The State of Innovation in Pain and Addiction

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BIO INDUSTRY ANALYSIS
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Where breakthroughs begin

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Pain and Addiction Therapeutics

Introduction

This report follows BIO's 2018 publication on pain and addiction R&D and investment trends. The 2018 report was part of a series of reports on highly prevalent chronic diseases that spotlighted underfunded therapeutic areas relative to their overall healthcare system burden and prevalence. The report demonstrated that venture investment for pain and addiction drug development was low relative to the overall healthcare system cost of these diseases.[1] Updated data found in this report illustrate that this discrepancy remains in place five years later, with pain and addiction drug development failing to benefit from the surge in biotech investment seen other areas in recent years. In fact, the amount of *venture capital (VC) raised for both pain and addiction companies in the U.S. in 2021 was $228 million, representing only 1.3% of total therapeutic VC funding in the U.S. In the same year, oncology companies raised $9.7 billion, or 38.3% of total therapeutic VC funding in the U.S.* This is highly concerning, as recent estimates show that societal costs in the U.S. for pain and addiction are in the trillions of dollars and more than one hundred million people now suffer from pain or addiction (**Figure 1**).

This report examines the impact that anemic funding has had on the clinical pipeline over the past five years. Additionally, this report provides updated data on clinical success rates, failed mechanistic strategies, and new trial initiations. Part I of the report focuses on the state of pain therapeutic innovation and Part II focuses on addiction therapeutics. These sections are followed by a discussion that examines potential considerations and solutions to this public health crisis. The appendix contains an updated categorization of all unique chemical entities marketed in the U.S. for pain and addiction.

[1] Thomas, D., Wessel, C. BIO Industry Analysis. The State of Innovation in Highly Prevalent Chronic Diseases, Volume II: Pain and Addiction Therapeutics, (2018) (www.bio.org/iareports)

DISEASE PREVALENCE AND SOCIETAL COSTS VS. VENTURE CAPITAL FUNDING FOR CANCER, PAIN, AND ADDICTION

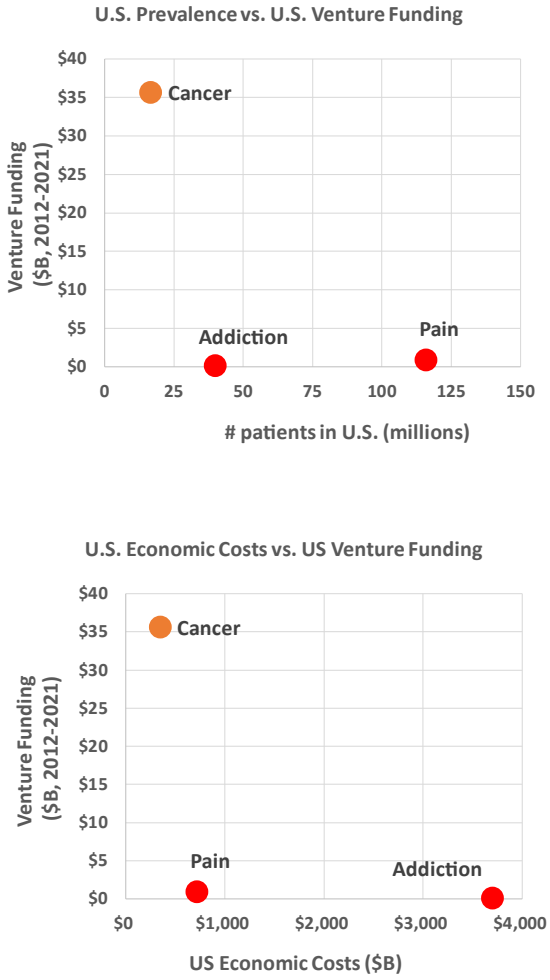

Figure 1. Venture Capital Funding for Oncology, Pain, and Addiction plotted vs. a) prevalence in the U.S. and c) total economic costs in the U.S.[2,3,4] Venture Capital funding is for U.S. therapeutic companies 2012-2021.

[2] Prevalence data: In 2019, The Surveillance, Epidemiology, and End Results Program (SEER) estimated **16.6 million cancer** cases in the U.S. (https://seer.cancer.gov/statfacts/html/all.html). **Pain** prevalence was **116 million** in 2011 based on the IOM report in 2012 (U.S. Institute of Medicine Committee on Advancing Pain Research, Care, and Education. Substance use disorder direct healthcare costs was estimated to be $118B in 2019 by Recovery Centers of America (insert link). **Substance Use Disorder** reached **40 million** according to the 2020 National Survey of Drug Use and Health (NSDUH) (https://www.samhsa.gov/data/release/2020-national-survey-drug-use-and-health-nsduh-releases)

[3] Economic cost data: Estimated U.S. economic costs for substance use disorder reached $3.7 trillion in 2019, according to the Recovery Centers of America (https://recoverycentersofamerica.com/resource/economic-cost-of-substance-abuse-disorder-in-united-states-2019). Economic costs include indirect costs due to job losses, early deaths, other social costs (such as criminal activity) in addition to direct healthcare costs. For pain, U.S. economic costs were estimated by the Institute of Medicine to be $721 billion in 2019 dollars (Gaskin, D., et al. Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research. The Economic Costs of Pain in the United States. Institute of Medicine (US) Committee on Advancing Pain Research, Care, and Education. Washington (DC): National Academies Press (US) (2011) $635 billion in 2010. U.S. economic cost for cancer was $342 billion in 2017, ($358 billion in 2019 dollars) according to the American Cancer Society, the International Agency for Research on Cancer, and the Union for International Cancer Control.

[4] Direct Healthcare spending data (Not shown): Cancer-attributable costs for medical services and prescription drugs in the U.S was $198B in 2015 ($225 in 2019 dollars) according to a 2022 report from the National Cancer Institute of the U.S. NIH, https://progressreport.cancer.gov/after/economic_burden. Estimated direct healthcare cost for pain is $300 billion ($340 in 2019 dollars) according to the 2012 report by the U.S. Institute of Medicine Committee on Advancing Pain Research, Care, and Education. Substance use disorder direct healthcare costs is estimated to be $118 billion in 2019 by Recovery Centers of America (https://recoverycentersofamerica.com/resource/economic-cost-of-substance-abuse-disorder-in-united-states-2019).

Key Takeaways for Pain Therapeutics

- The industry-wide clinical pipeline for pain therapeutics consists of 124 active clinical-stage drug programs vs 220 in our report five years ago, a decline of 44%.
    - For programs with novel chemical entities, there are now 75 vs. 125 programs five years ago, a decline of 40%.
    - The majority of novel chemical entities in the clinical pipeline act on targets with Food and Drug Administration (FDA) approval history. Only 26 of the 75 programs with novel chemical entities have new targets.

- Clinical success in pain drug development remains extremely difficult for novel drugs, with only a 0.7% probability of FDA approval from Phase I, compared to an overall 6.5% success rate for novel drug programs across all diseases. Phase III success rates were lower than all major disease categories with only one in five progressing to New Drug Application (NDA)/ Biologic License Application (BLA) filing stage.

- Excluding drugs for migraine headaches, there have been no drugs with novel targets approved in the last five years for pain. Seven novel chemical entities for migraine headaches were approved, all targeting the Calcitonin Gene-Related Peptide (CGRP) pathway. Three additional novel chemical entities were approved during this same five-year period for targets with an FDA approval history: one anesthetic drug for surgery targeting the gamma-amino butyric acid (GABA) pathway, one serotonin receptor agonist, and one new opioid drug. Thus, the total available Active Pharmaceutical Ingredients (APIs) for pain in the U.S. increased from 77 to 87, and the total number of targets for marketed drugs increased from 12 to 13. (**Appendix A1**)

- Venture capital into U.S. companies with novel drug programs in pain totaled $0.86 billion over the last 10 years. By comparison, oncology venture investment raised during the same 10 years was $35.7 billion.

Key Takeaways for Addiction Therapeutics

- The clinical pipeline for addiction therapeutics increased 34% since our report five years ago. The addiction pipeline now consists of 39 clinical-stage drug programs vs. 29 five years ago. However, the majority of drug programs (77%) target previously approved pathways. There are only eight drug programs with novel chemical entities specific to treating Opioid Use Disorder

- Novel addiction treatments have the lowest Phase II success rate, with 14 of 15 Phase II programs failing over the last decade. The lack of recent Phase III transitions made it infeasible to calculate an overall success rate for addiction.

- Only one new chemical entity was approved by the FDA for substance use disorder in the last five years. However, this drug is new only to the U.S., as it had been marketed in the U.K. since 1992 for managing opioid withdrawal symptoms. Thus, the total available APIs for substance use disorders in the U.S. has increased from 13 to 14. (**Appendix A2**)

- Venture investment into companies with novel addiction drug programs over the last 10 years is estimated at $130M, 270 times less than oncology.

List of Figures and Charts

INTRO

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Part I. Pain

Fate of the 2017 Clinical Pipeline for Pain

The current status of the 2017 clinical pipeline programs is outlined in **Figure 2**. Of the 220 programs active in 2017, 77% are now suspended. Only 13% (29) of the original programs remain in active clinical trial development while 10% (21) transitioned to FDA approval. Of the 21 approved drugs, seven target CGRP (Calcitonin Gene-Related Peptide, a new target for migraine), and 14 programs work through well-established targets for pain (*e.g.* opioid receptors, cyclooxygenases, and sodium channels).

