PAIN RESEARCH

Timefor nonaddictive relief of pain

Greater insight into the biology of pain will likely identify potential drug targets

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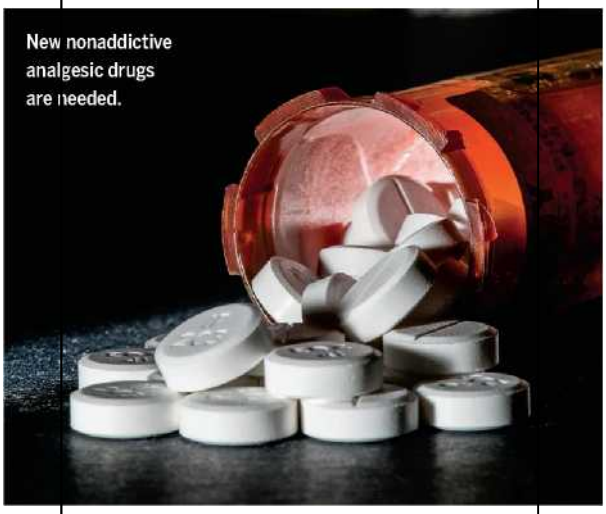
Much has been written recently about the prevalence of chronic pain (*1*), the dramatic increase in opioid prescriptions in the United States over the past 15 years, the concomitant rise in opioid dependency and addiction, and the quadrupling of deaths from opioid abuse. Although indispensable for managing acute severe traumatic pain and pain in a palliative setting, most opioids are prescribed either by dentists or by primary practitioners for chronic nonmalignant pain, and marketed aggressively to consumers for the latter, despite no scientific evidence supporting such treatment beyond 12 weeks (1). On the contrary, chronic opioid use can itself lead to pain. Most abuse (perhaps 70%) involves access to opioids that are prescribed for others—a diversion problem.

In the United States, the public health response to this crisis has involved education for patients and prescribers, attempts to restrain pharmaceutical companies from direct-to-consumer advertising, and the development of Risk Evaluation and Mitigation Strategies (REMS) by the U.S. Food and Drug Administration (FDA). Unfortunately, REMS are limited by the uneven quality of data available (there is no national abuse-surveillance system) and the prolonged time scale over which addiction might be ameliorated. Addictive drugs, such as opioids, induce adaptive changes in gene expression in brain reward regions, representing a mechanism for tolerance and habit formation with craving and negative affect that persist long after consumption ceases, thus setting the stage for relapse (2).

As the challenge of measuring the effectiveness of such interventions is contemplated, one must also be mindful of unintended consequences. For example, legalization of marijuana, now accessible for unrestricted or medicinal purposes for pain relief to approximately one-third of the U.S. population, prompted drug cartels to depress the price and increase the supply of heroin and the synthetic opioid fentanyl (3)—a move that was exaggerated by increased restrictions on the overprescription of opioids. This fostered drug switching to heroin, increasingly mixed with fentanyl, and a rise in addiction to these drugs.

The relative absence of an opioid abuse epidemic in Europe by comparison has been attributed to differences in prescribing practices, the absence of direct-to-consumer advertising, differential emphasis on non-pharmaceutical approaches to pain relief, greater social cohesion, and more robust state-supported safety nets for the unemployed in Europe (4). However, even within the United States, there are striking differences in reported opioid abuse and death rates in adjacent states *(5)* and within different segments of the population.



/Текстнарисунке: New nonaddictive analgesic drugs are needed./

The FDA has reacted with revised drug labeling, approved formulations [including those that delay release to slow brain penetrance; mixed opioid receptor agonists and antagonists; tamper-resistant preparations; and depot injection (which delays release) of buprenorphine to treat dependence], educational initiatives, and the collection and disposal of unused drugs. The FDA also called for a National Academies of Sciences, Engineering, and Medicine working group, which is currently considering the addition of societal impact to estimations of individual risk- benefit in the drug approval process. It is not clear how effective any of these approaches will be; delayed-release formulations were a major contributor to the crisis because they require high-dose pills, which can be abused.

To make headway, these various initiatives must be complemented with an investment in basic research on pain and in revolutionizing the approach to analgesic drug development (6). Specifically, we need an enhanced understanding of the biology of pain and its manifestation in patients, an expansion of the repertoire of nonaddictive analgesics, and a shift in emphasis in drug development towards parsing variability of drug response such as to develop individualized, dynamic paradigms for rational drug administration.

PAIN RESEARCH

Pain is a syndrome that is poorly understood, and research on pain is poorly resourced relative to its prevalence and cost, especially in terms of shattered lives and lost productivity. No analgesic drugs directed at novel targets have been approved in the past 5 years. Much more detailed insights into the molecular mechanisms that lower the nociceptive threshold (to reduce injury), distort pain perception, and drive spontaneous pain are necessary to develop treatments that reverse and potentially cure these perturbations of the nervous system. Among the things that require deeper understanding are whether inflammatory and neuropathic pain are distinct or overlapping *(7, 8);* how chronic widespread pain arises in the absence of peripheral pathology; the contribution of heritability to pain in the absence of a clear pattern of Mendelian inheritance (2, 9); and the transition from acute to chronic pain. Also unclear are the mechanisms by which sex and aging influence the perception of pain and the interrelationship between sleep and pain. Quantitative biomarkers of pain and its relief that translate from model systems to humans are urgently needed. Critical to answering all of these questions is the development of new models of pain—those that are spontaneous rather than evoked and reactive, those that incorporate the functional as well as the organic response to pain, and those that assess affective and cognitive components of pain.

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Precise molecular phenotyping of animal models of pain and patients will ultimately yield those models with the highest predictive validity for specific human pain phenotypes.

