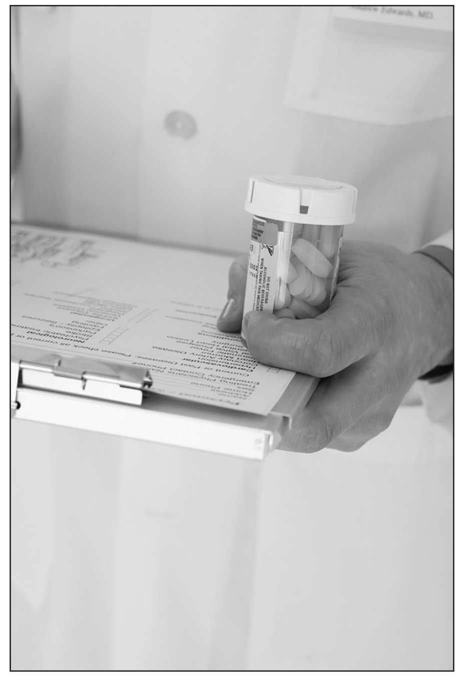

An Award for *The BackLetter*

A message from *BackLetter* editor-in-chief Sam Wiesel, MD:

An end-of-year wrapup at *The BackLetter* would be incomplete without expressing thanks to the International Forum for Back and Neck Pain Research in Primary Care—one of the world's elite back pain research organizations.

At its 2019 conference in Quebec City, the organizers gave *BackLetter* editor and lead writer Mark Schoene a surprise award for "an Outstanding Contribution to the field of Back and Neck Pain Research."

"Thank you for demonstrating the value and importance of intelligent and balanced journalism at a time when biased, divisive, and sycophantic journalism has become the norm," said Forum founder and epidemiologist Dan Cherkin, PhD, in presenting the award.

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Decline in Opioid Prescriptions for Low Back Pain

There was a significant decline in the proportion of commercially insured patients with low back pain who received a prescription for opioids from 2011 to 2016, according to a study presented at the 2019 annual meeting of the North American Spine Society in Chicago.

"After 2010 there has been a sharp decline in the proportion of patients who had prescriptions for opioids filled in the outpatient setting for low back pain," according to Micheal Raad, MD, of Johns Hopkins University and colleagues. (See Raad et al., 2019.)

There was also a parallel decline in opioid dosage over the same time frame. "Prescriptions that are considered to be associated with high overdose risk declined during the study period as well. This points towards an increasingly conservative approach to prescribing opioids for low back pain in the outpatient setting."

Commercially Insured Patients With Nonspecific Back Pain

These are encouraging trends. To what extent they represent broad national trends in opioid prescription for back problems is not clear. To achieve its goals this study had to exclude some important segments of the back pain treatment market.

This study only looked at commercially insured patients. US residents rely on a broad mixture of insurance programs. Only about two-thirds have private insurance.

"In 2016, private health insurance coverage continued to be more prevalent than government coverage, at 67.5 percent and 37.3 percent, respectively. Of the subtypes of health insurance coverage, employer-based insurance covered 55.7 percent of the population for some or all of the calendar year, followed by Medicaid (19.4 percent), Medicare (16.7 percent), direct-purchase (16.2 percent), and military coverage (4.6 percent)," according to the US government Census website. (See United States Census Bureau, 2019.)

The study also excluded anyone younger than 18 years and older than 64 years—though back pain is common among adolescents and the elderly. It did not include patients covered under Medicare and Medicaid, and US veterans' programs. And it excluded individuals with trauma, tumor, chronic pain, sciatica, disc herniation, and spinal stenosis.

After applying their exclusion criteria, Raad studied a total of 1,631,155 with isolated back pain symptoms. (See Raad et al., 2019.)

Steep Decline in Opioid Prescription

The number of patients who had an opioid prescription filled in the first 30 days after their visit declined from 27.7% in 2010 to 21.8% in 2016 ($P < 0.01$). Similarly, the average 90-day morphine milligram equivalent (MME)/day declined from 37.2 in 2010 to 34 in 2016.

One hopes that patients with other forms of health insurance—and with varying psychosocial and socioeconomic characteristics—are experiencing similar declines in opioid use for back pain. And that they are not migrating toward illicit and much more dangerous black market opioids.

Disclosures: None declared.

References:

Raad M et al., National trends in opioid prescribing practices for patients presenting with isolated low back pain in the outpatient setting, presented at the annual meeting, North American Spine Society, 2019, Chicago; abstract at www.thespinejournalonline.com/article/S1529-9430(19)30678-3/fulltext.

United States Census Bureau, Health Insurance Coverage in the United States: 2016, accessed December 2019; www.census.gov/library/publications/2017/demo/p60-260.html.

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Spinal Medicine Warped by a Succession of False Narratives?

Nobel Prize-winning economist Robert Shiller, PhD, recently published an essay and a book on the many narratives (i.e. stories) that help stimulate and power major economic events. (See Shiller, 2017.)

All of his points can also be applied in the medical realm—and especially the back pain area—where the interpretation and management of common symptoms have been driven by a series of stories, true and false.

Much of the progress in back pain research has come from recognizing false narratives and unproductive diagnostic and treatment models

Many of the common explanations for low back pain—that it typically represents an injury, that is typically can be diagnosed precisely, and that it can be treated definitively—are at least partially false. These falsehoods need to be knocked down and rooted out. And not just in research circles. Resolution of the back pain crisis will require wholesale changes in attitudes, beliefs, behaviors, and stories associated with this common symptom.

Shiller has pioneered the field of narrative economics (i.e. "the study of the spread and dynamics of population narratives, particularly those of human interest and emotion, and how these changes through time") and the influence of these stories on major economic events.

For example, Shiller pointed out that recessions may be partially based on a response to major economic events. However, they are also driven by human stories and population-wide beliefs that may or may not be true.