FATE OF THE 2017 CLINICAL PIPELINE FOR PAIN

2017 Status		2022 Status		
Phase	**Count**	**Remains in Clinic**	**Approved**	**Suspended**
I	65	10	0	55
II	88	11	1	76
III	53	7	11	35
NDA/BLA	14	1	9	4
Total	**220**	**29**	**21**	**170**
Percent	**100%**	**13%**	**10%**	**77%**

Figure 2. The status of programs active in the October 2017 clinical pipeline for pain (published January 2018) and current status as of October 2022. Suspended programs (73.6%), are either confirmed dropped programs by the company (*i.e.* removed from company websites), or inactive programs with no updates in more than three years (3.6%).

Of the 65 programs in Phase I, only 10 remain in the clinic (15%) and 55 are now suspended or inactive (84%). For Phase II programs, 76 of the 88 programs were suspended (87%), 11 of 88 (12%) remain in clinic and one transitioned through Phase III and FDA approval over the last five years. Of the 53 Phase III programs in 2017, 11 transitioned to FDA approval, 35 were suspended (66%) and seven (13%) remain in the clinic. All three BLA filing status programs were FDA approved, but only 6 of 11 NDA filing status programs were FDA approved.

Current Clinical Pipeline for Pain Therapeutics

The current clinical pipeline contains 124 clinical programs across all pain indications. This compares to 220 programs in 2017, a decrease of 44%. Although, 191 of the original 2017 programs are no longer in the pipeline as mentioned above, 95 new programs have been added over the last five years.

There is a wide variability in pipeline net change by pain indications, with some indications experiencing steep declines and others increasing over the five-year period. Of the 18 indications for pain listed in **Figure 3**, nine saw a decline of 50% or more since 2017. Postherpetic neuralgia, acute pain, migraine, chronic pain, low back pain, moderate to severe pain, each have 50% or fewer programs in 2022 vs 2017. Inflammatory pain and HIV-associated polyneuropathy did not have any active programs in the clinic as of October 2022. However, osteoarthritic pain and postsurgical pain increased in total net programs over the five-year period.

CLINICAL PIPELINE FOR PAIN BY INDICATION, 2017 VS 2022

Indication Name	2017	2022	% Change
Osteoarthritis Pain	16	18	13%
Neuropathic Pain	25	18	-28%
Pain Indications	19	15	-21%
Postsurgical Pain	12	15	25%
Migraine and Other Headaches	29	11	-62%
Diabetic Peripheral Neuropathy	12	8	-33%
Fibromyalgia	8	7	-13%
Chronic Pain	19	6	-68%
Moderate to Severe Pain	11	5	-55%
Acute Pain	14	4	-71%
Cancer Pain	6	4	-33%
Chronic Low Back Pain	23	4	-83%
Anesthesia	5	3	-40%
Chemotherapy Induced Peripheral Neuropath	3	3	0%
Postherpetic Neuralgia (PHN)	10	2	-80%
Sciatica	2	1	-50%
Inflammatory Pain	5	0	-100%
HIV-Associated Polyneuropathy	1	0	-100%
Total	**220**	**124**	-44%

Figure 3. The current pain pipeline by indication, sorted by highest to lowest number of programs in 2022. Biomedtracker's indication pathway categories are assigned to each program.

CLINICAL PIPELINE FOR PAIN BY PHASE, 2017 VS 2022

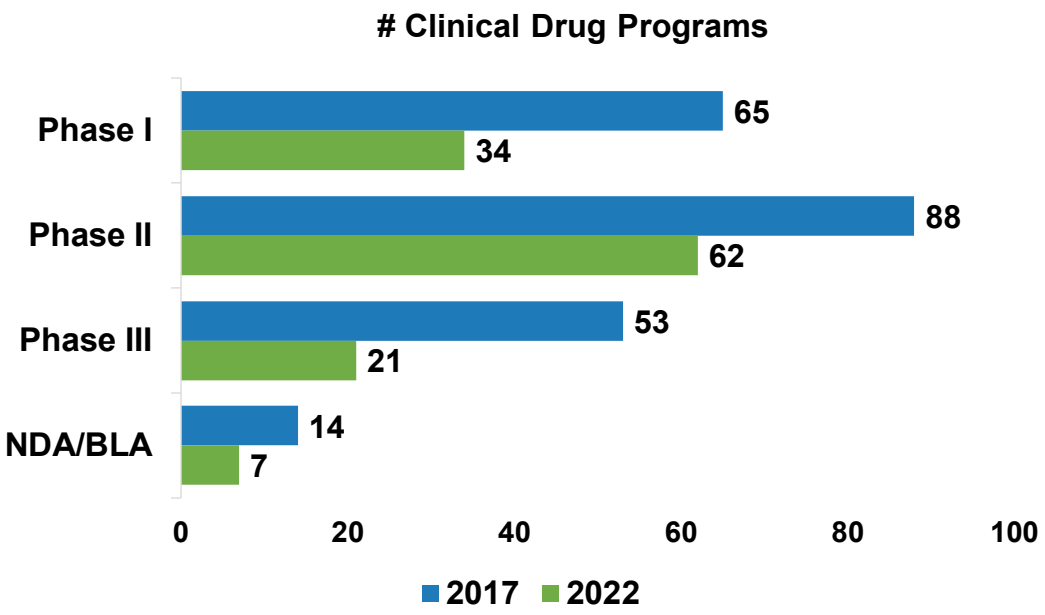

Figure 4. The pain pipeline by phase of development, October 2017 vs October 2022. Drug programs were downloaded from Biomedtracker and individually assessed for active status.

All four phases of the pain pipeline saw a decline (**Figure 4)**. The highest number of programs remains Phase II (62) followed by Phase I (34). There are now only 21 Phase III programs, down from 53 in 2017. NDA and BLA active filings are currently at seven, down from 14 in 2017. This 50% drop in the number of programs at the NDA/BLA filing stage, is due to the approvals of CGRP migraine drugs and reformulated products as well as the lack of successful Phase III programs.

Innovation Assessment of the Pain Clinical Pipeline

Clinical programs for pain with novel chemical entities declined 40%, from 125 back in 2017 to just 75 in 2022 (**Figure 5**). There was also a larger decline (48%) in the clinical pipeline for reformulated and repurposed drugs, from 95 to 49.

CLINICAL PIPELINE FOR PAIN BY DRUG TYPE, 2017 VS 2022

Innovation Type	2017	2022	% Change
Reformulated/Repurposed	95	49	-48%
Novel Chemical Entity	125	75	-40%
Total	220	124	-44%

Figure 5. The pain pipeline by program innovation type October 2017 vs. October 2022. Note this shows the number of programs, not number of specific APIs, thus the number of actual unique chemical entities in the clinic is slightly less than the number of indication pathways the drug can be developed.

Another way to assess innovation is to look at targets pursued in the clinic. This type of assessment shows the potential first-in-class breadth in the pipeline. For analyzing targets, we separated drug targets into three categories: 1) totally novel targets across all diseases (no FDA approval history), 2) new targets for pain, but with an FDA approval in another disease (usually repurposed drugs), and 3) targets that already have an FDA approved drug specifically for pain (usually reformulation programs). There are also a few programs with unknown targets but are described as reformulated or repurposed products by the company.

These categories are summarized at the top of **Figure 6**. There are now 26 clinical pain programs with a novel target. Thus 78% of pain programs in the clinic target a gene product previously validated by a prior FDA approval.

These 26 programs with a novel target are pursuing a total of 21 targets. Although seven novel targets in the 2017 pipeline are no longer active, 13 novel targets have been added. These new targets include epoxide hydrolase, Monoacylglycerol lipase, bradykinin receptors, axon termini, tricarboxylic acid cycle (TCA), transient receptor potential melastatin 8 (TRPM8), imidazoline receptor, IL-1/IL-19 cytokines, protease activated receptor, metalloproteinase, albumin cyclic peptide, nuclear factor (NF) -kappa B. There are also five targets with FDA approval appearing in the 2022 pipeline: histone deacetylase (HDAC), P1 adenosine receptors, an antibiotic target, sigma-1 receptor, and thrombin.

Program targets are listed in **Figure 6** according to their 2017 novelty status. CGRP remains listed as novel as these were first approved starting in 2018. Although cannabinoids have recently been approved for anorexia associated with weight loss in patients with AIDS and for certain seizures indications, there is no approval for pain. Six nerve growth factor (NGF) pain programs have been suspended and three remain in the clinic. NGF remains listed as a novel target as this only applies to anti-NGF strategies and NGF receptor antagonist strategies. There was a recombinant NGF approved in 2018 for a non-pain indication, but this is grouped separately from NGFR agonist programs.

Prior targets that are no longer in the clinic include: fatty acid hydrolase, epidermal growth factor nuclear receptor (EGR), innate repair receptor (IRR), lysophosphatidic acid (LPA) receptors, reactive oxygen species (ROS)/free radical scavengers, prostaglandin receptors, angiotensin receptors, nitric oxide synthase, amino-bisphosphonates, neprilysin, or the wingless-related integration site signaling (Wnt) pathway in the pipeline. In the decade prior to 2018, examples of failed target strategies included programs targeting the neurokinin-1 (NK-1) receptor, p38 mitogen-activated protein (MAP) kinase, histamine H3 receptor, mitochondrial peripheral benzodiazepine receptor (PBR), and collapsin response mediator protein 2 (CRMP-2).

