

Renewed Doubts About a Common Diagnostic Test—and the Safety of Novel Disc Injection Therapies

An award-winning study offers ominous news for spine specialists who want to continue using a common diagnostic test in an attempt to identify painful discs that might be candidates for invasive interventions—from injections to fusion surgery. (See Cuellar et al., 2015.)

And it may have profound implications for the myriad disc injection therapies under development around the world. It raises doubts about their long-term impact—and the way their long-term risks are being investigated in animal studies and human clinical trials.

The goal of many of these experimental intradiscal therapies—involving the injection of steroids, growth factors, stem cells, statins, and/or other medications—is to prevent or slow the development of disc degeneration. However, the mode of delivery of these compounds may itself lead to long-term degeneration and clinically significant back problems.

Discography, or provocative disc injection, remains a popular diagnostic method, used up to 70,000 times per year in the United States. The goal is to identify painful discs by examining whether the pressurized injection—with or without the use of contrast medium—recreates a patient’s “usual” back symptoms.

Yet, according to various reviews, discography has no proven diagnostic or prognostic value as a stand-alone test. (See Willems et al., 2013; Chou et al., 2009; Eck, 2014.)

A series of studies by the Stanford Discography Project over the last 15 years raised doubts about the ability of provocative discography to reliably identify symptomatic discs—those that might be responsible for patients’ usual back pain.

A 2009 study by the same group documented that discography also appears to result in radiologic damage to the disc. And the new study shows that provocative discography increases the risk of developing long-term, clinically important back problems. (See Carragee et al., 2009.)

“Lumbar provocative discography leads to more surgery, more imaging events, low

back-related adverse events, and more physician visits. Clinicians should counsel patients about the risk of clinical disc problems after provocative discography,” said spine surgeon and coauthor Michael P. Stauff, MD, of the University of Massachusetts in presenting the study at the 2015 annual meeting of the International Society for the Study of the Lumbar Spine (ISSLS) in San Francisco.

Given the current evidence, Stauff suggests that provocative discography should not be employed in the evaluation of chronic back pain and disc degeneration.

“Given the results of the Stanford Discography Project, which has demonstrated poor specificity, radiographic worsening of disc degeneration, and a higher rate of clinical disc problems, I do not believe that there is any role for lumbar provocative

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FDA on Epidural Injections

Physicians in the United States deliver millions of epidural steroid injections to people with back and leg pain every year. According to recent reviews, most of these injections do not have clinically important effects. But they do pose risks.

Unfortunately, according to a recent article by FDA scientists in the *New England of Medicine*, there is not enough evidence to determine the exact number of serious adverse events related to spinal steroid injections—or the safest injection techniques.

The FDA has never given formal approval to spinal epidural steroid injections. So epidural and related steroid injections are an off-label treatment in the U.S.—part of the practice of medicine not regulated by the FDA.

This highlights a significant gap in the U.S. regulatory process. Some common interventions are not regulated at all, and

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Placebo Effects Growing

In a surprise finding, the magnitude of placebo effects in some drug trials in the United States seems to be growing.

This makes it difficult for companies developing novel pain-relieving drugs to demonstrate their benefit. Interestingly, there is no evidence of rising placebo effects in drug trials in other countries.

Why would American study subjects get greater pain relief from placebo medications than people in other countries?

Alexander H. Tuttle and colleagues from McGill University examined 84 placebo-controlled clinical trials on chronic neuropathic pain (pain related to nerve injury or disease) conducted around the world from 1990 to 2013. Over that period, the degree of pain relief experienced by subjects in the placebo group in these trials rose steadily, reaching an impressive average of 30% in 2013.

The researchers found that rising placebo effects occurred only in studies conducted entirely in the U.S. So what might account for this unusual pattern of placebo-related pain relief?

Tuttle et al. found that several factors appeared to distinguish U.S. trials from those in other countries. U.S. drug trials have grown steadily longer over the course of this review from an average of four weeks in 1990 to 12 weeks in 2013. Trials in the U.S. have also grown steadily larger, from an average of 50 patients in 1990 to an average of 700 patients in 2013. (See Tuttle et al., 2015.)

“The data suggest that longer and larger trials are associated with bigger placebo responses,” said Jeffrey Mogil, the senior author of the new study in a statement accompanying the new study. “This, in turn, tends to result in the failure of those trials—since it makes it harder for pharmaceutical companies to prove that the drug being tested is more effective than treatment with a placebo.”

The cause of this pattern remains a mystery. “It remains to be determined why the United States is an outlier with respect to its clinical trials,” said Tuttle.

However, it is possible that some aspect of U.S. life is boosting the effects of placebo medications. The U.S. is one of the only countries in the world to have direct-to-consumer advertising. And it may be that continual exposure to advertisements for gleefully effective drugs on television and radio has primed U.S. consumers to respond more strongly to placebos.

Alternatively, it may have something to do with the ceremony of the longer, larger clinical trials. Many of these trials are run by large contract research organizations with dedicated staff. These organizations may treat study subjects quite a bit differently than those organizing and running smaller trials. Some aspect of their organization and performance may be raising expectations and realization of pain relief.

Tuttle et al. report that there have been similar reports of rising placebo effects in studies of antidepressants and antipsychotic drugs, though no hint that the placebo effects were stronger in the U.S. All these studies have something common—subjective self-reported outcomes.

It is important for researchers to get to the bottom of this issue. According to some reports, 90% of new medications for neuropathic pain and cancer pain in recent years have not produced positive results in clinical trials. (See Marchant, 2015.) It is also possible that better understanding of factors that modulate placebo responses might lead to better nondrug treatments for pain and other conditions.

Disclosures: None declared.

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How Researchers and Healthcare Providers Fool Themselves—And What They Can Do About It

In the spine field, there is tremendous loyalty to unproven explanations for low back pain, unproven diagnoses, and unproven treatments—among researchers and healthcare providers alike.

This occurs among elite mainstream researchers and providers—as well as those on the edges of the field.

Many researchers and providers have tunnel vision for pet hypotheses and myopia for competing ideas. They engage in “confirmation bias,” seeking out information that supports their views, and ignoring information that does not. They publish scientific studies on the basis of these hypotheses—and all too often treat patients on the basis of half-baked ideas. One can argue that tens of thousands of patients in the United States every year receive back pain/spine treatments that are not based on sound science.