"A recession, for example, is a time when many people have decided to spend less, to make do for now with that old furniture instead of buying new, or to postpone starting a new business, to postpone hiring new help in an existing business, or to express support for fiscally conservative government. They might make any of these decisions in reaction to the recession itself (that's feedback), but to understand why a recession even started, we need more than a theory of feedback. We have to consider the possibility that sometimes the dominant reason why a recession is severe is related to the prevalence and vividness of certain stories, not the purely economic feedback or multipliers that economists love to model," according to Shiller.

This prominent economist pointed out that "narrative economics" is a field in its infancy. "To my knowledge, there has been no controlled experiment to prove the importance of changing narratives in causing economic fluctuations," according to Shiller. And he called for rigorous research on the nature and course of these narratives.

The same holds true in the back pain area. Addressing the back pain crisis—back

pain is still the leading cause of disability worldwide—will require careful study of how narratives affect the way back pain is perceived and managed. It will require identifying the most important false narratives.

And it will require identifying new narratives that are evidence-based and therapeutic.

Disclosures: None declared.

References:

Shiller R, Narrative Economics, Working Paper 23075, 2017; www.nber.org/papers/w23075.pdf.

Shiller R, Narrative Economics: How Stories Go Viral and Drive Major Economic Events, Princeton University Press, 2019.

Fear of Pain Driving Overtreatment

"Evidence-based back care" is likely to be ineffective unless it is accompanied by a wholesale population-wide shift in thinking about back pain.

In an eloquent essay in the *Washington Post*, James Hudson, MD, pointed out that modern medicine has elevated pain from a coping issue into a fearful disease that needs to be recognized and obliterated. (See Hudson, 2019.)

"Instead of learning from pain, we now regard it as an illness in and of itself. Insurance companies, health-care providers and drugmakers have all worked to increase the public's fear of pain, leading us to see it as something to be treated, eliminated, banished—never lived with or accommodated or managed—lest it destroy us. They turned our natural fear into big business; our fee-for-service system has multiplied treatments based primarily on the financial rewards for pharmaceutical companies, doctors and hospitals. That attitude shift is perhaps the most overlooked explanation for an opioid crisis that kills tens of thousands of Americans every year."

There are no safe and effective heroic cures for many forms of pain and for most forms of low back pain. But as long as patients and the medical system continue to believe in an outmoded back pain treatment model, progress will be slow in coming. Opioids are a case in point.

Hudson observed that opioids do have a role in palliative care—and in acute care. But their value diminishes in the long-term treatment of chronic pain. Risks usually outweigh the benefits of these potentially lethal medications.

"The fear of pain, and the belief that a pain-free existence is optimal or even possible, has been a catastrophe for patients. Before the opioid revolution, doctors understood that pain was important to keeping us safe, to be lived with and managed. Even if this meant we bore frequent episodes of discomfort, that was better than the nationwide crisis America faces today. Life isn't 'pain free.' If we want to end the epidemic of addiction, we need to relearn that lesson," Hudson wrote.

Disclosures: None declared.

Reference:

Hudson J, Our dangerous fear of pain: We used to know how to manage discomfort. Our quest to banish it brought on the opioid crisis, *Washington Post*, 2019; www.washingtonpost.com/outlook/2019/11/27/our-dangerous-fear-pain/?arc404=true.

Lancet Editor Takes Aim at a Dominant Form of Medical Evidence: Systematic Reviews

There was a time in spine research when randomized controlled trials (RCTs) were regarded as the highest form of evidence regarding the risks and benefits of various approaches to low back pain.

And indeed, there was a time—25 years ago—when a single RCT would serve as the focus for a cover story in the *BackLetter*. They were that rare.

However, there are now more than 12,000 RCTs on back and neck pain. So systematic reviews of RCTs, with and without meta-analysis, have come to serve as the evidence pinnacle in many areas.

But what if much of the underlying evidence assembled in systematic reviews is not accurate or honest? That would throw a major wrench into the evidence-based medicine movement. And the field of medicine may have been a little too trusting in taking some systematic reviews at face value.

Lancet editor-in-chief Richard Horton, MD, recently discussed a disturbing allegation. (See Horton, 2019.)

"Imagine if the entire edifice of knowledge in medicine was built upon a falsehood. Systematic reviews are said to be the highest standard of evidence-based health care. Regularly updated to ensure that treatment decisions are built on the most up-to-date and reliable science, systematic reviews and meta-analyses are widely used to inform clinical guidelines and decision making. Powerful organizations have emerged to construct a knowledge base in medicine underpinned by the results of systematic reviews."

He specifically targeted the Cochrane Collaboration—arguably the world's most respected producer of systematic reviews across medicine. "Cochrane's claims are big: trusted evidence, informed decisions, and better health. But what if the astonishing energy, commitment, and productivity of the systematic review community are poisoning rather than nourishing medical practice?"

Horton cited the work of Ian Roberts, who has repeatedly alleged that systematic reviews are full of biased, low-quality, and even fraudulent RCTs. As Roberts and Katharine Ker wrote in a 2015 *Lancet* commentary: "Systematic reviews of small trials increase waste by advertising to the scientific community inflated, often significant treatment effects that become smaller or absent when large, high-quality trials are done … Failure of systematic reviews to acknowledge the unreliability of small, single-center trials should raise concerns about the value for money provided by reviews."

"Imagine if the entire edifice of knowledge in medicine was built upon a falsehood. Systematic reviews are said to be the highest standard of evidence-based health care. Regularly updated to ensure that treatment decisions are built on the most up-to-date and reliable science, systematic reviews and meta-analyses are widely used to inform clinical guidelines and decision making. Powerful organizations have emerged to construct a knowledge base in medicine underpinned by the results of systematic reviews."

Roberts suggested that the Cochrane Collaboration and other systematic review organizations need to raise their level of skepticism about many of the trials in systematic reviews—particularly small trials.

"Efforts by Cochrane and others to locate all trials have meant that many low-quality, single-center trials, often with inaccuracies, are easily accessible. Most meta-analyses are dominated by such trials. The median number of trials in Cochrane reviews is six to 16, and the median number of patients per trial is about 80."

