

# Development of Innovative Therapies for Pain



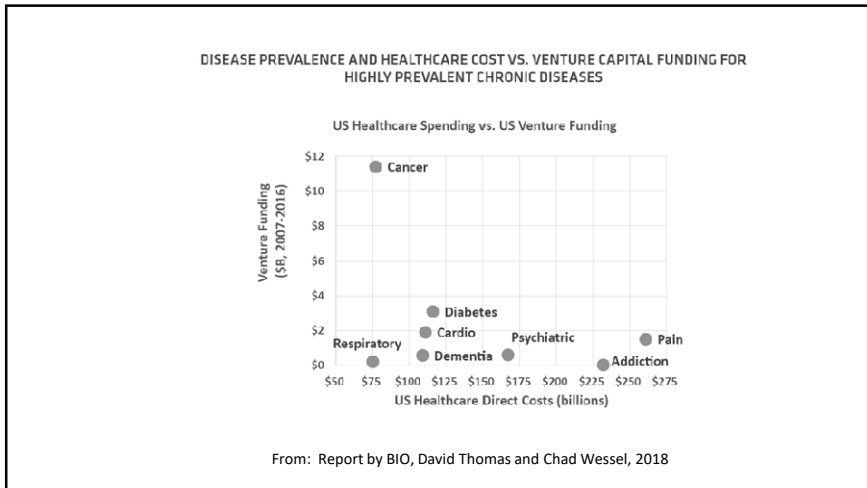
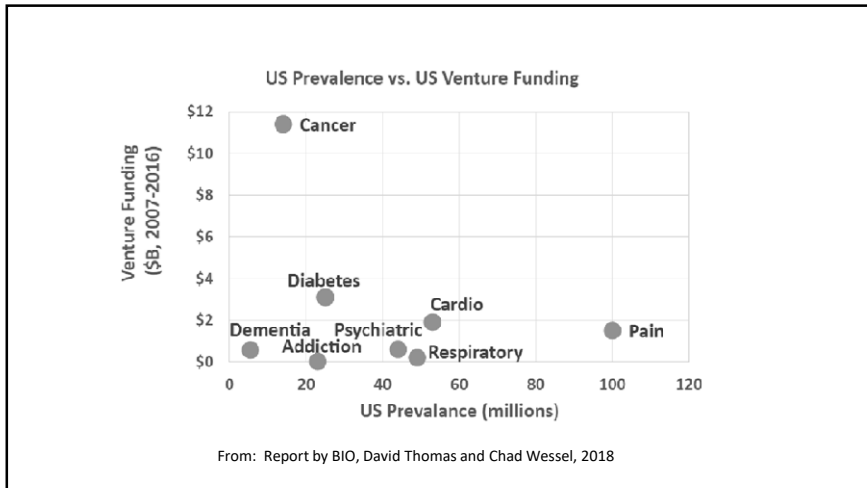
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 Centrexion Therapeutics  
 Professor Emeritus, Neurosurgery  
 Johns Hopkins University

## Clinical Stage Non-Opioid Pain Programs

Product Candidate	Pre-clinical	Phase 1	Phase 2	Phase 3	Anticipated Near-Term Milestone*
CNTX-4975 (Trans-capsaicin injection)		Moderate to Severe Knee OA Pain			Open label Victory-3 Q4 2019; Pivotal Victory-1 late 2019 to early 2020; Pivotal Victory-2 Q2/Q3 2020
CNTX-0290 (SSTR4 Agonist)		Neuropathic, Inflammatory & Mixed Pain			Licensed to Lilly
CNTX-6970 (CCR2 Antagonist)		Inflammatory Pain			Phase 2
CNTX-2022 (Lidocaine Gel)		Superficial Pain			Phase 1
CNTX-6016 (CB2 Agonist)		Neuropathic Pain			Phase 1/2

One of the largest clinical pipelines of novel, non-opioid and non-addictive chronic pain treatments, local injection, oral, intrathecal

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### Pathway to drug development

- How does a drug make from the test-tube to the bedside?
- Why is drug development so expensive?
- How successful has drug development been in the field of pain?



