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ORIGINAL ARTICLE

Reality and responsibility revisited: Stakeholder accountability in the effort to develop safer opioids

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ABSTRACT

This supplement is dedicated to an exploration of the science, potential utility, and the current state of abuse-deterrent formulations (ADF) of opioid analgesics. There are many stakeholders in the search for safer pain treatments in general, and safer opioid therapy in particular. Healthcare providers, patients, third-party payors, law enforcement and government regulators, the pharmaceutical industry, and the media all have a stake in seeing pain treated and addiction and overdose avoided. As it applies to ADFs, obviously not everyone has a stake in seeing that ADFs succeed commercially; but all stakeholders certainly have a responsibility to see that any potential advance, including ADFs, in protecting the public health is fairly and thoroughly evaluated. Particularly at a time of crisis. In this article, we revisit the framework used by Passik, Heit, and Kirsh (2006) to evaluate stakeholders' responsibilities with regard to both the opioid abuse and chronic pain epidemics. After evaluating the present status of aspirations delineated over a decade ago, we discuss the updated roles and responsibilities of each stakeholder, with emphasis on the role of ADFs as this technology was unavailable when the original manuscript was written.

INTRODUCTION

It took approximately 15 years from the earliest reports of AIDS and its beginning as a universally fatal disease to its transformation into a survivable chronic illness. And in only a few more years since then, we are on the threshold of a cure.[1] Fifteen years.

Some have suggested that an examination of the response to this public health crisis may uncover tactics that can be used to combat the opioid epidemic. Tragically, nearly 700,000 people have lost their lives secondary to AIDS, yet the response to this disease is a virtual prototype of how cooperation, activism, conflict, and resolution among stakeholders can effectively end a public health crisis. The response included contributions from a variety of stakeholders, including: (1) scientists and clinicians in the diagnosis and development of novel treatments of the disease; (2) activism and behavior changes of those at risk or suffering from the disease; (3) cooperation between regulatory and government bodies and the pharmaceutical industry to expedite development and approval of treatments indicated for the disease; (4) coverage for these treatments by third-party healthcare payors; and (5) the media raising awareness.[2]

Although it sometimes seems contradictory, the opioid epidemic did not emerge overnight. A subset of researchers and clinicians were warning of the potential implications of the trivialization of addiction as early as 2001, in response to the early rhetoric that largely underestimated this risk.[3] Disappointingly, in the same amount of time it took to virtually cure AIDS we have not been able to broadly implement "best clinical practices" in the use of opioids for pain. The reaction to the crisis of misuse, abuse, addiction, diversion, overdose, and death has been a virtual prototype of finger pointing, miscommunication, misinformation, misbehavior, and missed opportunities.

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Between 1999-2015, more than 183,000 Americans died of an opioid overdose.[4] As a result, many can see no other solution than to dramatically clamp down on the use of these medications, regardless of legitimate need. So much of the focus of activity meant to curtail the death and devastation, whether in the form of guidelines, policies, or laws, has focused upon dramatically decreasing the number of exposures to opioids rather than improving the quality of exposures that do occur. In some people's view, this represents a recipe of cruelty for those who need these medications, and ignores critical innovation from several stakeholders that could facilitate safer access to opioids.[5]

In an effort to combat the opioid epidemic, several tools and techniques have been developed: (1) virtually real-time prescription drug-monitoring programs, (2) "mass production" and rapid turnaround of liquid chromatography drug testing, (3) empirically tested psychotherapeutic approaches, (4) opioid take-back programs designed to decrease the amount of surplus medication, (5) genetic testing, and (6) potentially safer opioid products (ie, abuse-deterrent formulations [ADFs]).[6-9] It is truly ironic, given the unrelenting, ongoing opioid epidemic, that taken together, these advances could quite possibly make the present the *safest time there has ever been to prescribe opioid therapy – with the important proviso: in the hands of adequately trained and compensated pain practitioners*.

In 2005, Gourlay and Heit proposed a "universal precautions" approach to the treatment of chronic pain.[10] Their proposed approach parallels what is done in the world of infectious disease—appropriate precautions are taken with *all* patients. This approach has been adopted in the management of chronic pain with varying degrees of success, in part because for them to be successful, they must be adopted and supported by all stakeholders. The tools and techniques mentioned earlier must be utilized by providers, they must be embraced by patients, and they must be reimbursed by payors. A large reason for the success in the fight against AIDS was that efforts focused not only on treatment, but also on prevention. It seems that recent efforts in the opioid space are disproportionally focused on treatment of addiction (eg, availability of naloxone, medication-assisted treatment), while we have lost sight of prevention (ie, preventing legitimate pain patients from becoming addicts).