How Scientists Fool Themselves

Humans have a remarkable ability to fool themselves, according to an article by psychologist and biostatistician Regina Nuzzo, PhD, in *Nature*. (See Nuzzo, 2015.)

“Our brains evolved long ago on the African savannah, where jumping to plausible conclusions about the location of ripe fruit or the presence of a predator was a matter of survival,” Nuzzo explained.

However, in the complex modern world, those same tendencies can lead people astray.

“In today’s environment, our talent for jumping to conclusions makes it all too easy to find false patterns in randomness, to ignore alternative explanations for a result or to accept ‘reasonable’ outcomes without question—that is, to ceaselessly lead ourselves astray without realizing it,” Nuzzo added.

Specific Ways Scientists Fool Themselves

As part of a wide-ranging essay, Nuzzo offers some specific ways in which researchers fool themselves. By extension, healthcare providers often fall prey to the same issues:

- *Hypothesis myopia*. Collecting evidence to support one hypothesis, failing to look for opposing evidence, and ignoring all other explanations.



- *Texas sharpshooter*. “A cognitive trap that awaits during data analysis is illustrated by the fable of the Texas sharpshooter: an inept marksman who fires a random pattern of bullets at the side of a barn,

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An Explanation of Blind Data Analysis: Keeping Researchers Honest Through the Whole Study Process

BackLetter editors hear quite a few stories about research improprieties. Some of them involve researchers reportedly redoing their data analyses after getting results that contradicted their expectations.

Hearing about statements such as “Let’s run those numbers again with a different statistical model” is disappointing and dispiriting. The intent often violates the spirit of scientific investigation. However, researchers are developing new methods to avoid these problems and keep themselves honest. Blind data analysis is one method of doing so.

Astrophysicist Saul Perlmutter, PhD, explained the rationale for blind data analysis across multiple scientific fields in a recent article at *Berkeley News*. (See Sanders, 2015.)

“There is clear evidence in the literature that people tend to look for the errors in their analysis only when they get a surprising result or effect. This leads to people

re-examining their analyses, and since there are often alternative approaches and/or subtle hidden bugs, the final conclusions typically end up more in line with previous results,” Perlmutter said. In other words, researchers’ biases distort study results.

Here is a description of blind analysis from a Stanford University website: “In blind analysis, data are modified [by an independent party or computer program] so that the scientists don’t actually know what their results are until they’ve mostly completed their data analysis. The computer ‘knows’ the actual results, but displays them with random noise, systematic bias or scrambled labels in a way that enables the investigator to make analytic decisions without knowing whether they will help or thwart a particular hypothesis.” (See Nagel, 2015.)

Here is an explanation from Stanford researcher Robert MacCoun, PhD, a

staunch advocate of blind data analysis, in an interview at the same website.

“When I mention blind analysis to other researchers, many nod as if they are familiar with it, but they usually think I’m talking about double-blind methods that keep the participants and experimenters in the dark about which participants are getting a placebo vs. the actual treatment. Blind analysis is similar in spirit, but quite different in practice. In blind analysis, researchers analyzing the data can’t see the true results until they have completed the analysis. After lifting the blind, they can do more analysis, but they have to report those as ‘post-blind’—i.e., less credible—analyses,” noted MacCoun.

There is a more comprehensive article on blind analysis by MacCoun and Perlmutter at the *Nature* website. (See MacCoun and Perlmutter, 2015.)

Diagnostic Errors a Major Problem Across Medicine—Particularly in Spine Care

A new Institute of Medicine report asserts that diagnostic errors are extremely common across medicine—and have devastating consequences.

Spinal medicine is a complex area of medicine that is rife with diagnostic errors—missed diagnoses, wrong diagnoses and speculative diagnoses that are not clearly supported by scientific evidence.

What Is a Diagnostic Error?

So what is a diagnostic error, according to the new report by Erin P. Balogh, MD, and colleagues? (See Balogh et al., 2015.)

“The committee’s definition of diagnostic error is the failure to (a) establish an accurate and timely explanation of the patient’s health problem(s) or (b) communicate that explanation to the patient. The definition employs a patient-centered perspective because patients bear the ultimate risk of harm from diagnostic errors. Timeliness means that the diagnosis was not meaningfully delayed; however, timeliness is context-dependent. While some diagnoses may take days, weeks, or even months to establish, timely may mean quite quickly (minutes to hours) for other urgent diagnoses. A diagnosis is not accurate if it differs from the true condition a patient has (or does not have) or if it is imprecise and incomplete.”

The new report includes communication errors as an integral part of diagnostic errors. This makes it clear that treating healthcare providers not only have to arrive at accurate and valid diagnoses, they have to make sure that patients receive those diagnoses expeditiously. Patients often complain that healthcare providers and their staff just don’t communicate well. They are often slow to pick up the phone and seem needlessly resistant to modern communication methods such as email and text messaging.

“From a patient’s perspective, an accurate and timely explanation of the health problem is meaningless unless this information reaches the patient so that a patient and health care professionals can act on the explanation,” according to the report.

Most People Experience Diagnostic Errors

The extensive report by Balogh et al. suggests that most U.S. residents will experience at

least one diagnostic error over the course of their lifetimes.

Overall, the report found that about 5% of U.S. adults who seek outpatient care each year experience a diagnostic error. Post-mortem studies suggest that about 10% of patient deaths stem from diagnostic errors.

Diagnostic errors are responsible for 6% to 17% of adverse events in hospital settings, depending on the study source. “Diagnostic errors are the leading type of paid medical malpractice claims, are almost twice as likely to have resulted in the patient’s death compared to other claims, and represent the highest proportion of total payments,” according to Balogh et al.

Diagnostic errors—both errors of commission and omission—are extremely common in the spinal medicine realm.

One of the three cases of diagnostic error described at length in the IOM report concerned a man—a married father of two in his early 40s—with progressive neck discomfort. An imaging scan visualized a mass on his cervical spine. A neurosurgeon biopsied the lesion and sent a sample to a hospital pathologist. The pathologist suggested it was an “atypical spindle cell neoplasm.” The neurosurgeon concluded that this meant it was benign, removed it, and pronounced the patient “cured.”