"Inclusion of such trials in meta-analyses results in inflated treatment effects. Small trials are prone to publication and other selection biases, are often low quality, and, because single-center trials have less oversight than multicenter trials, they are more susceptible to misconduct," according to Roberts and Ker in a 2015 commentary. (See Roberts and Ker, 2015.)

This certainly has a bearing on systematic reviews of interventions in the world of spine care, where at least some of the RCTs in large systematic reviews are of questionable quality and provenance. And there may be a need for better ways of identifying bias and fraud in these trials.

Roberts has suggested trust could be restored if reviewers only included prospectively registered trials in systematic reviews—and then checked to see whether clinical trial data are real and accurate.

But only including prospectively registered trials would leave out a large segment of research in any field. Systematic reviews were originally developed as way of overcoming the biases and narrow scope of narrative reviews—where a single scientist would present the evidence that he/she regarded as important and timely. Systematic reviews, by contrast, were developed to gather and analyze the *entire body of evidence* on a particular intervention—or at least the entire body of evidence that meets certain quality criteria.

So it may be better to include a large body of trials in systematic reviews and then do sensitivity analyses to see how removing small, low-quality, and potentially biased trials might affect the results.

Disclosures: None declared.

References:

Horton R, Offline: The gravy train of systematic reviews, *Lancet*, 2019; 394:1790; www.thelancet.com/action/showPdf?pii=S0140-6736%2819%2932766-7.

Roberts I and Ker K, How systematic reviews cause research waste, *Lancet*, 2015; 386(10003):1536; www.thelancet.com/journals/lancet/article/PIIS0140-6736(15)00489-4/fulltext.

End Commercial Support for Back Pain Research?

The first in a series of articles on overuse and medical excess in the *BMJ* calls for disentangling medical research from commercial interests.

In the back pain field, and across much of medicine, this would require a major funding revolution. In the United States, for instance, about 60% of published medical research is industry funded. And that research, not surprisingly, is often biased toward industry interests.

"It's time to stop the endemic financial entanglement with industry that is distorting the production and use of healthcare evidence, causing harm to individuals and waste for health systems," according to a group of international experts on medical overuse, in a statement from the *BMJ*.

"If we want to produce trustworthy evidence and tackle the epidemic of medical excess, decision-makers at all levels within healthcare need to disentangle themselves from those profiting from that excess," said lead author Ray Moynihan, PhD, of Bond University in Australia. (See Moynihan et al., 2019.)

"Patients and the public deserve to have evidence they can trust," said *BMJ* editor-in-chief Fiona Godlee, MD. "Commercial influence has no place in scientific research, nor in the education and guidance of clinicians, nor in decisions about diagnosis and treatment. We hope that people around the world support our call for fundamental reforms."

This movement would require wrenching changes for governments, regulatory agencies, industry, and the practice of medicine.

Moynihan and colleagues offer some suggestions on pathways to financial independence from commercial interests. In the research realm, they argue for the following approaches:

- Governments should require independent production of evidence employed for healthcare decision-making, including the evaluation of new treatments, tests, and technologies.
- Governments should require that public healthcare organizations, including regulatory and health technology assessment agencies, receive no funding from industry. And that their advisers have no financial relationships with industry.
- Groups synthesizing research findings, including systematic reviews, should ensure that reviewers have access to all information on study methods and all relevant study results, including clinical study reports, and are conducted without industry funding and by authors with no financial relationships with companies that could benefit from the outcomes.

The source of funding for this ambitious effort, however, is not clear. And there appear to be huge barriers to getting from "here" to "there."

Disclosures: None declared.

Reference:

Moynihan R et al., Pathways to independence: Towards producing and using trustworthy evidence, *BMJ,* 2019; 367:l6576. doi:10.1136/bmj.l6576.

Spinal Imaging a Persistent Problem in Emergency Care

Excessive levels of spinal imaging continue to be a major problem in the United States.

Various studies suggest that high levels of imaging can lead to the discovery of irrelevant abnormalities, a cascade of diagnostic and treatment procedures, and unnecessary downstream costs.

Previous studies have suggested that emergency departments have a persistent problem with imaging. A new study confirms that.

Jina Pakpoor, MD, of Johns Hopkins University and colleagues studied emergency department patients aged 18 through 64 via a national commercial claims database in the period from 2011 to 2016. They excluded patients with evidence of trauma—and those with prior visits for low back pain. (See Pakpoor et al., 2019.)

A total of 134,624 emergency department encounters met their inclusion criteria. Roughly one-third of patients (33.7%) had an imaging scan over the course of the study.

There was a slight downturn in imaging rates over the years. The proportion of visits that included imaging decreased from 34.4% in 2011 to 31.9% in 2016.

X-rays accounted for most of the imaging. Over the entire study period, 30.9% of patients had x-rays, 2.7% had CT scanning, and 0.8% had an MRI.

There was significant geographic variation in imaging rates. Patients in the southern United States were about 10% more likely to have imaging than patients in the western region.

"West Virginia had the highest use, with imaging performed in 52.1% (930/1785) of ED visits. Tennessee and South Carolina followed, with 44.6% (1777/3984) and 43.5% (2628/6048) of visits, respectively. States with the lowest use were Utah, with imaging performed in 18.1% (193/1069) of ED visits; Arizona, with imaging performed in 20.1% (497/2475) of visits; and Minnesota, with imaging performed in 20.4% (197/967) of visits," according to Pakpoor et al.

By its design, this study only looked at patients with commercial insurance claims. So it is not entirely clear whether these patterns would also apply to people covered under US government programs (e.g. Medicare, Medicaid, and US military and veterans' program) or other forms of insurance.

Disclosures: None declared.

Reference:

Pakpoor J et al., Use of imaging during emergency department visits for low back pain [published online ahead of print November 19, 2019], *American Journal of Roentgenology*; doi:10.2214/AJR.19.21674.

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trial. Our study did not show any clinically important effect of three months of oral antibiotic treatment in patients with chronic low back pain, Modic changes, and a former herniated disc. Our results do not support the use of antibiotic treatment for chronic low back pain and Modic changes," according to the research team.