Abuse-deterrent opioids were nothing more than science fiction in the early to mid-1990s. During this same period, immediate-release (IR) opioids often carried large amounts of the active opioid drug in a single tablet, and these tablets required minimal tampering effort to alter their route of administration to achieve a greater high. These IR products soon became the "coin of the realm" for abusers and drug dealers, and they were greatly overprescribed at pill mills, illegitimate practices of every stripe, and by duped healthcare providers. Many stakeholders forget that prior to the introduction and subsequent notoriety and abuse of OxyContin, IR opioid formulations were already widely sought after by those who would use them solely for nonmedical purposes. This lapse in memory has led to a disproportionate focus on extended-release/long-acting (ER/LA) opioid formulations in the regulation of opioid therapy. Further, it has led to recommendations on how to conduct opioid therapy, such as the Centers for Disease Control's (CDC) Chronic Pain Guidelines, that discourages ER/LA opioid use in favor of IR products.[11]

However, epidemiological data and common clinical practice are at odds with the CDC's guidelines. Recent epidemiological studies support long-standing clinical observations—IR products are more frequently misused and abused than ER/LA products by abusers and patients with chronic pain, and diverted and preferred by abusers.[12-14] Further, these data support the common clinical recommendation that ER/LA opioids should be prescribed as part of a multifaceted program to help contain loss of control in chronic pain patients on IR products.[12-14] It stands to reason, that if a patient was switched to an ER/LA opioid because his clinician had noticed signs of loss of control on IR opioids (but still felt that opioids were warranted), a product with the greatest potential safety profile offering the greatest potential protection against worsening abuse would be desirable (eg, an ADF).

A framework for assessing stakeholder's past and future performance: Reality and responsibility revisited

In 2006, Passik, Heit, and Kirsh provided a commentary in this journal entitled "Reality and Responsibility: A commentary on the treatment of pain and suffering in a drug-using society."[1] In that article, the role of all stakeholders that had an interest in the continued availability of opioid therapy (read: "everyone"—we will all either personally suffer with pain or someone close to us will) and rendering it as safe as possible, was outlined.

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In the original commentary, the authors began by outlining two concurrent epidemics—chronic pain and opioid abuse. Both epidemics remain ongoing today, however, it can be argued that the chronic pain epidemic regularly takes a back seat to the opioid epidemic. Importantly, widespread disagreement on how to solve these epidemics remains.

For these reasons, just over a decade after the original commentary was written, we will use the same framework to provide a progress report (of sorts) and an update to the role and responsibility of each stakeholder (as we see it). Additionally, since the writing of the original commentary, several ADFs have been successfully developed, approved for use by the United States (US) Food and Drug Administration (FDA), and marketed. As such, we will outline the utility of these formulations within this framework, as well as emphasize the need for an honest appraisal of the currently available body of science related to ADFs and their role in the ongoing opioid epidemic. At the very least, we seek to gain recognition by all stakeholders that the absence of evidence does not constitute evidence of an absence of a societal and public health benefit of ADFs, and to encourage patience and support, monetary and otherwise, while the needed epidemiological data are obtained.

Healthcare providers

The authors laid out a series of recommendations and expectations of clinicians to essentially "up their game" by conducting more deliberate and individualized opioid therapy. It was recommended that healthcare providers (HCPs) (1) conduct, and periodically repeat, a risk assessment given the patient's individual and family history, (2) spend sufficient time deciding how to deliver opioid therapy and what safeguards to implement, (3) consider whether to treat the person alone, co-treat with an expert, or refer the patient out to an expert provider entirely, and (4) discuss and set appropriate guidelines and goals of successful opioid therapy with patients to ensure clear expectations around opioid continuation.

Status. In some respects, HCPs have made great strides in incorporating some forms of risk management techniques into their practices (urine drug testing being the most common).[15] However, heavy burden of communication around goals, expectations, and metrics of success and failure have occurred to a lesser extent. We believe this is due to a lack of training and the ongoing time pressure on most clinicians involved in the treatment of chronic pain outside of expert centers.

