ANESTHESIOLOGY

Estimates of Probabilities of Successful Development of Pain Medications: An Analysis of Pharmaceutical Clinical Development Programs from 2000 to 2020

Dermot P. Maher, M.D., M.S., M.H.S., Chi Heem Wong, Ph.D., Kien Wei Siah, Ph.D., Andrew W. Lo, Ph.D.

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ABSTRACT

Background: The authors estimate the probability of successful development and duration of clinical trials for medications to treat neuropathic and nociceptive pain. The authors also consider the effect of the perceived abuse potential of the medication on these variables.

Methods: This study uses the Citeline database to compute the probabilities of success, duration, and survivorship of pain medication development programs between January 1, 2000, and June 30, 2020, conditioned on the phase, type of pain (nociceptive *vs.* neuropathic), and the abuse potential of the medication.

Results: The overall probability of successful development of all pain medications from phase 1 to approval is 10.4% (standard error, 1.5%). Medications to treat nociceptive and neuropathic pain have a probability of successful development of 13.3% (standard error, 2.3%) and 7.1% (standard error, 1.9%), respectively. The probability of successful development of medications with high abuse potential and low abuse potential are 27.8% (standard error, 4.6%) and 4.7% (standard error, 1.2%), respectively. The most common period for attrition is between phase 3 and approval.

Conclusions: The authors' data suggest that the unique attributes of pain medications, such as their abuse potential and intended pathology, can influence the probability of successful development and duration of development.

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Despite the prevalence and societal costs of pain in the United States, investment in pain medication development is low, due in part to poor understanding of the probability of successful development of such medications

What This Article Tells Us That Is New

- This study examined outcomes and parameters of 469 pain pharmaceutical development programs of 399 unique active pharmaceutical ingredients between 2000 and 2020
- Development of new medications with high abuse potential decreased since the peak of the opioid epidemic, while development programs for low abuse potential medications increased
- The probability of successful development programs was 27.8% for high abuse potential compounds and 4.7% for low abuse potential compounds
- The probability of successful development of a treatment for nociceptive pain was 13.3%, and that for a treatment of neuropathic pain was 7.1%
- Development of pain medications in large phase 3 safety and efficacy trials took an average of 30 months

The exact definition and taxonomy of pain has been revised several times by the International Association for the Study of Pain (Washington, D.C.). Broadly, it currently includes nociceptive pain, caused by specialized pain receptors detecting adverse stimuli; neuropathic pain, caused by damage or disease affecting the nervous system; and the recently added category of nociplastic pain, caused by the altered behavior of pain receptors. Many pathologies are composed of overlapping components of two or sometimes all three of these categories.[1] There are many potential causes of pain, such as cancer, inflammation, and tissue injury, as well as injury or lesions of the nervous system. The proportion of adults in the United States reporting at least one painful health condition increased from 120 million (32.9%) in the period between 1997 and 1998 to 178 million (41%) in the period between 2013 and 2014.[2] An estimated 50 to 100 million adults in the United States live with chronic pain that can substantially restrict their work, social, and self-care activities.[3]

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Dermot P. Maher, M.D., M.S., M.H.S.: Johns Hopkins University School of Medicine, Baltimore, Maryland.

Chi Heem Wong, Ph.D.: Sloan School of Management, Laboratory for Financial Engineering, Electrical Engineering and Computer Science Department, and Computer Science and Artificial Intelligence Laboratory, Massachusetts Institute of Technology, Cambridge, Massachusetts.

Kien Wei Siah, Ph.D.: Sloan School of Management, Laboratory for Financial Engineering, Electrical Engineering and Computer Science Department, and Computer Science and Artificial Intelligence Laboratory, Massachusetts Institute of Technology, Cambridge, Massachusetts.

Andrew W. Lo, Ph.D.: Sloan School of Management, Laboratory for Financial Engineering, Electrical Engineering and Computer Science Department, and Computer Science and Artificial Intelligence Laboratory, Massachusetts Institute of Technology, Cambridge, Massachusetts.

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Despite the widespread prevalence and high societal costs of both pain and addiction, investment in therapeutics in both areas remains underfinanced. This has taken place for a variety of reasons, not least of which is the poor understanding of the probability of successful development of pain medications.[4] A poor understanding of the probability of successful development prevents accurate modeling of the risks involved in pain pharmaceutical development and could lead investors and drug developers to instead pursue safer, more well-understood therapeutic areas. An accurate understanding of the probability of successful development of new pain medications would remove part of the unknown risks of investment in this space, which could further increase growth and lead to a more robust pipeline of new pain medications. Additionally, a knowledge of probabilities of successful development will help anesthesiologist and pain physicians, many of whom are very active in the drug development process, to better focus research and academic efforts.