So what about the small statistically significant advantage in favor of antibiotic therapy? A review at the *New England Journal of Medicine Journal Watch* offered the following comment: "Whether the small statistical benefit is a hint that the infection hypothesis might apply to some undefined subset of patients—or is just a chance finding—remains unclear." (See Mueller, 2019.)

A *BackLetter* editor asked Rachelle Buchbinder, MD, of Monash University and the Cochrane Musculoskeletal Injury Group how healthcare providers and researchers should respond to this study.

Given the limited evidence supporting this treatment, Buchbinder suggested that all further research on antibiotics for Modic changes in the face of low back pain should be conducted in research settings. This treatment should not enter standard clinical practice based on the evidence to date.

"Physicians should not be using antibiotics in usual care to treat low back pain," she responded. "Not only is antibiotic therapy ineffective [according to the new RCT] there are much broader issues regarding antibiotic resistance that may harm the general population.

"I am not sure that *any* further trials should be conducted, at least not without a strong rationale as to why the trial is needed," she added.

"Avoid Experimenting Outside of Clinical Trials"

Lead author Bråten also believes that further investigations should be confined to research settings.

"I believe that any antibiotic treatment for back pain belongs in a trial setting, and that clinicians should avoid experimenting outside clinical trials," he explained in a recent email. "However, I do understand the temptation for patients with chronic back pain to try antibiotic treatment. It is also important to understand the pressure that clinicians can be put under to prescribe antibiotics. Clear advice to clinicians, based on high-quality evidence is therefore warranted. This is of particular importance considering the issue of antimicrobial resistance that also concerns not only that individual, but society as a whole," according to Bråten.

"If any further trials testing antibiotics in back pain were to be initiated, I think it might be wise to narrow down the target population to those patients with increased probability of treatment effect," according to Bråten.

"That is, find a subgroup of patients with a biologically plausible effect of treatment," he explained. "Ideally, this subgroup should be defined by microbiological evidence of infection. This might be difficult but exploring non-invasive methods and potential biomarkers could be of value in selecting subgroups of patients for targeted treatment."

Elusive Goal: Specific Back Pain and Specific Cures

As mentioned above, antibiotics for Modic changes and chronic back pain has been one of the most widely publicized treatments over the past few years. And many researchers and clinicians, not to mention doctors and patients, had hoped that this research process would finally identify a specific form of low back pain that responded to a specific therapy.

And in deflating some of those hopes, the study by Bråten et al. has come under some caustic criticism (see some of the specific criticisms below.) But this study was carefully designed and conducted. And Bråten said he is confident about the study design and conclusions. "I sincerely do not think the criticisms of the AIM Trial so far pose any major threats to the conclusions."

So where will this process go from here? Bråten suggests that further clinical trials may be necessary to reconcile some of the conflicting results in the two major RCTs conducted to date. He said he would welcome such trials.

Should a Single RCT Justify a Change in Clinical Practice?

Here is some background on the new study from Norway—and its importance.

In 2013 Hanne Albert, PhD, and colleagues from Denmark launched a tsunami of publicity by concluding that one form of low back pain may stem from low-grade infection of the intervertebral disc—and that lengthy antibiotic therapy (three months or more) might lead to significant or even permanent symptom relief. (See Albert et al., 2013.)

Scores of websites and publications around the world reported on this treatment in glowing terms. Some observers speculated that Albert et al. might win the Nobel Prize. And multiple clinics, including some associated with the authors, began offering this treatment approach to patients—with considerable "hype."

However, a *BackLetter* article in the wake of this RCT asked the question "Should a single RCT *ever* justify a widespread change in clinical practice? And the answer from prominent researchers was an emphatic and universal "no." (See Schoene, 2013.)

Martin Underwood, who chaired the development of the National Institute for Health Care Excellence (NICE) guidelines on persistent low back pain, told the *BMJ*, "These are promising preliminary findings, but it is too soon to start changing practice on their basis until they have been replicated in other studies and in other populations." (See McCartney, 2013.)

Details of the Norwegian RCT

The AIM Trial looked at 180 patients with chronic back pain, a previous disc herniation, type 1 or type 2 Modic changes, and pain intensity scores of at least five on a zero to 10-point scale over the preceding two weeks, 10 representing maximal pain. The mean age of study subjects was 45. Fifty-eight percent of the patients were women.

To avoid potential contaminating effects of surgery, the study excluded any potential subjects who had had disc surgery over the past year. And it excluded anyone who had had antibiotic treatment in the past month.

The patients were randomly allocated to one of two treatment approaches: (1) three months of oral treatment with the antibiotic amoxicillin 750 mg three times per day; or (2) a similar schedule and duration of treatment with a placebo pill made from cornstarch.

The primary outcome instrument was the Roland-Morris Disability Questionnaire, employed at baseline, three months, and 12 months. And the primary outcome measure was the difference in RMDQ scores between the antibiotic and placebo groups at 12 months.

The secondary outcome measure repeated the analysis in each of the Modic score types. So they were able to calculate differences in treatment responses between patients with Modic type 1 and Modic type 2 changes.

The results were clear. There was a small statistically significant advantage in favor of the antibiotic group as a whole (for

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Why Is There Such a Need for Replication Studies?

This studies on antibiotics for Modic changes and chronic back pain provide an excellent lesson for the spine field. The study from Norway comes at a time when the spine community, and medicine at large, have identified a tremendous unmet need for replication studies.

In general, the spine community has been overly reactive and responsive to "discovery" studies over the years, i.e., RCTs and other studies which purport to document diagnostic and treatment breakthroughs. Many treatments have entered the clinical marketplace, and stayed there for years, on the basis of a single clinical trial or small group of trials. The spine field has not had a distinguished tradition of replication.

In a recent invited lecture at the National Institutes of Health in Bethesda, Mary, study methodology expert Johan Ioannidis, MD, of Stanford University pointed out that the vast majority of medical discoveries end up being invalid. This is simply the way the evidence usually stacks up. (See Ioannidis, 2019.)

