Neurotherapeutics (2020) 17:765–769
https://doi.org/10.1007/s13311-020-00935-1

EDITORIAL

Aligning New Approaches to Accelerate the Development of Non-opioid Analgesic Therapies

Christine N. Sang[1] · William K. Schmidt[2]

Accepted: 21 September 2020 / Published online: 14 October 2020

The opioid epidemic has transformed pain research, not only in the sense of urgency with which analgesics are being developed, but also in the way in which hypotheses are being tested. This paradigm shift requires a look at both preclinical and clinical data with a perspective that follows traditional pharmaceutical approaches while incorporating new technologies. Moreover, with the launch of the National Institutes of Health (NIH) Helping to End Addiction Long-term (HEAL) Initiative in April 2018, the collaborative effort with the US Food and Drug Administration (FDA) and NIH has become ever more important.

In the previous *Neurotherapeutics Special Issue on Pain* (2009), our focus was on the advances in the field of neuropathic pain with an emphasis on the successful drug development program of gabapentin as the model for analgesic drug development. The treatments were almost entirely small molecules and the innumerable potential factors that contributed to failures to achieve clinically meaningful analgesic effects were focused on issues such as the ability of the compound to reach the target site. In 2020, many of the tools and technologies that have facilitated the discovery of analgesic targets and analgesic drug development were adapted from other therapeutic indications. These include the development of monoclonal antibodies to transmembrane protein 119 that enable immunostaining of microglia [1]; advances in transcriptomics [2, 3]; the development of subtype-selective small molecule radioligands [4]; and the improvement of viral and non-viral vectors and gene editing technologies [5].

Many of these innovations have revolutionized the landscape of new analgesics entering clinical trials. Table 1 presents a summary of 214 tracked compounds in development (as of December 31, 2019) that we have been following for the past 3 years; Table 2 presents the data by primary indication. The tables are extracted from a larger database that is available for download on www.paintrials.org/analgdrugdevt. All of the entries are based on publicly available data that are referenced by hyperlinks within the table. These include 179 compounds in active clinical development, 8 compounds that were recently approved (2018), and 27 compounds that were discontinued or where no development has been reported for extended periods of time. It currently takes, on average, 12.8 years to develop new therapeutics; for orphan drugs, it can take 2.3 years longer [6]. Central nervous system (CNS) drugs have even higher failure rates [7]. Even then, the road to an approved new drug is uncertain. Wong et al. [8] evaluated the probability of successful development for 21,000 unique drugs from January 2000 through October 2015; only 15% of CNS drugs entering phase 1 clinical trials received FDA approval.

Clearly, innovations are needed to accelerate the development of novel, more effective, and less addictive analgesic compounds with fewer adverse effects than the commercially available drugs in use today. These include better preclinical and clinical methods with predictive and prognostic biomarkers to develop drugs with a higher chance of success in gaining approval. Indeed, Dr. Francis Collins, Director of the NIH, has challenged the industry to discover improved methods for analgesic drug development and to reduce the development time for new drugs by 50% in order to address the opioid crisis in the United States. The NIH committed up to $1 billion to this effort in April 2018 to increase the number of novel compounds going into the pipeline and improve their chances of success in gaining FDA approval.

With these considerations in mind, this special *Neurotherapeutics* issue includes the insights of representatives from the FDA, academia, industry, and the NIH. This

✉ Christine N. Sang
csang@bwh.harvard.edu

[1] Translational Pain Research, Brigham and Women's Hospital, Harvard Medical School, 75 Francis Street, Boston, MA 02115, USA

[2] NorthStar Consulting LLC, Davis, CA, USA

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Table 1 Summary of analgesic drugs in development by therapeutic target (December 31, 2019)