In our previous report there were 12 mechanistic strategies for FDA approved drugs used to treat pain. **Figure 6** shows the number of programs for these original 12 targets is now 70, down from 157 five years ago. Within this group, the opioid programs have declined 74% (54 down to 14), vanilloid receptor programs declined 44% (9 down to 5), and most of the other strategies declined by only a few programs. Three of the 12 target classes are no longer being pursued in the clinic. However, it was not just reformulated opioid drug programs that declined, repurposed drug programs also decreased from 29 to 26 programs. Five targets in the repurposed category in 2017 are no longer being pursued.

CLINICAL PIPELINE FOR PAIN BY TARGET CLASS, 2017 VS 2022

Summary Table for Target Type

	2017	2022
New Drug Targets (as of 2018)	26	26
FDA approved target (ex-pain)	29	26
FDA approved target (for pain)	157	70
Not disclosed	8	2
Total	**220**	**124**

Targets with FDA approval history for pain prior to 2018

	2017	2022
Sodium channels	21	20
Opioid receptors	54	14
Cyclooxygenase	14	12
Adrenergic receptors	6	6
Vanilloid receptors	9	5
SER receptors	12	4
Glutamate modulation	6	3
GABA modulation	4	3
SNARE	2	1
Calcium channels	10	0
Monoamine transporters	3	0
Phosphodiesterases	0	0
Reformulation, ND	16	2
Subtotal	**157**	**70**

Targets with prior approval history, but new for pain

	2017	2022
Cannabinoid receptors	7	8
Glucocorticoid receptors	1	3
Stem cells	2	3
Nicotinic Acetylcholine Receptors	0	3
P2 adenosine receptors	1	2
Chemokine receptors	1	1
Somatostatin Receptors	1	1
Histone Deacetylase (HDAC)	0	1
P1 adenosine receptors	0	1
Antibiotic target	0	1
sigma-1 receptor	0	1
Thrombin	0	1
Prostaglandin receptors	2	0
Angiotensin receptors	4	0
Nitric oxide synthase	5	0
Aminobisphosfonate	4	0
Neprilysin	1	0
Subtotal	**29**	**26**

New Drug Targets (No approval history before 2018)

	2017	2022
NGF/NGFR (antagonist)	6	3
AAK (AP2 Associated Kinase)	1	2
IL-10 receptors	1	2
Multi-target [vapor anaesthetic]	0	2
CGRP receptors	7	1
Chondroitinase	1	1
PAC receptor	1	1
Glycine transporters	1	1
HGF receptors	1	1
Epoxide Hydrolase	0	1
Monoacylglycerol lipase	0	1
Bradykinin receptors	0	1
Axon termini	0	1
TCA Cycle	0	1
TRPM8 (CMR1)	0	1
Imidazoline Receptor	0	1
IL-1/IL-19	0	1
Protease activated receptor	0	1
metalloproteinase	0	1
Albumin cyclic peptide	0	1
NF-Kappa B	0	1
Fatty acid hydrolase	2	0
EGR nuclear receptors	1	0
Innate Repair Receptor	1	0
LPA receptors	1	0
ROS/free radical scavanger	1	0
WNT pathway	1	0
Subtotal	**26**	**26**

Figure 6. Target strategies in the current pain pipeline, October 2022 vs. October 2017 (published January 2018). The drug targeting strategy listed is based on the primary target of the novel compound under development, and categorization is as of 2017. CGRP drugs were approved starting in 2018, creating a 13th target class for pain. However, they are listed above as novel according to their 2017 status. NGF is also listed as novel as of 2017 – although no antagonists (anti-NGF mAbs) have been approved, there was a recombinant NGF approved (Oxervate) for Ophthalmic Wound Healing in 2018. For combination drugs, only the most active pain component is listed.

Clinical Development Success Rates for Novel Pain Drugs

Looking at novel molecule success rates, we found pain to have one of the highest clinical trial failure rates of any major disease category.[5] As shown in **Figure 7**, novel pain drug development's current overall probability of success from Phase I to approval is 0.7%, compared to 6.5% across all disease area programs for novel drug candidates. Additionally, this is less than the Phase I to approval success rate observed in our previous report (2%) which examined data from 2006-2015. It should be noted that the current overall industry probabilities have also decreased, from 7.7% to 6.5%.

Phase I saw a decline in the most recent decade, dropping from 57% to 40%. Novel pain drug development programs in Phase II had a 14% chance of success in transitioning to Phase III, which is similar to the 16% success rate calculated in our previous report. Phase III success cratered to 21%, with only 5 of 24 Phase III programs reaching NDA/BLA filing compared to 39% for the 2006-2015 time period. Although five failed NGF programs contributed to the low Phase III success rate, there were 12 additional targets with suspended programs.

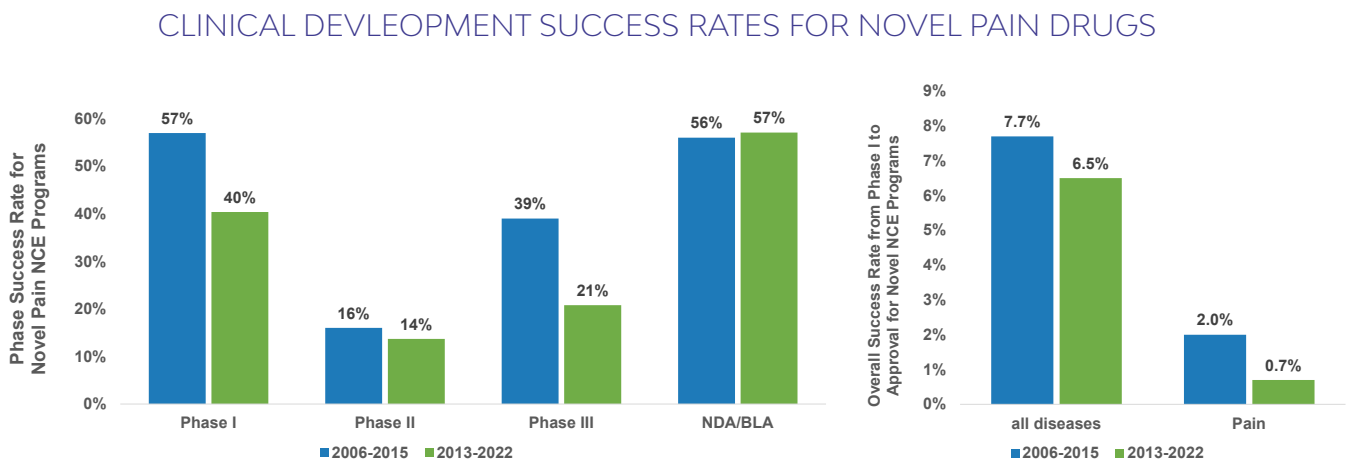

Figure 7. Clinical success rates for novel drug programs (both small molecule NMEs (New Molecular Entities) and new biologic drug programs) across all pain indications. Left: Phase success rates comparing two 10-year periods, 2006-2015 (from BIO's 2018 report) and the latest decade 2013-2022. Right: Likelihood of Approval from Phase I to Approval. Total NME transitions: N=244 for pain 2006-2015, N=225 for pain 2013-2022, and N=8,476 for all diseases 2006-2015, N=10,741 for all diseases 2013-2022.

[5] Thomas, D., et al. BIO, 2021, and PharmaPremia from Citeline (Accessed at www.bio.org/iareports)

Trends in Investment and Clinical Trial Starts for Pain Therapeutics

Venture investment into U.S. companies with lead pain products from 2012 to 2021 totaled $1.8 billion. However, only $0.86 billion went to companies developing novel drug molecules, as 48% of pain funding went to companies developing reformulated or repurposed drugs.[6]

No trend can be identified in the novel pain data for the decade, with seven years below $200 million and three years in the $200-$300 million range (**Figure 8)**. However, there is a clear upward trend for novel oncology drug development, to roughly $10B in 2021 from below $1B in 2012. This totals to $35.7 billion over the last decade, 41x more than investment in pain. During 2012 to 2021, 11 companies with lead drugs in pain were financed each year, on average. By comparison, there were 109 oncology companies financed each year, suggesting that early-stage investors currently prioritize other disease areas, such as oncology, over pain.

