

Anyone Seeking Medical Information on the Web Is Being Tracked

Anyone who researches medical topics on the Internet would do well to read a short new study in *JAMA*. It demonstrates the degree to which third parties track Internet users seeking medical information at prominent and not-so-prominent websites.

Medical ethicist Matthew S. McCoy, PhD, of the University of Pennsylvania and colleagues recently investigated the prevalence of web tracking of people seeking information about COVID-19. (See McCoy et al., 2020.)

“Prior research has shown that web pages visited by individuals seeking health information frequently contain code that initiates data transfers to third parties, such as online advertisers. These transfers often include URLs of visited pages and users’ IP addresses. When third parties have code on multiple web pages, they can build detailed profiles of specific individuals’ browsing behaviors and interests. This practice, known as ‘web tracking,’ can reveal sensitive information about individuals’ health conditions and concerns to parties who wish to profit from it,” according to McCoy and colleagues.

They used Google Trends to identify the top 25 search queries for COVID-19 and the coronavirus in May of 2020. They then identified the top URLs for these queries. They used an automated tool called webX-ray to detect third-party tracking.

“For each web page, we recorded data requests from third-party domains—that is, domains other than that of the website being visited.... We also recorded the presence of third-party cookies, data stored on a user’s computer, which often serve as persistent identifiers that allow users to be tracked across multiple websites,” according to McCoy et al.

An astonishing 99% of Web pages included a third-party data request. A

whopping 89% included a third-party cookie.

Aggressive third-party tracking was most common at commercial websites. They were less common, but still impressively prevalent, at government and academic websites.

No one should imagine that is a problem confined to COVID-19 Internet searches. *BackLetter* editor Mark Schoene, who spends several hours per day on the Worldwide Web reading research and seeking information, says he is painfully aware of being tracked continually.

“Before I started covering my tracks a little more carefully, I would get inundated with advertisements for products and services relating to whatever I was researching.”

“I ended up using a variety of browsers, including ones offering alleged trackless searching. I dropped off many social media sites”

“But I imagine my efforts to remain anonymous have been largely in vain. I am sure if I ever apply for life insurance the agent will tell me the policy has been denied because of my degenerative disc disease, spinal stenosis, disc herniations, Modic changes, high-intensity zones, osteoporosis, spondylolisthesis, vertebral compression fractures, and cervical myelopathy,” according to this *BackLetter* editor and writer.

Disclosures: None declared.

Reference:

McCoy MS et al., Prevalence of third-party tracking on COVID-19-related web pages, *JAMA*, September 8, 2020; doi: 10.1001/jama.2020.16178.

THE BACKLETTER®

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The Back Letter® (ISSN 0894-7376) is published monthly by Wolters Kluwer Health, Inc. at 14700 Citicorp Drive, Bldg 3, Hagerstown, MD 21742. Customer Service: Phone (800) 638-3030; Fax: (301) 223-2400; E-mail customerservice@lw.com. Visit our website at LWW.com. Publisher, John Ewers.

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SUBSCRIPTION RATES: Individual: US \$269.00, international \$392.00. Institutional: US \$639.00, international \$771.00. In-training: US \$138.00, international \$179.00. Single copy: \$62.00. GST Registration Number: 895524239. Send bulk pricing requests to Publisher. Single copies: \$52. COPYING: Contents of *The Back Letter*® are protected by copyright. Reproduction, photocopying, and storage or transmission by magnetic or electronic means are strictly prohibited. Violation of copyright will result in legal action, including civil and/or criminal penalties. Permission to reproduce must be secured in writing; go to the newsletter website (www.backletter.com), select the article, and click “Request Permissions” under “Article Tools,” or e-mail customerservice@copyright.com. Reprints: For commercial reprints and all quantities of 500 or more, e-mail reprintsolutions@wolterskluwer.com. For quantities of 500 or under, e-mail reprints@lw.com, call 866-903-6951, or fax 410-528-4434. PAID SUBSCRIBERS: Current issue and archives are available FREE online at www.backletter.com.

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Grim News About Opioid Overdose Deaths During the COVID-19 Pandemic

An article in the June *BackLetter* suggested that one of the demographic groups that would be hardest hit by the COVID-19 pandemic would be individuals struggling with drug and complex dependency issues.

“Due to 20 years of intemperate and excessive opioid prescription for chronic pain, millions of patients are struggling with addiction and complex opioid-dependency problems in the United States. Roughly two million American have a substance abuse disorder—most typically involving opioids. And about half of these individuals have a substance abuse disorder and a mental health problem. They are in every back care practice—especially those that prescribe or have prescribed opioids for chronic pain. And as many as eight million Americans may be on long-term opioid therapy—many on perilously high-dose prescriptions,” according to that article. (See Schoene, 2020.) And, of course, millions more are addicted to heroin, fentanyl, cocaine, and other street drugs.

That *BackLetter* article predicted a major wave of problems, among people with addiction/dependency issues, related to the social isolation and insecurities created by COVID-19—and a near-total lack of treatment services available during the first wave of the pandemic.

That prediction, unfortunately, seems to be proving true, at least based on the sketchy data that is available.

The *Wall Street Journal* recently performed a study of opioid overdose deaths in the current year. “The Journal, through data and public-records requests, asked the 50 largest counties by population for

information on overdoses this year. Among the 30 that provided numbers, 21 of them showed overdose deaths trending up from last year,” according to Jon Kamp and Arian Campo-Flores. (See Kamp & Campo-Flores, 2020.)