Therapeutic target	Phase 1	Phase 2	Phase 3	NDA/BLA submitted	NDA/BLA approved	Recently discontinued
α2δ-1		1	1			
5-HT_2 antagonist		1				
$Alpha_2$ agonist		1				
AMPA glutamate		1				
COMBINATION products	2	8	5	3		2
BIOLOGICS*	15	23	13		2	8
Bisphosphonate			2			1
Cannabinoid (CB1, CB2)	3	2				
Ion channel: calcium (CaV channel)			1			
Ion channel: sodium (NaV channel)		2				1
Ion channel: potassium (KV channel)		1				
CCR2 cytokine antagonist	1					
CGRP antagonist		2	1	2	3	
Corticosteroid			4			
Opioid: mu agonist	3		5	3		7
Opioid: kappa agonist			1			
Opioid: delta agonist	1					
Opioid: endomorphin	1					
Opioid: enkephalinase inhibitor	1					
Opioid: other (NOP, undisclosed)		1	1			
Opioid: prodrug	2					2
GnRH antagonist			1			
Ergot alkaloid			2			
Imidazoline agonist (I2)		1				
JAK1, pan-JAK inhibitor		1		1	1	
Local anesthetic	2	2	1	1		
Neurostimulation		2	1			
NGF inhibitor			2			
NMDA antagonist		2				1
NSAID (COX-1, COX-2)	2	2	1	1		
PDE9 inhibitor		1				
Prostaglandin synthase inhibitor						
Sigma channel blocker		1				
Soluble epoxide hydrolase (sEH) inhibitor	1					
Soluble guanylate cyclase (sGC)		1				
Somatostatin SSTR4 agonist	1					
Superoxide dismutase mimic		1				
Syk inhibitor		1				
Triptan		1		1		
TrkA inhibitor	1	1				1
TRPA1 antagonist		1				
TRPV1 agonist (capsaicin, resiniferatoxin)	1	2	1			
Wnt inhibitor			1			
Other mechanisms of action	6	9	3		2	4
Total	43	72	47	12	8	27

*BIOLOGICS (unless otherwise included above) include the following: ammonia-oxidizing bacteria (AOB), anti-CCP vaccine (citrullinated peptide dendritic cell immunotherapy), dipeptide aspartyl-alanyl diketopiperazine (DA-DKP), autologous bone morphogenetic protein (BMP-7), autologous gene therapy targeting BCL11A protein, BCG vaccine, chondroitin-sulfate-ABC endolyase, IL-1 inhibitor, IL-6 inhibitor, IL-10 inhibitor, IL-23 inhibitor, innate defense regulator (IDR), innate repair receptor peptide (IRR), gene encoding type VII collagen (COL7), NF-kB decoy, PACAP-38 inhibitor, P-selectin inhibitor, PEGylated uric acid specific enzyme, plasmid gene therapy encoding hepatocyte growth factor (HGF), proteoglycan aggrecan mimetic, stem cells, transthyretin (TTR) protein, type VII gene replacement

issue is organized into four sections, ranging from clinical outcome assessments, to approaches to modulating peripheral and central nervous system targets, to opportunities for federal funding that are reserved for analgesic drug development.

Section I: Emerging Clinical Technologies includes two papers that address the development of clinical outcome assessment endpoints in clinical trials that each consider the complexity of the multidimensional pain experience. St. Clair et al. [9] present an overview of the regulatory considerations when selecting and developing analgesic clinical trial endpoints in specific populations, with an emphasis on formulating measurement strategies that consider the comprehensive view of the patients' pain experience in determining clinical benefit, defined as how a patient feels, functions, or

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Table 2 Summary of analgesic drugs in development by primary indication (December 31, 2019)

Primary indication	Phase 1	Phase 2	Phase 3	NDA/BLA submitted	NDA/BLA approved	Recently discontinued
Arthritis: ankylosing spondylitis		1				
Arthritis: axial spondyloarthritis					1	
Arthritis: juvenile rheumatoid arthritis (JRA)		1				
Arthritis: osteoarthritis, hip or knee	5	17	10	1		4
Arthritis: other	1		1			
Arthritis: rheumatoid arthritis	2		1	1	1	2
Bladder pain (BPS/IC)	1	1				1
Cancer pain	1					
Chemotherapy-induced peripheral neuropathy (CIPN)	1		1			
Chronic low back pain (LBP)	1	1	2			
Chronic pain (general)	5	1	2	2		7
Chronic pain: Anal fissure			1			
Complex regional pain syndrome (CRPS)			1			1
Dermal pain, other		1				
Dermal pain/itch: prurigo nodularis (PN)			1			
Dermal: topical		1				
Endometriosis pain			1			
Fibromyalgia		5				
Gout		3	1			
Headache: cluster		1			1	
Inflammatory pain, unspecified	1					
Irritable bowel syndrome (IBS)		1				
Migraine: acute or chronic	2	3	3	2	2	
Migraine: prevention	1	1	1	1	1	
Musculoskeletal pain	1					
Neuropathic pain, unspecified	4	4				6
Neuropathic: diabetic peripheral neuropathy (DPN)	2	6	2			
Neuropathic: postherpetic neuralgia (PHN)	1					
Neuropathic: sciatica			1			
Ocular pain			2			
Opioid respiratory depression		1				
Oral: mucositis		1	1			
Oral: Sjogren's syndrome		1				
Post-amputation pain		1				
Postoperative pain: acute	8	8	7	5		5
Postoperative pain: chronic						
Rare disease: epidermolysis bullosa (EB)		2	3			
Rare disease: familial amyloid polyneuropathy (FAP)			1			
Rare disease: other		1	1			
Rare disease: pemphigus vulgaris (PV)			1			
Rare disease: sickle cell pain / disease	4	4	1		2	1
Ulcerative colitis (Crohn's)		2				
Uremic pruritus			1			
Unspecified pain	2	3				
Total	43	72	47	12	8	27