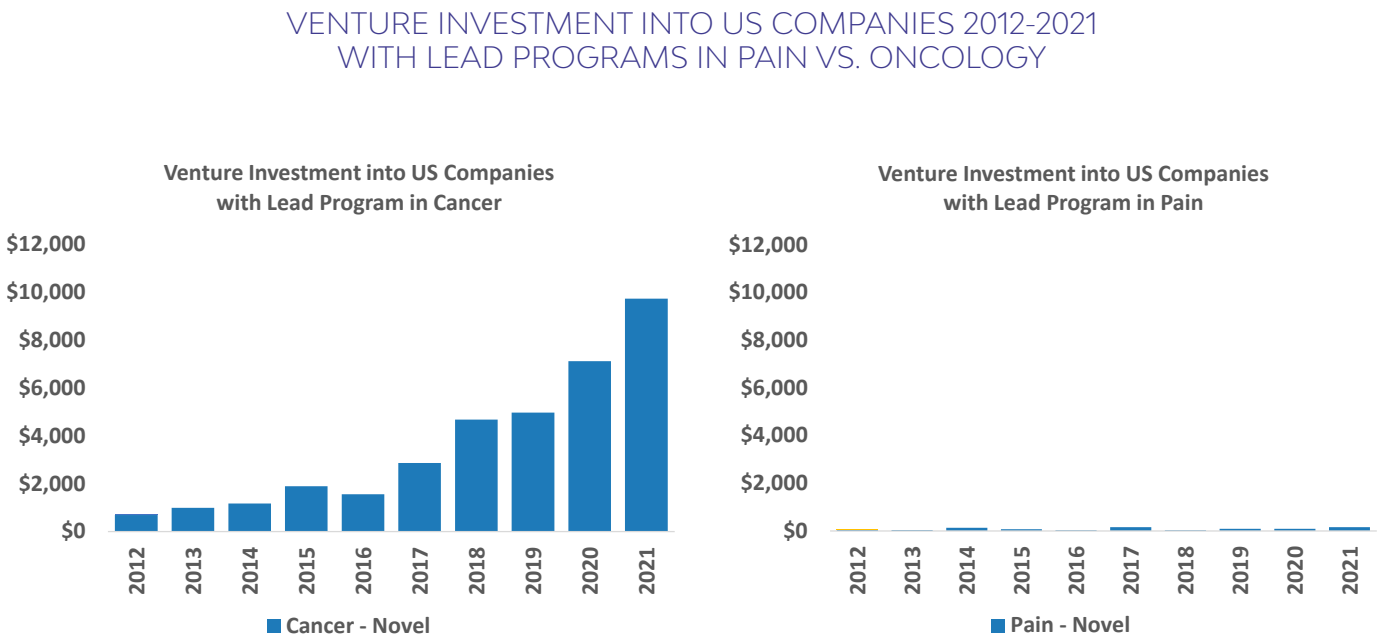

Figure 8. Left: Venture funding of companies with lead products in oncology, 2012-2021. Right: Venture funding of companies with lead products in pain, 2012-2021.

For public company investment, pain-focused emerging therapeutic companies raised a total of $5.5 billion through IPOs and FOPOs for the last decade. This compares to $155.6 billion for oncology. No discernable trend can be seen in the year-to-year amounts raised for pain companies

[6] To calculate the level of private company venture capital investment into pain, we identify companies with lead compounds in pain and sum their total venture funding each year. This can underestimate the venture funding for some companies, as some companies have broader pipelines outside their lead programs. Although most capital in a small company will tend to be used for a lead asset, this is not always the case. A more comprehensive method for assessing investment across the industry is based on quantifying the number of clinical trials starts by phase over time. For this broader industry R&D activity (which includes large and small public companies), we turn to the number of trial starts. Approximating average dollar costs to this would give an approximate spend per year but we have left this to number of trials due to variability and lack of detailed data of such numbers.

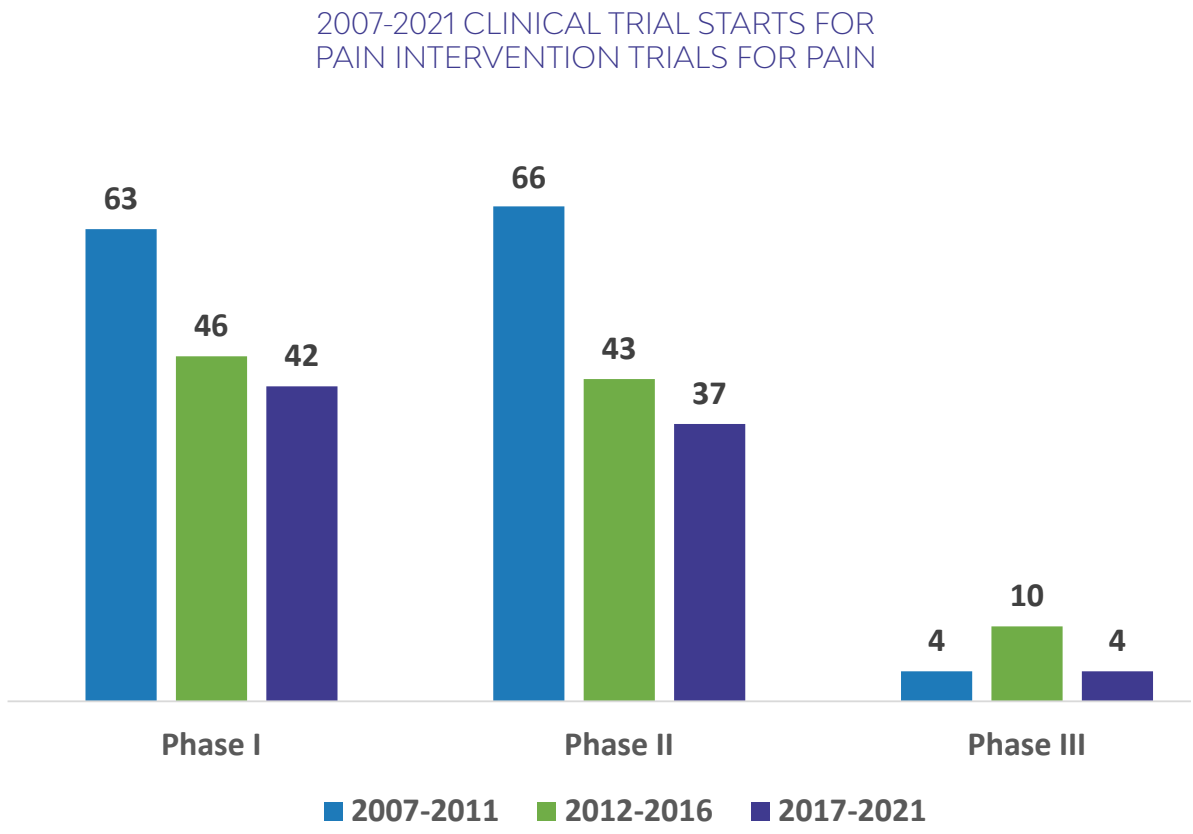

Figure 9. Clinical trial starts for Pain, 2007-2021 in five-year periods by phase. TrialTrove data for 2007-2016 was accessed October 2017 and data for 2017-2022 was accessed September 2022. Trials were individually assessed for novelty of drug (no prior approval history of the active compound) and trial phase cohorts de-duplicated.

Figure 9 shows clinical trials with novel products initiated since 2007, displayed in three five-year periods. A total of 315 novel clinical trials have been initiated over the 15 years (TrialTrove dataset). The number of clinical trial starts has declined over time, with 133 initiations occurring in the first five-year period (2007-2011), 91 in the second (2012-1016), and only 83 in the third (2017-2021).

The trend of consecutive declines over the five-year periods holds for Phase I and II, but not phase III. Phase III trial starts for novel drugs experienced an increase during the 2012-2016 period (from a total of four in 2007-2011 to 10). This is in part due to an increase in CGRP programs advancing to Phase III. The period following this (2017-2021) returned to four Phase III starts. Phase I and II starts show similar trends across the three five-year periods.

Part 2. Addiction

Fate of the 2017 Addiction Clinical Pipeline

Figure 10 shows the fate of drug programs by phase of development in 2017. Examination of the current status of the 2017 clinical pipeline for addiction therapeutics showed that 45% (13 of 29) of the programs were suspended and 45% remain in the clinic as of October 2022. The remaining 10% (3) were approved by the FDA during the last 5 years. Two of the approved drugs were reformulations of naloxone and buprenorphine for opioid use disorder. One approved drug (lofexidine) is new to the U.S. but has been marketed in the U.K. since 1992 for managing opioid withdrawal symptoms. Most of the clinical pipeline programs (25 of 29) were in early Phase I or II trials in 2017 and account for most of the suspended programs. There were only two drugs in Phase III at that time with the outcome split: one suspended and one approved.

FATE OF THE 2017 CLINICAL PIPELINE FOR ADDICTION

2017 Status		2022 Status		
Phase	**Count**	**remains in clinic**	**Approved**	**Suspended**
I	13	7	1	5
II	12	5	0	7
III	2	1	0	1
NDA/BLA	2	0	2	0
Total	**29**	13	3	13
Percent	**100%**	45%	10%	45%

Figure 10. The current status of programs from the October 2017 clinical pipeline for Addiction. Suspended programs (45%), are either confirmed dropped programs by the company (i.e. removed from company websites), or inactive programs with no updates in more than three years.

The Current Clinical Pipeline for Addiction Therapeutics

The current clinical pipeline for addiction has 39 clinical programs vs 29 five years ago, an increase of 34%. As shown in **Figure 11**, 17 are for treatment of opioid use disorder. This indication has seen the largest increase (183%) since 2017. Alcohol and smoking use disorders have nine and eight programs, respectively. Both indications have seen an increase since 2017. For cannabis, meth, and cocaine combined there are only five programs.