This study basically showed a series of snapshots of trends in different states that likely will likely add up to a significant worsening of the opioid crisis:

- The Southern Nevada Health District, which covers Clark County, including Las Vegas, said fentanyl fueled an 8% increase in fatal drug overdoses for the first half of this year.
- In Los Angeles County, overdoses rose 48% in the first month and a half of the pandemic compared with the same period a year earlier.
- Early figures show that the overdose tally in Ohio’s Franklin County reached 580 by late August, said county coroner Anahi Ortiz. That is near the entire total reported for 2019.
- Counties in Indiana, Minnesota, and Michigan also showed increases.
- “Authorities in other places, including traditional hot spots for opioid deaths like parts of Appalachia and New England, are also reporting more drug deaths.”
- Suspected overdoses rose almost 18% after stay-at-home orders were implemented across the country in mid-March, compared with the early 2020 period before the pandemic struck.

COVID-19 has been a cruel blow for people with drug addiction and dependency. And it came at a time when the United States had just begun to turn the corner in the opioid crisis. The number of opioid



overdose deaths in the United States had dipped slightly from 2017 to 2018, after years of rising numbers. Those ominous numbers seem to be climbing again.

Disclosures: None declared.

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Trends in Drug Poisonings, Suicide, and Alcohol-Induced Deaths

Nobel Prize-winner Angus Deaton and economist wife Elizabeth Case coined the phrase “deaths of despair” to describe rising death rates due to drug overdoses, suicides, and alcohol poisonings among poorly educated, eco-

nomically deprived, and socially marginalized non-Hispanic white men and women in the United States.

This was a group that the rising tide of prosperity over the last 40 years in the United States had left behind. This trend

resulted in a net loss of longevity in the United States over the last few years.

These problems came hand in hand with a variety of other health complaints,

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Should Researchers Follow the Path of Their Mentors or Blaze New Trails?

Some of the most important knowledge transmission in medicine and science occurs in an age-old fashion—from mentor to mentee, master to apprentice, leader to follower, and teacher to student. These relationships date back thousands of years but have rarely been studied.

Mentor/mentee relationships play a major role in both spine and back pain research—as they do in every area of medicine and science. Many who follow this field have sat around at spinal medicine conferences and speculated as to which students or mentees of influential researchers and prominent clinicians might become future leaders of the field.

Many mentees look like up-and-comers, as their careers grow in the shadow of their mentors. However, predicting which ones will truly become leaders is a little like betting on horse races. The ultimate performance on the track usually confounds hopes and expectations.

Some mentees stick to their mentors like glue, doing the same type of research, mining the same ground, and coauthoring articles for years and decades. Others break away early and attempt to blaze new trails.

Are Mentor/Mentee Relationships the Key to Become Successful?

A recent study in the *Proceedings of the National Academy of Sciences* by Yifang Ma and colleagues argued that mentorships are vital parts of a scientist's education. "Mentorship is arguably a scientist's most significant collaborative relationship." (See Ma et al., 2020.)

Albert Einstein agreed with them. And Einstein felt that great mentors did not simply engage in the transmission of codified information—of the type that can be found in textbooks and university lectures. Rather they passed on deeper and more important attitudes and habits.

"The value of an education," Einstein concluded, "is not the learning of many facts but the training of the mind to think something that cannot be learned from textbooks."

The type of information passed on by great mentors is sometimes referred to as

"tacit knowledge," knowledge that cannot be easily expressed verbally.

Here is a definition from Wikipedia: "Tacit knowledge can be defined as skills, ideas and experiences that people have but are not codified and may not necessarily be easily expressed. With tacit knowledge, people are not often aware of the knowledge they possess or how it can be valuable to others. Effective transfer of tacit knowledge generally requires extensive personal contact, regular interaction and trust. This kind of knowledge can only be revealed through practice in a particular context and transmitted through social networks. To some extent it is 'captured' when the knowledge holder joins a network or a community of practice" (https://en.wikipedia.org/wiki/Tacit_knowledge#:~:text=Tacit%20knowledge%20or%20implicit%20knowledge%20down%20or%20verbalizing%20it).

What Is the Best Way of Achieving Success?

In many areas of spine/back pain research, the best way of achieving a successful career is to work with one of the influential leaders in the field in a mentor/mentee relationship. These key figures have enormous influence on research and its funding, on clinical care opportunities, and gaining influence in professional societies.

But this is the superficial side of mentorship. The great mentors and teachers offer something more—something that might influence a scientist across an entire career.

"Communicating codified knowledge is relatively straightforward," said Brian Uzzi, PhD, the senior author of the new study on mentorship. "It's written down in books and presentations. But it's the unwritten knowledge we intuitively convey through our interactions and demonstrations with students that makes a real difference for mentees."

"Face-to-face interaction is essential. When we teach by doing, we are conveying tacit knowledge we don't even realize we have," said Uzzi, the co-director of the Northwestern University Institute on Complex Systems. "If we limit the face-to-face channel by which tacit knowledge is communicated, we potentially slow down the pace of learning and scientific breakthroughs, and that will affect us all."

Ma and colleagues recently attempted to quantify the influence of mentors. As mentioned earlier, mentorship has barely been studied with careful research methods. "Of all collaborations, comparatively little research exists on the link between mentorship and protégé success," they explained.

There is considerable debate as to the ideal function of mentors. Should they encourage their mentees to follow the trail of the mentor, in terms of research topics and clinical methods? Should they encourage their mentees to be trailblazers—and establish their own distinctive professional pathways? Or should they simply concentrate on passing on codified knowledge?

A Study of 40,000 Scientists and 1.6 Million Studies

Ma and colleagues recently attempted to fill in this void with a study of 40,000 scientists who published 1,167,518 articles in biomedicine, chemistry, math, or physics between 1960 and 2017.

The researchers studied genealogical data on scientists who worked in biomedicine, chemistry, math, or physics between 1960 and 2017. They used the ProQuest Dissertations and Theses databank, an official record of advisor/student relationships taken from PhD theses, and supplemented it with additional crowdsourced data from AcademicTree.org and the Mathematics Genealogy Project to ensure they correctly matched mentor/mentee relationships.

To account for the fact that more successful mentors naturally attract more talented students, the researchers grouped mentors with similar records and reputation based on factors including institutional resources, productivity, number of students, citations, and other measures of a mentor's skills. They compared the performance of students within the same mentor peer group.

