Pain Medicine

Pain Medicine 2011; 12: 1361–1375
Wiley Periodicals, Inc.

A Physician-Driven Solution—The Association for Medical Ethics, The Physician Payment Sunshine Act, and Ethical Challenges in Pain Medicine

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Disclosure: Neither Dr. Charles Rosen nor Dr. Danielle Perret receives any compensation from any medical manufacturer.

Abstract

The practice of contemporary pain medicine is laced with a number of significant ethical challenges. Considerable difficulties include the overutilization of interventional procedures, the application of under-evidenced treatment modalities, and potentially superfluous opioid prescribing. As with many other fields in medicine, including orthopedic surgery, relationships with industry are both common and pervasive, and influence our medical practice through education, publications, and research. This article highlights these ethical challenges and broaches several physician-driven solutions: The Association for Medical Ethics, the Physicians Payment Sunshine inspired by it, and other non-legislative reforms are discussed.

Key Words. Ethics; Conflicts of Interest; Lumbar Disc Replacement; Industry; Association for Medical Ethics; Opioids; Chronic Pain; Orthopedics; Physician Payment Sunshine Act

The United States constitutes only 4.6% of the world's population but consumes 80% of the global opioid supply and 99% of the global hydrocodone supply [1]. The history of opioid prescribing and its rapid recent increase for chronic noncancer pain in the United States is highlighted in this article as the consequences of that—including costs to health care and society, and morbidities and mortalities. Overall, several other problems also plague pain medicine. Namely, there is frequent application of interventional techniques to clinical practice with minimal evidence-based literature support, overutilization is rampant, and relationships with industry can be ethically problematic. Some pain physicians, perhaps driven by the pressure to increase revenue, may perform an excess number of procedures. Some, perhaps in desperation to palliate pain and suffering, may use a new technique before efficacy is proven. They may invest in a radiology or ambulatory center to which they refer patients. Some pain physicians may be lax in the employment of diagnostic block guidelines or in the prescribing of opioid analgesics. All of these scenarios represent significant ethical and legal challenges for the pain physician.

To balance any finger-pointing at the contemporary pain physician, the reader should consider some of the other obvious challenges of pain medicine [2]. In a culture that values objectivity and the quantifiable such as physical examination findings, there is an inherent and frustrating subjectivity to pain assessment. Additionally, although American medicine traditionally views the mind and body as separate entities, pain truly defies this concept, making it difficult both to assess and to manage. Pain patients are also often "difficult" in terms of their social characteristics and medical and psychiatric comorbidities. For treatment options, there are large gaps in the available evidence. Evidence to treat pain does point toward multidisciplinary and multimodal approaches, but these approaches seem to be at odds with the current bias of our medical culture toward efficacy and efficiency and oftentimes profitability. Additionally, in pain medicine, there are many clinical uncertainties. Almost all treatment options, including opioid analgesic medications and interventional treatments, have inherent and significant risks. Finally, as noted by Crowley-Matoka et al., "In a system that prioritizes both efficacy and efficiency, pain patients—for whom neither diagnosis nor treatment decisions may be clear cut—are all too often a poor 'fit.' Chronic pain, in particular, is the source of much conflict between physicians and patients precisely because it so often defies biomedical efforts to 'fix' it, while consuming considerable time, effort and resources in the process. Immersed in an increasingly evidence-based medical culture, physicians often feel at a loss, uncomfortable, or perhaps even vulnerable in the

face of the considerable clinical uncertainty often surrounding pain management" [2].

Interventional Pain Management

Interventional pain management is defined by the Medicare Payment Advisory Commission as "minimally invasive procedures including percutaneous precision needle placement, with placement of drugs in targeted areas or ablation of targeted nerves; and some surgical techniques such as laser or endoscopic discectomy, intrathecal infusion pumps and spinal cord stimulators; for the diagnosis and management of chronic, persistent or intractable pain" [3]. Regarding these procedures, it is expected by the larger medical community that the practice of interventional pain is based on evidence-based medicine (EBM). The ethical challenges that face the pain medicine practitioner are the minimal availability of EBM, its sometimes inappropriate use, the overemployment of procedures as a substitute for clinical diagnosis, the overemployment of procedures to increase revenue, the adoption of experimental procedures prematurely by pain physicians, and a lack of a true standard of care within the interventional world.

Interventional Procedures

In a review of a particular closed case, Helm et al. demonstrated that even among expert reviewers, there is no one true method of performing any one particular interventional procedure [4]. The authors mention the dilemma of "standard of care" in the pain medicine world. In medical–legal jargon, "standard of care" refers to any treatment that is considered an accepted method by the majority of physicians in that field and is a minimum standard of care below which is considered malpractice. Helm et al. argued by tackling a particular legal case where three experts could not agree on standard of care that standard of care in medicine is an evolving concept: "there does not exist currently any one way of doing [pain] procedures" [4]. The interventional pain ethical challenge begins with this concept: that there may be no true "right" or "wrong." However, this stance is also commonly used to justify any treatment even if it falls below the standard of care.

Interventional pain management has been criticized for lack of a significant sturdy body of evidence, and few pain physicians would argue this premise; not surprisingly, this lack of EBM probably explains the general lack of standard of care. There is, in general, fair (or poor) evidence for established techniques, and this is coupled with a near constant influx of new techniques, which, for the most part, lack evidence. Good evidence is required, therefore, in order to balance the continued unopposed growth of new complex interventional procedures. Without this, patient safety may be at stake. Additionally, from an economic viewpoint, pain interventionalists will inevitably contribute to the increasing cost of U.S. health care. Manchikanti et al. described the full impact of interventional pain management in these terms: overuse, abuse, waste, and fraud; inappropriate application of EBM; and organizational issues related to multiple societies [5].