### Why is Understanding New Drug Development Important

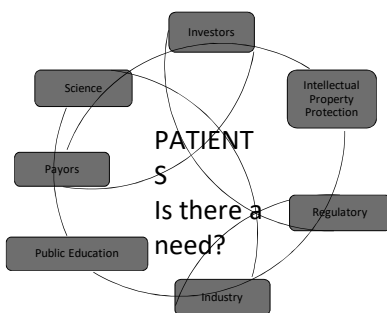
Patient advocates lead the way in spurring the development of new drugs

FDA weighs risk and benefit—if chronic pain is viewed as a benign condition the safety bar goes up.

Educate about issues with payors

Patients have more impact than physicians, pharmacists, pharma in investment in new treatments

### Elements for Innovation



### Pathway to Development of New Drug

- Preclinical (10% of candidates make it to human testing)
- Phase 1
  - Healthy volunteers
  - Dosing, safety
- Phase 2
  - Confirm the indication
  - Initial safety
- Phase 3
  - Safety (exposures to 1500 to 2000 subjects), 1 year data
  - Efficacy in 2 blinded randomized placebo-controlled trials
- Submission of NDA (new drug application)
- Approval (1 year process)
- Commercialization
- Total cost estimates range from \$1-3B

### Path to a New Treatment: Risks

- Risk multiplies
- If risk is 50% at each stage, then the risk to filing an NDA is
  - $0.5 \times 0.5 \times 0.5 = 12.5\%$

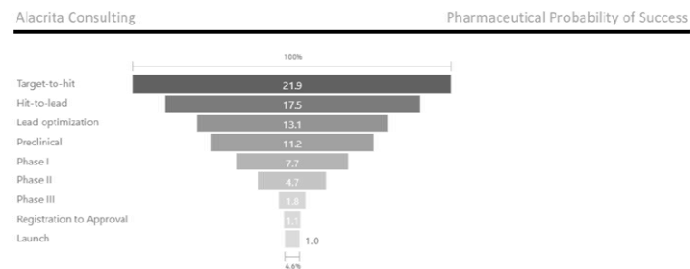


Figure 2. Number of Assets Needed for One Launch, by Development Phase, starting with Target-to-Hit.

### Intellectual Property

- IP lasts 20 years from the date of filing
- Getting to market launch of a new product within 20 years is often challenging
- Potential investment incentive
  - Provide 10 years of data exclusivity for novel non-opioid therapy for chronic pain (current exclusivity is 5 years)

### Probability of Success<sup>2</sup> by Clinical Trial Phase and Therapeutic Area

	P1 to P2	P2 to P3	P3 to Approval	Overall
Oncology	57.6	32.7	35.5	3.4
Metabolic/Endocrinology	76.2	59.7	51.6	19.6
Cardiovascular	73.3	65.7	62.2	25.5
Central Nervous System	73.2	51.9	51.1	15.0
Autoimmune/Inflammation	69.8	45.7	63.7	15.1
Genitourinary	68.7	57.1	66.5	21.6
Infectious Disease	70.1	58.3	75.3	25.2
Ophthalmology	87.1	60.7	74.9	32.6
Vaccines (Infectious Disease)	76.8	58.2	85.4	33.4
Overall	66.4	48.6	59.0	13.8
Overall (Excluding Oncology)	73.0	55.7	63.6	20.9

Source: Chi Heem Wong, Kien Wei Siah, Andrew W Lo. "Estimation of clinical trial success rates and related parameters." *Biostatistics* 20(2): April 2019, Pages 273-286. Published online: 31 January 2018. DOI: 10.1093/biostatistics/kxx069

## Regulatory

- A new drug must be shown to be safe and efficacious
- For chronic pain, efficacy must be shown at 3 months in 2 independent studies
- Primary efficacy typically pain reduction in average daily pain, 0-10 scale
- Change in pain needs to be statistically significant and clinically meaningful
- Safety has to be demonstrated out to 1 year
- See [clinicaltrials.gov](http://clinicaltrials.gov)

## New Therapies for Pain: Report Card

- Record of innovation
  - All agreed that collectively we are not doing well
  - Academia/Industry/Government
- Only two NCEs FDA approved to treat pain over the last decade
- There are 1700 novel drug clinical-stage programs in oncology, but only about 100 for non-opioid drugs
- Success in pain drug development has been difficult—only a 2% probability of FDA approval from phase 1