Empirical studies in fields where replication practices are common suggest that *most* of the initially claimed, statistically significant effects are false positives or are substantially exaggerated.

He explained that there are currently about 120 million studies floating around in the medical literature. Almost all claim to have statistically significant, important findings.

Most of these assertions end up being untrue. "Most scientific discoveries end up having negative value," said Ioannidis.

"It is far more likely they will confuse us, generate false negatives, lead people astray, lead to more waste downstream, and build on something that is a false negative claim or an exaggerated claim, rather than something that will save the world," according to Ioannidis.

And he emphasized that replication studies are in many respects more important than original "discovery" studies. These "discovery" studies are generally small with significant methodological flaws—and will ultimately have meager influence.

"We need replication," said Ioannidis. "We need to take all these tentative discoveries and try to replicate them and see what still survives different efforts to reproduce these results either exactly the same way or through different angles of triangulation."

So any time readers see a sensational study with the promise of a diagnostic or treatment breakthrough, wait for the replication studies before acting on it. And it may take several years or more before the value of any spinal treatment becomes clear.

Anyone who doubts this need only recall the train of scientific evidence on treatments for low back pain. Over the quarter-century history of the *BackLetter* any number of treatments for back pain, specific and non-specific, were touted as treatment breakthroughs or even "cures."

Yet in 2020, after thousands of RCTs and other studies, the vast majority of back pain treatments have proven to have marginal or trivial effects. This is not a field that is replete with miracle cures.

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patients with both types of Modic changes) but no clinically important differences. In the subgroup analysis, patients with type 1 Modic changes fared better with antibiotic therapy than those with type 2 changes.

However, the advantage in the type 1 Modic group—a mean 2.3 points—was well less than the pre-defined minimal clinically important difference.

Adverse events were more frequent in the antibiotics group. Serious events were rare. So the chief adverse event concern is the potential contribution to antibiotic resistance.

What Constitutes a Clinically Important Outcome?

The authors had pre-defined a clinically important outcome as a difference of 4 points on the RMDQ at one year. Judging from the rapid responses at the BMJ site, and the comments of the scholars who reviewed the study for the BMJ, this was the most controversial aspect of this study.

"Most scientific discoveries end up having negative value. It is far more likely they will confuse us, generate false negatives, lead people astray, lead to more waste downstream, and build on something that is a false negative claim or an exaggerated claim, rather than something that will save the world," That is why replication studies are so important. And often more important than the original "discovery" studies. —Johan Ioannidis, MD

The authors of the previous study from Denmark, and several BMJ reviewers, suggested that setting a minimal clinically important difference of four points on the RMDQ was out of line with research standards in the back pain field. And that setting a difference of two points on the RMDQ—as is common in back pain trials—might have been a more realistic and useful standard. And indeed, the authors of the original Danish RCT had employed a two-point standard.

BMJ reviewer Chris Maher, PhD, of the University of Sydney suggested that employing a different outcome standard might have been useful.

"I would encourage the authors to reconsider their portrayal of the result and rather than advocate that the treatment should not be used, take a more nuanced approach. It would be reasonable to note that the treatment is effective but it typically has modest effects that are somewhat larger in the subgroup with Modic type I changes. This is a perfect scenario where shared decision-making could be used so that an appropriately informed patient

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Does a Replication Study Have to Duplicate a Previous Study *Exactly*?

One of the criticisms of the recent Norwegian study on antibiotic therapy for chronic back pain and Modic changes is that it did not perform an exact replication of the previous RCT by Hanne Albert , PhD, and colleagues.

"The stated aim of this RCT [from Norway] was to replicate my own trial of oral antibiotics and chronic back pain patients with Modic type 1 changes (MC1). The AIM study was NOT a replication of my own trial as they used a different patient group, their back pain was less disabling, they used a different Roland Morris Disability Questionnaire (RMDQ) scale, and a different antibiotic," said Albert, in the "Responses" section at *BMJ*. (See Albert, 2019.)

However, study methodology expert Johan Ioannidis, MD, pointed out in a recent speech at the National Institutes of Health that replication studies don't have to be exact duplications of the original study—and often aren't.

The studies most likely to have exact duplication of methods are basic science studies. Replication trials involving human subjects often diverge significantly from the original "discovery" RCTs, due to changes in the understanding of disease processes, the context of the disease, the evolution of research measures, etc.

In an article at the NIH website by Eric Bock, Ioannidis pointed out that there are three clusters of reproducibility. "One is reproducibility of methods, which means 'to repeat exactly as possible the experiment and computational procedures.' Next is reproducibility of results, which means 'we're doing another study on new participants, samples and observations and we hope to get a result that is consistent, compatible—ideally as close as the original.' The final one is 'reproducibility of inference,' which means scientists ask others about their conclusions. They may disagree about what the results mean."

The new study would fall into the second category. It is not exactly the same as the study from Denmark. However, it addresses the treatment of low back pain and Modic changes with somewhat similar but not identical study and treatment methods. And it deserves to be taken seriously.

Antibiotics for Back Pain

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could decide if the likely benefit is worth the likely harms and inconvenience."

However, the Norwegian authors gave an excellent rationale for their study approach. They pointed out that the treatment advantage for the antibiotic group in the original Danish RCT was an impressive 8.3 points. And they observed out that if the symptoms in the Modic type 1 group did indeed stem from infection, three months of antibiotic therapy should have had a dramatic effect.

"Our trial's predefined minimal clinically important between group difference of 4 points on the RMDQ is larger than that used in some other randomized trials of patients with low back pain. However, it can be considered conservative given the results of the trial we were reassessing and the proposed rationale for the treatment that an infection leads to Modic changes and low back pain. If the symptoms were mainly because of an infection with C acnes, we would expect a large symptom improvement with effective antibiotic treatment," according to Bråten et al.