They found that one mentor in each group seemed to have hidden talent for identifying key problems and coming up with innovative solutions. They were often scientific prizewinners.

To assess protégé success, the researchers considered only those students who

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studied under a mentor before that mentor won a scientific prize—to control for selection bias and the halo effect a prizewinning mentor casts over students.

Which Mentees Performed Best?

So which mentees did the best? Those who followed in their mentors' footsteps or those who broke new ground? The answer was clear.

After controlling for differences in mentorship skills and mentee talent, the researchers found that the most impactful mentors are those who teach students to think independently and communicate their unique viewpoints effectively.

“Paradoxically, protégés achieve their highest impact when they display intellectual independence from their mentors. Protégés do their best work when they break from their mentor’s research topics and coauthor no more than a small portion of their overall research with their mentors” according to Ma et al.

Ultimately, Ma et al. felt the study confirmed the views of Einstein about the passing on of tacit knowledge.

Interestingly, Einstein had a prominent opponent in his debates about the key to enlightened mentorship. Legendary inventor Thomas Edison disagreed with Einstein and felt strongly that the passing on of codified knowledge rather than tacit knowledge was the key to future success. Edison actually developed a test for students and potential employees to assess their codified knowledge (i.e. their basic knowledge of science). And he felt that performance on this test was a major predictor of future research success and scientific prominence. (See Dennis, 1984.)

One little coda to this debate speaks volumes, however. Einstein took Edison’s test and flunked it. However, he still managed to put together a pretty good career as the most influential physicist of the 20th century. And many of his mentees achieved similar levels of success—suggesting but not proving that tacit knowledge might trump codified knowledge.

Ma and colleagues hope that their study might stimulate a flurry of further studies to determine whether their findings are true—and generalizable to other areas of science and medicine.

Mentors and Mentees Fall into a Variety of Complex Roles in Real-Life Settings

In some respects, this study may have oversimplified the roles of mentors and mentees.

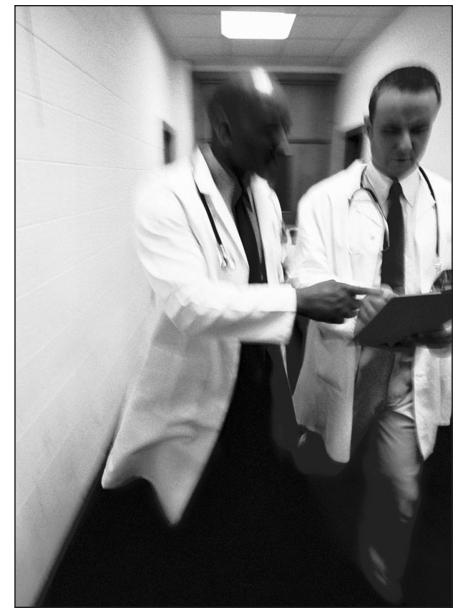
BackLetter editor Sam Wiesel, MD, Chairman of the Department of Orthopedics at Georgetown University Medical Center, pointed out recently that mentors and mentees fall into a variety of roles in real-life settings. And that it is often difficult to draw firm conclusions about the nature of those roles and relationships. Wiesel has been a spine surgeon for more than 40 years and chairman of a major department of orthopedics for more than half that time.

After controlling for differences in mentorship skills and mentee talent, the researchers found that the most impactful mentors are those who teach students to think independently and communicate their unique viewpoints effectively.

“Some mentors simply play the role of getting students and residents interested in the field—and giving them a basic introduction to it. Others treat their mentees almost as employees, getting them involved in the mentors’ projects and research. Some key on helping their mentees develop curiosity and open-mindedness,” said Wiesel.

“Some mentors focus heavily on leadership and organizational roles. Some key on developing technical skills—diagnostic and surgical,” he explained. Some transmit what the authors of the new study refer to as codified knowledge and others transmit tacit knowledge. Some do both.

Wiesel noted that the qualities and talents of mentees, residents, and students go a long ways towards determining these relationships. “Some mentees can take direction but don’t work well independently. Others have bright ideas but can’t do the necessary research and clinical work to explore them. Others can do the work but don’t have the bright ideas. Some become partisans and spend their careers promoting and defending



a certain set of ideas—often those of their mentors,” according to Wiesel.

A few mentees seem to be able to do it all. “They have bright ideas, can work independently, and quickly establish distinctive careers in research and clinical work,” said Wiesel. They often go on to become future leaders in the field.

Good mentors have to play different roles with all these personalities, Wiesel stressed. They have to recognize their mentees’ talents, skills, and aptitudes—and then help bring the mentees along as far as they can—in areas where they work best.”

So mentors and mentees, teachers and students, masters and apprentices play complex and variable roles in human life. This complexity makes it difficult to draw broad conclusions about these relationships—or to do definitive research in this area.

Disclosures: None declared.

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new guideline didn't provide references to studies that support these points.

The editors of the *BackLetter* have never run across these assumptions in a major guideline on the treatment of a broad range of musculoskeletal conditions before. Various acute musculoskeletal injuries and pain conditions—acute neck pain, acute thoracic disc herniations, spinal compression fractures, knee contusions, elbow tendinitis, stress fractures, wrist strains, muscle and tendon tears, hamstring sprains, and many more—would appear to have substantially different pain mechanisms, natural histories, pace of healing, and responses to different treatments.

So these conditions may not be truly comparable. In many ways, they appear to be “apples and oranges.” As a result, some observers would suggest they shouldn't be analyzed together in a single, large-network meta-analysis. Also, this is something of a hypothetical approach. To suggest it is the “best available evidence” on interventions for all these conditions is a stretch. There are alternative ways of analyzing and characterizing this body of evidence.

Reckless Approach?

Chris Maher, PhD, of the University of Sydney and the Cochrane Collaboration Musculoskeletal Group suggests this is an unconventional way of viewing painful musculoskeletal conditions. “There simply isn't adequate evidence to support lumping multiple conditions together like this. These are heterogenous conditions that don't respond to treatment in the same ways.