## Current Model

- Most pain trials have failed
- Typically, in phase 2
- Tanezumab, major disappointment
- Exceptions
  - Migraine
  - Spinal cord stimulation

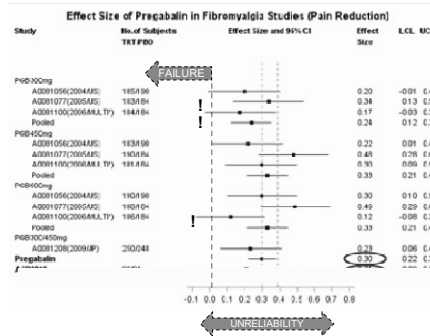
## Is Pain Investable? Issues We Confront

- Finite capital resources—highly competitive investment environment
- Investors demand ROI
- What are the elements that make for an investable environment
  - Unmet need
  - Science
  - IP
  - Regulatory
  - Clinical trials
  - Payors
  - Public education and patient advocacy

## Why has Innovation for Pain Treatment Glacially Slow

- Lack of targets?
- Animal models inadequate
  - Rigor
  - Proper measures
- High failure rate of clinical trials
  - Better clinical trial science
  - Improved “assay sensitivity”
  - Less placebo response
  - Faster/better/cheaper
- Lack of investor dollars
- Resourcing the FDA
  - Not necessarily paid well
  - Open to criticism from all sides (e.g., recent approval for Alzheimer’s drug)

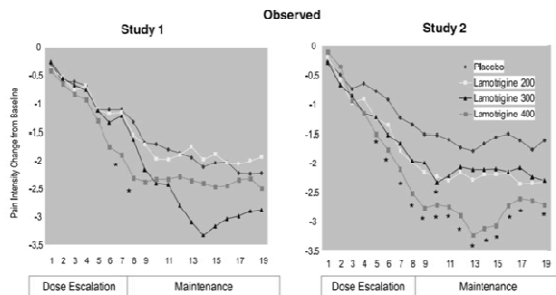
## Clinical trials are unreliable and have a high failure risk



- Pregabalin is FDA-approved for fibromyalgia and represented in all treatment guidelines
- Observed effect sizes in similar studies ranged from 0.12 to 0.48
- 3/10 studies failed (slipped below p<.05)
- The coefficient of variation of this set of studies is 40% - unacceptable in any other area
- Failure is common: 53% of Phase 3 trials fail to confirm efficacy observed in Phase 2

Courtesy of Paul Blahunka, Astellas Inc.

## Replicate trials often do not replicate



Vinik AI et al, Pain, 2007

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clinicaltrials.gov/ct2/home

Explore 390,644 research studies in all 50 states and in 219 countries.

See listed clinical studies related to the coronavirus disease (COVID-19)

ClinicalTrials.gov is a resource provided by the U.S. National Library of Medicine.

**IMPORTANT:** Listing a study does not mean it has been evaluated by the U.S. Federal Government. Read our [disclaimer](#) for details.

Before participating in a study, talk to your health care provider and learn about the risks and potential benefits.