The opioid crisis has highlighted the need for new therapeutics with low abuse potential to treat chronic pain. While pharmaceutical companies recognize this need, because of the subjective nature of pain—in addition to poorly defined phenotypes of pain response in human populations, a general lack of reliable biomarkers, and the high placebo response—the conduct of clinical trials for new drug approval in this space is a lengthy and costly proposition.[3] While there are numerous risks involved in the development of new pain treatments, an understanding of the potential opportunities in this field will hopefully encourage further development.

This study examines the outcomes and parameters of clinical development programs for pain medications. We first compute the individual probability of successful development for pain medication development programs between 2000 and 2020. We then analyze them by the type of pain treated (nociceptive *vs.* neuropathic) and the abuse potential of the medications. We then examine the duration and survivorship of these clinical trials across their various phases and outcomes. Our results allow for improved financial allocation and pipeline optimization in this therapeutic area.

Methods

Data

The data used are publicly available, and the study is not considered human subject research. Institutional review board approval was not sought. We extracted clinical trial metadata from the June 30, 2020, snapshot of Citeline's Pharmaprojects and Trialtrove databases, provided by Informa Pharma Intelligence (United Kingdom). These databases are widely available commercially, as well as through an academic license. Clinical trial metadata were retrieved from the Trialtrove database, while the approval data were obtained from the Pharmaprojects database, both of which are required to identify drug development programs. An example of the data found in this database is provided in Supplemental Digital Content Table 1 (http://links.lww.com/ALN/C862). Citeline databases incorporate more than 40,000 unique public domain sources from clinical development programs in more than 165 countries, including nightly feeds from official sources such as ClinicalTrials.gov, primary sources such as institutional press releases, financial reports, study reports, and drug marketing label applications, and secondary sources such as analyst reports by consulting companies. The use of secondary sources reduces potential biases that may arise from the tendency of organizations to report only successful trials, especially those before the U.S. Food and Drug Administration Amendments Act of 2007, which requires all clinical trials to be registered and tracked *via* ClinicalTrials.gov. These databases contain information from both U.S. and non-U.S. sources. The databases currently have information on more than 265,000 clinical development programs in a diverse range of therapeutic areas. Additional information regarding the source databases can be found at https://pharmaintelligence.informa.com. We consider a drug approved if it is approved in any country. All clinical trials used in this analysis have end dates after January 1, 2000, and starting dates before June 30, 2020.

We filtered our data to include only clinical development programs that have been tagged by Citeline as being developed for either nociceptive or neuropathic pain. The definition of neuropathic and nociceptive pain was in line with pain taxonomies provided by the International Association for the Study of Pain.[5] For example, a clinical trial for the treatment of postherpetic neuralgia was considered neuropathic pain, and treatment of postsurgical pain was considered nociceptive pain. The database encodes each unique triplet of trial identification number, drug, and disease as a data point. A single trial may therefore appear as multiple data points. The database does not indicate if a medication is intended to be marketed and sold as a prescription medication or over-the-counter medication.

We dichotomized medications to have either high or low abuse potential based on clinical trial information, evidence from other medications in the same class, and the pharmacologic properties of the compound, such as strong agonism at the μ-opioid receptor, the benzodiazepine receptor, or other receptors known to be involved in the development of addiction or chemical dependency. Consideration was given to using formal definitions of abuse from regulatory agencies, such as the Food and Drug Administration's 2019 guidance document.[6] It should be noted that the abuse potential of many medications early in their development will not be fully elucidated and would not meet the criteria set forth by these formal guidelines despite strong biologic plausibility of abuse potential. Unless a medication has compelling data to suggest that it has abuse potential, it was

classified as having a low abuse potential. Medications classified as having a high abuse potential were not limited to opioids for the purpose of this analysis.

Statistical Analysis

We apply the method of Wong *et al.*[7] to estimate the probability of successful development of pain medication programs using historical clinical trial metadata. This method was applied in Wong *et al.*[8] and Lo *et al.*[9] to investigate the clinical success rates of oncology programs and of vaccine and anti-infective therapeutic development programs, respectively. We briefly describe this method, with sections reproduced from the aforementioned articles for expositional convenience.

We say that a drug development program has reached phase i if it is observed, or can be inferred, that there is at least one trial in phase i. It is possible that a clinical trial can be repeated in multiple development paths. For example, the results of the phase 1 trial can be used as supporting evidence for the safe use of a drug, allowing that drug to be used for different indications without additional phase 1 testing. There also exist clinical trials where different drug combinations are tested for the same indication in different arms. Because of these multiplicities, computing the probability of successful development cannot be done simply by dividing the number of phase i+1 trials by the number of phase i trials for the same drug–indication pair—we need to identify specific drug development paths.