DRUG DEVELOPMENT

Although analgesics that target heterotrimeric G protein-coupled μ opioid receptors cause constipation and respiratory depression, studies in mice revealed that receptor activation without the recruitment of ß-arrestin to the receptors enhanced analgesia while reducing respiratory and gastrointestinal effects; such biased ligands are in clinical development ***(10)***. Mixed μ and δ opioid receptor agonists, as well as mixed μ agonists and κopioid receptor antagonists, show promise in segregating analgesic from abuse potential in preclinical models (*11*). Presently, the most common default option to opioids is nonsteroidal anti-inflammatory drugs (NSAIDs) that target cyclooxygenase (COX) enzymes. COX enzymes depress the synthesis of prostaglandin (PG) E_2 and PGI_2, which evoke pain by sensitizing neurons in the pain pathway. Although selective targeting of COX-2 decreases the frequency of gastrointestinal adverse effects, it also suppresses the synthesis of PGI_2, which is a platelet inhibitor and vasodilator, and thus presents a cardiovascular risk. However, recent preclinical studies suggest that NSAID efficacy might be largely conserved while the cardiovascular risk is reduced by targeting the macrophage microsomal PGE synthase downstream of the COX enzymes ***(12)***. The good news is that there are emerging drug targets to control pain, including voltage-gated sodium and calcium channels such as Nav1.7 and Cav2.2, potassium channels, the transient receptor potential cation channel subfamily V member 1, the cannabinoid receptor type 1, excitatory amino acid receptors, nerve growth factor, proinflammatory cytokines, such as interleukin 6 (IL-6), nitric oxide synthase, and enzymes involved in the synthesis of tetrahydrobiopterin (a cofactor in the synthesis of several neurotransmitters). Yet, for emerging and existing analgesics, it would be beneficial to explore two other areas. There is a need to understand the biology of the placebo response ***(13)*** so as to maximally exploit it. Complementary approaches to analgesia ***(14)***, such as acupuncture, yoga, cognitive behavioral and mindfulness techniques, and meditation, should be rigorously assessed to determine whether they provide value beyond placebo, and to determine their efficacy at an individual level.

DRUG RESPONSE VARIABILITY

A major challenge is how to assess and parse variability in drug responses. Here, multi-omics, advanced imaging, and remote sensing data can be integrated with studies of sensory, spinal cord, thalamic, and cortical neurons that are derived from induced pluripotent stem cells from patients in pain. Thus, patients are stratified based on their molecular pain phenotype. This approach can also parse variability of drug response and the implications of network perturbations by drugs that are administered alone and in combination. Such parsing and stratification would constitute a basis of screens for novel analgesics, which could improve the prediction of abuse liability and adverse drug responses.

Large, commercially driven, randomized clinical trials have thus far yielded no useful information on individual risk or benefit from NSAIDs. To gain insight into pain at the individual level, we must identify biomarkers that serve as guides for drug efficacy and risk of adverse effects. Deep phenotyping studies should be complemented by information harvested at scale. For example, crowdsourcing approaches or electronic health records linked to biobanks can be used to characterize the frequency of the diverse subphenotypes of pain. This information would help to prioritize further studies and the design of clinical trials.

"Pain is a syndrome that is poorly understood, and research on pain is poorly resourced..."

PAYING FOR IT ALL

The scientific agenda described here is ambitious and expensive, yet necessary if we are to emerge from the growing opioid crisis. A major initiative to develop novel, nonaddictive analgesics cannot be addressed merely by reallocating existing resources within the U.S. National Institutes of Health (NIH) budget. Instead, a serious expansion of NIH funding supported by investment in analgesic research by the private sector is necessary. The cost of the opioid epidemic in the United States has been roughly $80 billion ***(15)***, whereas sales of Oxycontin alone are approximately $35 billion. These costs and profits are likely to escalate despite increasing awareness of this crisis. For example, as sales of Oxycontin have dropped domestically, the owners of its maker, Purdue Pharma, have begun to deploy strategies to push its adoption abroad for which it was fined in the United States. We suggest the formation of a public-private partnership to create a $10 billion research fund that would be administered by the NIH over the next 5 years to support the research initiatives outlined in this article. This will complement the $1 billion allocated more broadly to address the opioid epidemic in the 21st Century Cures Act.

Given the origins of the opioid epidemic, the pharmaceutical industry has a societal obligation to contribute. The lawsuit filed in 2014 by the city of Chicago against five opioid manufacturers, and the recent settlement reached by the city with Pfizer, suggests that the industry bears some legal responsibility for misleading marketing claims. Legal liability aside, however, a substantial investment by the industry at large would not only create good will, but would likely serve its own collective financial interest, given the potential market for novel nonaddictive analgesics.

Here, it is worth drawing lessons from the AIDS crisis. Just like the opioid epidemic, the AIDS crisis required intervention at many levels—social, educational, cultural, medical, political, and financial—from diverse stakeholders to curb its escalation. In the case of AIDS, the eventual commitment of substantial fiscal resources and their utilization to support preclinical, clinical, and population-based research depended on an integrated effort by activists, politicians, and scientists from academia and industry. Encouragingly, this broad-based strategy worked, converting the inevitable lethality of AIDS to a reasonably well controlled, chronic disease. A further encouraging parallel is that the benefit from such initiatives in the United States extended to the domain of global health, curbing the spread of AIDS and the medical and social burden of the disease worldwide. If we are to deal with this crisis, we need bipartisan support from Congress for a major investment, together with industry and in partnership with academia and the FDA, in the science of pain and the accelerated development of a repertoire of new nonaddictive analgesic drugs, rationally deployed and financially accessible at the individual level. ■

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