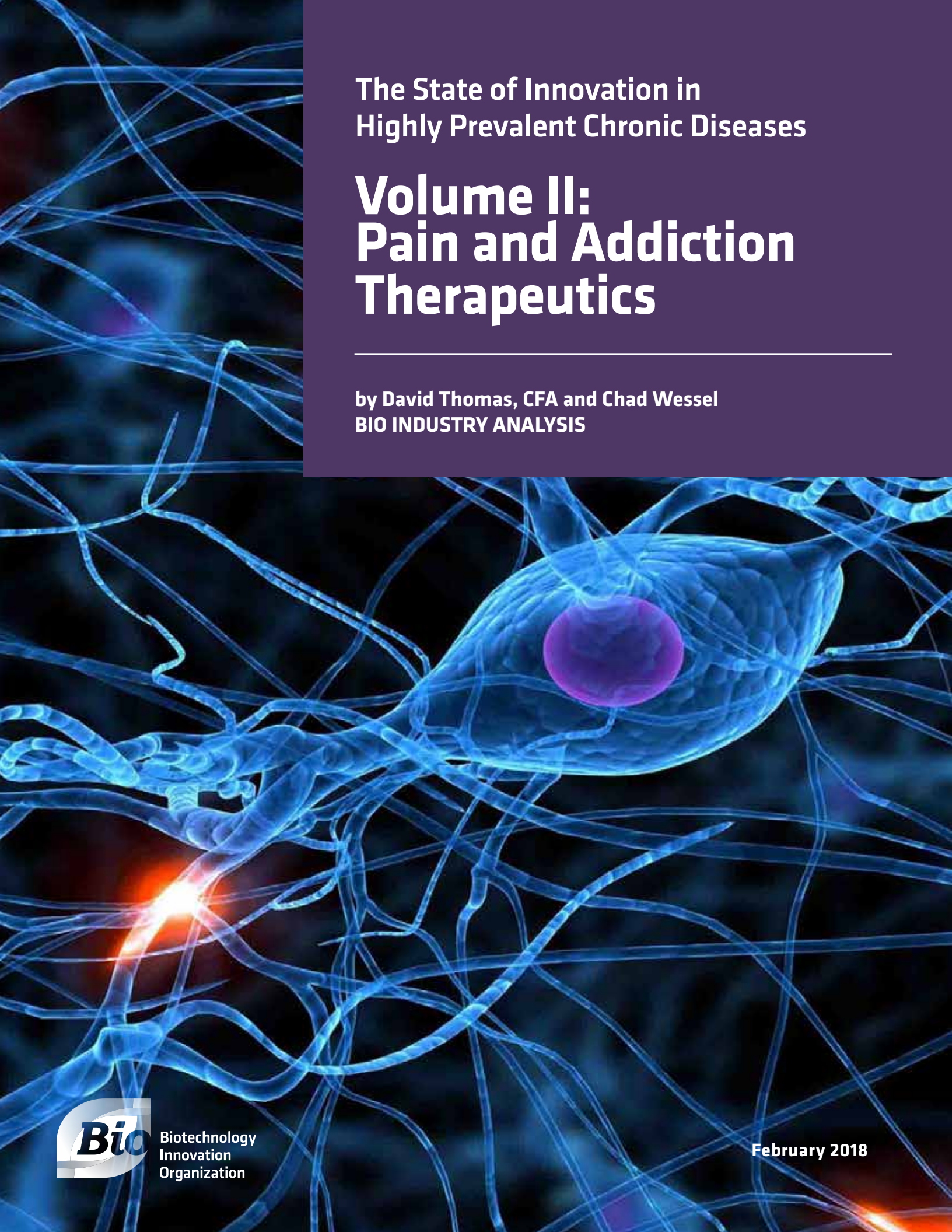

The State of Innovation in Highly Prevalent Chronic Diseases

Volume II: Pain and Addiction Therapeutics

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BIO INDUSTRY ANALYSIS

Biotechnology Innovation Organization

February 2018

Introduction

The following report is the second in a series on the current funding and R&D landscape of highly prevalent, chronic diseases. In our previously published research, emerging company investment for drug development in many of these common diseases was shown to be declining over the last decade and low relative to the prevalence and cost of these diseases (**Figure 1**).[1] The persistence of this trend could have implications for the future output of innovative medicines in these disease areas. The cause for concern is magnified by the impact these chronic disease areas are having on the overall healthcare system in the US. Thus, it is important that barriers to therapeutic innovation are identified and removed.

This volume takes an in depth look at the state of innovation in pain as well as addiction therapeutics. Chronic pain affects as many as 100 million people in the US alone.[2] Total economic and direct healthcare costs for treating pain in the US have been estimated to be as high as $635 billion annually, higher than the costs for cancer, Alzheimer's, or cardiovascular disease.[3] Addiction to drugs and alcohol affects more than 23 million Americans and continues to rise, in part due to abuses of pain medications.[4] Total economic and direct healthcare costs for substance abuse is an alarming $700 billion per year.[5]

Herein, we analyze all drugs marketed in the US for pain and addiction, as well as potential future drugs that are progressing through the clinical pipeline to meet the urgent needs of patients. The pipeline analysis aims to assess the depth and breadth of innovation given the large unmet need in pain management and addiction treatment. Historical clinical success rates and failed mechanistic strategies are also identified, as well as trends in venture financing and investment into new clinical trials.

Key Takeaways

- There have been only two novel chemical entities FDA approved to treat pain over the past decade.[6]
- The industry-wide pain pipeline consists of 220 clinical-stage drug programs, with 125 of these testing novel chemical entities in the clinic, 87% of which are for non-opioid receptors. These are relatively low numbers when compared to the current pipeline for oncology (2,617 total programs and 1,700 novel drug clinical-stage programs).
- Over the past decade, the biopharmaceutical industry has been working to develop abuse deterrent formulations, with 142 clinical trials initiated and 12 FDA approvals for abuse deterrent pain products.
- Clinical success in pain drug development has been extremely difficult for novel drugs, with only a 2% probability of FDA approval from phase I, compared to an overall 10% success rate across all diseases.
- Private company investment, as measured by venture capital into US companies with lead stage programs in pain, is 3.6% of total drug development venture funding. For venture funding of novel R&D, pain has received 17 times less venture capital than oncology over the last decade.
- There are only 15 active clinical-stage programs with novel compounds intended for addiction treatment: 10 for substance abuse, two for alcohol, and three for smoking cessation.
- Venture investment for addiction drug R&D is nearly non-existent.