Specifically, we make the assumption that each program must make the transition from phase 1 to phase 2 to phase 3 to approval, in this order, and model the possible states in a drug development program as a Markov chain. We infer missing transitions in the development paths arising from incomplete records. This is plausible since each of these stages involves distinct predefined tests, all of which are required by regulators in any new drug application. If we observe data for phases 1 and 3 but not phase 2 trials for a given drug–indication pair, our idealized process implies that there was at least one phase 2 trial that occurred but is missing from our dataset. Accordingly, we fill in the successful completion of phase 2 in these cases. It has been demonstrated that failure to fill in missing transitions will result in underestimation of the probabilities of success.[8] A further explanation of this analysis and the number of development programs in each category is provided in Supplemental Digital Content Section 2 (http://links.lww.com/ALN/C862).

Since it is common for drug candidates to skip phase 1 and move directly to phase 2 or 3 based on initial safety trials of the drug, filling in unobserved phases will lead to a more accurate probability of successful development estimates. There exist some rare cases where phase 2 trials are skipped, as with the example of Aduhelm (aducanumab, BIIB037), the recently approved Alzheimer's medication by Biogen (USA).[10] Since skipping phase 2 trials is motivated by compelling phase 1 data and is approved by the regulatory authorities, imputing the successful completion of phase 2 trials in these cases is a reasonable approximation. We make the standard assumption that phase 1/2 and phase 2/3 trials will be considered as phase 2 and phase 3 trials, respectively. A further exploration of the validity of this assumption is provided in Supplemental Digital Content Section 2 (http://links.lww.com/ALN/C862).

We call the estimated probability of a drug development program transitioning from phase i to phase i+1 the "phase i probability of success" (PoS), and the "estimated overall probability of successful development" is defined as the estimated probability of a drug development program going from phase 1 to regulatory approval in at least one country. To simplify this terminology, we will henceforth omit the qualifier "estimated" when referring to the probability of successful development, so it should be understood that all probability of successful development values reported in this article are statistical estimates of unobservable population parameters.

The probability of a drug development program transitioning from phase i to phase j (PoS_{ij}) can be computed using the simple ratio $\mathrm{N}_j/\mathrm{N}_i$, where N_i is the number of drug development programs that have reached phase i (where i = 1, 2, or 3) of the drug development process and are not in active development between phase i and phase j (where j = 2, 3, or "A," which denotes regulatory approval, and $i < j$), and N_j is the number of drug development programs among the former that made it to phase j. $\mathrm{PoS}_{1\mathrm{A}}$ is also known as the "overall probability of success."

The probability of a drug development program transitioning from phase 1 to approval ($\mathrm{PoS}_{1\mathrm{A}}$), estimated directly using this method, is called the "path-by-path" estimate of the overall probability of successful development, and is reported for all probability of successful development calculations. It should be emphasized that because of the treatment of in-progress drug development programs, path-by-path probability of successful development estimates are not multiplicative, *i.e.*, $\mathrm{PoS}_{12} \times \mathrm{PoS}_{23} \times \mathrm{PoS}_{3\mathrm{A}} \neq \mathrm{PoS}_{1\mathrm{A}}$. In contrast, the "phase-by-phase" estimates used in some previous studies[11–14] do multiply, *i.e.*, $\mathrm{PoS}_{12} \times \mathrm{PoS}_{23} \times \mathrm{PoS}_{3\mathrm{A}} = \mathrm{PoS}_{1\mathrm{A}}$. In keeping with methods of previous analyses, standard error is reported.

In addition to the probabilities of success, we looked at the duration of clinical trials involved in the drug development programs. We consider whether a drug development program made it to the next phase and tag the associated clinical trials as being successful or failures. It is possible for clinical trials to be completed but for the development program not to progress into the next phase. By our definition, these are tagged as failures. We used the start and end dates as provided by Citeline to compute the duration of the clinical trials. The duration measures the time between the enrollment of the first subject and the date when the last subject received an intervention or was examined for getting

data for the primary outcome or the date when a trial was abandoned for any other reason. The Kaplan–Meier estimators for the clinical trials are defined by $\hat{S}_t = \prod_{i=1}^{t}(1-\frac{d_i}{n_i})$, where d_i and n_i are the number of events and number of records at risk at time i, respectively.

Results

Through analysis of the Citeline database, we counted 1,623 data points corresponding to 469 clinical development programs and 399 unique active pharmaceutical ingredients. The number of new development programs known to start in each year, by indication, from 2000 to 2020 is plotted in figure 1A. The number of neuropathic and nociceptive pain development programs launched track closely, rising between 2000 and 2010 before gradually declining.