When prescribing opioids, HCPs need to assess risk in both the individual and household environment (ie, household risk) and consider use of an ADF when appropriate. Communicating the pros (eg, potentially safer, tamper-resistant formulation for themselves, family, friends, and community) and cons (eg, possible increase in out-of-pocket costs, dose adjustment period) of ADFs to patients will add time and effort. If a HCP feels an ADF is indicated, they are likely to have to lobby for it with payors, fulfill prior authorization requirements, and/or demand exceptions be made to safeguard their patient and those around them. HCPs play a critical role in obtaining real-world, epidemiologic data to determine if ADFs reduce abuse, as they are almost solely responsible for patient access. To achieve this, HCPs must strategically incorporate ADFs into best clinical practices by using them as a risk reduction tool.

Patients

In the original commentary, authors urged patients to work with their HCPs to develop a mutually agreed-upon treatment plan, strictly adhere to said plan, and take their medications only as prescribed without altering the delivery system (ie, tampering).

Status. It is difficult to assess the current state of adherence; however, it is safe to say that it is far better than the dismal performance routinely reported in the media. Patients taking their medications as prescribed and achieving improvement in their functioning and quality of life rarely make the news. A recent study reports aberrant behavior rates on low dose opioids in minimal risk patients are exceedingly low,[16] further supporting the notion that the vast majority of patients suffering from chronic pain are responsible, compliant, and are not abusing with their opioid medications.

While it is likely that the majority of patients are able to adhere to their treatment plans, it is unclear how often patients needing assistance are afforded the necessary structure. Monitoring and care to identify and help guard against escalating aberrant behaviors in patients has likely helped a subset of patients, however, there remains room for improvement.

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Patients suffering from chronic pain, for whom it is appropriate, are entitled to receive opioid therapy, regardless of whether others in their communities abuse the same medications. However, patients with chronic pain are obligated to take all possible precautions to ensure they are not negatively contributing to the opioid epidemic. Precautions include: (1) behavioral modifications (eg, adherence to treatment plans, safe storage of opioid medications) to prevent opioids from reaching abusers, (2) utilization of the safest available opioids (currently ADFs) to mitigate risk if abusers do obtain opioids, (3) advocacy (eg, demand safer opioid formulations from their HCPs and payors reimburse for them, speak up for chronic pain patients) to bring awareness to the chronic pain epidemic and to educate other patients on responsible opioid use, and (4) monetary (eg, pay for new technologies) to ensure that advances in technology continue to be in existence.

Third-party payors

In 2006, Passik, Heit, and Kirsh discussed the need for payors to be supportive of different levels of care for patients, based on risk, and the need to move away from minimally monitored, drug-only pain therapy for the majority of opioid patients.[1]

Status. Payors should be commended for their early recognition of the opioid misuse problem and certain targeted efforts to combat it (eg, limiting acute pain medication quantities, urine drug testing). Nonetheless, there is still a long way to go. A number of the fail-first policies and prior authorization measures typically employed, lie along a continuum from the merely absurd to socially irresponsible. The negative contribution by payors to the opioid epidemic has gone largely unrecognized to date.

Reimbursement policies related to ADFs suffer from a Catch 22 like dilemma—most payors require data demonstrating the real-world impact of ADFs on misuse, abuse, diversion, and addiction prior to adding the products to their formulary. However, until ADFs are universally covered, routinely prescribed, and utilized in a broad enough fashion, there will not be sufficient data to adequately assess their impact and satisfy payors. Expanded reimbursement for ADFs (even if only guaranteed for the period in which their impact is being assessed) and broader coverage of care based on patients' level of risk is critically needed to help provide HCPs, the tools they need to prevent and/or treat misuse, abuse, diversion, and addiction.

Law enforcement and government regulators

In the original commentary, the authors suggested that law enforcement and regulators strive for a fair balance in their practices and policies. They should simultaneously allow, stakeholders to combat the opioid epidemic and patients suffering from chronic pain, reasonable access to needed treatments.

Status. Regulations and laws, on both the state and federal level, have done a great deal to end the scourge of pill mills and ensure greater physician oversight of pain clinics. Laws related to pain practice have varied greatly, some have been reasonable and supportive of best practices. While laws mandating the use of prescription drug-monitoring programs have increased practitioner burden; they have facilitated a needed increase in usage of these systems. However, room for improvement remains as a mandatory requirement to check these systems for every patient at every visit, regardless of individuals' adherence history and level of risk, likely represents wasted effort and associated costs.