1 Thomas, D., Wessel, C. (2008) Emerging Company Trend Report, BIO Industry Analysis. (2017) (www.bio.org/iareports)
2 Medical Expenditure Panel Survey (MEPS), (2008). Definition of chronic includes joint pain or arthritic pain.
3 Gaskin, D, Richard, P. 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).
4 Defining The Addiction Treatment Gap, Open Society Foundations (2010).
5 https://www.drugabuse.gov/related-topics/trends-statistics
6 Since 2007, novel chemical entities approved in pain, with no prior approval history, are: 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. The majority of chemical entities approved in pain since 2007 have been reformulations or have pre-2007 US market history.

DISEASE PREVALENCE AND HEALTHCARE COST VS. VENTURE CAPITAL FUNDING FOR HIGHLY PREVALENT CHRONIC DISEASES

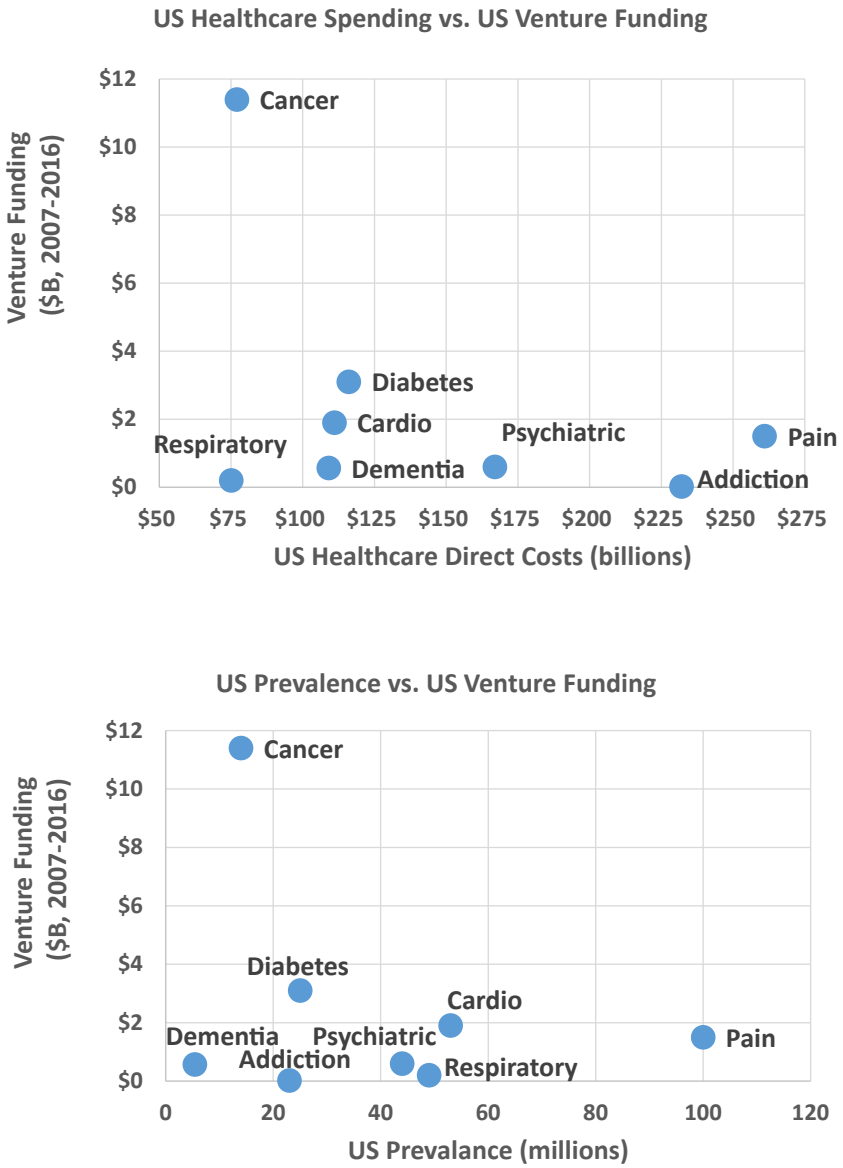


Figure 1. Prevalence and Cost vs. Venture Capital Funding 2007-2016 for Oncology, Psychiatry and other highly prevalent, chronic diseases. [Source for prevalence: Cardiovascular: 2015 data from Circulation, Heart Disease and Stroke Statistics – 2016 update; Psychiatric Disorders: 2010 data from NAMI for "Mental Illness"; Endocrine: 2007 data compiled by CDC; Cancer: 2014 data from SEER, Pain: MEPS, 2008. Source for healthcare cost: Health Affairs, 35, No. 6 (2016), Pain: The Journal of Pain, 2012. Source of venture data: BIO Industry Analysis, Emerging Company Trend Report, 2017.]

Overview of FDA Approved Pain Therapeutics

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.[7] Nociceptic, neuropathic, and migraine pain can each be chronic in nature and each type affects millions of people globally. In this report, we consider treatments for all indications for pain under development: chronic, moderate to severe, postsurgical, and acute pain, as well as cancer pain, inflammatory pain, arthritic pain, fibromyalgia, neuropathy, sciatica, and migraine. We excluded drugs used for general anesthesia in the surgical setting but include local anesthetic agents, as some of these reformulated products have applications in the chronic setting.

FDA Approved Medicines for Pain

Analyzing the EvaluatePharma and Biomedtracker databases for FDA approved drugs indicated for treating pain, we found 77 novel chemical entities that treat pain based on 12 mechanistic strategies (see **Figure 2)**.[8] The majority of these drugs are now available as generic medicines, either in their original formulation or as new formulations (*e.g.,* different salt forms, extended release capsules, or as combination products). Roughly a third of these were first marketed prior to 1950, and two thirds prior to the year 2000. In the last decade, only two novel chemical entities, with no prior approval history, have been approved for pain treatment: 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. The majority of chemical entities approved in pain since 2007 have been reformulations or have pre-2007 US market history.[9]

When examining the 12 mechanistic strategies, the most prescribed pain drugs in the United States fall into the following three categories: 1) cyclooxygenase inhibitors (NSAIDs and other prostaglandin modulators), 2) opioid receptor modulators ("opioids"), and 3) direct sodium channel blockers (the "caines," such as lidocaine and benzocaine). Beyond these three mechanistic strategies, each of which has a long market history, the nine other categories tend to be more specialized in the type of pain being treated, with five strategies only having one drug representative (listed in **Figure 2**).