The number of clinical development programs for compounds believed to have a high abuse potential increased by about sixfold between 2000 and 2010, from 7 programs in 2000 to 45 in 2010, before declining to 17 programs in 2014 and hovering around that level thereafter as seen in figure 1B. On the other hand, the number of development programs launched for drugs believed to have a low abuse potential averaged about 4 per year between 2000 and 2010 before rising to 16 in 2013. It then fluctuates around an average of 7.5 between 2014 and 2019.

The overall probability of successful development (PoS_{1A}) for nociceptive pain and neuropathic pain are 13.3% (standard error, 2.3%) and 7.1% (standard error, 1.9%), respectively, leading to an overall success rate of 10.4% (standard error, 1.5%) for pain medications as seen in table 1. The difference in the development rates between the two indications is driven mainly by the lower probability of transition between phase 2 and phase 3 (PoS_{23}) for neuropathic pain (38.5% *vs.* 61.3%).

From table 1, we see that the overall probability of successful development programs with high abuse potential is 27.8% (standard error, 4.6%), which is about six times greater than the overall probability of successful development of programs with low abuse potential compounds (4.7%; standard error, 1.2%). While programs with high and low abuse potential compounds have similar probability of successful transition from phase 1 to 2 (PoS_{12}; 62.4% and 67.2%, respectively), they have very different transition probabilities from phase 2 to phase 3 (84.1% *vs.* 42.6%) and from phase 3 to approval (62.8% *vs.* 20.9%).

We define a clinical trial to be a "success" if it leads to a higher phase in the development program, and define it as "failed" if the development program was terminated at that phase. Figure 2 summarizes the duration of the clinical trials, while the Supplemental Digital Content Figure 4 (http://links.lww.com/ALN/C862) shows the survival curves of the clinical trials by indication, phase, and eventual status. The duration of a clinical trial is defined as the number of days from the initiation to the conclusion of subject enrollment or trial termination. It should be noted that characterization of a particular development pathway or individual trial as a success or failure in no way reflects the medications' clinical effectiveness or lack thereof.

For those development programs targeting neuropathic pain, we see that while both failed and successful trials have similar survival curves in phase 2, failed trials typically end earlier than successful ones in phases 1 and 3. The differences between the median duration of successful and failed trials are 3.3, 0.7, and 7.2 months for phase 1, 2, and 3 clinical trials, respectively.

For clinical development programs involving nociceptive pain, successful trials typically end earlier than failed ones in phase 1, but the two have similar survivorship profiles in phases 2 and 3. The differences between the median duration of successful and failed trials are −0.37, 0.97, and 2.4 months for phases 1, 2, and 3, respectively.

We show the distributions of the durations of development, together with their fitted gamma probability density functions, by indication and phase in Supplemental Digital Content Figures 5 and 6 (http://links.lww.com/ALN/C862) for completeness.

Discussion

Our study analyzes 469 pain pharmaceutical development programs of 399 unique active pharmaceutical ingredients, an increase over the 2019 study by Hwang *et al.*,[15] which analyzed 119 pain development programs that were engaged in clinical trials between 2000 and 2013. Compared to that study, we obtain a higher probability of successful transition from phase 1 to phase 2 (PoS_{12}; 66.5% *vs.* 51.5%) and transition from phase 2 to phase 3 (PoS_{23}; 51.6% *vs.* 11.4%). They did not report probability of successful transition from phase 3 to approval (PoS_{3A}), as six out eight of the phase 3 trials they were studying failed, and the remaining two were still under development at the time of their writing. The differences in the probability of successful development can be attributed to sampling differences and the differences in the methods used to compute the probabilities.

Our study indicates that only approximately 1 in 10 phase 1 medication development programs are eventually granted marketing approval, with notable differences between medications with either high or low likely abuse potential, and between medications to treat nociceptive and neuropathic pain. This overall success rate is slightly lower than the 15.0% for central nervous system drug development programs, as reported in the study by Wong *et al.*,[7] but is similar to the success rate observed for all medications.[11] The higher probability of successful development could represent a more thorough biologic understanding of pain signaling pathways targeted by medications with high abuse potential compared to the novel mechanisms offered by alternative medications with lower abuse potential. The