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survives (in the contex of the drug product; the disease state; the patient population; pain measurement that includes not only physical but also emotional and social functioning; and the relevant stakeholders). Goldstein et al. [10] present an approach to evaluating pain and function by using a mobile platform for measuring pain, emotions, and associated bodily feelings. Moreover, they have developed and validated predictive models using artificial intelligence/machine learning tools to demonstrate that the best predictors of future pain in patients with chronic low back pain are not simply pain intensity but the interactions between (1) bodily expressed fatigue with negative affect and (2) positive affect with past pain.

Section II: Approaches to modulating targets presents two reviews of novel peripheral targets for analgesic drug development and six novel CNS targets. Ciotu and Fischer [11] survey an enormous literature of mediators and antagonists acting on peripheral sensory neurons that include some now familiar targets (e.g., substance P, calcitonin gene-related peptide, tumor necrosis factor-alpha) and others that are less familiar and, hence, of interest for developing novel therapeutics (lysophospholipids, trypsin, and a Disintegrin and Metalloproteinase with Thrombospondin motifs (ADAMTS)). Krajewski [12] discusses purinergic P2X3 and P2X2/3 receptors on sensory nerves that are critical for sensory transduction. Clinical studies have shown promise in treatment for bladder pain and pain associated with osteoarthritis. Bannister and Dickenson [13] review supraspinal mechanisms for pain control and discuss the supraspinally mediated analgesic actions of opioidergic, anti-convulsant, and anti-depressant drugs. Donnelly et al. [14] discuss glial cell mechanisms in chronic pain focusing on ways that microglia and astrocytes contribute to chronic pain and point to potentially druggable hemichannels and proteases produced by reactive microglia and astrocytes that may regulate acute or chronic pain. Li et al. [15] discuss adenylyl cyclase subtype 1 (AC1) as a key intracellular protein that causes both presynaptic and postsynaptic forms of long-term potentiation (LTP); inhibiting AC1 may block behavioral sensitization and injury-related anxiety in animal models of chronic pain. Hughes and Todd's review [16] focuses on inhibitory neurons in the spinal cord that are critical for setting pain thresholds; they discuss how disinhibition of spinal dorsal horn interneurons can produce aberrant sensory processing associated with chronic pain states. Ji et al. [17] present neuromodulation techniques (e.g., vagal nerve stimulation, auricular electroacupuncture) that may release specialized pro-resolving mediators (SPMs), which are lipid molecules produced during the resolution phase of inflammation. Recent studies suggest that SPMs inhibit inflammatory pain, postoperative pain, neuropathic pain, and cancer pain in rodent models via immune, glial, and neuronal modulations. Wagner et al. [18] discuss epoxy fatty acids (EpFAs) formed as metabolites of membrane lipids that may limit pain and inflammation by controlling endoplasmic reticulum stress and blocking mitochondrial dysfunction. These authors have recently developed a series of small molecule inhibitors of soluble epoxide hydrolase (sEH) that stabilize EpFA *in vivo* as a new approach for reducing acute and chronic pain.

In *Section III: Additional insights into peripheral and central nervous system mechanisms*, Song et al. [19] review the interactions between and among various small non-coding RNA species (including lncRNAs, circRNAs, and miRNAs) and their ability to regulate protein expression from mRNA in neuropathic pain.

In *Section IV: The Future*, Iyengar et al. [20] present the NIH HEAL Initiative, with the goal of accelerating the discovery and development of non-addictive pain treatments. This issue also includes three *Original Articles* that show the use of specific strategies to reduce hyperalgesia in rodent models of neuropathic pain [21, 22] and the development of analgesic tolerance to the chronic use of MK-801 resulting from the sensitization of presynaptic N-methyl-D-aspartate receptors and associated glutamate release [23]. Additionally, this issue includes articles and commentaries that address strategies for regeneration and restoration in neurodegenerative disorders; we view these papers as opportunities for potential cross-fertilization.

Tremendous progress in recent years in the understanding of pain targets has led to the development of over 200 compounds for acute and chronic pain, but the approval of new analgesics has been disappointing. We look forward to seeing at least some of these advances realized to bring new analgesics to the patients. This would require that new approaches to preclinical and clinical drug discovery be aligned in order to accelerate the development of non-opioid analgesic therapies.

Required Author Forms Disclosure forms provided by the authors are available with the online version of this article.

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