Aspirin is an example of a drug in the category of cyclooxygenase inhibitors, generally used to treat mild to moderate pain; aspirin has been on the market since the early 1900s.[10] 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"[11]). 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 category, 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.

7 Chakravarty, A., et. al. Migraine, neuropathic pain and nociceptive pain: towards a unifying concept. Med Hypotheses. 74(2):225-31 (2010)

8 EvaluatePharma database (www.evaluategroup.com) accessed December 2017, Bomedtracker (biomedtracker.com) accessed December 2017. Other eferences 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)

9 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).

10 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 has been used for thousands of years to treat pain.

11 Federal Register of October 5, 1983 (48 FR 45466). https://www.fda.gov/ohrms/dockets/ac/98/briefingbook/1998-3454B1_03_WL37.pdf

The third category 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.

UNIQUE CHEMICAL ENTITIES MARKETED IN THE US FOR PAIN

	Mechanistic Strategy	Physiological Outcome	API Count	Unique Chemical Entities on Market
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	19	morphine, hydromorphone, oxymorphone, oxycodone, buprenorphine, codeine, hydrocodone, prodine, meperidine, fentanyl, sufentanil, levorphanol, pentazocine, butorphanol, nalbuphine, dezocine, tramadol, tapentadol
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 CRGP, leading to vasoconstriction	9	ergotamine, dihydroergotamine, sumatriptan, almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, zolmitriptan
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.)	3	topiramate, valproic acid (divalproex), butalbital
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

Figure 2. Unique FDA approved Active Pharmaceutical Ingredients (APIs) for pain still active as of January 2018 (prescription, generic, or OTC) categorized by primary mechanistic target strategy and physiological strategy. 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 US 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.)

The fourth category, 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.[12] As will be described later, this CRGP pathway is a promising target for numerous Phase III product candidates in the pipeline today.

Category five, 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.

The direct voltage-gated calcium channel modulators (category 6) 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.[13]

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.

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.

Current Clinical Pipeline in Pain

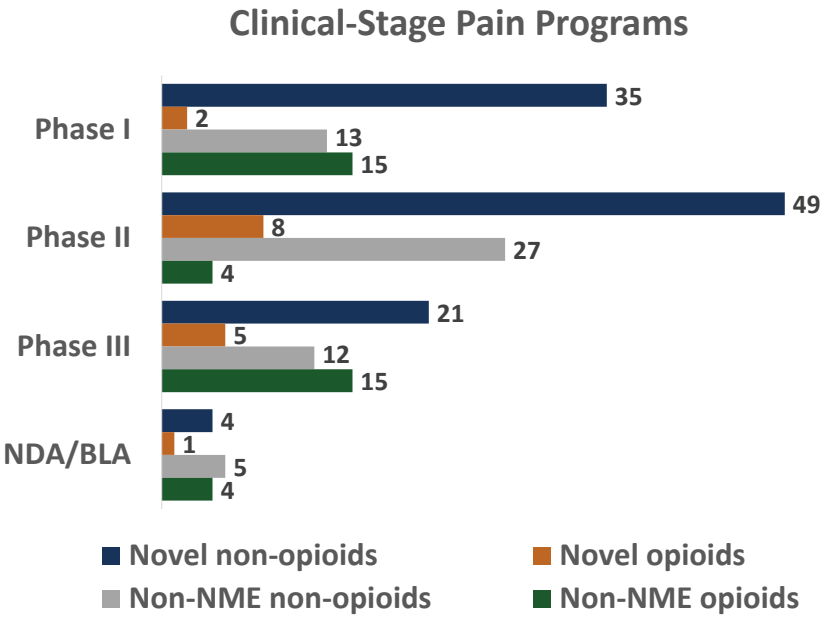
There has been progress over the last few decades in advancing our understanding of the biologic mechanisms underlying pain. As mentioned above, the serotonin receptor subtype 1B/1D inhibitors were a turn of the century example of newly defined targets spawned out of basic biological research followed by industrial breakthroughs in biochemical specificity. Since the last of these migraine-indicated triptans were approved, however, there has been relatively few new targets that have an FDA approved drug associated with them. The selective cyclooxygenase-2 (COX-2) inhibitors were another example of industry's progress in drug target selectivity. Unfortunately, the complexity of COX-2 tissue expression in non-targeted organs led this group to be withdrawn. After this period in the early 2000s there have been only a few examples of new drug class approvals in pain.

The current clinical pipeline includes 220 ongoing clinical programs for pain indications. Of these 220 programs, 125 have completely novel drugs indicated for pain. Furthermore, 87% of these novel programs are pursuing non-opioid receptor targets (See **Figure 3**).

[12] 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).

[13] Patel, R., et.al. Mechanisms of the gabapentinoids and α2 δ-1 calcium channel subunit in neuropathic pain. Pharmacol Res Perspect. Apr; 4(2) (2016)

2017 DRUG PIPELINE FOR PAIN
125 NOVEL DRUG (NME/BIOLOGIC), 95 REFORMULATION (NON-NME) PROGRAMS



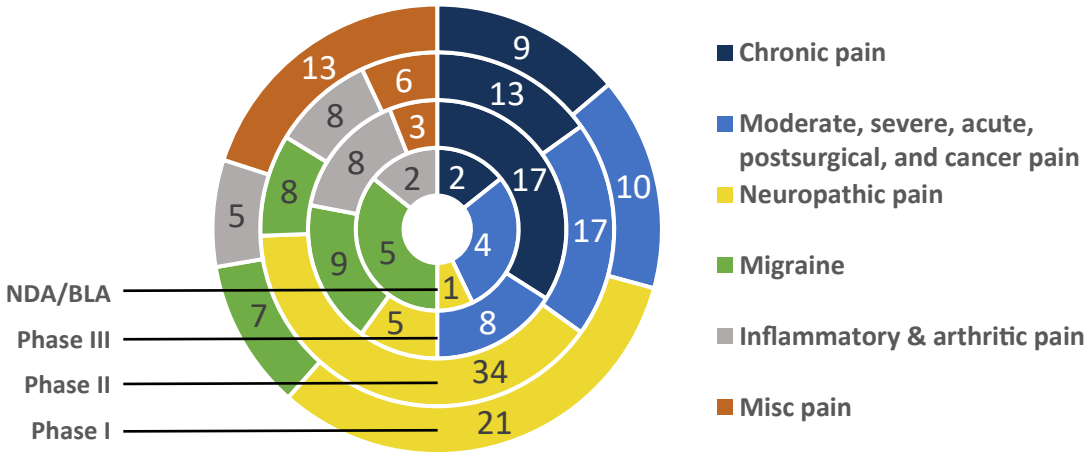


Figure 3. **The currently active pain pipeline, based on Biomedtracker's methodology. Top: Pain pipeline by phase of development. Novel drugs that do not have an approval history, non-NME drugs that are reformulated or repurposed products, and each group split by opioid receptor activity. For combination 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: Radar plot by earliest (outer) to latest phase (center) and by type of pain. Biomedtracker indications for chronic pain, and chronic lower back pain are combined, postsurgical pain, and moderate to severe pain, acute and cancer pain were combined. Neuropathic pain includes general neuropathic pain along with Biomedtracker indications for neuropathies, neuralgia, sciatica, and fibromyalgia. Migraine and other headaches are grouped separately. Misc pain includes many phase I programs that are not specified as to the type of pain, and a few local anesthetics.**