However, the pathologist did further staining procedures and ultimately determined the lesion to be a malignant synovial cell carcinoma. Twenty-one days after surgery, the pathologist sent the report to the neurosurgeon’s office, where it was immediately lost. So neither the neurosurgeon nor the patient learned that the initial mass was malignant.

Six months later, onerous neck symptoms returned. The patient went on to have seven additional operations along with numerous rounds of chemotherapy and radiation. He died two years later.

There were multiple errors in this sad case. The pathologist, the treating neurosurgeon, and the neurosurgeon’s office staff all made needless errors that may have hastened the patient’s death.

Errors of Commission and Omission

Readers can find endless variations on all manner of diagnostic errors in the medical



literature. Nancy Epstein, MD, and colleagues recently described a case with diagnostic errors at two phases of the care process. It again involved a mass on the cervical spine.

A man in his early fifties sought medical care after experiencing neck and limb discomfort. He underwent enhanced MRI of the cervical spine. (See Epstein et al., 2015.)

The original radiology report suggested that the man had a small disc herniation at C4/5; a moderate size, broad-based bony ridge at C5/6, causing mild cord compression; and moderate bilateral foraminal stenosis—in other words, mild degenerative abnormalities.

The first physician in this case apparently did not read the imaging scans and instead trusted the interpretation of the radiologist. Unfortunately, the radiologist missed a right-sided tumor at C5/6, which filled the right neural foramen with extension into the spinal canal.

Two years later, the patient again sought medical care, presenting with severe and worsening quadriparesis (muscle weakness affecting all four limbs). His tumor—which ultimately proved to be a benign meningioma—had expanded 6.7-fold over the intervening years. He recovered eventually, but as a result of the diagnostic errors, he had to undergo a much more challenging surgical procedure.

Two errors in this case prevented timely and accurate diagnosis. The most obvious was the radiologist’s misreading of the initial MRI scan. The second error was the apparent decision of the first treating physician not to read the MRI scan and instead to trust the erroneous radiology report.

In several commentaries published with this report, various neurosurgeons suggested that if the treating physician is capable of interpreting this type of MRI scan (e.g. an orthopaedic surgeon, a neurologist, or neurosurgeon), the appropriate standard of care

Two Separate Gauntlets for New Drugs, Devices, and Technologies in Spine Care and Elsewhere

Many casual observers believe that the FDA is the only government agency that regulates the uptake of new drugs, devices, and technologies. Yet, the Center for Medicare and Medicaid Services (CMS)—the agency that regulates interventions in the U.S. government’s massive retirement and disability programs—has overlapping responsibilities with the FDA.

Unfortunately, the conflicting standards at the two agencies may be hindering the development and dissemination of beneficial medical interventions. This is a particular concern for devices (surgical and otherwise), which sometimes can gain approval at the FDA and fail to pass scrutiny at CMS.

“The FDA approves drugs and devices based on evidence that the product is ‘safe and effective,’ whereas CMS makes coverage determinations based on whether the product is reasonable and necessary,” according to a recent article in *Health Affairs* by Liz Richardson of the Brookings Institution.

To some extent, these evidence requirements are complementary. The FDA requires careful clinical trials to demonstrate safety and efficacy in refined patient populations.

“For CMS, however, the primary concern is how the product performs under normal clinical conditions in typical Medicare patients, who are usually much more diverse and have more comorbidities than the patients who are enrolled in a premarketing clinical trial,” according to Richardson. (See Richardson, 2015.)

There are a variety of initiatives underway. Parallel review by the two agencies would streamline the approval process by having both agencies vet new treatments and technologies at the same time. It is being evaluated in pilot programs.

Some observers think that CMS has the capacity to mitigate some of the problems with the dual approval process by issuing more flexible coverage decisions, particularly “coverage with evidence development.”

Under this scenario—also being evaluated in pilot programs—CMS would have additional options beyond simply approving or not approving coverage of a drug, device, or other intervention.

CMS could also issue “temporary approval” and reimbursement for a new technology pending further research. Recipients of the new interventions would have to be enrolled in prospective clinical studies that could subsequently be used to reevaluate and potentially revise the coverage determination.

Unfortunately, because of political considerations, the future of both types of programs is up in the air at the moment.

Disclosures: None declared.

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Richardson L, Health policy briefs, *Health Affairs*, 2015; 34(9). www.healthaffairs.org/healthpolicybriefs/brief.php?brief_id=143.

Diagnostic Errors

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would be to do so, preferably before reading the radiology report.

There are no simple, sure-fire ways of avoiding diagnostic errors. They often involve complex issues in busy, complicated care environments. Readers, however, can find details about various diagnostic errors, and potential solutions, in the IOM report at the web address in the references below.

The report also offers a table with broad goals for improving diagnosis and reducing diagnostic errors (see Table I). This table reflects the view from 30,000 feet rather than real-life error prevention on the ground. But healthcare providers who want to work on these issues can certainly flesh out these recommendations into more realistic human terms.

Beguilingly Complex Issues

BackLetter readers might want to peruse a recent eloquent column in the *New York Times* on the challenges of diagnosis in a busy internal medicine practice in the Big Apple. It describes the ever-present possibility of diagnostic errors in a real-life healthcare setting. These errors are common. Diagnostic

accuracy in U.S. medicine is estimated to be only in the range of 80% to 90%. (Diagnostic accuracy is lower in the spine field.)

Danielle Ofri, MD, described a “bursting-at-the-seams” day in the clinic featuring patients with a broad array of symptom presentations.

She described the difficulty of triaging the patients based on the potential severity of their illnesses. “Every patient presented a wide range of possibilities, from totally benign complaints to catastrophic illness,” she recounted.

She discussed the difficulty of coming up with a quick differential diagnosis (i.e. all possible and/or likely explanations for the patients’ symptoms) and the challenge of homing in on the right possibilities.

“As I raced through my day trying to avoid falling too woefully behind schedule, I was also struggling to be as thorough as possible. The ulcer gnawing at the pit of every doctor’s stomach is, “What if I miss something serious?” according to Ofri.