The terms "overuse," "abuse," "fraud," and "inappropriate" paint an overall vision of profound corruption, which may seem harsh when one considers the counterarguments. Chronic pain does have an immense economic impact. As pointed out by Freburger et al., there is an annual increase of 11.6% in the overall prevalence of low back pain [6]. Additionally, literature reveals that chronic pain is indeed a chronic issue: chronic pain lasts for months to years with tendencies to recur and relapse [5,7]. For the majority of pain patients who are not surgical candidates, the evidence for nonpharmacologic modalities (physical therapy, heat and cold modalities, transcutaneous electrical nerve stimulation, acupuncture, chiropractic care, traction, etc.) is also poor. The evidence for pharmacologic modalities is similarly poor: the evidence for opioid analgesic use, for example, in the setting of low back pain is extremely limited [8–12]. With growing numbers of patients with chronic pain seeking treatment, does lack of evidence across the board translate to justification to ignore the problem? The ethical impetus to palliate pain and to offer treatment is a strong one that deserves additional consideration. With this in mind, Bogduk and Fraifeld admitted to the lack of solid good evidence in the form of randomized controlled trials, arguing that these are too expensive and difficult to produce in pain medicine [13]. Randomized controlled trials are expected to compare an experimental variable with placebo and/or with standard of care; for interventional pain, both represent inherent challenges. The authors propose, therefore, implementation of observational evidence to perhaps replace randomized controlled trials, to justify interventional pain treatments. To complicate and foster this argument, Manchikanti et al. point out reverse discrimination: good EBM is sometimes inappropriately applied to deny interventional procedures when "lack of [randomized controlled trial] evidence" is incorrectly interpreted as "evidence for the lack of effectiveness" [5,14,15].

Among other issues in the ethical–legal world of interventional pain medicine, Benyamin et al. highlighted the "explosive growth of physicians performing these procedures without training" [16], citing that further delineation of competency criteria is needed in this young field. Given the minimal criteria (a quantity log of all procedures and cases only) for competency required by the Accreditation Council of Graduate Medical Education and given the number of freestanding nonaccredited fellowship training programs (that seemingly lack regulation), it is no wonder that several agencies are seeking to establish pain medicine as an independent residency. Regardless of whether pain medicine remains a fellowship training program or is converted into a full residency training program, however, competency assessment should be instituted promptly and more fully. Competency assessment, not training type, is perhaps the underlying problem.

Additionally, Benyamin et al.'s discussion of the validity of diagnostic blocks is worth mentioning. Diagnostic facet joint nerve (medial branch nerve) blocks have moderate to strong evidence in the diagnosis of axial low back pain based on multiple studies using the strict criteria of 80% analgesia post-procedure, with the ability to perform previously painful movements [17–22]. Many physicians, however, use a 50% relief criterion (or less) or only use a single diagnostic block, which may underscore the validity of the procedure. The employment of more strict criteria will lead to improved diagnostic efficacy and "less misutilization of the healthcare system" [16]. In this case of facetogenic pain diagnosis, using a criteria of >80% relief and use of a double diagnostic paradigm lead to a diagnostic decrease in prevalence from 73% to 53% with one block and a decrease to 31% in double diagnostic blocks [16]. Improved diagnosis, therefore, may lead to less unnecessary neurolytic (radiofrequency) procedures, as well as other costly (and potentially complicated) therapeutic interventions.

The secondary interest of practice profit may play a large role in interventional pain management [23]. By its very nature, the traditional fee-for-service practice design, for example, incents the physician to overutilize potentially lucrative procedures [24]. Furthermore, when there are several equal choices, physicians may unconsciously resort to the option that most favors their own interest [25]. The dilemma of practice profit is well-articulated by Schofferman [23]: on one hand, physicians are entitled to reasonable profit, and the benefits of profit are many, including improved and more efficient patient care, better medical product development, and better outcomes with more satisfied patients. Physicians, however, are not entitled to unreasonable profit. With the modern problems of shrinking reimbursements, greater patient care-related paperwork (non-reimbursed time), higher overhead, and more time demands, the following unreasonable measures may occur. Physicians may limit their practice to only profitable patients; they may refuse to provide pharmacologic pain management or nonpharmacologic noninterventional pain management such as rehabilitation care. Physicians may also perform additional unwarranted interventional procedures on patients. Additionally, many pain physicians may invest in an ambulatory surgery center to which they refer patients [23].

Orthopedic Surgeries

Interventional procedures present ethical challenges for the orthopedic surgeon as well. The Charite disc replacement study might serve the reader as an example of the profound conflicts of interest regarding medical research and medical practice patterns and their relationships with industry. The Charite disc (DePuy Spine, Raynham, MA, USA) was approved following a randomized prospective study that compared 205 disc replacement patients with 99 control patients [26]. Seventy-six subjects (27% of experimental patients) were labeled as "training" patients and received the disc replacement but were excluded from the final results for efficacy; these patients represent the initial complications that usually occur with a new procedure. The 99 patients in the control group underwent a procedure that had a 60% failure rate and was universally out of favor when the study commenced [27]. As this was a noninferiority study, the experimental group had a very low bar to clear for approval. Major end points of success were based on radiographic appearance and lack of reoperations or neurologic injury, among others. Continued pain, requiring daily narcotics, was not considered a major end point of success or failure, although the overriding goal of the operation was to essentially relieve back pain. This is significant because two-thirds of experimental patients remained on narcotics after 2 years [28]. At the Food and Drug Administration (FDA) approval hearing, comments critical of the study design were made by the FDA statistician, who noted that slight changes of certain statistical parameters may have to lead to non-approval of the device [29]. This study is wrought with inherent bias: a majority of the authors of the study were paid consultants of the company making the device, hence there were highly vested internal interests to have the device approved for use in the United States. In general terms, studies of this nature with this type of bias may result in the widespread use of medical products or of interventional procedures that are not independently evaluated, do not improve patient outcomes compared with other treatments, and which may be dangerous.