The current clinical programs in pain can be grouped into 26 mechanistic strategies. These strategies' targets are different than previously discussed (FDA approved) mechanistic strategies. Among these 26 strategies, there are new enzyme and receptor targets modulated by small molecules, neuropeptides inhibited by antibodies, and cell-based approaches, under investigation for pain.

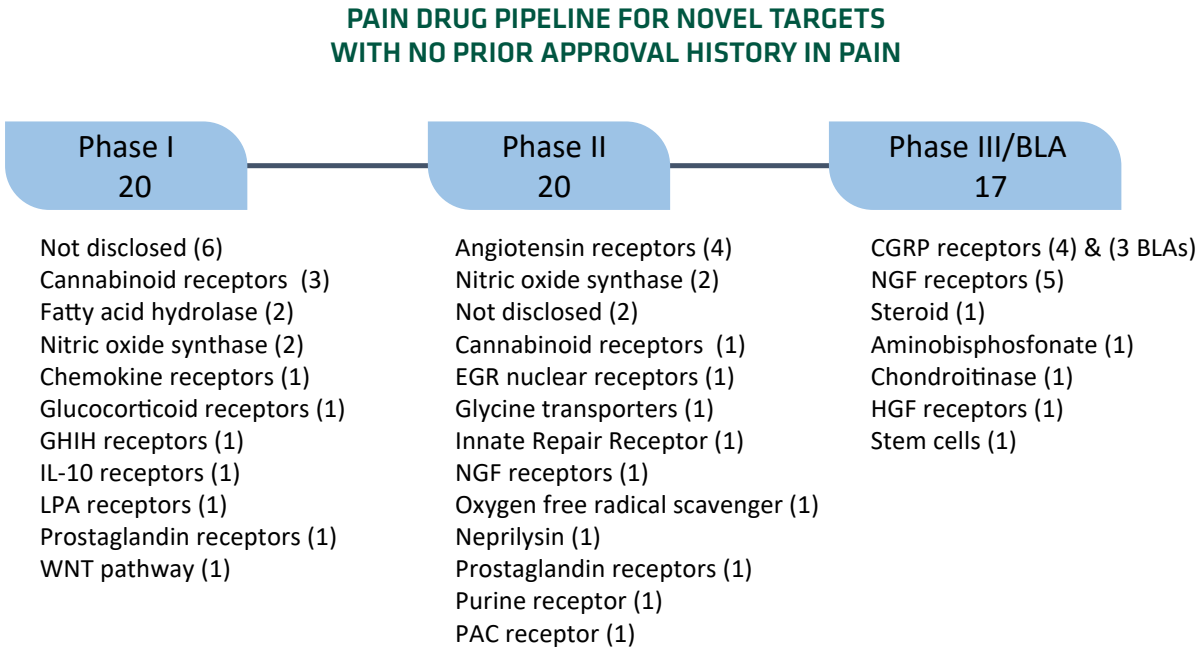


Figure 4. The breadth of completely new target strategies in the currently pain pipeline. The drug targeting strategy listed is based on the primary target of the novel compound under development. For combination drugs, only the novel active component's target is listed. Pipeline data by phase of development was obtained from Biomedtracker.

The 17 novel Phase III and NDA/BLA candidates listed in **Figure 4** are spread across seven mechanistic strategies. Furthest along, with three BLAs filed with the FDA in 2017, are the calcitonin gene-related peptide (CRGP) antibodies. This peptide is implicated in pain transmission through vasodilation and other physiological roles. The antibodies bind CRGP, rendering it unable to impact downstream activity. Nerve growth factor (NGF) antibodies are also represented, with 5 Phase III trials ongoing. NGF is a large neuropeptide involved in the maintenance of sensory neurons. Phase III programs also include representative candidates including the use of hepatocyte growth factor, chondroitinase, bisphosphonates, steroids, and stem cells.

However, when compared to the level of innovation occurring in other diseases, the need for greater investment in pain research and development is clear. For comparison, the oncology pipeline currently has 2,671 total active clinical programs, more than 10 times the number found in the pain pipeline (220).[14] The number of clinical programs in a single oncology sub-indication is closer to that found in the pain pipeline. For example, breast cancer has 158 active clinical development programs, lung cancer 180, and leukemias 211 – each slightly below the total pain pipeline. However, when we compare the number of *novel* drugs only (new molecular entities and new biologics), the novel pain pipeline consists of fewer programs: breast cancer (n=137), lung cancer (n=168), and leukemias (n=200) vs. pain (n=125).

To predict what may enter the clinical pipeline in the near future, we examined all preclinical pain programs in the Biomedtracker and EvaluatePharma databases. We found that 13 of the 59 preclinical programs listed had drugs for unique targets not currently in the clinic or previously approved, indicating further advances may be on the horizon.

[14] Data for oncology R&D pipeline is taken from the BioMedTracker database, and current as of January 2018. A total count by disease area can be found in Thomas, D., Wessel, C. Emerging Company Trend Report, BIO Industry Analysis (2017) (www.bio.org/iareports)

Trends in Venture Investment and R&D Activity (Clinical Trial Initiations) in Pain

Uncovering the exact dollar amounts that private and public companies are spending on pain drug development has limitations. Nevertheless, we have outlined below a few methods of approximating the level of private company venture capital investment (emerging, non-public biotech companies) and the broader industry R&D activity (combining small, midsize, and large public companies and private biopharmaceutical companies). For small private companies, we identify companies with lead compounds in pain and assess venture funding over time. This tends to underestimate the venture dollars ultimately used for pain R&D in small companies, as some companies have broad pipelines. Although most capital will tend to be used for the 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.