CLINICAL PIPELINE FOR ADDICTION BY INDICATION, 2017 VS 2022

Substance Abused	2017	2022	% Change
Opioids	6	17	183%
Alcohol	7	9	29%
Nicotine	6	8	33%
Cannabis	2	2	0%
Methamphetamine	1	1	0%
Cocaine	3	1	-67%
General	4	1	-75%
Total	29	39	34%

Figure 11. The change in the addiction clinical pipeline, October 2017 vs October 2022. Drug programs were downloaded from Biomedtracker and individually assessed for active status. Top: Addiction pipeline by phase of development and by novelty criteria: Novel drugs are those with no history of approval for the active chemical entity whereas non-NME drugs are reformulated or repurposed products. For combination drugs, only the novel active component is used to categorize as novel. If no novel compound is present in the combination drug, the "Non-NME" label is used. Bottom: Phase by type of addiction. General addiction includes many Phase I programs that are not specified as to the type of addiction, as well as others that are designed to treat a variety of addiction disorders.

Figure 11 shows programs for reformulations, repurposed drugs, as well as novel chemical entities. For programs specific to treating Opioid Use Disorder, only 8 of the 17 listed in **Figure 11** are programs with novel chemical entities.

Figure 12 shows addiction programs by phase of development. Each trial phase has increased since 2017, but the number of NDAs has declined from two to one. There are now currently 18 in Phase I, 15 in Phase II, and five programs in Phase III.

CLINICAL PIPELINE FOR ADDICTION BY PHASE, 2017 VS 2022

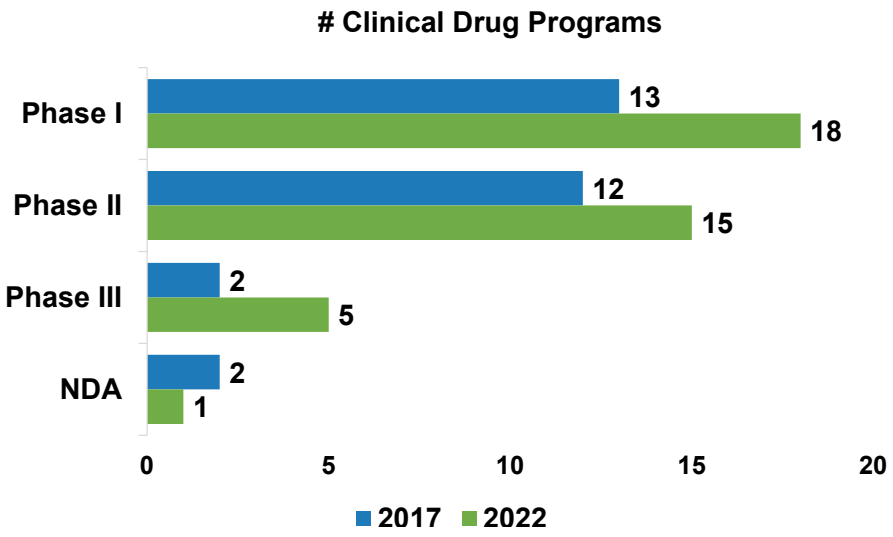

Figure 12. The current addiction clinical pipeline (as of October 2022). Drug programs were downloaded from Biomedtracker and individually assessed for active status. Top: Addiction pipeline by phase of development and by novelty criteria: Novel drugs are those with no history of approval for the active chemical entity whereas non-NME drugs are reformulated or repurposed products. For combination drugs, only the novel active component is used to categorize as novel. If no novel compound is present in the combination drug, the "Non-NME" label is used. Bottom: Phase by type of addiction. General addiction includes many Phase I programs that are not specified as to the type of addiction, as well as others that are designed to treat a variety of addiction disorders.

Innovation assessment of the Current Addiction Clinical Pipeline

More than half of the 39 clinical programs in the current addiction pipeline are novel chemical entities (**Figure 13**). This is an increase of 53% from the 15 new chemical entities observed in the 2017 pipeline. There are 16 clinical programs testing reformulated and repurposed drugs for addiction, in-line with the 14 observed in the 2017 pipeline.

CLINICAL PIPELINE FOR ADDICTION BY CHEMICAL TYPE, 2017 VS 2022

Program Type	2017	2022	% Change
Novel Chemical Entity	15	23	53%
Reformulation/Repuropsed	14	16	14%
Total	29	39	34%

Figure 13. The current addiction clinical pipeline (as of October 2022) by type of drug being developed. Programs designated NME by FDA and Biomedtracker are separated from non-NME (reformulations and repurposed drugs). Drug programs were downloaded from Biomedtracker and individually assessed for active status.

Breaking the addiction pipeline into target strategies reveals 30 of the 39 programs (77%) are targeting pathways with an FDA approval history. As shown in **Figure 14**, the majority (20) use similar mechanisms as previously approved drugs for addiction, while others (10) are using mechanisms that have been proven effective in other diseases. Among the previously FDA approved addiction target groups, 14 of the current programs target opioid receptors and five use a monoamine modulation approach for addiction. For programs using validated targets in other diseases, cannabinoid receptors, glutamate receptors, PDE (phosphodiesterases), and GABA receptors remain top targets. Peroxisome proliferator-activated receptors (PPARs), adrenergic receptors, and calcium channels were targets observed in our previous report that no longer have active trials.

Novel targets for addiction include nicotinic acetylcholine receptors (3 programs), 11-beta-hydroxylase (2 programs), and one program each for aldehyde dehydrogenase and orexin receptors. Two novel antibody programs are in trials for cocaine and methamphetamine. The vaccine and engineered cholinesterase programs to treat cocaine substance abuse disorder observed in 2017 are no longer active.

CLINICAL PIPELINE FOR ADDICTION, BY TARGET CLASS, 2017 VS 2022

Novel Drug Targets (No FDA approval history)

Target Class	2017	2022
Nicotinic Acetylcholine Recep	2	3
11-beta-hydroxylase	2	2
Aldehyde Dehydrogenase	1	1
Cocaine (mAb)	0	1
Methamphetamine (mAb)	1	1
Orexin receptors	0	1
Cholinesterases	1	0
Immune System	1	0
Subtotal	8	9

Targets with FDA approval history, but new for addiction

Target Class	2017	2022
Cannabinoid receptors	2	4
Glutamate Receptors	1	3
PDE Enzymes	2	2
GABA Receptors	1	1
PPAR gamma	2	0
Adrenergic Receptors	2	0
calcium channels	1	0
Subtotal	**11**	**10**

Targets with FDA approval history for addiction

Target Class	2017	2022
Opioid receptors	5	14
Serotonin Receptors	3	3
Monoamine transporters	1	2
Unknown	1	1
Subtotal	**10**	**20**

Total	**29**	**39**

Figure 14. The current addiction clinical pipeline by target type (as of October 2022). Drug programs were downloaded from Biomedtracker and individually assessed for target type. For combination drugs, only the most active API is used to categorize.

R&D Investment for Addiction Therapeutics

Venture investment into U.S. companies with lead products in addiction has been low relative to pain over the past 10 years. Using the "company lead product indication" methodology, we found $400 million invested over the last decade. More than 60% of this funding ($250 million) went to a single company that also develops drugs for pain in addition to addiction. Total venture funding in the last five years was spread across six companies. The total amount of venture capital raised for addiction-focused companies is low relative to pain (3x less funding) and oncology (150x less funding) over the same period.

Assessing clinical trial starts for addiction therapeutics was not possible due in part to indication tagging differences in the TrialTrove database. To assess R&D investment trends across the broader public biopharmaceutical industry, we analyzed IPOs and follow-on offerings from public companies specifically focused on addiction (**Figure 15**). For IPOs, only three addiction-focused companies went public over the last 15 years. For follow-on offerings, we found only two addiction-focused companies raising funds on the public market over the last 15 years.

INVESTMENT INTO ADDICTION-FOCUSED COMPANIES, 2012-2021

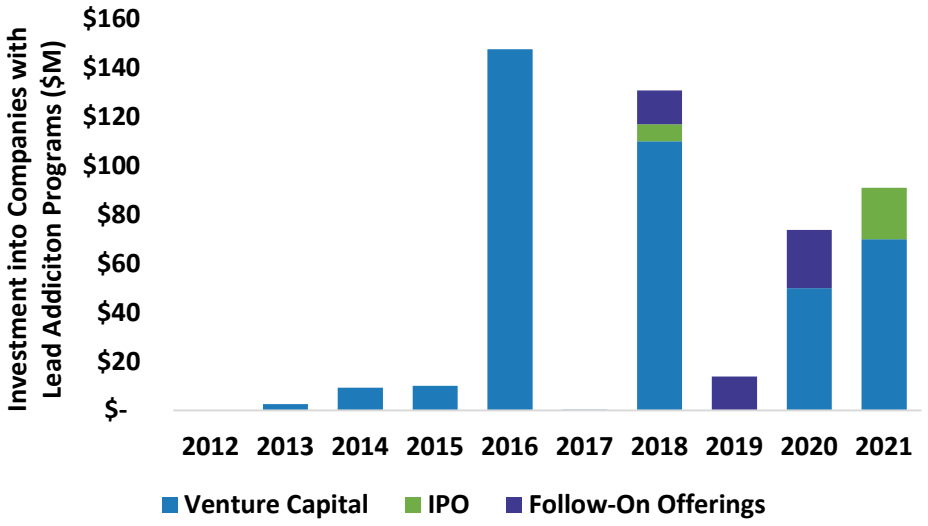

Figure 15. Total investment into companies with lead programs in Addiction for Venture Capital, IPOs and Public Follow-On Offerings, 2012-2021.