Some orthopedic surgeries may also have limited evidence. Although lumbar spine fusions, with or without laminectomy, have definite indications (structural instability, fractures, tumors, and scoliosis), many of the 300,000 fusions performed each year in the United States are performed solely for degenerative disc disease. Although surgical success and outcomes are excellent when surgery is performed for an indication of structural instability such as spondylolysis, spondylolisthesis, fractures, tumors, or scoliosis, the results of the few long-term prospective, randomized controlled studies—Level 1 evidence—evaluating fusion for degenerative disc disease compared with nonoperative care indicate that nonoperative care may be best in these cases [30–33]. However, the amount of money gained by device manufacturers is so great that industry-sponsored research performed by physicians on their payroll to stretch the indications for fusion is irresistible. For example, pedicle screws cost up to $2,000 each, intervertebral cages cost $4,000, rods cost $1,000 each, and usually, a unit of manufactured bone graft substitute such as bone morphogenetic protein (such as Infuse) costs $3,000–5,000; together, this lineup results in tremendous profits. It is careful analysis of both the level of evidence presented—usually Level III or less—as well as the full financial disclosure of the authors and funding that would better serve the medical community in deciding whether fusion surgery is indicated or not. At the current time, huge amounts of health care dollars are wasted on fusions performed for degenerative disc disease alone for which there is scant proven evidence of efficacy.

For technology-based orthopedic and pain medicine, it is perhaps more important to demand guidance on the how, why, when, and what technology rather than simply ask whether or not technological developments should be used [34]. Technology "demands that we become more stringent in understanding its use, limitations, and delimitations in specific rather than purely generalized contexts" [35]. As pain medicine is a palliative practice aiming to relieve suffering, the guidelines must not be too stringent to deny the physician the ability to account for and interpret the intricacies and variables of each patient's clinical encounter; this "art" of medicine differentiates pain management from mere technology. Somehow, in this amalgamation of the humanistic art of medicine and interventional technology, we need to balance the goals of pain reduction and improvement in function and quality of life "using the best available evidence in the most cost effective way" [16]. Right now, we have many excuses: that good EBM is not warranted or that observational evidence will instead suffice, that guidelines are mere suggestions, and that the lack of standard of care means the freedom of lack of regulation as does the lack of competency assessment. In order to avoid being labeled as a culture with excuses, we can work harder to erase the excuses that exist. We can also remind our medical colleagues that EBM does not equal randomized controlled trials alone; "EBM is the integration of the best research evidence, clinical expertise, and patient values as the basis for medical decisions" [36]. Additionally, as Weiner and Levi suggested, physicians should always simply provide the treatment that is best supported by the available evidence [37]. The treatment should be commensurate with the patient's values and desires, and if everything else is equal, the treatment with the least risk and lowest cost should be the one provided; physicians should periodically critique their own practice outcomes and be willing to change things if required. By following the aforementioned values, interventional pain medicine can be practiced in a more ethical manner without extraordinary effort.

Opioid Prescribing for Chronic Pain

There is no doubt that undertreating pain violates ethical principles [38]. There is also no question that opioid analgesics play a vital role in the management of acute postoperative pain and cancer-related pain. More recently, opioid analgesics have been promoted, chiefly by pharmaceutical companies, for use in the arena of chronic pain treatment. In chronic pain practices, as many as 90% of patients are reported using opioids for analgesia [39,40]. The pharmaceutical industry has also been successful in decreasing prescribers' concerns regarding chronic opioid use in the community [41]. The appropriateness of this extension of opioid prescribing remains unclear. As we transcend the "Decade of Pain Control and Research" (as the years 2001–2010 were declared by the U.S. Congress), and as hospitals and outpatient clinical offices alike have implemented pain as the "fifth vital sign," and as we continue to focus on ensuring that inpatient and outpatient pain is adequately treated, what are the consequences of the growing number of community patients taking opioids? A 2010 commentary from the British Medical Journal entitled *Bad Medicine: Pain, Ignorance, Opioids and Bliss* warns that contemporary pain medicine is likening to the Victorian era—when nearly everyone took "tincture of opium" [42]. Certainly, in the United States, half of the patients who took opioid analgesics in 2001 were taking long-term prescription opioids in 2005 [43]. Additionally, in the last decade, opioid prescribing has increased significantly for patients with chronic pain [44,45]. In many instances, physicians may be prescribing chronic opioid analgesics for the treatment of psychosocial stress, anxiety, insomnia, and/or depression in lieu of somatic or visceral pain. In one of the author's (DP) own experiences in an academic pain practice, many patients on long-term long-acting opioid analgesics for many apparent nonpain diagnoses have been referred for continuation of care. Referrals also often include patients on chronic long-acting opioids for the treatment of fibromyalgia, a diagnosis where the use of opioid analgesics is extremely controversial and usually not recommended [46]. Finally, for this broad population that is now on chronic opioid therapy, there exists an important question: do most pain clinics or community prescribers have the multidisciplinary resources—the physical therapists, pain psychologists, and administrative support staff—needed to adequately address chronic opioid patients' needs?