2007-2016 VENTURE INVESTMENT INTO US COMPANIES WITH LEAD PROGRAMS IN PAIN VS. ONCOLOGY

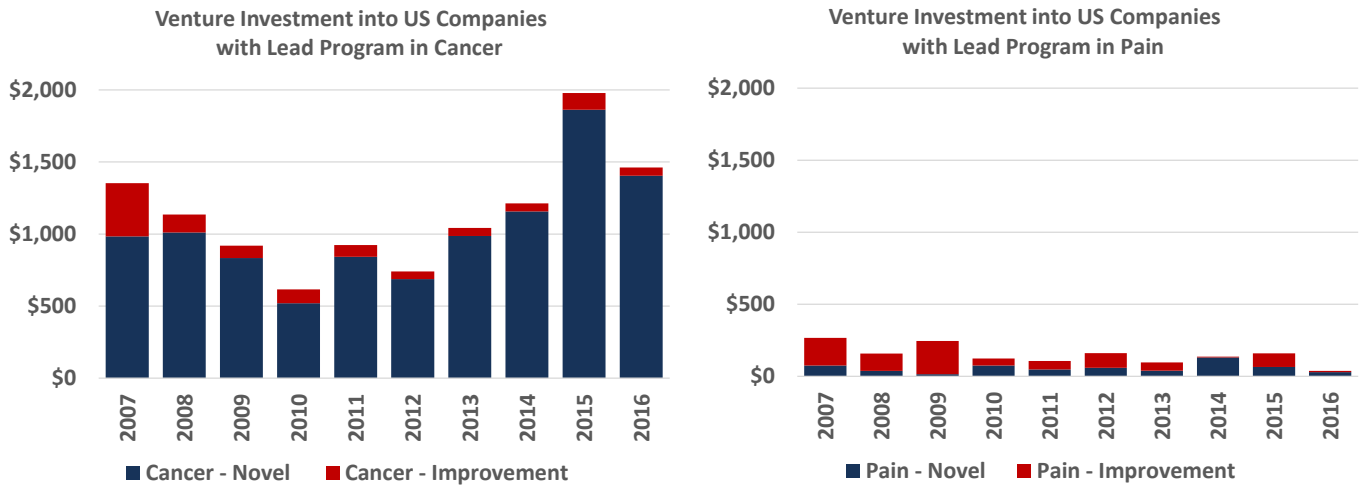


Figure 5. Left: Venture funding of companies with lead products in oncology, 2007-2016. Right: Venture funding of companies with lead products in pain, 2007-2016. Blue bars denote novel drug in lead program of company. Red bars indicate drug improvement (reformulation, repurposing) for the lead asset under development.

Venture investment into US companies with lead pain products from 2007 to 2016 totaled $1.5 billion. Using the "lead product" method for tracking venture investment, we also assessed whether the funded company was developing "drug improvement" reformulations or truly novel drug candidates. The funding for all novel pain drugs was only $576 million over the ten-year window, which is 17 times less than the funding received for novel oncology drugs ($10.3 billion). During the period from 2007 to 2016, six companies with lead drugs in pain were financed each year, on average. By comparison, there were 68 oncology companies financed each year, suggesting that early-stage investors currently prioritize other disease areas, such as oncology, over pain.

2006-2016 CLINICAL TRIAL STARTS FOR PAIN INTERVENTION TRIALS FOR PAIN

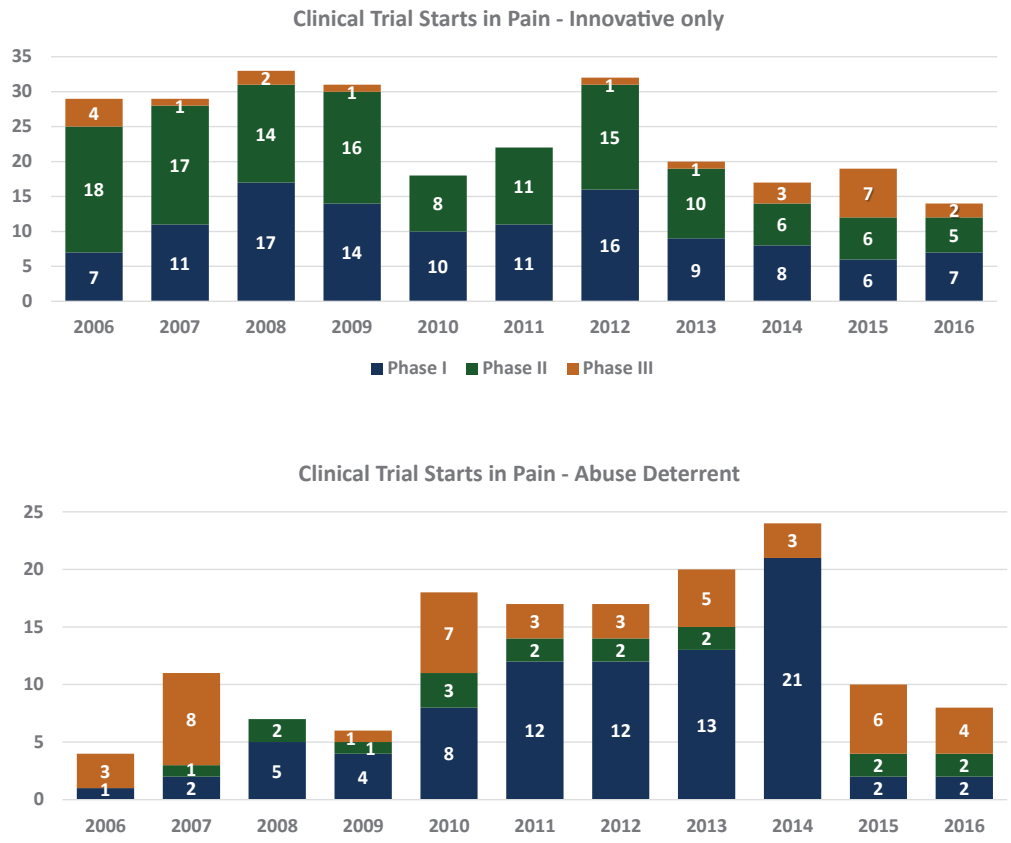


Figure 6. Clinical trial starts for Pain, 2006-2016. TrialTrove data accessed November 2017. Top: total of 1,930 clinical trial starts were retrieved from TrialTrove (on November 2017). Top: Trials were individually assessed for novelty of drug (no prior approval history of the active compound) and trial phase cohorts de-duplicated. A total of 290 novel drug intervention trials were initiated. Bottom: Trials were individually assessed for physical modification into abuse deterrent formulations of previously approved opioids, and all trial starts counted by year.