Success Rates for Addiction Therapeutics

Calculating an overall success rate from Phase I to approval is not possible due to the low number of transitioning Phase III clinical programs and NDA filings over the past decade. In fact, only one novel drug candidate moved through Phase III to NDA over the last 10 years. There is, however, data for the early clinical pipeline. For addiction trials with novel drugs in Phase I, there have been nine transitions with an above average success rate of 67% (the industry average for NMEs is 50%). For Phase II, there have been 15 Phase II trial transitions. Unfortunately, 14 of the 15 Phase II programs failed, pushing the Phase II success rate down to 6.7% (vs. an industry average of 28% for NMEs in Phase II).

Discussion

At the time of our first report on pain and addiction therapeutic innovation, in early 2018, the opioid crises had become a top public health priority in the United States. Governments and companies were stepping in to address the issue. For example, the NIH launched the HEAL Initiative (Helping to End Addiction Long-term) in April 2018 to help companies move candidates for pain and addiction along the clinical translation pathway. Companies outlined in our 2018 report had progressed 220 pain programs into the clinic and 29 clinical programs for substance abuse. Five years later, the clinical pipeline for pain and addiction looks very different.

For pain, the number of programs plummeted by 44%, with 170 programs suspended in just five years. Although reformulated products in the pipeline decreased by 48%, this did not account for the overall drop. Unfortunately, numerous innovative pain programs also failed, including 13 novel targets no longer being pursued in the clinic.

The current pain pipeline for novel chemical entities has only 75 clinical programs, which is nowhere near the level of innovation we would like to see to better ensure true transformations in how patients suffering from pain will be treated in the near term. With an overall success rate of just 0.7%, the odds suggest a challenging environment for the next wave of non-opioid, non-addictive medications.[7] Digging deeper into individual pain indications shows an even more anemic pipeline. For example, consider that to treat post-surgical pain, for which opioids are prescribed in the majority of current cases, there are only five novel chemical entities in clinical development. There are only 4 novel treatments for chronic lower back pain and one for cancer pain in the clinic.

For addiction, 23 of the 39 clinical programs have novel chemical entities across all forms of substance abuse. However, the late-stage pipeline has been so inactive we could not calculate a Phase III or NDA/BLA success rate. For programs specific to treating Opioid Use Disorder, there are only eight novel clinical-stage programs in development. It is highly concerning that there are only eight novel drug programs for a crisis that is now at record annual deaths and economic costs to society raises. Overdose deaths due to opioids alone reached 80,816 in 2021 and economic costs are now estimated to be 1.5 trillion annually in the U.S.[8,9] Estimates for alcohol and drug abuse place the country's total economic costs at $3.7 trillion annually affecting more than 23 million Americans.[10]

Placing the addiction crisis and pipeline in perspective, consider the war on cancer and the response to COVID-19. The oncology clinical pipeline has 3,300 total drug programs vs. only 39 for addiction and 124 for pain. Oncology is associated with $200 billion in total economic costs and roughly 600,000 deaths in the U.S., and the biopharma industry and its investors are aligning and prioritizing innovation with the threat. During the Covid-19 pandemic response, biopharma companies quickly launched more than 1,000 drug programs with 500 of these making it into clinical development.[11] Within two years, we saw successful vaccines, antibodies, and small molecules emerge from this pipeline to meet the crisis. We also saw significant investment from both private and public sources to translate science into useful medicines in record time. Moving the needle for therapeutics requires extraordinary investment and numerous shots on goal to ensure success.

Investment in pain and addiction remains out of proportion to the current societal problem. Venture Capital for both pain and addiction companies in the U.S. in 2021 was $228 million, representing only 1.3% of total therapeutic VC funding in the U.S. In the same year, oncology companies raised $9.7 billion, or 38.3% of total therapeutic VC funding in the U.S.

7 https://www.bio.org/iareports. Success from Phase I to FDA approval was calculated in this study to be 0.7% for the period 2012-2022. With the industry-wide success rate at 6.5% for novel chemical entities, pain's 0.7% is approaching an order of magnitude underperformance and is below any of the 12 major disease areas tracked by Biomedtracker

8 https://www.cdc.gov/nchs/pressroom/nchs_press_releases/2022/202205.htm

9 https://beyer.house.gov/news/documentsingle.aspx?DocumentID=5684

10 DEFINING THE ADDICTION TREATMENT GAP, Open Society Foundations (2010).

11 www.bio.org/iareports

What can be done to incentivize more investment and breakthroughs to treat pain and addiction? A strong regulatory and policy environment that provides a solid foundation for companies developing innovative treatments for pain and addiction to succeed is the starting point. Unfortunately, policy decisions over the last several years do not incentivize innovation and, unfortunately, favor prescribing and coverage of less safe and less effective pain and addiction treatments. Unless these policies change, there will not be the level of investment required to address this national health emergency.

For example, the newly enacted Inflation Reduction Act may create downward pressure on the development of small molecule medicines, which due to their ability to penetrate the brain are essential to the future of innovation in pain and addiction.

Recent innovative drug launches in chronic, highly prevalent indications and in addiction have faced challenges to coverage and access, creating uncertainty in the investor community.[12] As long as reimbursement policies favor generic pain and addiction drugs even when they may be less safe or effective for the patient suffering from these diseases it will be a struggle to achieve the level of investment required to achieve the change we need.

It is also important that specific needs and solutions to combat substance use disorder are recognized. There continues to be a need for education regarding the stigma of "addiction". Insurance companies, physicians and the entire health system need to treat addiction as a disease with a physiological basis. Historical personal stigmas surrounding addiction often constrain clinical trial enrollment as many patients are reluctant to seek help. Lastly, an expansion of the Opioid Public Health Emergency to a Substance Use Disorder Public Health Emergency should be considered. This would acknowledge the full breadth of the addiction crisis and enable medicines to enter the market faster through streamlined use, approval and coverage pathways.

Continued funding of basic brain research is also needed to support innovation in both the pain and addiction fields. Expanded funding for discovering and validating new targets, combinations of different therapeutic approaches as well as combinations with non-drug technologies will help move basic brain research closer to novel chemical entity discovery by companies. For basic research, there remains a need for developing animal and in silico models that are able to predict safety and efficacy in humans, biomarkers for stratifying patient populations, and utilization of modern approaches to data monitoring to better predict what treatments work best and for whom.

Even in the face of the tough scientific hurdles, low clinical success rates, financial challenges, and amid continued threats from policymakers, emerging companies are developing drugs for 27 new targets for pain and addiction. Although more drug candidates are needed, this is evidence emerging companies have the ability to explore untested drug mechanisms and are willing to translate them into clinically meaningful therapies. The Biotechnology Innovation Organization (BIO) and member companies view innovation as the key to changing the paradigm for the treatment of pain and addiction. Developing and providing solutions to the pain and addiction crises in the U.S. will require continued funding for basic and translational research, a health care system that values improved care for pain and substance abuse disorder patients, and a policy environment that incentivizes innovation.

[12] https://www.pewtrusts.org/en/research-and-analysis/issue-briefs/2021/05/policies-should-promote-access-to-buprenorphine-for-opioid-use-disorder

Appendix 1. FDA Approved Pain Therapeutics

There are now 87 novel chemical entities that are marketed in the U.S. to treat pain based on 13 mechanistic strategies (**Figure A1**).[13,14] This compares to 77 novel chemical entities and 12 mechanistic strategies in our previous report published January 2018. The 10 novel chemical entities approved since our last report are shown in bold in **Figure A1**. Seven of these are migraine drugs for a new target, the CGRP receptor. The other four are recently approved novel chemical entities that have targetswith a previous approval history: remimazolam (GABA receptors), Lasmiditan (Serotonin receptors), and oliceridine (Opioid receptors). Note that there were 21 approvals since 2017, but only 10 were novel chemical entities with the balance being reformulations of previously approved drugs.

In the prior 10 years, 2007-2017, only two novel chemical entities were FDA approved to treat pain: 1) milnacipran, an SNRI drug approved for depression ex-US since the 1990s, received its first FDA approval for fibromyalgia in 2009 and 2) tapentadol, a novel opioid drug FDA approved in 2010.[15]

The majority of prescribed pain drugs in the United States fall into the following three mechanistic strategy categories: cyclooxygenase inhibitors (NSAIDs and other prostaglandin modulators), opioid receptor modulators ("opioids"), and direct sodium channel blockers (the "caines," such as lidocaine and benzocaine). Beyond these three mechanistic strategies, the categories tend to be more specialized in the type of pain being treated, with five strategies only having one drug represented.