When one considers the history of both ancient and modern medicine, opioid analgesics have been on a roller coaster ride. Ballantyne and Fleisher pointed out that prior to the 20th century and throughout most of medicine, cure of disease was so unusual that symptom control and the palliation of suffering became the major roles of the physician; opioids, of course, were key players in this role and were oftentimes freely dispensed [47]. International drug regulations that came into being in the 20th century were devised to control the import, distribution, and trade of narcotics but also had the effect of forcing physicians to self-control the prescribing of opioids. Opioid prescribing then became severely limited. Physicians and patients both feared opioid addiction in an exaggerated fashion; clinicians also regularly feared loss of license or censure secondary to opioid prescribing. Together with the "criminalization of opioids," both acute and chronic pain were undertreated, and patient care, by the traditional ethical standard of benevolence, was sub-adequate. The situation was so dire that activism eventually ensued, and finally, after many years of political lobbying, opioid prescribing was reinvigorated—so much that it was extended into the treatment of chronic pain [48,49]. This was then followed by the era of patient-centered care and patient satisfaction, which continues today.

Patient satisfaction, fortunately or not, now plays a major role in health care. The Joint Commission on Accreditation of Hospitals added pain intensity measurement and assessment to its list of other quality measures to assess health care outcomes (after concluding without consulting EBM that acute and chronic pain are major causes of patient dissatisfaction in the U.S. health care system) [50]

with the unintentional, perhaps unhealthy, consequence that opioid prescribing increased dramatically [51]. Do clinicians now feel threatened to prescribe opioids because they are judged by patient satisfaction outcomes that document pain scores? As Ballantyne and Fleisher eloquently addressed the issue: "Here the moral issue is whether prescribing opioids to drive up patient satisfaction metrics is justified" [47].

The same authors suggest reasons to challenge the idea that opioid prescribing is always justifiable in the chronic pain setting of non-severe pain—mild to moderate in intensity—or with a personal or family history of addiction or drug abuse. However, a study by Passik et al. found that patients with a history of substance abuse were less likely to display aberrant drug-related behavior than someone without such history [52] and that a patient's refusal to cooperate with non-opioid analgesics and with nonpharmacologic pain therapies [47] may be reasons to avoid opioids. In this era of patient-centered care and patient-directed decision-making, however, the patient may not agree with the clinical decision to avoid opioids. This presents a profound dilemma for the modern pain physician who seeks to comply with the contemporary patient-centered care vision.

The Risks and Benefits of Opioids in the Chronic Pain Setting

Many physicians also still believe that opioids, except in the context of high-dose monotherapy, remain the answer. They would perhaps argue that development of safer analgesics and safer methods of controlling drug-related adverse events is where improvement is needed. There are rational reasons to use opioids in the setting of chronic pain because some chronic pain conditions respond to opioid therapy and because there are, indeed, risks to the undertreatment of chronic pain. These risks include the following: fatigue and decreased exercise tolerance [53]; mood changes and an increased stress response, including depression, suicidal thoughts, anxiety, and fear [54–56]; sleep disturbances and insomnia [57]; disability [56]; and obesity [58]. To balance the argument, one may reply that there are risks to opioids, especially regarding the side effects of chronic opioid use. These include the inevitable development of dependence, as well as sedation, constipation, endocrine effects, and even hyperalgesia—although the clinical significance of opioid-induced hyperalgesia (OIH) remains uncertain [59]. Opioids may be tumorogenic [60], and there may be significant cognitive effects of opioids in chronic noncancer pain [61]. There are actually few long-term studies of opioid-tolerant patients with chronic noncancer pain (and breakthrough pain) that monitor adverse opioid-related events. Adverse events recorded during a recent study (long term = 18 months) involving fentanyl buccal tablet as a breakthrough agent occurred in 88% of patients [62]; an observational study on oxycodone use in the chronic noncancer pain population (long term = 3 years) also recorded adverse events in 88% of patients [63]. Although not all adverse events are opioid-related, these numbers still resonate loudly.

The ethical dilemma in the prescribing of opioids for chronic pain also includes the risk or cost to society as a whole. Ballantyne and Shin argued that opioid use for chronic pain comes at a high price to society because the goals of treatment are not met (they argue that opioid therapy typically provides only marginal benefit in the setting of chronic pain) [64–67] and because opioid misuse, abuse, and opioid-related deaths increase with increasing opioid prescribing practices [68–71]. As an example, the number of individuals abusing controlled prescription drugs in the United States increased 94% between 1992 and 2003 [72]. When one considers diversion data—in 2007, more than half of those taking pain relievers for nonmedical purposes obtained the drug from a friend or relative [68]—one can begin to appreciate the true cost to society. If the goal of pain medicine is to balance the opioid pendulum, the pendulum arm must avoid going too far toward widespread use and too far toward avoidance, which is a factor even in fearful dying persons. Proper balance requires full risk stratification, and denying opioids to some patients with chronic pain may, in some cases (or in many cases), be ethically justifiable [47]. The stratification should also consider the available evidence. The evidence for opioid analgesic use specifically in the setting of low back pain, fibromyalgia, or daily headache, for example, is very limited or the evidence does not show a clear benefit [8–12]. As pointed out in *Research Gaps on Use of Opioids for Chronic Noncancer Pain: Findings From a Review of the Evidence for an American Pain Society and American Academy of Pain Medicine Clinical Practice Guideline*, recently published guidelines recommend "judicious use of opioids in appropriately selected patients . . . who have not responded to other treatments and analgesic medications" [73]; not surprisingly, most of the guidelines were developed by consensus alone due to the lack of substantial evidence [74–78]. The current national force, despite this lack of evidence, is expansion of opioid prescribing, not containment.