Norwegian Study Not an Exact Replication of the Original RCT

Other rapid responders at the BMJ website criticized the Norwegian RCT for not being an *exact* replication of the original study from Denmark. However, as an adjoining article points out, replication studies in complex clinical areas often diverge significantly from the original RCTs. They often employ similar but not identical methods. And that is true of the Norwegian study.

Several commenters suggested that if the new study from Norway had used the same standards and methods as the RCT from Denmark, it would have successfully confirmed the effectiveness of antibiotic therapy for patients with low back pain and type 1 Modic changes.

"An honest and transparent conclusion would have been that their trial confirmed the Albert trial regarding the efficacy of oral antibiotic treatment for MC1 patients but not for patients with MC2," said Albert in her rapid response comments.

However, doing post-hoc revision of study methods and study findings is an exercise fraught with hazard. And it certainly isn't warranted in this situation. The Norwegian researchers performed a careful and thoughtful study. This RCT survived an extensive and transparent review process at BMJ. The journal accepted the study methods and published the conclusions.

If critics are dissatisfied, they have the option of performing further research to test the conclusions of both RCTs.

The reviewers of the Norwegian study, and those who made rapid responses at the BMJ site expressed a number of other criticisms and reservations about the new study. These are too long and elaborate to discuss in a newsletter format.

However, the editors of the *BackLetter* would strongly suggest that readers take a look at the Norwegian RCT, the rapid responses, and the peer reviewers' notes. BMJ has made all these available through "Open Access." It is a great opportunity to examine the study results and the complex issues that come into play in this type of clinical trial. And to consider whether the take-home messages of the Norwegian and Danish trials are accurate.

However, at the end of the day there is one certain take-home conclusion. The results of the Danish RCT have not been replicated. And the future of antibiotic therapy for chronic back pain and Modic changes remains uncertain.

Disclosures: None declared.

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Evidence in *Multiple Areas* Trending Against Antibiotics for Back Pain in the Presence of Modic Changes

The evidence on antibiotics for low back pain in the presence of Modic changes seems to be growing more contradictory by the month.

A recent email from Peter Fritzell, MD, and the Nordic Research Group suggested that evidence from multiple areas is trending against the use of antibiotics in the management of low chronic low back pain and Modic changes.

They argued that antibiotics currently have no proven role in the treatment of back pain/Modic changes. These points mirror similar reservations about antibiotic therapy for low back pain/Modic changes expressed in recent *BackLetter* editions.

Three Recent Studies

Fritzell et al. pointed to three recent studies. A cohort study with 13-year follow-up by Peter Udby, MD, and colleagues—recently discussed at length in the *BackLetter*—found that Modic changes had no long-term negative association with back pain, disability, or sick leave. Surprisingly, Udby and colleagues found that patients with Modic changes had significantly less disability and sick leave than those without these characteristic changes to the endplate and vertebral body. (See Udby et al., 2019; Schoene, 2020.)

They also pointed to the study that serves as the focus of this month's *BackLetter* edition—the AIM trial by Lars Christian Haugli Bråten, MD, and colleagues. That RCT found only a borderline advantage for antibiotic therapy in patients with Modic type 1 and/or Modic type 2 changes. That advantage achieved statistical significance but came nowhere close to satisfying the study's definition of a "clinically important" treatment effect.

Questions About the Role of Bacterial Infections

A third recent study, by Fritzell et al., questioned the role of bacterial infection in the genesis of Modic changes. (See Fritzell et al., 2019.)

"It has been suggested that LBP may be the result of a low-grade infection caused by the anaerobic skin bacterium *Cutibacterium acnes* (formerly *Propionibacterium acnes*). This is based on studies that have found this bacterium using culture of degenerative lumbar disc material, and researchers have suggested that some patients with LDH/LBP could be treated with antibiotics. Hypothetically, haematogenous spread of bacteria to a disc may cause pain through host release of pro-infammatory substances. Some researchers have argued that we indeed may face a paradigm shift in the treatment of LDH/LBP. Others argue that isolation of bacteria from discs during LDH surgery is likely due to contamination. A causative relationship has been suggested between a low-grade infection in vertebrae adjacent to a degenerated disc and an infammatory process identifed on magnetic resonance imaging (MRI), i.e. Modic type 1 changes," according to Fritzell et al. (See open access study by Fritzell et al. for further details.)

However, the study by Fritzell and colleagues raised doubts about this relationship. They studied the level of bacterial infection in two different groups: (1) forty adult patients with lumbar disc herniations and low back pain; and (2) twenty adolescents who underwent scoliosis surgery. The latter are an excellent control group, in that none of them exhibited disc degeneration or disc degeneration-associated low back pain.

"We found that such bacterial findings in discs and vertebrae were rare in both groups, and almost always detected in conjunction with abundance of the same agent on the skin or in the wound," according to Fritzell et al. There was no association between preoperative Modic changes and bacterial findings.

A Warning About Antibiotic Therapy

As the Nordic Research Group noted in their email, "In short, the three studies from Denmark (Udby et al), Norway (Bråten et al) and Sweden (Fritzell et al) complement each other and support the conclusion that bacteria are not generally speaking associated with Modic changes and LBP/leg pain. Consequently, based on our studies, and, as we see it, based also on the current level of scientific evidence, low back pain/leg pain should not be treated with antibiotics," said Fritzell et al.

And they added a key point of emphasis. "As there is a global concern about antibiotics and resistance, we consider this to be a crucial message to both the profession and the public."

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Violence, Chronic Pain, and Fatigue

Women who have experienced domestic abuse appear to have nearly twice the risk of developing chronic widespread pain and persistent fatigue—compared with those who have not experienced such abuse, according to a study by J. S. Chandan of the University of Birmingham in the UK and colleagues. (See Chandan et al., 2019.)

They performed a retrospective cohort study of 18,547 women who had been exposed to domestic violence. Each woman was compared to four matched control subjects who had not been exposed to such violence. They assessed the prevalence of fibromyalgia and/or chronic fatigue syndrome (CFS).

Domestic violence was associated with a steep increase in risk of pain, fatigue, and other symptoms.