[13] In this report, we consider treatments for all indications and types of pain under development. Indications include chronic, moderate to severe, postsurgical, and acute pain, as well as cancer pain, inflammatory pain, arthritic pain, fibromyalgia, neuropathy, sciatica, local anesthetic agents and migraine. Pain can be classified into either nociceptic pain (the more common pain associated with injury, heat, and other external factors), and neuropathic pain, which arises internally from damaged nerves or other diseases affecting the somatosensory system. Migraine headaches tend to be classified as either a complex mix of both of these types, or a complex neuropathic pain. Nociceptic, neuropathic, and migraine pain can each be chronic in nature and each type affects millions of people globally. Chakravarty, A., et. al. Migraine, neuropathic pain and nociceptive pain: towards a unifying concept. Med Hypotheses. 74(2):225-31 (2010)

[14] EvaluatePharma database (www.evaluategroup.com) accessed December 2017, Bomedtracker (biomedtracker.com) accessed December 2017. Other references include Advokat, C., et al. Julien's Primer of Drug Action, 13th edition (2014) and Waller, D., et al. Medical Pharmacology & Therapeutics, 4th edition (2014)

[15] Reformulations and repurposed drugs are categorized as "non-NME" in the Biomedtracker database. Examples of FDA approved chemical entities with prior approval history include pregabalin (Lyrica) and duloxetine (Cymbalta), originally approved in depression, approved for Fibromyalgia in 2007 and 2009; Botox, approved for wrinkles in 2002, received an sBLA approval in 2010; Capsaicin was sold OTC prior to the 2009 FDA approval of Qutenza in postherpetic neuralgia (PHN).

APPROVED ACTIVE CHEMICAL ENTITITES FOR PAIN IN THE U.S., 2022

	Mechanistic strategy	Physiological Role	API Count	Unique Chemical Entities
1	cyclooxygenase inhibition	inhibition of prostaglandin synthesis, leading to vasoconstriction and anti-inflammation	24	salicylate, aspirin, methyl salicylate, acetaminophen, ibuprofen, naproxen, fenoprofen, ketoprofen, flurbiprofen, nabumetone, indomethacin, nepafenac, etodolac, bromfenac, ketorolac, sulindac, diclofenac, meloxicam, piroxicam, oxaprozin, mefenamic acid, meclofenamate, tolmetin, diflunisal
2	opioid receptor modulation	inhibition of neurotransmitter and neuropeptide release	20	morphine, hydromorphone, oxymorphone, oxycodone, buprenorphine, codeine, hydrocodone, prodine, meperidine, fentanyl, sufentanil, levorphanol, pentazocine, butorphanol, nalbuphine, dezocine, tramadol, tapentadol, **oliceridine**
3	voltage-gated sodium channel modulation	inhibition of sodium release and electrical signalling	10	benzocaine, tetracaine, lidocaine, bupivacaine, ropivacaine, articaine, chloroprocaine, dibucaine, pramoxine, butamben
4	serotonin receptor agonists	indirect inhibition of CGRP, leading to vasoconstriction	10	ergotamine, dihydroergotamine, sumatriptan, almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, zolmitriptan, **lasmiditan**
5	monoamine modulation	sedative effect via multiple receptors/transporters	4	droperidol, levomepromazine, duloxetine, milnacipran
6	voltage-gated calcium channel inhibition	inhibition of neurotransmitter and neuropeptide release	3	gabapentin, pregabalin, ziconotide
7	GABA modulation	increase in GABA or GABA-like CNS inhibition directly (GABA receptor) or indirectly (Glu receptors, etc.)	4	topiramate, valproic acid (divalproex), butalbital, **remimazolam**
8	adrenergic receptor antagonism	beta blocking mediated vasoconstriction	1	propranolol
9	phosphodiesterase inhibition	cAMP-inducing smooth muscle vasoconstriction	1	cilostazol
10	SNARE inhibition	blocks acetylchloline release and neurotransmission	1	onabotulinumtoxinA
11	vanilloid receptor modulation	inhibition of neurotransmitter and neuropeptide release	1	capsaicin
12	sodium channel inhibition with monamine modulation	sedative effect via multiple receptors/transporters	1	carbamazepine
13	CGRP receptors	vasoconstriction	7	**erenumabc, fremanezumab, galcanezumab, eptinezumab, atogepant, rimegepant, ubrogepant**

Figure A1. Unique FDA approved Active Pharmaceutical Ingredients (APIs) for pain still active as of October 2022, categorized by primary mechanistic target strategy and physiological strategy. Bold APIs were approved in the last five years: eight CGRP receptor antagonists, as well as remimazolam (GABA receptors), Lasmiditan (Serotonin receptors), and oliceridine (Opioid receptors). The list does not include herbal extracts and adjuvant medicines that assist the anti-pain compounds, drugs for general anesthesia for the surgical setting, and excludes enantiomer isolations, herbal extracts and supplements. Source: EvaluatePharma, Biomedtracker, fda.gov, company websites. (Drugs that were once sold in the U.S. but are now discontinued (withdrawn due to side effects or deemed illegal by law) are not shown in this list. For example: the opioids heroin, anileridine, propoxyphene; cocaine for local anesthesia; three COX-2 inhibitors (celecoxib (Celebrex), rofecoxib (Vioxx), and valdecoxib (Bextra); the anti-pyretic propoxyphene, phenylbutazone, phenacetin (the precursor to Tylenol), NSAIDs benoxaprofen and phenylbutazone.)

Aspirin, which has been on the market since the early 1900s, is an example of a drug in the category of cyclooxygenase inhibitors, generally used to treat mild to moderate pain.[16] Since the turn of the 20th century, this category of drugs has gone through three development periods. First was the approval of acetaminophen (Tylenol) in 1955 (its precursor phenacetin was introduced in the early 1900s but withdrawn in 1983 for its "high potential for misuse and its unfavorable benefit-to-risk ratio"[17]). The second development was a new class of NSAIDs in the 1970s and 1980s, which included ibuprofen (Advil, Motrin) and naproxen (Aleve). In the late 1990s, a third class was introduced as industry researchers created more selective inhibitors for a specific cyclooxygenase enzyme (COX-2) known to be involved in peripheral inflammation. However, while innovative at the biochemical level, drugs in this class were withdrawn from the market due to cardiovascular toxicity issues that occurred with certain patients (*e.g.,* celecoxib (Celebrex), rofecoxib (Vioxx), and valdecoxib (Bextra).

The second mechanistic strategy, opioid receptor modulators, includes medicines to treat more severe pain. These have a long history dating back thousands of years, beginning with use of poppy resin extract. In the 1800s, the active compounds in poppy seed resin (morphine and codeine) were isolated and, by the turn of the century, sold in purified form. By the early 1900s, not only were purified morphine and codeine sold, but so were related semi-synthetic compounds heroin, oxycodone (the active ingredient of today's Oxycontin), oxymorphone, and several other opioids. In the 1940s and 1950s, new fully synthetic opioids prodine and meperidine (Demerol) were introduced, having little structural similarity to the semi-synthetic opioids but maintaining similar potency. From 1960 to the 1980s, more potent synthetic opioid receptor modulators were brought the market including fentanyl and carfentanyl (respectively 100 and 10,000 times more potent than morphine). By 1990, 18 active opioid substances were introduced to the U.S. market, many of which are still widely used today, albeit in reformulated composition.

The third mechanistic strategy includes medicines that target voltage-gated sodium channel modulation (*e.g.*, inhibition of sodium release and electrical signaling), which have been primarily used in acute setting as local analgesics. The currently marketed chemical entities were introduced a century ago as chemists designed non-addictive substitutes for cocaine. For example, benzocaine, first synthesized in 1890, is still available over the counter (OTC) to treat skin and dental pain. Some of these chemical entities have been formulated for more chronic use. An example is bupivacaine in a liposome formulation that can be used for postsurgical analgesia, reducing the need for opioid use.

The fourth mechanistic strategy, serotonin receptor agonists, is relatively new compared to the previously discussed mechanistic strategies. The first FDA approved drug in this class, sumatriptan, was approved in 1998 for migraine headaches. Eight more have been approved since then. These drugs work by activating specific serotonin receptors known as 5HT1B and 5HT1D and are indicated for migraine headaches. Activation of these receptors eventually leads to a dampening of neural calcitonin gene-related peptide (CRGP) production, and ultimately an attenuation of the vasodilation that accompanies headaches.[18] As will be described later, this CRGP pathway is a promising target for numerous Phase III product candidates in the pipeline today.

Mechanistic strategy five in **Figure A1**, monoamine neurotransmitter modulators, include drugs that have psychiatric indications (*e.g.*, anti-psychotic, anti-depressant) that have also been utilized to treat pain. This is likely due to the breadth of targets these drugs impact. For example, some of these drugs have both transporter and receptor activity, as well as anti-histamine activity. One example is duloxetine (Cymbalta), a serotonin, norepinephrine reuptake inhibitor (SNRI) antidepressant, was approved by the FDA for peripheral diabetic neuropathic pain in 2005.

[16] Acetylsalicylic acid (Aspirin) is a derivative of salicylic acid, a cyclooxygenase inhibitor also marketed in late 1800s. Salicylic acid is the key ingredient in willow tree extract and was used as for thousands of years to treat pain.
[17] Federal Register of October 5, 1983 (48 FR 45466). https://www.fda.gov/ohrms/dockets/ac/98/briefingbook/1998-3454B1_03_WL37.pdf
[18] Durham, P. Calcitonin Gene-Related Peptide (CGRP) and Migraine, Headache; 46, S1 (2006) and Ahn, A. et.al. Where do triptans act in the treatment of migraine? Pain. 115(1-2): 1–4 (2005).