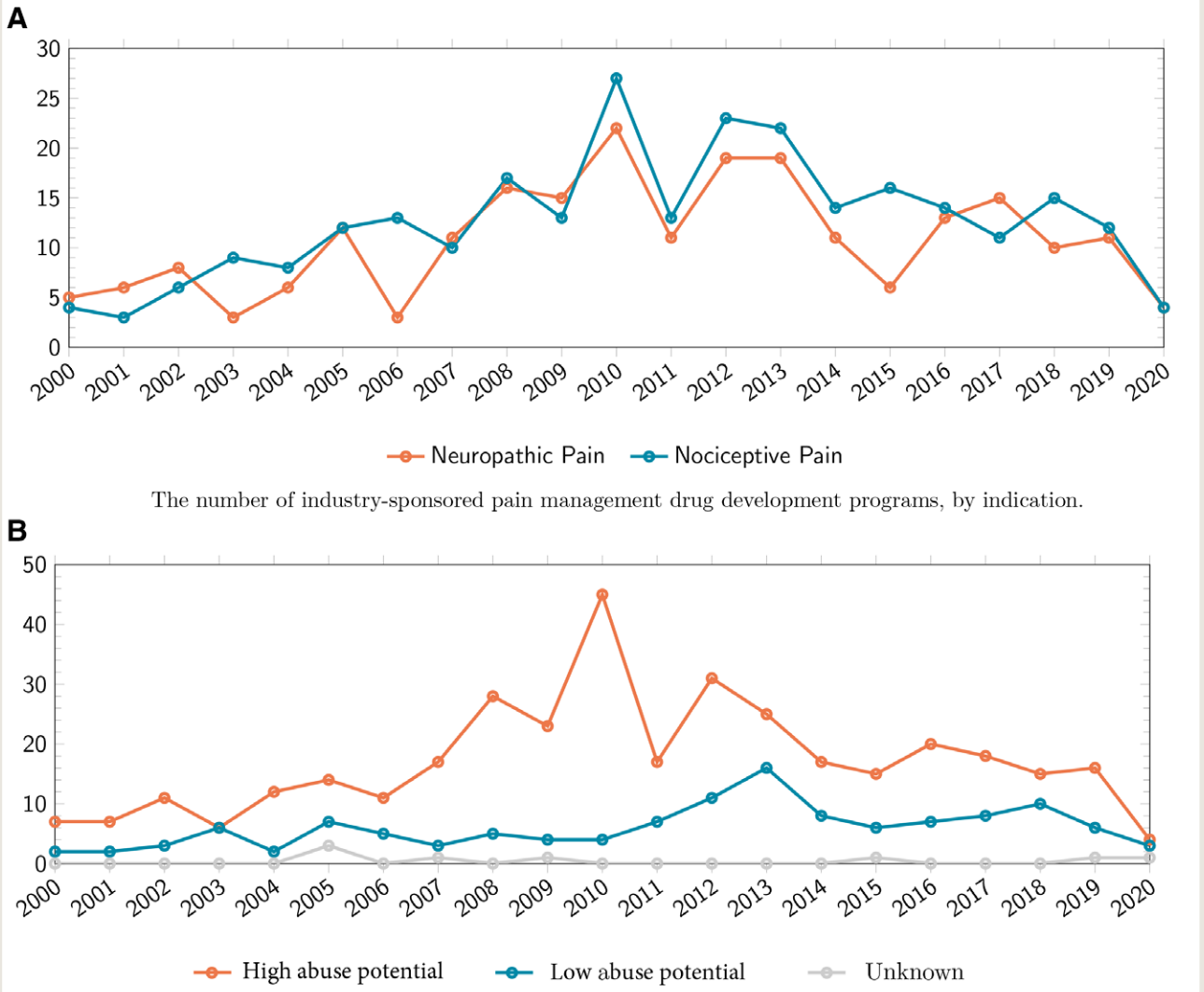

Fig. 1. The number of industry-sponsored pain medication development programs, by indication (*A*) and classified by whether the compounds were believed to have a high or low biologic plausible abuse potential (*B*) initiated per year from January 1, 2000, through June 30, 2020. The fall in 2020 can be attributed to partial data for the year.

differences in probability of successful development between nociceptive and neuropathic pain medications may also be attributable to a difference in the biologic understanding of nociceptive and neuropathic pain, to their different patient populations, or the design of studies needed to evaluate treatments in these different settings.