“To me it makes no sense to suggest that you would manage these musculoskeletal conditions in the same manner because they varied so widely. Take a look at Table I in the Supplement to see how heterogenous the conditions are. I don't know anyone who would lump together tennis elbow, ankle sprain, shoulder dislocation, rib fracture, and hip fracture. And then they were reckless enough to attempt a treatment effect estimate for massage and exercise [and other therapies] across all those conditions,” he pointed out. (See Supplemental Appendices, Qaseem et al., 2020.)

“Who in their right mind massages a fractured rib or prescribes an exercise program for a hip fracture? Who would mobilize or

apply acupuncture to a fractured humerus?” This is an example of network meta-analysis taken to an extreme, Maher suggested.

This guideline could theoretically apply to an enormous swath of pain conditions. As mentioned above, the guideline research team acknowledges using the work “injuries” loosely.

“We did use injury in the broad sense, and included any acute, non-low back-related musculoskeletal pain (pain with duration <4 weeks or defined by authors as ‘acute’) in an outpatient setting,” said Jason Busse, DC, PhD of McMaster University, the lead author of one of the systematic reviews supporting the guideline. (See Busse et al., 2020)

So from the perspective of a primary care provider, “acute musculoskeletal injuries” might include all acute pain that appears to have a musculoskeletal origin, intermittent and/or recurrent pain, and the initial symptoms related to numerous chronic conditions. Dozens of painful injuries and conditions would meet these criteria.

Is it really possible that a limited set of treatments would apply in all those pain conditions? From an intuitive perspective, it seems unlikely. However, the authors of the ACP/AAFP guideline and supporting meta-analyses disagree and have defended their results vigorously (see below).

A Basic Framework for Treatment?

The leaders of the American Academy of Family Physicians (AAFP) and the American College of Physicians (ACP) hope that the new guideline can provide a basic framework for the treatment of multiple types of musculoskeletal injuries and pain and convince healthcare providers to move away from the use of opioids for these indications.

“This guideline is not intended to provide a one-size-fits-all approach to managing non-low back pain,” said Gary LeRoy, MD, president of the AAFP. “Our main objective was to provide a sound and transparent framework to guide family physicians in shared decision making with patients.” But is it a sound framework on which to build a rational treatment approach?

“As a physician, these types of injuries and associated pain are common, and we need to address them with the best

treatments available for the patient. The evidence shows that there are quality treatments available for pain caused by acute musculoskeletal injuries that do not include the use of opioids,” said Jacqueline W. Fincher, MD, president of the ACP. “There are a number of recommended interventions that are not opioids to choose from, and topical NSAIDs should be the first line of treatment.”

Despite the ACP's enthusiasm for this guideline, it is not at all clear that it presents an accurate view of therapeutic options—and their likely results.

So patients and healthcare providers should take these results with a grain of salt, rather than accept them solely on the authority of these two professional societies. The ACP/AAFP guideline should be viewed as an experiment rather than a validated treatment approach.

However, readers can certainly take these results under advisement and see if they help patients respond to acute injuries and pain conditions.

What About Other Recent Reviews?

Healthcare providers and patients can also look at other recent systematic reviews and guidelines to find contrasting results and recommendations.

For example, the US Agency for Healthcare Quality and Research (AHRQ) is in the process of conducting a massive review of treatments for acute pain, including back, neck, and other forms of musculoskeletal pain. AHRQ recently published a rough draft of the review for the purposes of peer review and commentary. (See AHRQ, 2020.)

The authors of the AHRQ review chose not to analyze all treatments for all acute musculoskeletal pain conditions in a single network meta-analysis.

Instead, the AHRQ employed more traditional systematic review methodology based on analysis of head-to-head randomized controlled trials for each individual condition category (e.g., head-to-head trials on treatments for low back pain, neck pain, other musculoskeletal pain, etc.) in conducting the evidence review and meta-analysis. And the AHRQ review came to very different conclusions compared to the ACP/AAFP review, at least in this preliminary draft.

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Table I: American College of Physicians/American Academy of Family Physicians Recommendations on the Treatment of Acute Musculoskeletal Pain

<p>Recommendation 1: Topical NSAIDs. <i>ACP and AAFP recommend that clinicians treat patients with acute pain from non–low back, musculoskeletal injuries with topical nonsteroidal anti-inflammatory drugs (NSAIDs) with or without menthol gel as first-line therapy to reduce or relieve symptoms, including pain; improve physical function; and improve the patient’s treatment satisfaction (GRADE: strong recommendation; moderate-certainty evidence).</i> [Moderate-certainty evidence = the true effect is likely close to the estimated effect but there is a sizeable possibility it is substantially different] (See Qaseem et al., 2020b.)</p>
<p>Recommendation 2a: Oral NSAIDs and Oral Acetaminophen. <i>ACP and AAFP suggest that clinicians treat patients with acute pain from non–low back, musculoskeletal injuries with oral NSAIDs to reduce or relieve symptoms, including pain, and to improve physical function, or with oral acetaminophen to reduce pain (GRADE: conditional recommendation; moderate-certainty evidence).</i> [Conditional recommendation = benefits probably outweigh risks or burden but there is appreciable uncertainty]. (See Qaseem et al., 2020.)</p>
<p>Recommendation 2b: Acupressure and TENS. <i>ACP and AAFP suggest that clinicians treat patients with acute pain from non–low back, musculoskeletal injuries with specific acupressure to reduce pain and improve physical function, or with transcutaneous electrical nerve stimulation to reduce pain (GRADE: conditional recommendation; low-certainty evidence).</i> [Low certainty-evidence = The true effect may be substantially different from the estimated effect.]</p>
<p>Recommendation 3: Opioids Including Tramadol. <i>ACP and AAFP suggest against clinicians treating patients with acute pain from non–low back, musculoskeletal injuries with opioids, including tramadol (GRADE: conditional recommendation; low-certainty evidence).</i></p>

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For example, here is a look at the conclusions of the two reviews on acute neck pain. The new guideline from the ACP and the AAFP—based on direct and indirect comparisons in its network meta-analysis—recommended three non-opioid pain medications and two nonpharmacologic treatments for neck pain. (See details below.)