Looking at clinical trial starts over the last decade shows a more robust interest in pain. **Figure 6** shows the results from our analysis of TrialTrove data, where we individually assessed 1,950 clinical trials launched since 2006 for novelty of drug (no prior approval history of the active compound) and trial phase cohorts removed to avoid double counting. A total of 290 novel drug intervention trials were initiated between 2006 and 2016. However, we found clinical trial initiations (based on our analysis) declined 25% in the recent five-year period (2012-2016, n=111) compared to the prior five-year period (2007-2011, n=149). Phase III trial starts have totaled fewer than four per year in every year since 2006, with the exception of 2015. (The increase in 2014-2015 is attributable to the anti-CRGP migraine trials.) The low numbers of Phase III trial starts will be addressed in the following section on clinical trial success rates.

Trials were also individually assessed for physical modification into abuse deterrent formulations (ADFs) of previously approved opioids, and all trial starts counted by year. We observed a total of 142 ADF trials initiated since 2006, with a large increase over the 2010-2014 timeframe, perhaps coinciding with reports of additional unmet need in the opioid area. Although the majority were Phase I starts, there were 43 Phase III trials initiated during this period. There has been progress made in reformulating approved opioids into abuse deterrent versions as seen by the increased clinical activity in 2010-2014 and the 12 ADFs for six different opioids (morphine, oxycodone, oxymorphone, fentanyl, tapentadol, and tramadol) approved recently.

Based on our analysis of venture investment in small biotechnology companies and the number of clinical trials starts data (which includes public companies, large and small), publicly traded companies appear more active in the development of pain medications than small privately held companies.

Clinical Development Success Rates for Novel Pain Drugs

Evidence of the drought in new products for treating pain can be understood when the staggering degree of failure of clinical programs is considered over the last decade. Looking at new molecular entities in pain, we found one of the highest clinical trial failure rates of any major disease category.[15] As shown in **Figure 3**, novel pain drug development programs in Phase II had only a 16% chance of success in transitioning to Phase III, and only a 39% chance of transitioning from Phase III to NDA filing. These high Phase II and Phase III failure rates were a major contributor to the low overall probability of success (only 2.0%) for drug programs moving from Phase I all the way to FDA approval, compared to 9.6% across all disease areas.[16]

CLINICAL DEVLEOPMENT SUCCESS RATES FOR NOVEL PAIN DRUGS 2006-2015

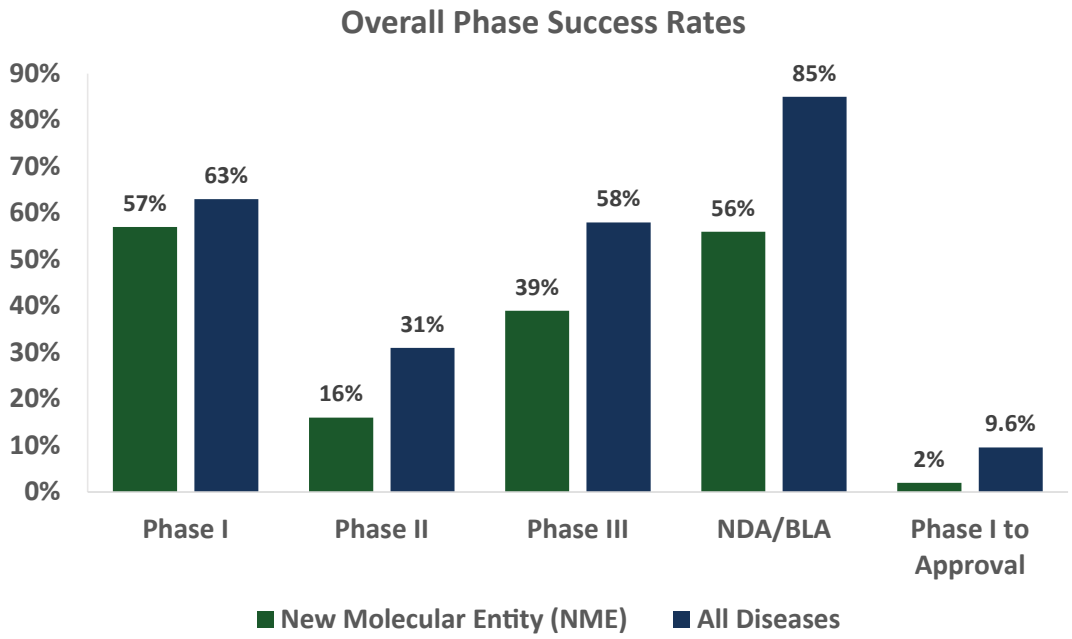


Figure 7. Clinical success rates for all Pain indications compared to overall industry probabilities, 2006-2015. Data is based on approximately 10,000 drug programs in the Biomedtracker database. (Thomas, D., et al. BIO, BioMedtracker, Amplion. Clinical Development Success Rates 2006-2015 (2016) (Accessed at www.bio.org/iareports)

Analyzing the R&D programs that were active in the period 2006-2017, we found that 183 clinical programs targeting new targets are now suspended. Examples of failed strategies are numerous and include targets such as the NK-1 receptor, p38 MAP kinase, AMPA glutamate receptor, metabotropic glutamate receptor (mGlu5), histamine H3 receptor, mitochondrial peripheral benzodiazepine receptor (PBR), and collapsin response mediator protein 2 (CRMP-2). The current pipeline includes novel chemical structures and modalities directed at targets that have experienced failure in the past. This reflects scientific advancement based on learned experiences and have the potential for success. For example, the Nerve Growth Factor (NGF) target has seen 12 failed programs but has six active novel clinical development programs.[17]

[15] Thomas, D., et al. BIO, BioMedtracker, Amplion. Clinical Development Success Rates 2006-2015 (2016) (www.bio.org/iareports)

[16] The low success rate for novel drugs was not observed for the non-NME pain drugs (those that are mostly reformulations of older APIs). The non-NME drugs had an overall 25% success rate.

[17] Other ongoing programs with a prior history of failure include cannabinoid receptors (CB1 and CB2), chemokine receptors, vanilloid receptor TRPV1, fatty acid hydrolases, and the receptor for CRGP.

Overview of FDA Approved Addiction Therapeutics

According to sources compiled by the NIH Institute of Drug Abuse, the abuse of tobacco, alcohol, and other drugs is costing the US more than $740 billion annually in costs related to healthcare, lost work productivity, and crime. In terms of direct healthcare costs, tobacco remains at the top of the list ($168 billion, 2010), followed by opioid abuse ($28.5 billion, 2013) and alcohol abuse ($27 billion, 2010).[18] This report examines currently available therapeutic options and the current pipeline for substance use disorders (including opioids, alcohol, nicotine, stimulants, and cannabis).