"Among women who had been exposed to domestic abuse or violence, the incidence rate ratio for developing fibromyalgia was 1.73 (1.36-2.22). The incidence rate ratio of developing CFS was 1.91 (1.11-3.33)," according to the authors.

"Recent UK estimates suggest that 27.1 per cent of women have experienced some form of domestic abuse, with a large proportion of these cases expected to be women who have suffered violence at the hands of an intimate partner," said Chandan in a statement accompanying the study. So this is not an uncommon problem and risk factor.

"Considering the prevalence of domestic abuse, and the fact that patients experiencing fibromyalgia and CFS often face delays in diagnosis due to a limited understanding generally of how these conditions are caused, it is important for clinicians to bear in mind that women who have survived abuse are at a greater risk of these conditions."

"We hope these first of their kind research findings will change healthcare practice and will be of assistance in the early diagnosis of fibromyalgia and CFS in women who have been abused," he added.

"Survivors of domestic abuse can experience immense physiological and psychological stress," said coauthor Julie Taylor.

"The changes that happen in the body as a result of such stress can lead to a multitude of poor health outcomes such as what we see in our study here."

"However, more research needs to be done to establish the biopsychosocial pathways that cause this link between abuse and these types of health conditions.

"This is a very complex relationship and it is important to emphasize that not all women who have been abused will develop fibromyalgia or CFS, and that having these conditions does not mean there has been domestic abuse in the past."

Disclosures: None declared.

Reference:

Chandan JS et al., Intimate partner violence and the risk of developing fibromyalgia and chronic fatigue syndrome [published online ahead of print December 6, 2019], *Journal of Interpersonal Violence*; doi:10.1177/0886260519888515.

An Award for The BackLetter

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"Periodically one has the good fortune of coming into contact with someone who is a true master at what he or she does," Cherkin explained. This could be a teacher, a researcher, an auto mechanic, a parent, a clinician. It is not just their job titles, it is how they execute their jobs that matters. Unfortunately, these masterful contributions usually go unheralded even when they are noticed and appreciated.

"It has occurred to several of us associated with the Forum that we have such a person within our midst…While he does not publish or present original research, he has made a major mark on the field to which many of us have devoted our careers," Cherkin added.

Our goal at *The BackLetter*—and that of our team of writers, editors, board members, reviewers, and contributors—has always been to provide critical, accurate, and balanced coverage of spine and back pain research in plain language that any professional in this broad field could understand. Our work departs from conventional medical journalism in a couple of respects. We employ an elaborate research process that starts with comprehensive literature searches and a direct reading of the medical literature—followed by an extensive review effort.

Mark and I work closely with Randi Davis, our publisher at Lippincott Williams & Wilkins, in pursuit of this goal.

This award from an elite research organization gives us hope that we are making progress in this quest.

"Our goal at *The BackLetter*—and that of our team of writers, editors, board members, reviewers, and contributors— has always been to provide critical, accurate, and balanced coverage of spine and back pain research in plain language that any professional in this broad field could understand."

The BackLetter has followed the development of the Forum since its inception in Seattle in 1995—and was one of the first publications to recognize the importance of the Forum's work.

The Forum began when Cherkin and a group of international colleagues decided to stage a one-time gathering of the world's most prominent back pain researchers in the primary care area in Seattle in 1995.

Until that time specialists, particularly spine surgeons, had dominated spine research. And the primary care perspective was almost completely absent from that research effort.

There were only 15 or so prominent primary care researchers in the entire world in 1995 and fewer than 100 people at the conference.

But the "one-time meeting" was so successful that it led to the formation of a detailed research agenda, a delightfully informal research society, and a rapidly growing international research movement. There are now hundreds of primary care researchers playing roles not only in research but also in information dissemination and policy making.

The Forum has now staged conferences in 11 countries on five continents. *The BackLetter* has provided coverage from 13 of those meetings. We look forward to following future research developments at Forum XVI in Sydney, Australia in 2021.

Sam Wiesel, MD
Executive Editor, *The BackLetter*
Chairman, Department of Orthopaedics
Georgetown University Medical Center

MEETING CALENDAR

American Academy of Orthopaedic Surgeons Annual Meeting
March 12-16, 2020
2019 Las Vegas, Nevada
Contact: AAOS
9400 W. Higgins Road
Rosemont, IL 60018
Tel: 847-823-7186
Fax: 847-823-8125
www.aaos.org

47th Annual Meeting, International Society for the Study of the Lumbar Spine, Combined with SpineWeek, 2020
April 27-May 1, 2020
Melbourne, Australia
Contact: Katarina Olinder Eriksson, Administator, ISSLS
c/o Institute of Clinical Sciences
Sahlgrenska Academy
University of Gothenburg
PO Box 426 SE-405 30
Gothenburg, Sweden
Tel: 46-31-786-44-36
E-mail: katarina.olinder@gu.se

American College of Rheumatology/ Association of Rheumatology Health Professionals 2020 Annual Meeting
May 16-20, 2020
Washington DC
Contact: American College of Rheumatology
Association of Rheumatology Health Professionals
Rheumatology Research Foundation
2200 Lake Boulevard NE
Atlanta, GA 30319
Tel: 404-633-3777
Fax: 404-633-1870
www.rheumatology.org

International Association for the Study of Pain 2020 World Pain Congress
August 4-8, 2020
Amsterdam, The Netherlands
Contact: IASP
1510 H Street NW, Suite 600
Washington, DC 20005
Tel: 202-856-7400
Fax: 202-856-7401

Scoliosis Research Society 53rd Annual Meeting
September 9-12, 2020
Phoenix, Arizona
Contact: Scoliosis Research Society
555 East Wells Street, Suite 1100
Milwaukee, WI 53202
Tel: 414-289-9107
E-mail: meetings@srs.org

Eurospine 2020
October 7-9, 2020
Vienna, Austria
Contact: Eurospine, Spine Society of Europe
Attn: Judith Reichert
Schild Seefeldstrasse 16
8610 Uster-Zurich,
Switzerland
Tel: 41-44-994-1404
www.eurospinemeeting.org