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Table I. Goals for Improving Diagnosis and Reducing Diagnostic Error

- Facilitate more effective teamwork in the diagnostic process among healthcare professionals, patients, and their families
- Enhance healthcare professional education and training in the diagnostic process
- Ensure that health information technologies support patients and healthcare professionals in the diagnostic process
- Develop and deploy approaches to identify, learn from, and reduce diagnostic errors and near misses in clinical practice
- Establish a work system and culture that supports the diagnostic process and improvements in diagnostic performance
- Develop a reporting environment and medical liability system that facilitates improved diagnosis through learning from diagnostic errors and near misses
- Design a payment and care delivery environment that supports the diagnostic process
- Provide dedicated funding for research on the diagnostic process and diagnostic errors

Trick Question: Is Seeking Back Care From a Physician a Waste of Time and Money?

Those who want to make spine care more cost-effective can do something that has nothing to do with diagnosis and treatment. They can stop wasting their patients' time and money and streamline their healthcare services.

Kristin N. Ray, MD, et al. recently used data from the U.S. National Ambulatory Medical Care Survey and the American Time Use Survey to calculate how much time patients have to spend making a single visit to an office-based physician in the United States.

"Using American Time Use Survey data, we determined that patients spent on average 123 minutes obtaining medical care, including 86 minutes of clinic time and 38 minutes travel time," according to Ray et al. (See Ray et al., 2015a.)

This investment in time earned patients about 20 minutes of face time with the physician.

Unfortunately, racial and ethnic minorities, individuals with lower levels of education, and the unemployed had to invest significantly more time to see a physician—both in travel time and waiting in the clinic.

For instance, a white Hispanic individual had to spend 25 extra minutes at the clinic than a white non-Hispanic—but not in face time with a physician.

Time Investment Clearly Excessive

This time investment for a simple physician visit is clearly excessive. Patients with common back pain and other run-of-the-mill ailments have to spend about a quarter of an average workday to see a doctor.

These data should provide motivation to streamline patient visits as well as come up with alternate modes of medical care delivery.

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And, of course, she had to do all of this in the rushed environment of modern American healthcare.

"If I had the luxury of an hour with each patient, I would have the time to carefully sort through every possibility," Ofri said. But like many healthcare practitioners, she only had five to ten minutes to complete this daunting task—"to push the majority of diagnoses to the bottom of the list, come up

Tallying the Costs of Wasting Time on Medical Care

In another recent study, Ray et al. tallied the actual costs—the so-called "opportunity costs" of seeking medical care. They explained the rationale. (See Ray et al., 2015b.)

"Time spent seeking healthcare represents a burden to patients, lost productivity to employers and society, and a potential inefficiency within healthcare systems. The Institute of Medicine has identified improving timeliness of care, including reducing waiting time, as 1 of the 6 key quality goals in the US healthcare system. Patient time burden (measured in minutes) and patient time costs (measured in dollars) are 2 methods of measuring the time spent by patients traveling to, waiting for, and receiving medical care," according to Ray et al.

They explained that "opportunity costs" are a way valuing patient time on the basis of the value of foregone activities—work and other activities that patients might have performed had they not gone to see a doctor.

Employed Individuals Lose 1.1 Billion Hours of Work Time Because of Medical Appointments

The opportunity costs of long travel and clinic times are substantial. Employed individuals lost about 1.1 billion hours of work time in seeking physician care in 2010. The opportunity costs lost per medical visit work out to about \$43. In other words, the patient, his or her employer, and/or society are investing \$43 in addition to the direct costs of the medical care. A lot of that cost is being squandered in useless waiting.

with the most likely few at the top—being careful, of course, to keep in the rare but life-threatening possibilities—and then explain to the patient what I think," she said. And then, move on to the next patient in line. (See Ofri, 2015.)

Disclosures: None declared.

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The sum of \$43 per visit does not sound like a lot until one multiplies this sum by the total number of physician visits in the U.S. Then these costs become onerous: \$52 billion per year.

Should Physicians Move Beyond Ancient Communication Methods?

So what are the solutions? There are numerous ways of streamlining medical care. Better logistics and efficiency at medical clinics would be a good start.

There is an opportunity for more extensive use of "modern" technologies to facilitate communication between physicians and patients—such as telephone calls, e-mail, and texting. There is no reason why physicians have to linger in the mid-20th century in their communication methods.

Walk-in medical retail clinics, after-hours clinics, telemedicine services, and even "Uber-type" house call services—all offer the opportunity to deliver healthcare, including spine care, more efficiently.

Disclosures: None declared.

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Novel Disc Injection Therapies

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discography,” according to Stauff. [Editor’s note: The mention of “poor specificity” refers to the elevated number of misleading, false-positive results associated with discography.]

The study drew an enthusiastic response and won a “Best Paper” award at the ISSLS conference. Several members of ISSLS suggested discography should no longer be used routinely to investigate suspected discogenic pain.

“The use of any procedure requires careful consideration of risks and benefits,” said Bradley Weiner, MD, professor at Weill Cornell Medical College and chief of spine surgery at Houston Methodist Hospital.

“From several studies now, it appears there are real risks associated with discography and limited benefits. For years, there has been an opinion about discography that goes something like: ‘While it’s a bit unpleasant, it’s an otherwise benign procedure—and while the information provided isn’t the greatest, it’s the best thing we have for discogenic pain.’

“Given that we now know that the procedure is not benign and that the findings are not very helpful diagnostically or prognostically; there appears to be little indication for it. We would not tolerate this from any other diagnostic intervention,” according to Weiner.

What About a Modified Version Of Discography?

What about performing a modified version of discography to limit the potential damage related to the procedure? In most discography protocols, the physician administering the test injects the degenerated disc suspected of being the source of discogenic pain, as well as one or two healthy control discs for comparison purposes. What about just injecting the suspected painful disc—in order to avoid damaging the healthy control discs?

Unfortunately, this is not a viable strategy, according to Stauff. “The use of control discs is the most troubling part of the test based on our results because discs that were normal or less severely [degenerated] than the disc in question were subjected to the needle puncture and low pressure injection and put at risk for [accelerated] disc degeneration.”