There are many reasons why potential medications fail to progress through the clinical development phases, including a lack of efficacy, concerning safety signals, lack of financial incentive to continue development, insurmountable regulatory issues, manufacturing issues, legal challenges, and prohibitive development costs or timeframes. When considering providing financial support for a medication development campaign, an understanding of the probability of successful development and the average time needed for development are crucial variables in modeling risk. The probability of successful development varies considerably by therapeutic class.[11] Even within a single therapeutic area, variation is observed between medications intended to treat one disease compared to others, such as human immunodeficiency virus medications achieving more frequent approval compared to other anti-infection medications.[12]

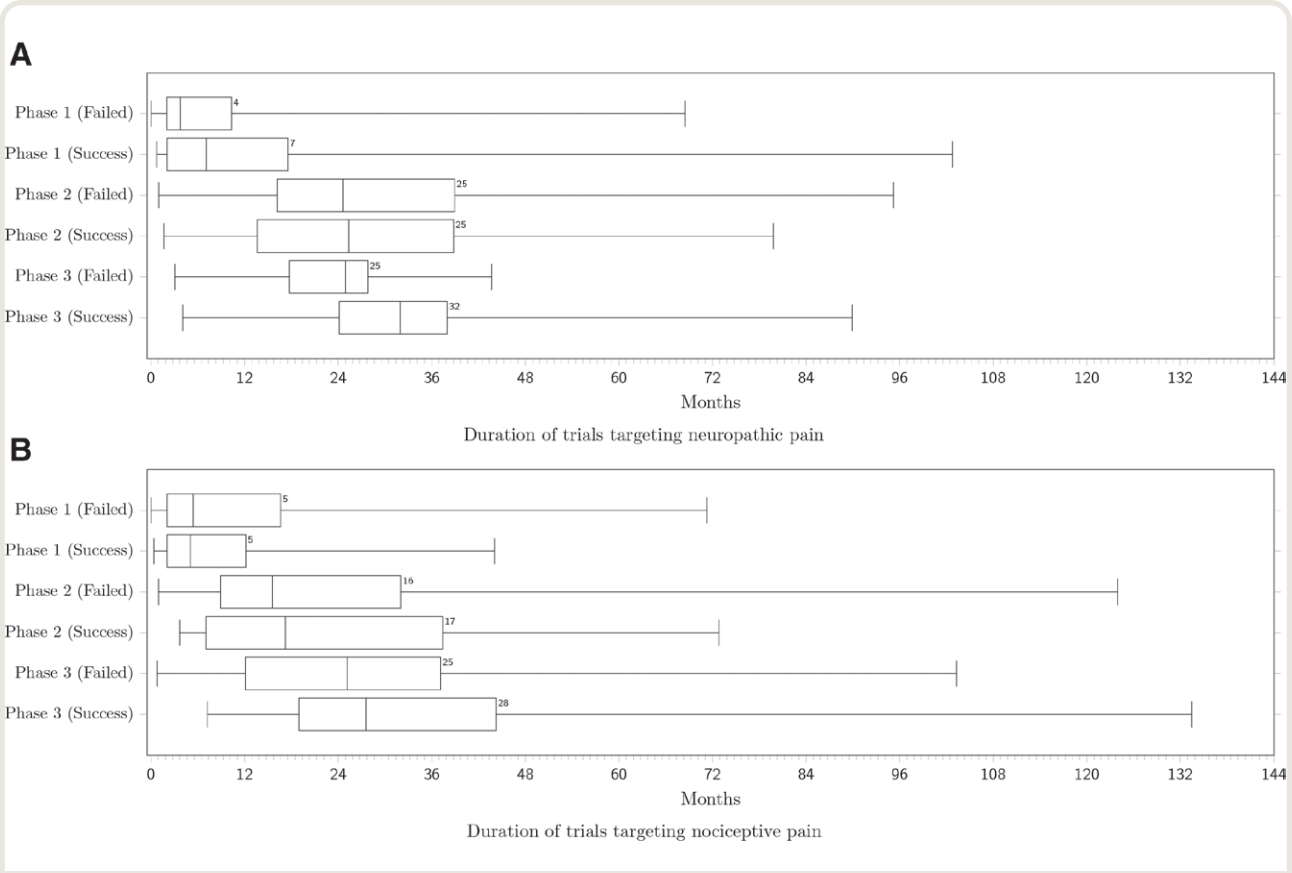

Fig. 2. Boxplots summarizing the duration of industry-sponsored pain management drug development programs, classified by development phase and indication. (*A*) neuropathic pain and (*B*) nociceptive pain. The numbers on the boxplots indicate the median duration.

Similar variation has been observed in the development of medications to treat pain.[15] The presented data add to the existing knowledge by demonstrating that specific medication attributes, such as addictive potential and therapeutic target, will alter the probability of successful overall development and probability of the transition from one phase of development to the next. The data do not allow determination of the reasons for pain medications to proceed in development or not. It is likely that each of the reasons for continued development or not are represented in the dataset with specific medication attributes increasing or decreasing the probabilities of successful development.