Ultrashort-Acting Fentanyl

To illustrate this point, consider the agenda to expand fentanyl buccal tablet use, an ultrashort-acting high-potency opioid analgesic, which is currently indicated for breakthrough pain in cancer, to the noncancer chronic pain patient. The studies that demonstrate that the fentanyl buccal tablet can be "safe" and "effective" in the chronic noncancer pain patient population are sponsored by the pharmaceutical manufacturer [61,79].

These studies are dependent on the ambiguous idea of breakthrough pain itself. Breakthrough pain is defined as a transient pain flare that may occur in patients with otherwise stable, persistent pain controlled with long-acting around-the-clock opioids [80,81]. The concept that breakthrough pain even exists in the noncancer pain population, however, is highly debated [82]. Breakthrough pain was

originally described in the cancer patient population and is generally accepted as a therapeutic challenge in the treatment of cancer pain. The International Association for the Study of Pain task force on cancer pain, however, reported that despite its widespread acceptance, the definition of breakthrough pain varies widely by country and by physician specialty; the definition even varies widely among cancer pain specialists [81]. The definition of breakthrough pain may represent a myriad of occasions, including underlying disease progression, OIH, long-acting opioid underdosing, long-acting opioid end-of-dose failure, opioid tolerance, and probably most common, pain exacerbated by voluntary movements or movement-evoked pain. As movement-evoked pain appears to be less responsive to opioid analgesics, breakthrough pain in the chronic noncancer pain patient population may represent the limited efficacy of opioids in the chronic pain setting [83]. A recent publication by Manchikanti et al. summarized the evidence, however, and concluded that "there is no significant evidence of any type of breakthrough pain in chronic noncancer pain" [84]. The reader might therefore question the use of breakthrough pain medication in chronic noncancer pain. For those that continue to argue that breakthrough pain exists, its nonspecificity makes prescribing difficult: pain medicine guidelines call for individualized patient assessment when prescribing opioids, but is this actually possible when breakthrough pain is so nonspecific? As suggested by Nicholson, do physicians encourage patients to focus on their pain by the increased clock watching that "breakthrough" prescribing might require or promote [85]? To further these arguments, the available evidence, via results of a 2009 clinical study review published in the *British Journal of Anaesthesia*, suggests that the treatment of breakthrough pain with short-acting immediate release (IR) opioids is of no additional benefit in terms of long-term analgesic efficacy [86]. The authors do suggest, however, that because breakthrough pain peaks within about 10 minutes [87–89] while short-acting IR opioids have an onset of action of about 30–60 minutes [90], ultrashort-acting fentanyl formulations are an argument worth considering.

Ultrashort-acting fentanyl formulations do show efficacy for the short-term treatment of breakthrough pain in both cancer pain and noncancer pain patient populations [90–94]; these studies do not address any long-term impacts of the short-acting breakthrough pain agent, however, such as those that may affect the long-term analgesia of long-acting opioids. Currently, there is mixed evidence on ultrashort-acting fentanyl. To address the inherent concerns of breakthrough fentanyl, a recent study indirectly promotes fentanyl buccal tablet for breakthrough pain because it shows that there is no sufficient evidence, consistent with previous findings [44], of a difference in abuse liability among different oral opioid formulations, and there is no apparent relationship between higher opioid doses and aberrant drug-related behavior [52] (however, the population studied was highly select and highly screened and would not likely translate directly into the routine clinical practice setting). Although a recent *Journal of the American Medical Association* publication does show a relationship between higher opioid doses and risk of overdose, patients receiving both regularly scheduled opioids and as-needed opioid analgesics, although ultrashort-acting fentanyl was not specifically studied, were not found to have an increased risk of overdose (after adjustment) [95].

There is, however, evidence that suggests that fentanyl-related misuse and abuse is already a serious issue—even without the addition of ultrashort-acting fentanyl. Fentanyl-related emergency room visits increased more than 50-fold from 1994 to 2002, a rate much higher than prescription increases [96]. In a long-term noncancer-related breakthrough pain study on fentanyl, there were two reports of nonfatal accidental overdose and one additional report of fatal diversion when the spouse of a patient died [62]. In addition, there have been several post-marketing reports of serious adverse events related to improper patient dosing or selection of non-opioid-tolerant persons [97]. As Markman stated in his 2008 editorial, *Not So Fast: The Reformulation of Fentanyl and Breakthrough Chronic Non-Cancer Pain*, "The tradeoff of uncertain benefit for increased risk seems hardly worth it for patients, clinicians, and society as a whole . . . Good faith and reasonable judgment in the prescription of opioids, as called for in consensus guidelines, must be grounded in clinical science if the benefits and risks are to be weighed. In the absence of appropriately conducted outcome studies, more opioid use will likely occur in the patients most at risk for harm" [82]. The pharmaceutical industry might respond differently: "If all possible questions had to be answered for every drug prior to approval for marketing, no drug would ever be brought to the market . . ." [98]. The bottom line is that the current mixed evidence needs to be sorted out so that physicians and patients both have a clearer understanding of the indications and limitations of this next generation of high-potency opioids. In the end, however, physicians are well aware that rapid onset opioid formulations are outstandingly addictive (with rapid onset of euphoria) and that injected opioids have a greater potential for addiction than ingested formulations. While it would not be ethical to test the addictive potential of ultrashort-acting fentanyl, emergence of this medication will likely have a predictable consequence—a higher rate of problematic use than other slower onset preparations. Only the future will tell the fate of ultrashort-acting fentanyl. Waiting to witness the predictable future, and allowing the development of the problems that will likely result from more widespread use of a high-potency, ultrashort-acting opioid, however, may not be ethical in and of itself.