“Eliminating the control disc injection would mitigate this as a problem for traditional provocative lumbar discography, but it also may worsen the specificity of a test that already has poor specificity. For this reason, a pressurized injection into one disc would not likely yield clinically meaningful information. Early data [from other studies] does show promise for injecting a local anesthetic into a disc to gauge the change in a patient’s low back pain, but these data are preliminary at this point,” he added.

Implications for Other Intradiscal Therapies

In the new study, discography led only to degeneration and long-term back problems in a minority of patients who underwent the procedure. But at this juncture, there doesn’t appear to be any way to make an accurate prediction regarding which patients might be vulnerable to long-term degenerative problems after disc puncture and injection.

This vulnerability may relate to the health of the disc or discs undergoing injection, the genetic characteristics of the patient, and/or other exposures and influences.

“The effects of discography were not uniform,” said senior author Eugene Carragee, MD, in a recent interview. “There were people who underwent discographic injections at the three levels who had good-looking discs ten years later—and didn’t have any back problems.”

“But there are also people whose discs degenerated quickly. Where you say afterwards, ‘We never should have put a needle in that disc,’” said Carragee.

“When we began the Stanford Discography Project in 1997, we never imagined that discography could result in disc degeneration and long-term clinically important back problems. We thought that infection from repeated injections would pose the most significant risk. So these findings were a surprise to us,” Carragee explained.

As mentioned above, this pattern of results seems to have implications for the many intradiscal interventions currently under development around the world.

Companies are vying for position in an effort to come up with effective intradiscal therapies. Many involve the injection—and repeated injection—of intervertebral discs with needles of substantial size.

Currently, there does not appear to be any easy or convenient way to assess the safety of these injection procedures, except

with long-term human studies. None of the widely employed animal models of disc degeneration (which are commonly used to assess the effects of intradiscal injection) appears adequate for this task.

“Many intradiscal injection therapies seem to be staking their safety claims on animal models. But this isn’t realistic,” said Carragee.

“When you inject a disc in a genetically identical animal model—New Zealand rabbits, for instance—you see a consistent rate of progressive radiologic damage over time,” said Carragee. “It is easy to do studies in genetically similar animal models. But their relevance to the human situation isn’t clear.”

“In humans we have a very different expression of disc disease. As our study showed, after disc injection in humans, you get a variable rate of radiologic damage and a delayed incidence of clinically important back problems,” he explained.

The development of clinically important back problems in the new study wasn’t apparent for several years after disc puncture and injection, said Carragee. “It took about five years to see differences in back problems between the discography group and the control group,” he said. This suggests there is a need for a long time frame in studies of intradiscal injections.

“This raises questions about many of the intradiscal therapies,” Carragee commented. “To say that the needle punctures aren’t going to make any difference just isn’t realistic.”

“Some of the intradiscal therapies would appear to be riskier than discography because they will involve the injection of large proteins—through a much larger needle than we used for the discography study. If you use a smaller needle for these injections, you can disrupt the three-dimensional structure of the protein being delivered to the disc,” he said.

Given the results of the Stanford Discography Project, the developers of intradiscal therapies will now have to assess the long-term risk/benefit profile of these interventions more carefully.

“I think this is a critical issue for the spine field going forward,” said Carragee, who is Editor-in-Chief of *The Spine Journal*. “There is a lot of money at stake. It is such a contentious issue that it is sometimes difficult even to have a civilized discussion about it. But we need to address this issue up front before it becomes a bigger problem.”

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Discography Controversy Speaks to Larger Problems Across Spinal Medicine

The debate over discography speaks to some larger issues—and larger problems—in spine research and spine care. The Institute of Medicine recently kicked off a major effort to reduce diagnostic errors across medicine. (See article on page 136.)

This initiative will be a challenge to the spine field, which is especially vulnerable to diagnostic errors. Spinal medicine falls prey to the usual broad spectrum of common diagnostic errors: failure to recognize serious disease, coming up with the wrong shortlist of possible diagnoses, misinterpretation of patients' histories and clinical examinations, failure to interpret imaging and other diagnostic tests competently, and failure to communicate adequately.

However, spine care providers all too often run the risk of another type of diagnostic error, through the widespread use of unvalidated tests to diagnose speculative spinal conditions and diseases. This is a problem affecting multiple spine treatment professions.

Many common diagnostic procedures that purport to identify painful discs, facet joints, sacroiliac joints and soft tissue abnormalities have never been validated in adequate scientific studies—either in comparison with a “gold standard” or in rigorous long-term outcome studies. Yet these questionable diagnostic procedures are employed commonly and enjoy support from tens of thousands of practitioners and even from prominent professional societies.

But what if these tests aren't capable of arriving at accurate diagnoses—and don't lead to appropriate therapeutic procedures?

Then they become diagnostic errors—with the potential to cause grievous harm.

The spine field traditionally has been slow to move away from unproven interventions—including unvalidated diagnostic tests. Discography is a perfect example. It came into widespread use in the spine field in the 1990s, often as a method of identifying patients who might benefit from spinal fusion surgery for “discogenic pain” or “degenerative disc disease.” Discography became something approaching a “gold standard” for the identification of discogenic pain.

Warning signs about its ability to identify painful and nonpainful discs emerged as early as the turn of the millennium, with the publication of the first studies from the Stanford Discography Project. One early study showed that discography could result in elevated levels of false-positive results in patients without low back symptoms. Another suggested that discography was incapable of distinguishing clinically important from clinically unimportant pain. (See Carragee et al., 2000a; Carragee et al., 2000b.)

Yet these and other studies from the Stanford Discography Project did not appear to reduce the utilization of discography significantly. Discography remained popular even after the 2009 study by Carragee et al. suggested that it can cause long-term disc degeneration. So the potential for harm didn't dissuade all the proponents.

Even major professional societies haven't backed away from endorsing discography

as a diagnostic method—despite questions about its utility and validity. Fifteen professional societies (including major spine, neurosurgery, pain, radiology, and pain intervention societies) recently submitted a letter to the Agency for Healthcare Research and Quality regarding the diagnosis of specific forms of back pain (as it pertained to spinal injections). (See American Association of Neurological Surgeons et al., 2015.)