The challenges inherent in the design and interpretation of pain therapeutic development trials have led to the development of many innovative trial designs, including adaptive trials, clinical effectiveness trials, and enriched enrollment randomized withdrawal trials. These, however, can be both more expensive and lengthy to perform.[16] Our data indicate that the development of pain medications in large phase 3 safety and efficacy trials takes around 30 months, on average, with some trials requiring significantly greater duration. Another complication in the development of new pain medications is that animal testing using pain models does not simulate the multidimensional or subjective nature of pain.[17] Taken as a whole, these factors can lead to investors concluding that the pain medication market is relatively unattractive despite its market opportunities, high prevalence, and societal need, due to the high overall risks associated with pain therapeutic development. Nevertheless, the data indicate that in certain scenarios, certain types of assets have greater probability of successful development than others.

The comparative probability of successful development of different pain medication development programs is useful in forecasting financial performance and valuation of such programs. However, the treatment of pain has several additional peculiarities further complicating these financial assessments, such as long-term patient adherence and compliance. Using the Medication Possession Ratio, chronic compliance has been estimated to be highly variable with opioids (0.07 to 0.78) compared to the relatively high Medication Possession Ratios seen with nonopioid pain medications (0.7 and 0.81 for duloxetine and celecoxib, respectively).[18–20] This could reflect differences between the intended "as-needed" use of opioids and their actual habitual use, compared to the more consistent use of nonopioid

Table 1. Probabilities of Successful Development of Pain Medications, 2000 to 2020

	Phase 1			Phase 2				Phase 3			Overall		
Therapeutic Area	Paths	PoS_{12}	Standard Error	Paths	PoS_{23}	Standard Error	PoS_{2A}	Standard Error	Paths	PoS_{3A}	Standard Error	Paths	PoS_{1A}	Standard Error
Indication														
Pain (nociceptive)	257	69.3	2.9	160	61.3	3.9	18.1	3.3	77	37.7	5.5	218	13.3	2.3
Pain (neuropathic)	212	63.2	3.3	117	38.5	4.5	11.1	3.1	34	38.2	8.3	184	7.1	1.9
Total	469	66.5	2.2	277	51.6	3.0	15.2	2.3	111	37.8	4.6	402	10.4	1.5
Whether the compounds used are believed to have high or low abuse potential														
Low abuse potential	345	67.2	2.5	209	42.6	3.4	6.7	1.8	67	20.9	5.0	300	4.7	1.2
High abuse potential	117	62.4	4.5	63	84.1	4.6	42.9	6.8	43	62.8	7.4	97	27.8	4.6
Unknown	7	100	0.0	5	20	17.9	20	17.9	1	100	0.0	5	20.0	17.9
Total	469	66.5	2.2	277	51.6	3.0	15.2	2.3	111	37.8	4.6	402	10.4	1.5

The probabilities of success of pain management drug development programs, by indication and by whether the compounds used are believed to have high or low abuse potential, computed using data from January 1, 2000, to June 30, 2020. PoS_{12}, PoS_{23}, PoS_{2A}, PoS_{1A}, and PoS_{3A} are the probability of successful transition of pain pharmaceutical development programs from phase 1 to phase 2 (PoS_{12}), phase 2 to phase 3 (PoS_{23}), phase 1 to approval (PoS_{1A}), phase 2 to approval (PoS_{2A}), and phase 3 to approval (PoS_{3A}).

medications to treat painful pathologies such as neuropathic pain.

While opioids have well-described short-term benefits for the treatment of moderate pain, the evidence for opioids as an effective long-term treatment is controversial.[21] This ongoing controversy against a background of societal change provides an impetus for the development of consensus guidelines regarding the initiation, titration, and long-term maintenance of opioid therapy, and highlights the need to develop effective nonopioid methods for treating pain.[21]

The opioid epidemic in the United States is an ongoing, multifaceted challenge to American health care, one that continues to evolve in both nature and scope. The genesis of the epidemic is generally thought to have occurred as early as the 1980s, with the realization that opioids, when used on a chronic basis, are effective for the treatment of long-term or chronic pain.[22] These findings were published at the same time as the development and commercialization of opioids that were both easy to use and highly potent, including Vicodin in 1978 (Knoll Pharmaceuticals, USA), Oxycontin in 1996 (Purdue Pharmaceuticals, USA), transdermal fentanyl, also known as Duragesic, in 1990 (Alza Corporation, USA), and Percocet in 1999 (Endo Pharmaceuticals, USA). Finally, national concern for the undertreatment of pain led to a change in the instruments of practice, such as new joint commission guidelines.[22]

Our data suggest that pharmaceutical developers responded to increased sales of opioids with the further development of medications with high abuse potential that were not necessarily opioids. After 2010, the development of medications with high abuse potential decreased, with a rise in the initiation of development programs for (presumably) medications with low abuse potential.