### Find a study (all fields optional)

**Status**

Recruiting and not yet recruiting studies

All studies

**Condition or disease** (For example: breast cancer)

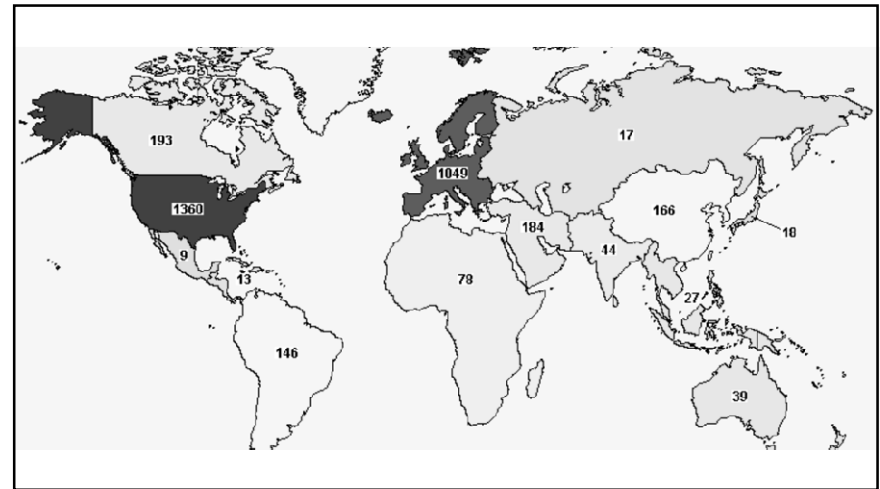
chronic pain X

**Other terms** (For example: NCT number, drug name, investigator name)

X

**Country**

X



clinicaltrials.gov/ct2/results?cond=chronic+pain&recrs=a&age\_v=&gndr=&type=Int&rst=&phase=2&Search=Apply

23 Studies found for: **Recruiting Studies | Interventional Studies | chronic pain | Phase 3**

Applied Filters:  Recruiting  Interventional  Phase 3

List By Topic On Map Search Details

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Showing: 1-10 of 23 studies 10 studies per page Show/Hide Columns

Row	Saved	Status	Study Title	Conditions	Interventions	Locations
1	<input type="checkbox"/>	Recruiting	Lidocaine Infusions for Chronic Pain in Children	• Pain, Chronic	• Drug: Lidocaine Infusion	• The Hospital for Sick Children Toronto, Ontario, Canada
2	<input type="checkbox"/>	Recruiting	Development/Testing of SUMMIT: a Tool to Help Patients Manage Pain While Tapering Opioids	• Chronic Pain	• Behavioral: SUMMIT • Behavioral: control	• VA Connecticut Healthcare System West Haven Campus, West Haven, CT

**Recruitment**

Not yet recruiting

Recruiting

Enrolling by invitation

Active, not recruiting

clinicaltrials.gov/ct2/results?cond=atopic+dermatitis&recrs=a&age\_v=&gndr=&type=Int&rst=&phase=2&Search=A...

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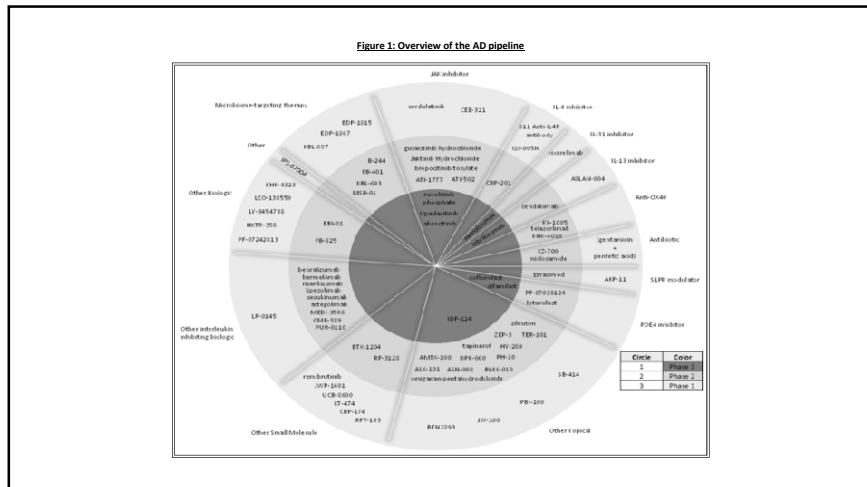
Home > Search Results

Modify Search Start Over

23 Studies found for: **Recruiting Studies | Interventional Studies | atopic dermatitis | Phase 3**

Also searched for **Eczema**. See Search Details

Applied Filters:  Recruiting  Interventional  Phase 3



**Has there been progress?**

- Recognition that pain care is often inadequate
- FDA reorganization
- NIH initiative under the HEAL program
  - Spurred by the drug overdose epidemic
  - Inadequately treated pain seen as one element in the crisis

**What Can You Do**

- Be aware of what is involved in developing a new treatment or a new drug
- Educate the public about the need
  - Scientists
  - Doctors
  - Payors
  - Congress
  - Public Agencies
  - Patients and their families
- Build awareness
- ADVOCATE