The AHRQ review, employing a more conventional meta-analysis of the results of head-to-head RCTs, couldn’t find convincing evidence regarding the use of any medication—opioid or nonopioid—for acute neck injuries or neck pain. And they didn’t find any conclusive evidence on nonpharmacologic treatments.

This raises the question that crops up frequently regarding treatment recommendations for back and neck pain: Which is the most accurate way of analyzing the existing body of evidence?

What Did the Guideline Say?

So what did the guideline say? The guideline panel, led by Amir Qaseem, MD, et al. concluded that the first line of treatment for pain due to musculoskeletal injuries in all parts of the body except the low back should be topical nonsteroidal anti-inflammatory drugs (topical NSAIDs) with or without the addition of menthol gel. (See

Qaseem et al., 2020.) (See Table I for the detailed recommendations, with evidence ratings.)

“The guideline also suggests that oral NSAIDs, acetaminophen, specific acupressure, or transcutaneous electrical nerve stimulation (TENS) are effective treatments and suggests against using opioids, including tramadol, except in cases of severe injury or intolerance of first-line therapies,” according to the ACP press release.

The guideline could not find enough evidence to recommend several common treatments for neck pain, including exercise interventions, spinal manipulation, mobilization, massage, supervised rehabilitation, or educational interventions.

Here is a brief description of the new guideline. Qaseem and colleagues from the ACP and the AAFP commissioned two systematic reviews to serve as the foundation of the guideline.

The first was a systematic review and meta-analysis of observational studies on predictors of long-term opioid use among patients prescribed opioids for acute musculoskeletal injuries—by John J. Riva, DC, MSc and colleagues. Not surprisingly, it found that protracted use of opioids (greater than 7 days) among patients with acute pain led to an unacceptable level of persistent opioid use.

“The overall prevalence of prolonged opioid use after musculoskeletal injury for high-risk populations (that is, patients

receiving workers’ compensation benefits, Veterans Affairs claimants, or patients with high rates of concurrent substance use disorder) was 27% (95% CI, 18% to 37%). The prevalence among low-risk populations was 6% (CI, 4% to 8%; *P* for interaction < 0.001),” according to Riva et al.

Network Meta-Analysis of 207 RCTs on Treatments for Acute Musculoskeletal Pain

The second review was the above-mentioned systematic review and network meta-analysis of randomized controlled trials on the treatment of acute non-low back injuries and pain conditions by Busse and colleagues.

The reviewers found 207 relevant RCTs on treatments for various acute injuries and pain conditions. They evaluated a total of 45 separate therapies directed at 32,959 participants.

Network meta-analyses differ substantially from more traditional meta-analyses of RCTs. Traditional meta-analyses—of the kind that are common across the spine field—focus on comparisons of RCTs of individual treatments for a particular condition.

A traditional review of the use of NSAIDs for acute neck pain might look at all RCTs which compared NSAIDs to a placebo among subjects with acute neck pain. If there were enough data from similar trials, the reviewers might combine the

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results of those head-to-head trials in a meta-analysis. However, this type of meta-analysis would only include treatments that have been tested in RCTs. They cannot make inferences about treatments that have not been evaluated in RCTs.

However, in routine clinical practice healthcare providers and patients have to choose among a broad range of treatments for acute pain: NSAIDs, opioids, acetaminophen, gabapentinoids, corticosteroids, non-drug treatments, and various combinations of treatments. The choices include therapies that have not been evaluated head-to-head in randomized controlled trials.

Network meta-analysis is a way of comparing three or more treatments when there is no direct evidence, or insufficient direct evidence, for the comparison of interest. Network meta-analyses allow the simultaneous comparison of any number of interventions as long as they have been compared to at least one common intervention.

Here is a fictitious example: If eight NSAIDs have been compared to a placebo in RCTs on acute neck pain but not against each other, a traditional meta-analysis would not be able to make any inferences as to whether one NSAID is superior to others.

A network meta-analysis, by contrast, would look at the relative performance of all these NSAIDs against a common comparator (in this case placebo) and use that to make inferences about their relative treatment effects. If one NSAID produced dramatically better results than the other seven NSAIDs when compared to placebo, a network meta-analysis might conclude it is superior to the others in the treatment of acute pain.

However, network meta-analyses are only valuable if the underlying clinical trials are sufficiently homogenous to facilitate reliable comparisons—and report enough data to make those comparisons. And critics of the ACP/AAFP guidelines suggest that the large number of clinical trials in this area are not sufficiently homogenous to support such a broad network meta-analysis. The authors of the ACP/AAFP guidelines, by contrast, believe that more than 200 trials on dozens of interventions are sufficiently alike to make these comparisons.

Complex Network Meta-Analysis

Busse et al. carried out this complex network meta-analysis. The following is a simplified bare-bones description. Readers should consult the published meta-analysis for further details. They can find more elaborate information on network meta-analysis at the Cochrane Collaboration website. (See Chaimani et al., 2020.)

To qualify for inclusion in the meta-analysis, studies had to be parallel-design RCTs of adult patients with acute pain from non-low back-related musculoskeletal injuries or pain conditions—with at least 10 patients in each study group.

Busse et al. included 207 RCTs that evaluated 45 different therapies for acute pain. Ninety-nine trials (48%) enrolled populations with diverse musculoskeletal injuries, 59 (29%) included patients with sprains, 13 (6%) with whiplash, and 11 (5%) with muscle strains; the remaining trials included various injuries ranging from nonsurgical fractures to contusions.