Several public health and regulatory measures have been instituted at the federal level to guide development and marketing. Since April 2010, the Food and Drug Administration has required that manufacturers of opioids provide a Risk Evaluation and Mitigation Strategy, which can include financial support for physician education specifically addressing opioid use.[23] Despite widespread physician engagement, it is unclear if Risk Evaluation and Mitigation Strategy programs have resulted in more responsible opioid prescribing or improved patient outcomes.[23] The number of campaigns to develop medications with high abuse potential decreased from a peak in 2010, but it is not clear if there is a direct link between increased regulatory efforts and decreased development. The Food and Drug Administration has also strongly encouraged the development of abuse-deterrent formulations of opioids, while acknowledging that these formulations will only decrease abuse by nonoral routes, not prevent or eliminate the development of addiction or dependency.[24,25] The rapid development and deployment of abuse-deterrent formulations possibly had the unintended consequence of some patients shifting to other illicit substances such as heroin, but

rarely to other prescription opioids.[24,26,27] However, the relationship between the introduction of abuse-deterrent formulations and the rise of heroin and other illicit opioid use may be driven by numerous other factors and have a weak, if even present, causal link.[24] Since 2015, the Food and Drug Administration has also provided industry guidance, requesting studies that demonstrate the actual abuse-deterrent properties of abuse-deterrent formulations, including phase 4 postmarketing studies.[25] This additional guidance does not seem to have decreased the number of development campaigns for medications with low abuse potential between 2015 and 2020. As of 2019, abuse-deterrent formulations account for only 2% of all opioid prescriptions, and about 25% of long-acting opioid prescriptions, as multiple abuse-deterrent formulation opioid analgesics have been voluntarily withdrawn by their application holders. In addition, onerous requirements by third-party payers, such as "prior authorizations," decrease physician willingness to prescribe these costlier medications. While effective on certain levels, the shortcomings of these programs underscore the need for additional pain treatment options with a lower risk of abuse.

This study has several limitations. First, as a retrospective study examining historical trends in drug development, the presented data cannot accurately predict the success of future development programs or identify new determinants of success. Each new product under development deserves appropriate consideration and due diligence. We used a commercially available dataset of drug development programs. While efforts were made to ensure its completeness, such as manually examining data points and comparing it to resources like ClinicalTrials.gov, there is the possibility that additional medications in developing studies were not captured in the analysis. There are also limited publicly available data available on proprietary medications, and for medications about which the drug sponsor does not wish to disclose any additional information such as the compound structure or the pharmacologic profile. The indications for which a drug is under development may also be subject to change and refined as its clinical development proceeds. Additionally, drugs were only classified as either nociceptive or neuropathic, and additional classification into subtaxonomies such as diabetic neuropathy, shingles, or surgical pain was not conducted. Conversely, drugs with only these tags were also not integrated into the primary pain taxonomy for the purposes of our analysis.

In conclusion, the data presented here indicate that there has been a decrease in the development of new medications with high abuse potential, including opioids, since the peak of the opioid epidemic around 2010. There has also been a concurrent increase in the number of development programs for low abuse potential pain medications, reflecting a societal need for such a paradigm shift in the management of pain. However, the overall probability of successful development is still highest for medications with high abuse potential and medications intended to treat nociceptive pain. There are many possible reasons for this, such as a greater familiarity with nociceptive pathology, relatively expedient readouts of the trial data, or more profound analgesia with opioid analgesics. Additionally, a poor understanding of neuropathic pain pathology, a lack of biomarkers, or a lack of effective targets may be limiting the successful development of these agents. The development of effective pain treatments without the potential for abuse should continue to be the pharmaceutical industry's goal in pain medication development.

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Competing Interests

Dr. Lo has received payment from Roivant Sciences (Basel Switzerland), BridgeBio (Palo Alto, California), Atomwise (San Francisco, California), AbCellera (Vancouver, British Columbia), Annual Reviews (San Mateo, California), Apricity Health (Austin, Texas), Aracari Biosciences (Irvine, California), Enable Medicine (Menlo Park, California), Lazard (New York, New York), QLS Advisors (Cambridge, Massachusetts), Quantile Health (New York, New York), and Think Therapeutics (Cambridge, Massachusetts) and is co-founder of QLS Advisors, a healthcare analytics and consulting company. The other authors declare no competing interests.

Correspondence

Address correspondence to Dr. Maher: 600 North Wolfe Street, Baltimore, Maryland 21287. dermotpmaher@gmail.com. This article may be accessed for personal use at no charge through the Journal Web site, www.anesthesiology.org.

Supplemental Digital Content

Supplementary Description of Methods and Analyses, http://links.lww.com/ALN/C862

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