Diversion Control Programs

At the time of the writing of this article, the FDA Advisory Panel, in a 25–10 vote, rejected the agency's risk evaluation and mitigation strategy (REMS) for long-acting opioid pain medications [99]. REMS, particularly for drugs with abuse potential, is a regulatory technique for dealing with the anticipated risks of new medications [98]. In theory,

premarketing risk assessment, pharmacovigilance, and risk minimization action plans (which may include physician and public education and targeted promotion, for example) have a goal to enhance access to appropriate drugs for the population that will derive most benefit while minimizing misuse, abuse, and overdose [98]. Interestingly, an early review of REMS, published in 2008 by three authors, all of whom have had past or have current affiliations with industry, stated that "The current epidemic of prescription opioid abuse is due, in part, to the large amount of opioid medication used per capita in the United States. Part of such overuse, when it occurs, is due to conflicts of interest" [98]. The article cites that even in high-risk populations, implementation of diversion-control programs can reduce misuse, abuse, diversion, and addiction by as much as 50% [100,101], but those conflicts of interest may limit program implementation. The first broad risk management program, developed largely by the manufacturer of OxyContin (Purdue Pharma, Stamford, CT, USA) after many rural area deaths were reported in the early 2000s, included both active and passive surveillance systems, media monitoring, educational training programs for health care providers, law enforcement, securing the supply chain efforts, and the provision of resources to communities and schools who suffered from local abuse problems. Unfortunately, it is not known if this seemingly comprehensive risk management program has had any effect on the abuse and diversion of OxyContin [98]. Only the future will determine the actual effectiveness of similar broad-based risk-management programs such as REMS. Due to potential inherent conflicts of interest, however, is it inappropriate for drug companies to be telling physicians exactly how to prescribe drugs? Moreover, should the drug companies be formulating their own REMS programs? The reader may be dubious as to REMS' purported conflict-free power to change negative outcomes. For now, the FDA committee agrees that the REMS plan is inadequate for curbing the abuse of prescription pain medications [99].

Relationships with Industry

An excellent 2008 review by Schofferman and Banja highlights contemporary conflicts of interest in pain medicine [102]. In the context of industry, these conflicts involve consultation work, editors and journals, continuing medical education (CME), research, and investments.

Consultation Work

The industry may require expert consultants to aid in product development, but these relationships should be fully disclosed. Schofferman and Banja noted that in many instances, "consultation" work is a simple disguise for "gifting," however. Physicians might be selected as consultants because they are or have the potential to become high users of a drug or product or perhaps because they are highly visible successful academicians and because the company wishes to link the physician's reputation to a product [23,103].

Journal Editors and Societies

Great influence on the practice patterns of physicians is exerted by the medical journals that physicians read and by the practice guidelines of the physicians' professional societies. These sources of information also form the basis for governmental guidelines for Medicare, Veterans Affairs hospitals, state workers' compensation boards, and private insurance carriers. Most people, including physicians, assume that editorial review is impartial and unbiased, which is why peer-reviewed literature is often followed in its recommendations. There is a similar trust of the practice guidelines by professional medical society committees.

However, this trust may be misplaced when one considers the often enormous personal fortunes that may be in the balance for editors and society officers. For example, in 2009, it was uncovered that the editor of a major journal in spine surgery had received $19 million over 6 years from a manufacturer of spinal implants; the manufacturer both advertises in the journal as well as has published research on its products in the same journal [104]. In 2008, the president-elect of the American Psychiatric Association, the most influential psychiatric society in the United States, was under scrutiny for not revealing fully that he owned $6 million in stock of a drug company that he founded that was concurrently applying for FDA approval of a new drug [105]. It is unreasonable that physicians in such positions of influence can be unbiased while at that same time, receiving huge sums from medical companies. Most bias is unintentional, however, and the recipients of financial compensation may not have any intention of being biased. Yet, it does not seem reasonable to assume that safeguards can prevent all of the forms of unintentional bias that can occur when someone is in such an influential position. Full financial disclosure must be present so as to allow subscribers of any journal, or members of any medical society, to decide for themselves if bias is a possibility. Going one step further, the Association for Medical Ethics (AME) has Ethical Rules of Disclosure that suggest that no one who is in an editorial position or a professional society officer should exceed $50,000 in money received from the industry (http://www.EthicalDoctor.org).

CME

Industry-sponsored CME is a powerful tool: it has been estimated that for every $1 spent by industry on CME programs, a return of $3.56 in revenue back to the industry is the outcome [106]. In 2008, over $1.04 billion was spent by medical manufacturers on CME as cited by the Accreditation Council for Continuing Medical Education. The industry funded approximately 60% of CME activities that year [107]. Private companies often arrange free CME for physicians, but funding is actually paid by medical manufacturers, and secondary interests can therefore threaten objectivity. Although CME is supposed to be without industry bias, private companies that supply CME with industry monies are actually accredited by the

American Medical Association to do so. A former editor-in-chief of the *New England Journal of Medicine*, Marcia Angell, calls this bias "a case of the fox not only guarding the hen house, but living in it" [108].

Mission statements of medical manufacturers often are inspirational, claiming a goal of improving health care for all. Yet, their legal and fiduciary duty is to make a profit, not to educate physicians but to market to them to sell their product. It should be clear that industry-funded CME is aimed at marketing, and industry-funded CME should not be accredited to meet state, medical society, or medical board requirements. Full financial disclosure of the presenters at CME activities and events should be obligatory, at least, to allow the audience to know the full extent of industry funding and bias.