In one section of that letter, they endorsed the use of several unvalidated diagnostic methods to “attribute” back pain to lumbar discs, facet joints, sacroiliac joints, and myofascial trigger points. The letter suggested that “disc stimulation” (another term for discography) could attribute pain to the disc.

Ironically, at least three of these societies have published evidence-based reviews and guidelines recommending against the use of discography as a stand-alone test for identifying painful discs. (See Chou et al., 2009; Eck et al., 2014.)

So the spine field is, in many respects, in an untenable position. It is using multiple unvalidated tests to identify candidates for various procedures. These tests don't have clear scientific support. Yet the field has not organized the types of long-term outcome studies necessary to determine the true value of these diagnostic methods. The spine field needs to document the utility and value of these diagnostic tests or start moving away from them. Otherwise, diagnostic speculation will morph into diagnostic error all too often.

Novel Disc Injection Therapies

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Stauff said he agrees with Carragee that there is a need for careful, long-term human trials to assess the risks and benefits of various intradiscal therapies under development.

“The radiographic and clinical disc problems found in the study were more significant in the experimental group but it was still in a minority of patients. One interpretation of this is that certain patients have a

genetic predisposition to getting disc degeneration that is potentiated by the disc injection, whereas the discs in other patients were not significantly changed at long-term follow-up,” Stauff explained.

“The underpinnings of this theory are in the genetic basis of disc degeneration that was demonstrated in the Twin Spine Study from Finland. (See Battié et al., 2009.) In traditional animal models using lab-raised animals, it is very difficult to replicate the typical genetic heterogeneity seen in humans.

For this reason, long-term human studies would better demonstrate risks and benefits,” he added.

Weiner points out that attention to these safety issues does not preclude the use of intradiscal injections to deliver therapeutic compounds—if they are proven to be effective. It simply suggests there is a need for a more sophisticated research process and a careful balancing of risks and benefits.

“Obviously, the ideal situation is that we have long term safety information on all

interventions—including intradiscal injections,” according to Weiner.

“That said, if the novel injections/interventions are therapeutic and the benefits are significant (reversing, preventing, or limiting the progression of degenerative disease), this is a scenario quite different than discography. We have not abandoned hip replacements knowing that many will fail in fifteen years—given the tremendous benefits during the therapeutically effective temporal window. The same may be true for some emerging intradiscal technologies—and it may be the case that the trans-annular approach may be the best and safest way to get there,” said Weiner.

Brief Summary of the New Stanford Discography Study

At the ISSLS meeting, Stauff presented a brief summary of the new discography study—a dual-cohort investigation led by Jason Cuellar, MD, PhD, of New York University (See Cuellar et al., 2015.)

Stauff explained that the goal of the new study was to “determine the clinical effects of provocative discography on the lumbar intervertebral disc.”

As mentioned above, a previous study from the Stanford Discography Project had found that discography resulted in accelerated disc degeneration in a minority of study subjects. The researchers wanted to determine whether the accelerated disc degeneration would translate into clinically important back problems.

The researchers’ working hypothesis was that would be no differences in clinically important back problems, number of surgeries, imaging events, or low back events between the two groups.

Description of the Two Cohorts

Here is a description of the two cohorts in this study. “Between 1997 and 1998, a cohort of 75 subjects was recruited and enrolled in a study of discography (L3–S1) in persons asymptomatic or minimally symptomatic for low back pain,” according to Carragee et al. in a previous study.

Subjects in the discography group were recruited from one of three patient pools. All the subjects had a history of vulnerability to disc disease or psychological problems.

There were 40 individuals with documented cervical disc disease; 25 subjects with a history of lumbar disc herniation and complete symptom resolution; and 10

subjects with no history of either cervical or lumbar disc illness but who did have a history of serious psychological distress consistent with a somatization disorder. From the same 3 subject pools, the researchers recruited 75 matched subjects who would not undergo discography. (See Carragee et al., 2009.) Baseline characteristics in the two groups were similar.

The experimental group underwent low-pressure discography at the L3–S1 levels with relatively small, 22- to 25-gauge needles. A positive discography result required both a painful response in the disc being targeted and a negative result in a control disc. MRI scans were obtained from both the group that underwent discography and the control group at baseline and ten-year follow-up; and both groups underwent thorough assessment at baseline, one, two, five and ten years.

Surgery and Imaging Events

The primary outcome measures were the number of lumbar surgeries and the number of MRI and/or CT events.

Secondary outcome measures were medical visits for low back pain, serious low back pain events (pain score greater than five out of 10), serious disability events, and work loss over the six months preceding final assessment.

The study found that patients in the discography group had a significantly greater level of clinically important back problems than the control group.

Regarding surgery, there were no differences between cohorts at five years. But by ten years, a different pattern emerged. In the experimental group, there were six surgeries in 11 subjects vs. 4 surgeries in three subjects in the control group. The results were statistically significant.

There was a similar pattern regarding imaging events. By 10-year followup, patients in the discography cohort had 21 imaging events vs. 11 in the control cohort—again, a statistically significant difference.

Regarding secondary outcome measures, medical visits, CT/MRI examinations, work loss, and prolonged back pain were all more frequent in the discography group compared to control subjects, according to Stauff.

Stauff acknowledged that the study had some limitations. There was incomplete followup, as is common in long-term studies. “Out of 150 patients, 40 were lost to follow-up”... according to Stauff. This level of

follow-up is not uncommon in long-term trials. Those who completed follow-up and those lost to follow-up had similar baseline characteristics.

“We had attrition in our study cohorts that is typical for long term studies. It would have been nice to have more complete follow up in both cohorts, but we still feel the data is valuable especially given the similarity in the patients that were lost to follow up,” Stauff commented. Subjects in this study also may have been at heightened risk of spine problems. “Subjects in the study were taken from pools of patients who were at greater risk of degeneration [compared with the general public or usual patients in medical settings],” according to Stauff.

However, Carragee points out that patients with a history of spinal disc degeneration and psychological issues are common in spine care practices, and that this was not an unrealistic group to study.

[*Editor’s Note:* Some of the data from the new study by Cuellar et al. also were presented by Eugene Carragee at the 2011 annual meeting of the North American Spine Society. (see [http://www.thespinejournalonline.com/article/S1529-9430\(11\)00591-2/abstract](http://www.thespinejournalonline.com/article/S1529-9430(11)00591-2/abstract).) They were then held back for further analysis. The revised study will be published shortly.]