UNIQUE CHEMICAL ENTITIES FDA APPROVED FOR ADDICTION

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

* prescribed only for symptoms of withdrawal (tremors, anxiety), for example clorazepate, oxazepam

Figure 8. Unique FDA approved active ingredients for addiction, marketed in the US as of January 2018 (prescription, generic, or OTC) categorized by primary mechanistic target strategy and physiological 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. *Benzodiazapines are prescribed for symptoms of withdrawal (tremors, anxiety), for example clorazepate, oxazepam (Source: EvaluatePharma, Biomedtracker, fda.gov, company websites.)

[18] https://www.drugabuse.gov/related-topics/trends-statistics#supplemental-references-for-economic-costs, accessed January 2018. References cited: U.S. Department of Health and Human Services. The Health Consequences of Smoking—50 Years of Progress. A Report of the Surgeon General. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health; 2014. Xu, X. et.al. Annual Healthcare Spending Attributable to Cigarette Smoking: An Update. American Journal of Preventive Medicine 2014;48(3):326–33. Centers for Disease Control and Prevention. Excessive Drinking is Draining the U.S. Economy. National Drug Intelligence Center. National Drug Threat Assessment. Washington, DC: United States Department of Justice; 2011. Birnbaum, HG. et al. Societal Costs of Prescription Opioid Abuse, Dependence, and Misuse in the United States. Pain Medicine 2011; 12: 657-667. Florence, C et al. The Economic Burden of Prescription Opioid Overdose, Abuse, and Dependence in the United States, 2013; Medical Care. Volume 54, Number 10, October 2016. (2004)

Drugs for Opioid Abuse Disorder

Currently available treatments for substance abuse disorder are all based on modulation of the opioid receptor, either antagonistically or agonistically but with different magnitude or effect compared to opioids used to treat pain. **Figure 8** lists the four active unique substances.

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.[19]

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 for heroin addiction. 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, Vivitrol, was approved in 2010 for opioid addiction.

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, but is often used in combination with naltrexone.

Levacetylmethadol: Levacetylmethadol (not listed in **Figure 8**) was discontinued by the manufacturer based on evidence of cardiac-related side effects and the FDA's addition of new label warnings.[20] 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.

Drugs for Alcohol Abuse Disorder

Only three classes of drugs are available for treating alcohol use disorder, working through three different mechanisms as categorized in **Figure 8**.

Disulfiram: Disulfiram is the oldest drug on the list in **Figure 8**, 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.

Naltrexone: As mentioned above, Naltrexone was originally approved in 1995 for treating alcohol dependence. The long acting version was approved in 2006.

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.

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

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

Drugs for Nicotine Addiction

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.[21]

Current Clinical Pipeline for Addiction Therapeutics

There are 29 programs in the substance abuse disorder pipeline according to data obtained from the Biomedtracker database. As shown in **Figure 9**, the majority (18) are for treatment of opioid, stimulant, or cannabis addiction, five are for alcohol abuse disorders, and three are for smoking cessation and nicotine addiction. Breaking this pipeline into novel programs (new molecular entity small molecule, new biologic, or new vaccine) reveals only 15 novel ongoing clinical programs (five are broadly defined for treatment of substance abuse disorders, five are specific for cocaine, methamphetamine, or THC, two are for alcohol, three are for nicotine/tobacco). There seems to be a lack of breadth and depth in today's addiction therapy pipeline. In contrast, consider pain's 125 or breast cancer's 137 novel investigational compounds, as mentioned previously.

The five novel drug programs indicated broadly for substance abuse disorders are all early-stage (in Phase I or II trials, not in Phase III trials) and cover five different strategies. Esketamine (a ketamine enantiomer), while also being developed for depression, is in Phase II for treatment of substance abuse disorders. Ketamine has a range of targets, including various glutamate receptors, opioid receptors, and ion channels.[22] A peroxisome proliferator-activated receptor (PPAR) gamma agonist in Phase II is being used both for substance abused disorders in general and specifically to treat nicotine addiction. There is one serotonin–norepinephrine–dopamine (SNDRI) reuptake inhibitor in Phase II, as well as one undisclosed product. The fifth program is a selective alcohol dehydrogenase 2 (ALDH2) inhibitor in Phase I that works to stop addictive cravings due to dopamine surges.[23]

The five novel drug programs indicated for specific drugs in the addiction setting fall into two broad groups. First, there are three programs in early clinical development that use therapeutic agents to inactivate abused drugs. These drugs act either directly, for methamphetamine (using an antibody that binds meth) and cocaine (using an enzyme that inactivates cocaine), or indirectly, by recruiting the immune system to recognize and destroy the illicit substance. The two other abuse-specific programs are the cannabinoid receptor antagonists being developed for marijuana abuse.

For alcohol abuse, three early-stage drugs are listed as novel. Two of these drugs are prodrugs of active substances used in the pain setting.[24] A prodrug to gabapentin (a derivative of gamma-aminobutyric acid (GABA), recently approved for moderate-to-severe restless legs syndrome and postherpetic neuralgia), reduces calcium channel activity and enhances GABA like effects. A prodrug of baclofen, also a derivative of GABA, is in phase II. An intranasal formulation of Naltrexone is also under development.

For nicotine addiction, there are three very distinct agents under development. First, cytisine is in early-stage clinical trials. It is believed to act similarly to varenicline (in **Figure 8**) as a partial agonist of nicotinic acetylcholine receptors. As mentioned above under substance abuse, a peroxisome proliferator-activated receptor (PPAR) gamma agonist is being tested for nicotine addiction. Lastly, a conjugate vaccine program against nicotine has been in clinical trials for well over a decade.

The 12 non-NME drugs in the addiction pipeline include three combination drugs and nine reformulations of approved drugs. It is important to note that some of these products are being tested in addiction indications for the first time, or are being developed into formulations or delivery systems that will increase patient compliance.

[21] Roddy, E. Bupropion and other non-nicotine pharmacotherapies. BMJ, 328 (7438): 509–511. (2004)
[22] Sleigh, J., et al. Ketamine – More mechanisms of action than just NMDA blockade. Trends in Anaesthesia and Critical Care, 4 (2-3): 76-81 (2014)
[23] Phase of product and target information in this section are based on Biomedtracker and company websites accessed January 2018.
[24] Prodrugs are drugs inactive until the body metabolizes them into the active chemical entity.