Is there any alternative to industry's role in CME? The alternative to industry paying for CMEs is for CME funding by physicians themselves. This can be possible either directly or via medical society membership dues. Medicine, in contrast to almost all other professions (from lawyers to accountants), has become normalized to the free "education" that is really CME-based marketing in disguise. Therefore, breaking away from this pattern will likely meet some resistance. Physicians, in recognizing the true educational value of CME conferences and courses, should keep in mind that CME budgets by industry are usually counted under marketing expenses. To keep costs lower for physician-funded events, the following suggestions are applicable: Courses do not have to be held in resort destinations. Speakers do not have to be highly paid industry consultants. Doctors can and should be able to pay for unbiased CMEs to keep current their medical knowledge for the sake of effective and proven care for their patients. It is our obligation.

Research

In many areas, the partnership of research investigators with industry for sponsorship may create a large conflict of interest. Unfortunately, the broad lack of disclosure that pervades all the medical specialties has resulted in the rapid use of new drugs, interventions, and devices that later may often be seen to be either ineffective or dangerous. Whether it is cardiac stents, orthopedic implants, interventional pain procedures, or psychiatric or diabetic drugs, it is the same story. Products are released and marketing is optimized for rapid utilization throughout medicine while little is revealed about the financial biases present and about the lack of true independent validation.

For example, in 2008, it was reported that a renowned Harvard psychiatrist, who long promoted the use of certain antipsychotic medications in children for the treatment of bipolar disorder, failed to report $1.6 million he was paid by drug manufacturers [109]. During the years 1994–2003, there was a 40-fold increase in the diagnosis of bipolar disorder in the United States, leaving one to speculate on the impact of these published studies, full of their secondary interests, on real patients.

The lack of financial disclosure in industry-sponsored research also, perhaps surprisingly, has its counterpart in National Institutes of Health (NIH)-sponsored drug research. In 2006, a House of Representatives subcommittee investigated what was called "the largest scandal in all of NIH's existence" by subcommittee chairman Rep. Edward Whitfield (R-KY) [110]. In the prior 3 years, 34 NIH scientists had been found to violate conflict of interest rules. Punishments ranged from letters of reprimand to suspension. Not a single scientist was fired.

More than one-third of institutional review board (IRB) members have relationships with the industry; more than one-half of all IRB members have no formal disclosure system [111]. Consider the outcomes of industry-sponsored research: in a survey of 527 articles published in *Spine* from January 2002 to July 2003, the odds ratio of industry-funded studies reporting positive results was 3.3 times that of the studies with any other funding source [112]. Moreover, consider the extent of this problem: a 2006 study published in *Pain* examined 176 migraine and acute pain trials and found only two studies that were sponsored by nonprofit sources [113]. Much of what we read as pain clinicians is sponsored, at some level, by the industry. At the minimum, therefore, all authors must disclose all relationships with industry and amounts of compensation received; this will be required specifically for public release as the Physician Payment Sunshine Act is implemented fully in 2013. This should pertain to all sources of funding for the research [114]—and to all IRBs. However, is this enough? Is there a single journal that might publish only nonprofit funded evidence?

Unfortunately, disclosure is the (only) current solution to "deal" with most of the aforementioned conflicts of interest. Overall, for the most part, current disclosure is a weak solution because it is largely ineffective and not specific regarding amounts of compensation received. As stated in the 2010 *American Academy of Pain Medicine Ethics Council Statement on Conflicts of Interest: Interaction between Physicians and Industry in Pain Medicine*, recent evidence suggests that disclosure in the current pre–Sunshine Act form does little to mitigate the potential conflict [115]. Furthermore, disclosure unfairly places the burden of managing the conflict on the reader or information receiver, charging the reader with determining how skeptical to be about the objectivity of the situation [116] and charging the reader with determining the magnitude of the effects of influence without knowledge of whether $10,000 or $1 million was received. To further complicate the situation, evidence suggests that disclosure can actually be counterproductive: speakers provide *more* biased advice after disclosing their conflict of interest [117]. Disclosure is often incomplete and generic, based on broad categories of compensation, and rarely verified: is this type of disclosure meaningful? No, it is not. To address this issue, more rigid disclosure recommendations are available [115]; these, for the most part, however, only

echo those made by Schofferman and Banja in 2008 [102], although they will dramatically be enhanced with the full transparency required in 2013 by the Physician Payment Sunshine Act.

Physician-Driven Solutions

Legislation: The Physician Payment Sunshine Act

On September 12, 2007, the Physician Payment Sunshine Act—S.2029—sponsored by Senators Kohl (D-WI) and Grassely (R-IA) was introduced. It requires public disclosure of all money transferred between medical manufacturers and physicians. On February 27, 2008, the Senate Special Committee on Aging, chaired by Senator Kohl, held senate hearings on the proposed legislation. One of the authors (CR) was invited to testify on the need for financial transparency in medicine and was the only physician to do so on behalf of this legislation [118]. The hearing culminated in all members, including the minority, being in favor of the legislation. Subsequently, in 2009, the bill was included in the Obama health care legislation and passed as part of that package in March 2010; the date of implementation is to be on 2013 [119]. The act stated, at that time, that any compensation to a physician over $100 by a medical manufacturer would need to be reported annually. A nonspecified governmental Website would then make the data public.

Between the time the legislation was proposed and its passage, much occurred. Political negotiations by industry began in an effort to mollify any negative effects of the bill on the industry. An initial effort was made to exempt third parties from the reporting requirements so that physician consultants could have their compensation remain unknown. Consultants began decrying that the government, to the detriment of the country, was curtailing research. The fact that no restriction on any flow of money was part of the bill, only disclosure of it, was not mentioned. Delay in implementation of the bill and certain exemptions in reporting of the payments to physicians involved in pre-FDA approval studies was sought with the view that information regarding which consultant was providing services to which company was a trade secret. The exemptions would allow consultants to receive undisclosed bonuses after FDA approval of products; practicing physicians reading the literature would not be privy to this information beforehand. Many changes were debated, and the ultimate bill incorporated some of these [119]. Still, the extent to which this law will affect the practice of medicine in this country will be enormous, particularly when it is fully implemented in 2013.