NASS 2020: Annual Meeting of the North American Spine Society
October 7-10, 2020
San Diego, California
Contact: North American Spine Society
7075 Veterans Boulevard
Burr Ridge, IL 60527
Tel: 630-230-3600
Fax: 630-230-3700
www.spine.org

Cervical Spine Research Society
December 10-12, 2020
Las Vegas, Nevada
Contact: Cervical Spine Research Society
9400 W. Higgins Road, Suite 500
Rosemont, IL 60018-4976
Tel: 847-698-1628
Fax: 847-268-9699
E-mail: csrs@aaos.org

Coming Soon:

- **Opioid Dependence and Addiction: What is the Difference?**
- **New Evidence that Factory Closings Spur Opioid Prescription**
- **Educational Attainment and Opioids: Crucial Relationship?**
- **Aerobic Exercise: Does it Stand Out as an Exercise Method for Back Pain?**
- **Diagnostic Validation Still Lacking for Disc-, Facet-, and SI-Joint-Related Pain**

THE BACKPAGE

PRP Injections for Back Pain: More Evidence Please!

Platelet-rich plasma (PRP) injections are growing in popularity as a treatment for low back pain (LBP) in the presence of disc degeneration. Numerous media articles have touted their effectiveness in treating a variety of musculoskeletal conditions. The science in this area, however, has failed to keep up with the hype.

So what is PRP? Here is an explanation from the American Academy of Orthopaedic Surgeons.

"Although blood is mainly a liquid (called plasma), it also contains small solid components (red cells, white cells, and platelets.) The platelets are best known for their importance in clotting blood. However, platelets also contain hundreds of proteins called growth factors which are very important in the healing of injuries."

To create PRP, the treatment team draws blood from the patient and then increases the concentration of platelets via centrifuge. (See https://orthoinfo.aaos.org/en/treatment/platelet-rich-plasma-prp.)

So does PRP have any therapeutic effect in the treatment of back problems? The answer is "no one knows."

Koji Akeda, from Mie University in Japan and colleagues recently reviewed the broad sweep of evidence on PRP in the management of chronic back pain. (See *J Pain*, 2019;12: 753-767.)

All the human studies, regardless of their methodology, reported PRP injections to be safe and effective. Akeda et al. expressed hope that this therapy would prove viable.

However, they noted the evidence is not conclusive or persuasive at the moment. "It should be noted that only one double-blinded study with contrast agents in a limited number of patients and without characterization of PRP preparation showed some positive effects in limited outcome measures. Therefore, it remains to be answered whether PRP has specific biological effects on pain generation in LBP patients."

Acetaminophen: Still Useless for Acute Back Pain

Acetaminophen has lost popularity as a treatment for acute back pain in the wake of a pivotal randomized controlled trial in the *Lancet* in 2014 showing it to be ineffective. "Our findings suggest that regular or as-needed dosing with paracetamol does not affect recovery time compared with placebo in low-back pain, and question the universal endorsement of paracetamol in this patient group," according to Christopher M. Williams, PhD, and colleagues.

But what about acetaminophen in combination with another analgesic medication? Benjamin Friedman, MD, and colleagues tested the effectiveness of ibuprofen plus acetaminophen vs. ibuprofen alone in the management of acute low back pain (LBP) in two urban emergency departments (EDs).

"Patients presenting with acute, non-traumatic, non-radicular LBP of no more than 2 weeks duration were eligible for enrollment immediately prior to discharge from an ED if they had a score > 5 on the Roland-Morris Disability Questionnaire (RMDQ)."

At one week after the ED visit, patients randomized to ibuprofen plus placebo reported a mean improvement in the RMDQ 9.7 of 11.9 (SD), while those randomized to ibuprofen plus acetaminophen reported a mean improvement of 11.1 (SD 10.7). "The 95% CI for the between-group difference of 0.8 was −3.0, 4.7. At one week follow-up, moderate or severe pain was reported by 15/53 (28%) patients in the ibuprofen + placebo group and 16/57 (28%) patients in the ibuprofen + acetaminophen group (95% CI for between-group difference of 0%: −17, 17%)," Friedman et al. reported.

These were not statistically significant nor clinically relevant differences. They concluded that acetaminophen was not effective in the combination treatment of acute LBP. (See *Academic Emergency Medicine*, 2019 [epub ahead of print]; https://doi.org/10.1111/acem.13898.)

Why Do Patients Use Black Market Pain Medications?

Black market medications such as fentanyl and carfentanyl are major causes of overdose death among people with chronic back and other forms of musculoskeletal pain.

Many people who utilize powerful black market pain medications were originally prescribed legal opioids by their doctors. It is not entirely clear why so many patients end up transitioning to riskier street medications.

Some of the proposed explanations include difficulty in obtaining long-term opioid prescriptions from MDs and difficulty in paying for them.

Many patients with diabetes face similar problems and end up acquiring medications and other diabetes supplies via the black market and trades with friends, family, and strangers.

In a study of 159 patients with diabetes, Michelle Litchman, PhD, of the University of Utah and colleagues looked at reasons why patients with diabetes are turning to the black market and other unorthodox sources for their medications and supplies.

And the main answer is "The health system is failing them."

And that is also true for many patients who transition from medical to black market opioids for chronic pain. Many patients become physically or psychologically dependent on a supply of opioids for pain after their doctors prescribe then. Then they have trouble—due to financial and logistical issues—obtaining medical opioids and turn to friends, family, and the black market for additional pain relief.

If US society is to resolve the huge opioid crisis, this issue will have to be addressed effectively and creatively. The answer lies not in giving patients an endless supply of opioids but in providing alternative pain therapies that do not lead to addiction and overdose. (See *J Diabetes Sci Technol*. 2019; Dec 4:1932296819888215.)

The Back*Page* Online

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- **Is Pain Just an Opinion—a Subjective Response to a Perceived Threat?**
- **The Electronic Health Record: Is It More Reliable Than a Microwave Oven?**
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