The direct voltage-gated calcium channel modulators have been approved for use in neuropathic pain indications. Examples include conotoxin ziconotide, a small peptide derived from snail toxins prescribed since 2004 as a long-acting medicine for chronic pain, as well as gabapentin (Neurontin) and pregabalin (Lyrica) which have been used to treat chronic neuropathic pain since 2002 and 2004, respectively.[19]

The direct or indirect gamma-aminobutyric acid (GABA) stimulators make up category 7. GABA, a key inhibitory neurotransmitter in the brain that dampens nerve excitation, has also been the target of pain drugs. For example, butalbital, a direct GABA receptor agonist, mimics some of the effects that GABA has on the nervous system. The other drugs in this group are difficult to categorize as some of the drugs have ambiguous mechanisms in their GABA modulating activity. For example, topiramate has been proposed to antagonize glutamate receptors (ionotropic kainate type) as well as other pathways that lead to increased GABA. Topiramate was approved in 2004 for migraine prophylaxis. The GABA analog, valproic acid (divalproex), available since the 1970s, is also believed to increase GABA levels but the mechanism is not yet known.

Mechanistic categories 8-12 each contain a single drug and each work in unique ways. Propanolol (8), on the market since the 1960s, works as a beta blocker (beta adrenergic receptor), leading to vasoconstriction and migraine prophylaxis. Phosphodiesterase inhibitor cilostazol (9) works through an indirect signaling pathway that leads to vasoconstriction. Botulinum toxin (10), marketed as Botox for headache pain in 2010, blocks the neurotransmission (synaptic vesicle release) of acetylcholine. Capsaicin (11) is the same active component of hot chili peppers and is the only compound approved that directly binds to the ionotropic vanilloid receptor. Its activity for pain derives from long exposure and desensitization of the nerve signaling. The last drug on the list, the anti-psychotic drug carbamazepine (12), works as a direct binder of sodium channels and, not surprising based on its structure, is a likely serotine reuptake inhibitor.

The new 13th category is for calcitonin gene-related peptide (CGRP). This peptide is implicated in pain transmission through vasodilation and other physiological roles. The antibodies that bind CGRP or small molecules that bind to its receptor block downstream activity of the receptor.

[19] Gabapentin binds to α2δ subunit of L-type calcium channel complex. The Gabapentin Receptor α2δ-1 is the Neuronal Thrombospondin Receptor Responsible for Excitatory CNS Synaptogenesis. Cell 139(2): 380–392 (2009). The α2δ-1-NMDA Receptor Complex Is Critically Involved in Neuropathic Pain Development and Gabapentin Therapeutic Actions. Cell Rep. 22(9): 2307–2321 (2018)

Appendix 2. Overview of FDA Approved Addiction Therapeutics

There are currently 14 unique chemical entities (active pharmaceutical ingredients, APIs) approved for addiction as shown in **Figure A2**. Since our report published in January 2018, only one new chemical entity was FDA approved. However, this drug, lofexidine, is new only to the U.S., as it has been marketed in the U.K. since 1992 for managing opioid withdrawal symptoms.

In addition, there were five approvals of reformulated or combination products of buprenorphine and naloxone over the last five years. Although these are not new APIs, recent drugs approved through the 501b pathway have demonstrated advantages in areas such as abuse deterrence, patient compliance and overall patient experience.

APPROVED ACTIVE CHEMICAL ENTITITES FOR ADDICTION IN THE U.S., 2022

Addiction Type	Mechanistic Strategy	Unique Chemical Entities (Examples)	APIs
Opioid Use Disorder	opioid receptor antagonist (competitive to opioid agonists drugs	naltrexone (Trexan, Vivitrol)	1
	opioid receptor antagonist (competitive to opioid agonists drugs	naloxone (in combination with buprenorphine) (Bunavail, Zubsolv, Suboxone)	1
	opioid receptor modulation (partial agonist)	buprenorphine (Subutex, Probuphine, Sublocade)	1
	opioid receptor agonist and nicotinic acetylcholine receptor antagonist	methadone (Dolophine)	1
	adrtenergic receptor agonist, inhibits the release of norepinephrine	**lofexidine (Lucemyra)***	1
Alcohol Use Disorder	opioid receptor antagonist (competitive to opioid agonists drugs	naltrexone (Revia, Vivitrol)	1
	alcohol dehydrogenase inhibition	disulfiram (Antabuse)	1
	GABA receptor modulation	acamprosate (Campral), and benzodiapines* (diazepam (Valium), oxazepam, clorazepate (Tranxene), chlordiazep-oxide (Librium))	5
Nicotine Use Disorder	monoamine modulation	bupropion (Zyban)	1
	nicotinic acetylcholine receptor partial agonist	varenicline (Chantix)	1
	nicotinic acetylcholine receptor agonist	nicotine (as patch)	1
Stimulant Use Disorder	no approvals (i.e. for cocaine, methamphetamine)	no approvals	0
Cannabis Use Disorders	no approvals	no approvals	0

Figure A2. Unique FDA approved active ingredients for addiction, marketed in the US as of October 2022, categorized by primary mechanistic strategy. Under substance abuse, the FDA approved drug levomethadyl (OrLAAM) is omitted as the patent holding manufacturer as discontinued sale of the product. See text for details. *Prescribed for mitigation of withdrawal symptoms (tremors, anxiety), for example clorazepate, oxazepam, and lofexidine. There are only 14 unique APIs listed - note that naltrexone is counted as one API but listed twice as it is approved for two indications. Sources used: EvaluatePharma, Biomedtracker, fda.gov, company websites.

The mechanistic strategies and unique chemical entities approved for substance use disorder are described below.

Naloxone: In 1971, the FDA approved naloxone (Narcan) for treating opioid overdose. Naloxone, a competitive opioid receptor antagonist, can work within minutes to block the effects of opioid overdose by competing for the same mu opioid receptors that opioids bind to, but act to decrease activity rather than increase activity. However, naloxone can also cause symptoms of withdrawal. It is now commonly prescribed as an oral drug in combination with buprenorphine such that the oral opioid is active, but any misuse by injection will be blocked.[20]

[20] Orman, J. et. al. Buprenorphine/naloxone: a review of its use in the treatment of opioid dependence. Drugs. 69 (5): 577–607 (2009)

Methadone: Termed a replacement or maintenance therapy for its ability to help individuals taper their use of other opioids, methadone is a mu opioid receptor agonist. Methadone, already approved in 1947 for pain relief, was approved in 1972 for treating opioid abuse and to help with the growing abuse of street heroin.

Naltrexone: The 1972 Drug Abuse Office and Treatment Act called for the development of non-addictive "blocking or antagonistic drugs" and "detoxification agents" that could be used to treat withdrawal in the case of heroin addiction. It was not until 1984 that a new, strong antagonist to the opioid receptors was approved. That drug was naltrexone, a potent antagonist of the mu opioid receptor. In 1995, it was approved for alcohol addiction. The original formulations of naltrexone required daily dosing, which raised issues with patient compliance. The more recent once-monthly formulation of naltrexone was approved in 2010.

Buprenoprhine: As a partial agonist at the mu opioid receptor, buprenoprhine works as a pain reliever and as a replacement or maintenance therapy for opioid addiction. It was originally approved as a standalone therapy in 1981 by the FDA.

Levacetylmethadol: Levacetylmethadol (not listed in **Figure A2**) was discontinued by the manufacturer based on evidence of cardiac-related side effects and the FDA's addition of new label warnings.[21] In 1993, OrLAAM, levomethadyl acetate, a structurally similar compound to methadone, was approved for opioid addiction in cases where methadone and buprenorphine have not proven effective.

Disulfiram: Disulfiram is the oldest drug on the list in **Figure A2**, approved in 1951. This drug inhibits the enzyme that normally breaks down alcohol, creating a sensitivity to alcohol such that, when drinking, immediate hangover symptoms and unwanted side effects arise, making it unfavorable to continue consuming alcohol.

Benzodiazepines: Four benzodiazepines have also been approved for use in the alcohol addiction setting. These work as a substitute for alcohol to help during the withdrawal stages as benzodiazepines work similarly to alcohol modulating GABA transmission.

Nicotine & varenicline: For nicotine addiction, nicotine itself has been used since the 1980s in patch or gum form to help addicts alter their smoking habit. Nicotine and the key ingredient of Chantix (varenicline) work by activating what is now known as the "nicotine receptor" (nicotinic acetylcholine receptor) in the brain. This in turn causes the release of several brain chemical messengers, including dopamine, which contribute to the addictive properties of nicotine.

Bupropion: Bupropion, originally approved for depression (as Wellbutrin in the 1980s), was approved in 1997 for smoking cessation (renamed Zyban for this indication). Bupropion is known to decrease appetite cravings and elevate dopamine levels but may have other relevant activity such as antagonizing acetylcholine receptors.[22]

Lofexidine, a structural analog of clonidine, activates α2-adrenergic receptors. Both drugs have been used to decrease opioid withdrawal symptoms. However, clonidine is used off label.

[21] FDA documents: https://www.federalregister.gov/documents/2011/06/06/2011-13884/determination-that-orlaam-levomethadyl-acetate-hydrochloride-oral-solution-10-milligramsmilliliter

[22] Roddy, E. Bupropion and other non-nicotine pharmacotherapies. BMJ, 328 (7438): 509–511. (2004)

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