Founding of the AME

The association was founded by one of the authors (CR) and Gemma Cunningham in 2005, with the intent to educate the public about the undue influence of industry on medicine and to make patient care objective, unbiased, and more ethical. One of the authors (CR) testified before Congress in support of the Physicians Payment Sunshine Act, and the association became nationally recognized in the media and government for its role in the passage of this patient-centered legislation in 2010. The purpose is to allow practicing physicians reviewing research to know the precise financial compensation, if any, provided to the researchers. This, in turn, would allow practicing physicians to judge for themselves the extent of any bias, if present, and to make an informed decision on whether to use the medical product or not. There are no dues; the only requirement initially was to electronically sign a sworn statement that the prospective member did not accept any money, personally, from any medical industry source. The beauty of the membership design involves new members who have a “clean slate” without industrial affiliations, which later allows easing of requirements to allow all legal industrial affiliations but on a more transparent basis. In 2009, there were more than 300 members and applicants for membership. The members hail from 11 different countries including Sri Lanka, China, Egypt, and Iraq. A Website http://www.EthicalDoctor.org was set up to advance and broadcast the goals of the association and its members.

The main goal of the AME is to promote full financial disclosure in the practice of medicine and in research. Namely, the association recognizes that the patient and the practicing physician have a right to realize if a drug or device manufacturer paid the authors of a positive study; the amount and nature of financial compensation should also be transparent. It was felt by association members that the amount of money involved makes a difference in the study interpretation. For example, if one reads the typically cryptic disclosures in a research article that an author merely has a “consultant” relationship or that “one or more authors may or may not have stock/royalty/options,” it means little compared with knowing that authors may have received millions of dollars from the manufacturers. This disclosure of specific information that may represent conflicts of interest makes the difference between a practicing physician using the product right “off the bat” or instead considering that there is a significant and concerning bias in the study and then deciding to wait a few more months or years for more unbiased results. The ultimate effect on the medical community is actually a large one because the speed of implementation of a poor product or intervention will be the difference in how many patients are negatively affected if the product has complications. For example, in the case of new drugs, the complication may be death [120].

In its goal to make financial transparency in research mandatory, the AME is unique in its position: it inspired and successfully lobbied for the Physician Payment Sunshine Act. With the passage of the act, “Medical Ethics” societies have sprung up and jumped on the AME bandwagon. To our knowledge, however, all of these organizations are sponsored either directly or indirectly by the industry to exert “control” over this issue. The AME is the only organization—as well as Website—that lacks industry funding. Being industry-free and supporting physicians is what gives credibility to the AME; the AME is therefore the

only nationally recognized medical ethics organization to address Congress. The AME is the only organization to be requested by Blue Cross Blue Shield nationally to implement a patient education program, one of its current and ongoing projects.

Other Solutions

For interventional procedures, training program requirements and competency assessment should be refined. More importantly, practicing physicians must self-discipline to utilize the available EBM to the fullest. Using strict criteria for diagnostic medial branch blocks, for example, may lead to less unnecessary neurolytic procedures and overall, less misutilization of the health care system. Self-monitoring will be challenging, especially when we are all faced with unconscious financial pressures. The interventional pain physician will need to focus on using the best available evidence in the most cost-effective way possible while meeting the goals of pain reduction and improvement in function and in quality of life.

For the prescribing of opioid analgesics, the pendulum must be restored and balanced. Again, EBM will provide guidance on proper opioid use. Use should be judicious in select patients, and multidisciplinary clinics should be consulted to initiate and provide multimodal therapy. Physicians should limit their reliance on pharmaceutical-sponsored research and wait for more clear outcomes and evidence when pharmaceutical-sponsored research is the only available evidence (as in the case of new fentanyl formulations). Diversion control programs should be implemented with follow through on research that demonstrates actual outcomes and effectiveness. Ideally, diversion control programs, such as REMS, should be independently formulated without pharmaceutical infrastructure.

In the context of industrial relationships, sweeping policy changes are warranted. CME should be provided at a reduced cost, at less expensive facility locations, and with reduced speaker honoraria; physicians themselves (or medical societies) should accept the additional funding required. Other CME settings that do not involve large groups or conferences should be explored. Regarding research and publications, full financial disclosure must be present so as to allow subscribers of any journal or members of any medical society to decide for themselves if bias is a possibility. The AME's Ethical Rules of Disclosure suggest that no one who is in an editorial position or a professional society officer should exceed $50,000 in money received from industry.

As biases are nearly impossible to completely eradicate from medicine, a better disclosure and bias-monitoring system is a key. With increased financial transparency throughout medicine, with increased physician insight into biases, and with increased physician-directed management of biased structures, such as CME and medical journals, physicians will drive solutions to our own ethical challenges. The AME will be our model of success.

Conclusion

Physicians have duties and obligations on both an individual level and a public level. They are to provide humanitarian care to the patient while doing no harm and, at the same time, to sustain the role of medicine for the overall public good [34]. The broad challenges facing the contemporary pain physician include the regulation of interventional techniques and the use of opioid analgesics in chronic noncancer pain. All physicians must realize the pervasive effects of the industry on medical practice and the many subtle ways in which they occur. We should be emboldened by the ideals and goals of the AME, as well as the new law of the land—the Physician Payment Sunshine Act. Medicine should return to being independent, unbiased, and guided only by what is best for the patient, not necessarily what the patient or medical manufacturers want. Medicine needs doctors to be the problem solvers. Medicine needs physician-driven solutions.

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