R&D Investment for Addiction Therapeutics

Venture investment into US companies with lead products in addiction has been virtually nonexistent over the past 10 years. Although using the "lead product only" methodology underestimates investment, as it only takes into account lead program disease indication, the picture is nonetheless bleak. We only identified $16 million invested across two addiction-focused companies over the last decade. Furthermore, both companies had lead products for alcohol dependence, not substance abuse. Assessing clinical trial starts in this area was not possible due to the lack of defined indication tagging for these three specific indications in Trialtrove. Thus, we were unable to assess R&D investment trends across the biopharmaceutical industry (emerging, mid and large biopharmaceutical companies as we did for our analysis of R&D activity for pain. However, based on our analysis of active clinical trial programs it is fair to assume it has not been substantial.

Due to the low number of active clinical programs over the past decade, it was not prudent to calculate success rates for addiction drug development using Biomedtracker data. However, suspended programs listed in the Biomedtracker database include eight for substance abuse, 12 for nicotine addiction (smoking cessation), and 14 for alcohol abuse. As suspended programs (38) outnumber ongoing programs (29), and not a single novel chemical entity has been approved in more than a decade, evidence suggests a low rate of success in this area.

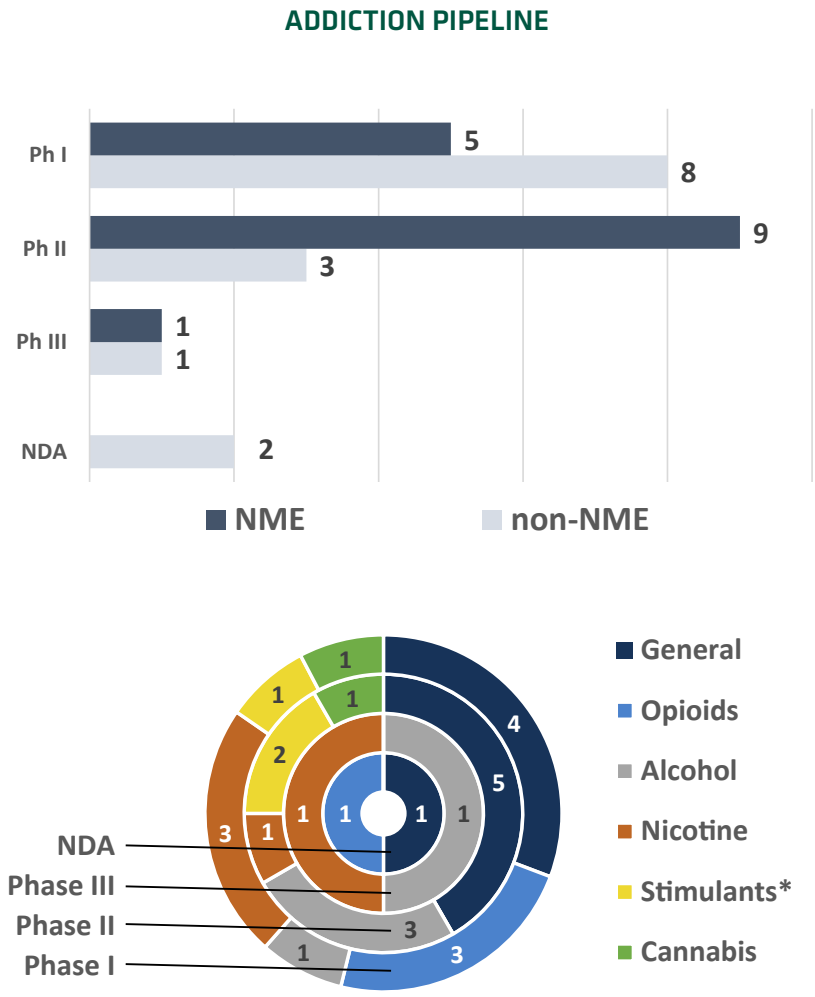


Figure 9. The addiction pipeline, based on Biomedtracker database, January 2018. Top: Addiction pipeline by phase of development and by novelty criteria: Novel drugs that do not have an approval history and non-NME drugs that are reformulated or repurposed products. For combination drugs, only the novel 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: Radar plot by earliest (outer) to latest phase (center) and by type of addiction. Geenral 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. *Stimulants only includes cocaine and methamphetamine.

Discussion

With 125 novel drug programs in the clinic to treat pain, there is potential for innovation to change how pain is treated through alternatives to current therapies. Recent innovative formulations of approved active substances have also led to safer pain medicines, with 12 ADFs approved in the last decade and a clinical pipeline of 95 non-NME programs progressing. The status of innovation in addiction treatments is very limited, with only 15 novel programs making their way through the clinic (only five of which might be applicable to opioid abuse).

When examining the current state of unmet need and public health burdens caused by both pain and addiction, policies that support an improved scientific understanding of the neurobiology of pain and addiction will allow for better identification of novel targets, while policies supporting efficient and effective regulatory environments and coverage for treatments in this area will provide more therapeutic options for patients with pain and addiction.

Advancing our understanding of the biology of pain and addiction and encouraging modern approaches to drug development and coverage would stimulate investment and novel R&D activity in these disease areas. For example, developing animal models that are better able to predict safety and efficacy in humans, biomarkers that could be used to stratify patient populations, development and utilization of modern approaches for diagnoses and drug development, and unleashing the power of data to better predict what treatments work best and for whom would all serve to incentivize innovation and change the paradigm of how we treat pain and addiction.

Additionally, barriers to access to and coverage of innovative medicines have a strong negative impact on investment. This can be a significant factor in disease areas where generic drugs are the predominantly prescribed medicines even when there are very large patient populations to treat. There are potentially 100 million people currently experiencing some form of chronic pain in the US and more than 90% of the prescribed medicines for pain have a generic option available. Recent drug launches in chronic, highly prevalent indications, even launches of highly innovative drugs, have faced challenges to coverage and access, creating uncertainty in the investor community.

The Biotechnology Innovation Organization (BIO) and member companies view innovation as the key to changing the paradigm for the treatment of pain and addiction. Advancements in science, more choices for patients, and a policy environment that stimulates investment in R&D are necessary to achieve this goal. (Please visit www.bio.org/opioid for more information).

Bio Industry Analysis

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Acknowledgements

We would like to acknowledge Cartier Esham, Danielle Friend, and Charles Crain for their review of this report.

Cover photo by Science Health (https://www.flickr.com/photos/42750848@N02/6461022819)