Disclosures: None declared.

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FDA on Epidural Injections

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there is no accurate, systematic gathering of evidence on their risks and benefits. The rationale for this hole in the regulatory system is not clear.

FDA Has Been Gathering Evidence on Serious Adverse Events Since 2009

Even though the FDA does not regulate epidural steroid injections, the agency is trying to assess evidence on adverse events related to them. Since 2009, the FDA has been gathering evidence on serious neurologic events associated with epidural steroid injections, according to a new report from Judith A. Racoosin, MD, and colleagues at the FDA. (See Racoosin et al., 2015.)

But because physicians report serious adverse events voluntarily—and sometimes just don't bother to submit accurate reports—the FDA evidence-gathering process is haphazard.

Serious Events Can and Do Occur

It is abundantly clear that serious and catastrophic events related to steroid injections can and do occur.

“Between 1997 and 2014, a total of 90 serious and sometimes fatal neurologic events were reported to the FDA Adverse Event Reporting System (FAERS), including cases of paraplegia, quadriplegia, spinal cord infarction, and stroke. (Compounded glucocorticoids used in epidural injections have been associated with fungal meningitis, but cases involving contaminated products were not included in the case series under consideration.) Potential causes of these adverse events included technique-related problems such as intrathecal injection, epidural hematoma, direct spinal cord injury, and embolic infarction after inadvertent intraarterial injection,” according to these FDA scientists.

Mandatory Warnings About Dire Events

In 2014, in response to these data, the FDA mandated that all injectable corticosteroid products carry warnings about potentially dire events: “Serious neurologic events, some resulting in death, have been reported with epidural injection of corticosteroids” and that the “safety and effectiveness of epidural administration of corticosteroids

have not been established and corticosteroids are not approved for this use.”

The agency determined that the class warning was warranted based on its analysis of FAERS cases and reports in the medical literature of serious neurologic events. The warning did not document differences in risk associated with various injection approaches (interlaminar, transforaminal, and caudal), locations of spinal injection (cervical, thoracic, lumbar, and sacral), or glucocorticoid formulations (solutions and suspensions), because the data suggested that each approach, location, and formulation was associated with some risk of neurologic injury, according to Racoosin et al.

Advice From an Advisory Committee of Experts

The FDA also convened an advisory committee meeting to get expert input on serious risks related to epidural steroid injections.

One key question for the committee was whether a contraindication was warranted to restrict the injection of steroids into the epidural space. Before and during the advisory committee meeting, the FDA received feedback regarding the scope of injection-related adverse events.

There was a wide range of opinions, from support for stronger labeling to arguments that the warning was too broad and should focus on particular approaches, spinal regions, formulations, or some combination thereof. Many advisory committee members expressed concern about the safety of cervical transforaminal injection of suspension glucocorticoid formulations and recommended that the FDA contraindicate suspension products for this use.

Some also thought that the FDA should modify its statement to say that the safety and effectiveness of the injections have not been established by the FDA.

Many observers suggested that the FDA should adopt the advisory committee's warning about the risks of cervical injection of suspension steroid formulas. However, the FDA has now rejected that recommendation—and will continue with its current warning about serious adverse events.

Not Enough Accurate Data About Rare Events to Support A Change in the FDA Warning

Racoosin et al. say there is not enough accurate information about the overall incidence of serious neurologic complications or of the

risks of particular formulas and modes of delivery to support any conclusive judgments.

“Without question, serious (sometimes fatal) neurologic events occur with epidural glucocorticoid injection. Given the large number of these procedures performed, these events appear to be rare; however, a population-based study would be needed to establish a valid estimate of their frequency. We find that available data do not currently support either a contraindication or a warning focused only on cervical transforaminal injection of suspension glucocorticoids. Although many experts think the risk is greatest with suspensions, the available data do not support comparative safety labeling implying that solutions are safer. Such labeling could encourage practitioners to use solutions, even though their relative safety and effectiveness remain an open question,” according to Racoosin et al.

They concluded the article by noting that some published studies support the benefit of epidural glucocorticoid injection, but others call that benefit into question.

“Patient selection may be the key to optimizing the efficacy of epidural glucocorticoid injection, and we encourage the medical community to work to identify the types of patients who might benefit most.”

[Editor's note: There has been a recent consensus process involving 13 specialty societies to identify the safest methods of epidural steroid injections and reduce the number of serious neurologic complications. (See Rathmell et al., 2015.) However, the article by Racoosin et al. in the *New England Journal of Medicine* indicates that the FDA has stopped short of endorsing many of these recommendations because of gaps in the evidence.]

Disclosures: None declared.

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Coming Soon:

- The Increasingly Vicious Opioid Overtreatment Crisis
- Balancing Patient Care With Societal Issues
- Opioids No Better Than NSAIDs for Acute Back Pain?
- No Indication That the Spine Field Has Reduced Excessive Care
- The Evidence on Marijuana as a Pain Treatment

Erratum

Three references were inadvertently left out of the article “Growing Furor Over Epidural Steroid Injections—And the Lack of Evidence Supporting Them” in the November 2015 edition of the *BackLetter*. (See *BackLetter*, 2015; 30(11): 121-130). The editors apologize for the omission. Here are the three references:

Chou R et al., Pain Management Injection Therapies for Low Back Pain, Technology Assessment Report, Agency for Healthcare Research and Quality, March 20, 2015; <http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0073206/>.

Chou R et al., Epidural corticosteroid injections for radiculopathy and spinal stenosis: a systematic review and meta-analysis, *Annals of Internal Medicine*, 2015; 163(5):373-81.

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Researchers Fool Themselves

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- draws a target around the biggest clump of bullet holes, and points proudly at his success,” according to Nuzzo.
- *Asymmetric attention.* Paying attention to, and rigorously scrutinizing, unexpected findings and giving expected findings “a free pass.”
 - *Just-so storytelling.* Concocting explanations after the fact “to rationalize whatever the results turn out to be.”

We All Need to Continually “De-bias” Ourselves!