“After reviewing the literature and consulting with our technical expert panel, we elected to combine all acute musculoskeletal conditions in our analyses. Upon consultation with a clinical pharmacologist, a pharmacist, and the technical expert panel, we included pharmacologic treatments with similar properties and clinical effects in single nodes, which was our primary network of interventions. We explored the appropriateness of these groupings by deriving the statistical consistency of each network and local loops of evidence for each outcome,” they explained.

This was a hybrid review. Busse et al. not only conducted a network meta-analysis, they also compared those results to more traditional pair-wise meta-analyses if two or more RCTs provided relevant data. They graded heterogeneity among RCTs with a standardized method.

They categorized treatments from most effective to least effective based on the estimates of benefits and risks obtained in the network meta-analysis. They assessed the certainty of the evidence using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach. They assessed bias with a modified Cochrane tool.

Busse et al. looked at several different outcomes: pain relief at two hours or less, pain relief at one to seven days, symptom relief, measures of physical function,

patient satisfaction with treatment, and various types of adverse events.

Advantage for Four Nonopioid Analgesics

Busse et al. found a small advantage for four non-opioid analgesics compared to other treatments. “In this network meta-analysis of RCTs in patients with acute pain from non-low back musculoskeletal injuries, we found high- to moderate-certainty evidence that topical NSAIDs, followed by oral NSAIDs, acetaminophen plus diclofenac, and acetaminophen, showed the most attractive benefit-harm ratio.”

These drugs all had roughly a one-point advantage on a 10-point visual analogue pain scale. That barely rose to a minimum clinically important difference.

Topical NSAIDs had the best benefit-to-risk profile. They provided pain relief comparable to oral NSAIDs without the gastrointestinal adverse effects associated with the oral formulations.

No opioid achieved a greater benefit than NSAIDs. And opioids, including fentanyl, tramadol, and opioid plus acetaminophen, caused greater harm relative to placebo than other medications.

“Our review found high- to moderate-certainty evidence that compared with placebo, tramadol failed to achieve important benefits and opioids caused significantly more adverse events. Our results demonstrating that opioids fail to achieve important benefits beyond interventions with less harm provide compelling reasons to avoid opioid prescribing in the setting of acute non-low back musculoskeletal injury,” according to Busse et al.

Busse et al. found that three nonpharmacologic treatments—acupressure, joint manipulation, and TENS—offered some pain relief without risk of gastrointestinal, neurologic, or dermatologic adverse events. However, the evidence supporting these nonpharmacologic treatments was of “low certainty” according to the GRADE assessment scale, “low certainty” signifying that “The true [treatment] effect may be substantially different from the estimated effect.”

Disclosures: None declared.

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Who Is Right?

Interpreting complex network meta-analyses on treatments for musculoskeletal pain is an intimidating challenge for healthcare providers and patients. The methods and language in these reviews are both complex. And the results often differ from those of more traditional systematic reviews.

A *BackLetter* editor asked Jason Busse, DC, PhD, if he is concerned that network meta-analyses and more traditional meta-analyses of head-to-head trials often come to different conclusions.

“Regarding neck pain, for example, I don’t believe a systematic review of head-to-head trials would agree with the conclusions of your review [on treatments for non-low back musculoskeletal injuries]. I don’t think there would be adequate evidence of the effectiveness of acetaminophen, topical NSAIDs, and maybe even oral NSAIDs.

“This raises the question: ‘Who’s right? Which view of the evidence should prevail?’”

“The concordance of network meta-analyses with head-to-head trials is critical, and this has been formally explored [in his recent systematic review],” Busse responded.

He explained that he and his colleagues formally assessed coherence (the degree to which direct and indirect comparisons of treatments are in agreement) in their recent network meta-analysis.

“We did this at both the level of the network (for each outcome) and for every comparison in the network. For our review, we found no evidence of incoherence at the level of the network for any outcome, and among the hundreds of individual comparisons, we only found evidence of incoherence in two comparisons,” he reported.

He said when he and his colleagues find incoherence in a comparison, they use the estimate supported by higher-certainty evidence. “Or, if the certainty of evidence is the same for both the direct and indirect evidence we use the network estimate but rate down the overall certainty of evidence due to incoherence,” he added.

Confidence in the Meta-Analysis Conclusions

“Thus, our results do give us confidence that direct and indirect data explored in our review were largely concordant. That being said, when there is only indirect evidence it is not possible to assess incoherence. In such situations, issues regarding intransitivity (i.e. important differences in the population, intervention, control, or outcomes) may warrant particular attention, and the threshold for rating down for intransitivity may be lower,” said Busse.

“In response to your question – who is right? And with your example [inadequate

evidence from head-to-head trials], I would look to the certainty of the evidence. Our review and network meta-analysis found moderate certainty of evidence to support topical and oral NSAIDs and acetaminophen (with or without diclofenac). This means that we are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

“Thus, further study, including head-to-head trials would certainly be reasonable. At the same time, clinicians need to make decisions with what evidence is available and our review provides this information,” he noted.

The *BackLetter* editor posed another question to Busse. “Do you worry at all that we are going to confuse consumers with the diversity of reviews—and the differing recommendations in guidelines?”

“The world of musculoskeletal medicine is already struggling to adhere to evidence-based guidelines. I worry that we are going to make this situation worse.”

“I strongly agree that both reviews and guidelines should be standardized so that consistent results emerge,” Busse responded. “Until standard criteria are required for reviews and guidelines, disparate results will persist and clinicians and patients will (likely) gravitate to the source that best fits their pre-existing beliefs,” he asserted.

Contradictory Recommendations on the Treatment of Acute Back Pain and Acute Neck Pain

In the wake of the new ACP/AAFP guideline on the treatment of acute injuries, the American College of Physicians recommendations on the treatment of neck pain and back pain differ substantially.

The new guideline on acute pain recommends topical NSAIDs as the first-line of treatment for neck pain, followed by oral NSAIDs and oral acetaminophen. It also recommends acupuncture and transcutaneous electrical nerve stimulation

[TENS] as treatments of less certain benefit.