Several laws have been implemented on the state and federal level since the original commentary was published, that place arbitrary dose limits on daily opioid prescribing. The obvious negative consequence of these limits is that HCPs are no longer able to provide individualized care, resulting in many patients suffering from intractable pain that was previously managed with high-dose opioids. Furthermore, while the authors acknowledge that there are potential benefits from these limits (eg, reduction in diverted dosage), it is also likely that additional negative consequences will emerge overtime (eg, inadequately medicated pain leading to changes in suicidality). In patients who are adequately assessed and monitored based on their level of risk, there is no medical or scientific justification to uniformly limit doses.[17,18] Alternative tools and techniques exist to assess and manage risk; these arbitrary dose limits have inhumane repercussions on some of the most vulnerable patients.

Some states have begun to implement regulations that aim to improve patient access to ADFs, including requirements for payors to reimburse for them; no such federal regulations exist. Expansion of regulations requiring mandatory coverage of ADFs

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will be a necessary step toward understanding the potential public health benefit of ADFs.

Pharmaceutical Industry

In 2006, Passik, Heit, and Kirsh encouraged the pharmaceutical industry to (1) develop potentially safer opioid products, (2) conduct more extensive post-marketing studies related to misuse, abuse, diversion, and addiction, (3) provide oversight of educational programs for fair and balanced content, and (4) closely monitor sales techniques to ensure they focused on providing opioids only to patients suited for them.[1]

Status. Pharmaceutical companies have made positive strides in nearly all of these areas, sometimes mandated specifically by regulators to do so and sometimes voluntarily. Currently ten ADFs have been approved with the majority being marketed.[19] The FDA has mandated several post-marketing studies related to opioid safety that are nearing completion, required implementation of Risk Evaluation and Mitigation Strategies, and has much firmer oversight of opioid promotional programs. Many companies have sought alternative ways to incentivize sales representatives without overemphasizing sales.

While ADFs are in their infancy, these formulations represent a step forward in the fight against the opioid epidemic. However, addicts have been shown to quickly adapt their behaviors in response to changes in formulations that make them more difficult to tamper with (ADFs).[20] For this reason, industry must continue to innovate, including advancements in ADF technologies, novel analgesics, and addiction treatments. Lastly, they have an obligation to make current and future products accessible to the general public through fair and competitive pricing.

Media

Finally, the authors urged the media to present an accurate representation of the opioid epidemic by (1) not suggesting addiction is solely a disease of exposure, (2) explaining the difference between addiction and physical dependence, and not using the terms interchangeably, and (3) covering both the successes and failures of opioid pain management in a clear and factual way.

Status. The media deserves to be commended for raising awareness of the public and helping marshal, the response to the opioid epidemic. That said, mainstream media coverage has tended to be inaccurate. Very few stories depicting positive patient outcomes related to opioids have made it past "specialty media" organizations to the general public.

We continue to urge the media to present a fair and accurate depiction of opioid use, both from the perspective of patients suffering from chronic pain and those suffering from addiction. It is also critical that the media avoid rushing to judgment on the utility of ADFs. The media has the responsibility to remain fair when it comes to ADFs; until adequate data are available, it is unclear exactly what impact these compounds will have on public health.

CONCLUSION

There has been overwhelming concern from every corner related to the opioid epidemic. However, that concern often seems to go only so far as calling for regulation and limitations with little action being taken. Few seem willing to support, economically and otherwise, partial and incremental advances meant to safeguard opioid therapy. There has been a ton of mischaracterization and mythology circulating; much outcry and misdirected action. Yet, there has been little recognition of the innovation and ingenuity that has gone into the development of ADF products or their potential contribution to the opioid epidemic solution. That contribution may be dramatic or it may be limited, but we all have a stake in finding answers to this vexing problem.

The response to AIDS, and the successes therein, show what can be accomplished when stakeholders come together and are motivated by the need to address a dire threat. While there is such a response now to the opioid overdose aspect of the pain and addiction epidemics, other aspects of these crises remain largely ignored. We have failed to make necessary changes in how we deliver pain management in the same amount of time it took to turn AIDS from a death sentence to a survivable disease. Many have sounded the alarm about both the problem of poorly treated pain and of abuse, addiction, overdose, and death related to prescription and illicit opioids. However, alarm is not enough. Stakeholders must face the realities of our dual public health crises and live up to our responsibilities to the public health.

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