Nuzzo suggests that scientists—and all people—need to continually de-bias themselves, by questioning their own findings and their own beliefs. As astrophysicist Saul Perlmutter, PhD, commented in the article, “Science is an ongoing race between our inventing ways to fool ourselves, and our inventing ways to avoid fooling ourselves.”

Some of the methods Nuzzo suggests include:

- *Devil’s advocacy.* Consider alternative hypotheses and test them against favorite hypotheses head to head.
- *Precommitment to a research plan.* Preplan and publicly declare a study plan—including data collection and analysis—before commencing a study. And do not deviate from the plan if expected results don’t materialize.
- *Team of rivals.* Invite academic or scientific adversaries to design and conduct a study together.
- *Blind data analysis.* This is the most complicated concept that Nuzzo presents. “Blind data analysis” is a common practice in experimental physics but is just beginning to be widely used in medical, biological, and social sciences. It is a way of blinding researchers to the progress of their own study analyses—so they don’t subtly alter the analyses to reach the conclusions they desire. (See “An Explanation of Blind Data Analysis” on page 135.)

Disclosures: None declared.

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THE **BACK**PAGE

The Myths of Low Back Pain Live On

In 1998, Richard A. Deyo, MD, published a widely cited list of myths regarding low back pain—touching on its nature, prognosis, diagnosis, and treatment. These myths have had remarkable staying power and are still being studied today. Here are the seven myths he identified in *Scientific American* (August 1998:49–53):

1. If you have a slipped disc, you must have surgery.
2. X-rays and newer imaging tests can always identify the cause of your pain.
3. If your back hurts, you should take it easy until the back pain goes away.
4. Most back pain is caused by injuries or heavy lifting.
5. Back pain is usually disabling.
6. Everyone with back pain should have a spine x-ray.
7. Bed rest is the mainstay of therapy.

There was widespread hope in the late 1990s that societies and healthcare systems would correct misconceptions about low back pain, restrain its treatment, and improve its long-term outcomes. However, despite an enormous effort, many modern societies have largely failed in this quest. By most accounts, Deyo's myths are alive and well across much of the modern world.

The latest evidence of this comes from Ireland, where Sudarshan Munigangaiah, MD, and colleagues asked 500 individuals about these myths at a Galway hospital.

Of the 500 responders, 59 people (11.8%) answered none of the questions correctly. Fifty-six (11.2%) answered one question correctly, 106 (21.2%) answered two questions correctly, 85 (17%) people disagreed with three

myths, 88 (17.6%) disagreed with four myths, 55 (11%) people answered five questions correctly, and 34 (6.8%) answered six questions correctly.

Therefore, only 17 of the 500 people (3.4%) disagreed with all seven of the myths.

"The findings from this study suggest that public health information regarding low back pain is inadequate and has not affected attitudes to low back pain in an Irish population," Munigangaiah et al. concluded. (See *European Journal of Orthopedic Surgery and Traumatology*, 2015 [Epub ahead of print]; PMID:26346961.

review by R. Andrew Moore and colleagues.

The researchers looked for clinical trials of NSAIDs for neuropathic pain conditions lasting two weeks or longer that compared NSAIDs to a placebo or to an active treatment. They found only two studies with a total of 251 subjects suffering from chronic back pain with a neuropathic component or postherpetic neuralgia. They could not find any evidence that NSAIDs delivered significant pain relief.

So patients and physicians are flying blind in this area. "There is no evidence to support or refute

physical conditions (55.3%), and mental disorders (35.0%)," according to Michael Von Korf, PhD, and colleagues. (See *Pain*. 2005 Feb; 113(3):331–9.)

The offices of spine specialists as well as primary care providers are filled with people who have both physical and psychological problems. And healthcare providers have to treat the whole patient. But where do they find the guidance to do so?

A new study suggests that people with psychiatric problems have been systematically excluded from studies of low back pain.

"In a sample of 400 highly-cited randomized trials across 20 common chronic disorders, we found that half had eligibility rules that prevented people with psychiatric problems from enrolling," noted lead author and Stanford psychiatrist Keith Humphreys, MD, in a Stanford University blog. (See <http://scopeblog.stanford.edu/2015/09/16/how-people-with-mental-illness-get-left-out-of-medical-research-studies/>.)

Seventy-five percent of the back pain studies they looked at had systematically excluded people with psychiatric disorders.

"People with conditions such as depression, anxiety disorders, alcohol problems and schizophrenia thus may face some added risk when they seek health care: People like them were often left out of the research that tells doctors what medical treatments work," according to Humphreys.

Including patients with psychiatric problems in key studies will be a challenge to researchers. They may be more difficult to study and follow-up. However, there is no other way forward than to make clinical trials more inclusive. (See *Journal of Psychiatric Research*, 2015; 70:28–32.)

The BackPage Online

See free online-only BackPage briefs at www.BackLetter.com. This month:

- Do People With Back Problems Have Spines That Resemble Those of Chimpanzees? Two Views
- Should Older Individuals Take Calcium Supplements to Prevent Spine, Hip, and Other Fractures?
- FDA Adds Patient Advisors

NSAIDs for Neuropathic Pain: Flying Blind

Neuropathic pain—pain related to injury or disease of the nervous system—is all too common in various spinal conditions. Sciatica related to a disc herniation would be an example.

The first line of treatment for neuropathic pain is often non-steroidal anti-inflammatory drugs (NSAIDs). More than a dozen NSAIDs are available for prescription use in the United States, with ibuprofen, naproxen, and aspirin available in reduced-strength, over-the-counter formulations.

But is there solid evidence from clinical trials to support the use of NSAIDs for neuropathic pain conditions? The answer is no, according to a recent Cochrane Collaboration

the use of oral NSAIDs to treat neuropathic pain conditions," the study found. (*Cochrane Database Systematic Review*, 2015; 10:CD010902 [Epub ahead of print].)

People With Psychiatric Disorders Excluded From Back Pain Research

Chronic back and neck pain have a strong overlap with psychological or psychiatric disorders.

For example, a 2005 study found that 35% of people in the United States with chronic spinal pain had a comorbid mental disorder such as anxiety or depression. "The vast majority (87.1%) of people with chronic spinal pain reported at least one other comorbid condition, including other chronic pain conditions (68.6%), chronic