The 2017 ACP guideline on the treatment of acute back pain, by contrast, only recommended nonpharmacologic treatments as first-line therapies, categorizing oral NSAIDs as a second-line treatment.

And the ACP has issued particularly confusing recommendations on acetaminophen for acute pain. The new guideline on the treatment of non-low

back musculoskeletal injuries recommends oral acetaminophen as a treatment for neck pain.

Yet the 2017 ACP guideline on low back pain recommended against the use of acetaminophen for acute back pain—based on a persuasive RCT that was not included in the new review. Patients and providers may well shake their heads over these divergent recommendations. (See Qaseem A et al, 2017.)

Will COVID-19 Lead to Long-Term Unrest and Health Problems?

A major question regarding the COVID-19 pandemic is whether it will lead to widespread social unrest—which could translate into increasing social inequities and a variety of health problems, including various forms of pain.

Italian political scientists Massimo Morelli and Robert Censolo recently reported that COVID-19 will likely have disruptive effects on society for an extended period of time. So every medical field needs to have contingency plans for various potentially disruptive scenarios.

They studied the effects of 50 previous epidemics on subsequent social disruption and unrest.

“Overall, the historical evidence shows that the epidemics display a potential disar-

ranging effect on civil society along three dimensions,” the authors write. “First, the policy measures tend to conflict with the interest of people, generating a dangerous friction between society and institutions. Second, to the extent that an epidemic impacts differently on society in terms of mortality and economic welfare, it may exacerbate inequality. Third, the psychological shock can induce irrational narratives on the causes and the spread of the disease, which may result in social or racial discrimination and even xenophobia.”

Morelli and Censolo asserted that pandemics and other massive health crises may be “social incubators” nurturing explosive long-simmering social tensions and inequalities. These issues could certainly have myriad effects on health, healthcare, and social welfare.

They suggested that cynical political leaders were already attempting to foment unrest to reinforce their power, citing the “law and order” campaigns of US president Donald Trump and Hungarian Prime Minister Viktor Orban as examples.

It is important to recognize that these projections could also be wrong.

Disclosures: None declared.

Reference:

Morelli M and Censolo R, COVID-19 and the Potential Consequences for Social Stability *Peace Economics, Peace Science, and Peace Public Policy*, 2020; doi:10.1515/peps-2020-0045.

Spondy Success

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new”—with relative rest and progressive rehabilitation.

But even athletes whose fractures do not heal completely often go back to normal athletic performance.

A retrospective study by Heath P. Gould, MD, and colleagues recently documented favorable outcomes among a cohort of professional baseball players with spondylolysis or spondylolisthesis. (See Gould et al., 2020.) [Editor’s note: Spondylolisthesis occurs when the pars fracture or fractures leads to the injured vertebra slipping forward relative to the vertebra below it.]

They performed a retrospective cohort study of 75 minor or major league professional baseball players in the United States who presented with a painful pars interarticularis defect between 2011 and 2016.

Forty-seven of the players were diagnosed with spondylolysis and the remaining 28 with spondylolisthesis. All but one of the athletes returned to baseball after rehabilitation.

The researchers studied pre- and post-injury performance among the players, using data from the Major League Baseball Injury Surveillance System. Unfortunately, 19 players had insufficient

performance data and had to be dropped from the analysis.

The researchers judged baseball performance with a variety of position-specific measures. Pitching performance, for example, was judged via earned run average—along with runs, home runs, hits, strikeouts, and walks per nine innings.

Overall, there were no differences between performance pre- and post-injury according to both primary and secondary outcome measures.

“Athletes with a diagnosed pars defect did not show a significant decline in performance after returning to competition after their injury episode,” according to Gould et al.

Baseball players with spondylolisthesis returned to play faster than those with spondylolysis alone. Major league players returned more quickly than minor league players. And position players returned faster than pitchers.

Gould and colleagues hope to begin large and more rigorous prospective studies to shed further light on the influence of pars fractures among professional players.

This study is a snapshot of a small subgroup of 56 baseball players who may or may not be representative of all players with spondylolysis or spondylolisthesis in that professional sport. And they were not followed over the long term.

According to a 2018 article in *Forbes*, there are more than 7500 players in major and minor league baseball at any given time. (See Brown, 2018.)

Even if only 5% of those athletes had a pars defect, there would be 365 players who might meet the inclusion criteria for a future study. And the prevalence of spondylolysis and spondylolisthesis is likely to be far higher than that, given the demands of baseball on the spine.

Disclosures: None declared.

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Trends in Drug Poisonings

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including disabling spinal pain, headaches, and orofacial pain.

Based on the work of Deaton and Case, many observers have assumed that deaths from these three causes tracked together and had similar social and economic causes.

A recent study by Meredith S. Shiels, PhD, and colleagues documents that death rates due to these causes did rise substantially from 2000 to 2017. During that period drug overdose death rates rose 3.6-fold, suicide death rates roughly 1.4-fold, and alcohol-induced deaths roughly 1.3-fold. (See Shiels et al., 2020.)

But they did not track together in the same groups and the same geographic locations. Death rates were highest among men for each cause. Drug overdose deaths (largely due to opioids) were highest among people aged 35 to 49 years—while suicide and alcohol poisoning deaths increased with age.

There is growing consensus that drug overdose deaths came in three waves in the United States. The first wave began in the

1990s and stemmed from the overprescription of opioids for pain management. The second wave began around 2010 and has been attributed to a surge in heroin availability. The third wave—likely related to a rapid increase in the availability of fentanyl—began around 2013.

Shiels et al. found that the rates of drug overdose deaths fell into what might be considered three waves, increasing by 11.4% per year from 2000 to 2006, 2.5% per year from 2006 to 2013, and 15% per year from 2013 to 2017.

The three groups with the highest rate of drug overdose deaths were whites, American Indians, and Alaskan natives. However, drug overdose deaths have risen in almost every ethnic group.

Rates were highest and increased most rapidly in the Northeast and Appalachia. However, drug overdose death rates increased significantly in nearly every state and have affected rural and urban counties, according to the study.

“It has been proposed that worsening opportunities in the labor market among White individuals, particularly those with no more than a high school education, have

contributed to increasing death rates from drug poisoning, suicide, and alcohol during middle age. However, other factors likely also contribute. Increasing drug poisoning, suicide, and alcohol-induced death rates in the US are not limited to White individuals; furthermore, demographic and geographic patterns of these three causes of death differ substantially, indicating a more nuanced and complex picture. Our findings indicate that these 3 causes of death merit individual consideration, and their underlying causes and optimal prevention strategies may differ in nature, intensity, and duration across populations and contexts.” according to the new study.

Disclosures: None declared.

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THE **BACKPAGE**

Gut Bacteria, Human Health, and Chronic Pain

There is a growing consensus that the composition of microbes in the human gut is likely to influence multiple diseases and their treatment. And they may even have an influence on acute and chronic pain.

“Disruptions in the delicate balance of microbes within the gut and other niches are associated with numerous disease states—including neurologic disorders, cardiovascular disease, gastrointestinal disorders, and even cancer. Accordingly, there is intense interest in targeting these microbes to promote overall health and to abrogate disease,” according to cancer specialist Jennifer Wargo, MD. (See *Science*, 2020; 369:6509.)

The greatest success in improving health by altering the makeup of the gut biome has come with the alleviation of treatment-resistant *Clostridium difficile* infection through the transplantation of fecal material.

“Numerous clinical trials have since been undertaken, using FMT [fecal microbiota transplantation] and other gut microbiota modulation strategies to treat diseases of the gut (such as CDI [*Clostridium difficile* infection], and inflammatory bowel disease, IBD) as well as other systemic diseases,” according to Wargo.

Learning how to relieve disease through alteration of the gut bacteria is likely to be a long, slow process. The first attempts to treat human disease with the transfer of fecal matter occurred in the 4th century BC—and researchers are just flirting with success 2400 years later.

A 2019 study of 156 subjects found that subjects who fit the criteria for fibromyalgia had significant differences in the composition of gut bacteria when compared to control subjects who did not.

However, it was not clear whether the difference in gut

biome composition was a potential cause or a consequence of the pain condition. “Results of this study provide evidence for alterations of gut microbiome alterations in FM. Further studies are needed to measure possible microbiome changes in other chronic pain conditions, and to explore potential causal correlations between the gut microbiome and FM,” according to Amir Minerbi, MD, et al. (See *Pain*, 2019; 160(11):2589–02.)

A 2019 review suggested that gut microbes might influence many types of chronic pain, including visceral, inflammatory,

field have generally focused on industry payments to individual physicians. However, hospitals often have their own set of potential financial conflicts. So Timothy S. Anderson, MD, and colleagues recently set out to document industry payments to teaching hospitals in the United States.

They used the database set up under the Physician Payments Sunshine Act to document payments to the hospitals.

“We examined 2018 CMS Open Payments program data to identify all nonresearch payments made by industry to teaching hospitals and determined that

interventions into computer games. Silja Litvin, PhD, and colleagues from Ludwig Maximilian University of Munich studied a mobile mental health intervention designed to reduce anxiety and increase resilience. They turned it into an iPhone game and then tested it in a 5-week randomized trial involving 358 subjects.

They randomly allocated the study participants to one of three interventions: (1) the gamified app; (2) the usual nongamified app; or (3) a waiting list for the gamified app. They measured anxiety and resilience with questionnaires administered at three time points over the course of the study.

The authors found that after five weeks, the subjects randomized to the gamified app had a statistically significant advantage over the two other groups. Additionally, the game group retained 21% more participants than the other groups.

The latter may be an important factor. Digital mental interventions often have major attrition problems, where users gradually lose interest in the digital treatments—and revert to their preintervention status.

“eQuoo [the gamified intervention app] was able to show that it not only had a significant and beneficial impact on the participant’s mental wellbeing but that gamifying therapies counterbalances sky-high attrition rates most mental health apps struggle with, especially in the demographic of 18-35-year-olds,” according to Litvin et al.

This should only be regarded as a pilot study that needs confirmation in a more rigorous independent trial. Lead author Litvin disclosed she is the majority shareholder in the company (PsychApps Limited) that developed the eQuoo computer game. (See *PLoS One*, 2020; 15(9): e0237220.)

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Beware: Researchers Are “Spinning” the Results of All Too Many Studies

Reducing Social and Physical Isolation to Fight Ill Health in the Wake of COVID-19

headache, neuropathic pain, and affect opioid tolerance. Ran Guo, PhD, and colleagues pointed out that gut microbes help modulate the excitability of the dorsal root ganglion and regulate inflammatory changes in both the central and peripheral nervous systems.

“Targeting gut microbiota through dietary intervention, pharmabiotic approaches, or faecal microbiota transplantation, represents a novel and potentially fruitful strategy for chronic pain management,” according to the authors. (See <https://www.sciencedirect.com/science/article/pii/S0007091219306385>)

Overlooked Conflicts-of-Interest in the Spine Field

Researchers trying to document the prevalence of financial conflicts-of-interest (COI) in the spine

91 percent of teaching hospitals received industry payments totaling \$832 million in 2018.”

They found substantial royalty payments, which likely reflect cooperative research partnerships—along with payments for gifts and educational activities.

“Hospitals should strengthen policies to prevent the institutional conflicts of interest that may arise from these payments while promoting beneficial industry collaborations,” according to Anderson et al. And they would also like to see the Sunshine Act expand its coverage of hospital payments. (See *Health Affairs*, 2020; 39(9):1583–91.)

Turning Treatments Into Digital Games

A new study hints that there may be potential in turning health