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Problems with Developments of Breakthrough Analgesics: Recent History via Scientometric Analysis

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ABSTRACT

This study evaluated 13 specific topics representing molecular targets for pain during the period 1982-2016. The evaluation was performed by measuring research efforts via a scientometric approach on one hand and by assessing successful outcomes of these efforts, as indicated by the development of FDA-approved analgesics, on the other. A number of new analgesics were developed during this period, some of them with a completely novel mechanism of action. However, the main problems with approved drugs, as well as drug candidates, are relatively low levels of clinical superiority in effectiveness and narrow spectrum of action in different types of pain, compared to opioids or NSAIDs. The most interesting feature of the scientometric analysis of the 13 analgesic discovery topics is the long-lasting growth in the number of articles. The total number of all PubMed articles persistently increased over each of many 5-year periods in every topic even without any success in the development of new analgesics. Scientometric indices of NIH-supported studies are not better at predicting successes in the discovery of new analgesics than indices applied to all publications without regard to the category of support. Thus, even the highly valued NIH-based funding system did not demonstrate a clear advantage for discovery efforts centered on pain-related molecular targets. The evaluated research efforts did not result in breakthrough analgesics that could demonstrably affect the current use of opioids or NSAIDs. Orthodox thinking—both in research and research funding—might be the main reason for the absence of breakthrough analgesics.

Introduction

A 2010 study[1] assessing analgesic drugs developed over the preceding 50 years demonstrated that very intensive research efforts directed at diverse molecular pain targets produced thousands of publications and the introduction of more than 50 new analgesics. Nevertheless, these analgesics did not have sufficiently broad effectiveness to demonstrably affect the use of opioids or nonsteroidal anti-inflammatory drugs for the treatment of pain. The status of the development of new analgesics has been characterized as "A lack of real breakthrough drugs".[1] Excessive use of opioids, especially for chronic nonmalignant pain, contributing to the opioid-overdose crisis, is the most dramatic illustration of the lack of true breakthrough analgesics.[2–4]

The aim of the current study was to use scientometric methods to evaluate pain research efforts that resulted in new analgesics introduced during the period 1982-2016. Scientometrics is the study of the quantitative aspects of the process of science as a communication system. Its methods have been used in a number of publications to assess research efforts related to drug discovery.[5–8] Pain mechanisms and their molecular drivers discovered in the previous searches for new analgesics were used to collect the appropriate pain targets.[9–12] The intensity of efforts to investigate pain-related molecular targets was assessed by analyzing scientometric indices based on the number of articles published in biomedical journals.

Progress, in many fields of medicine, has often been associated with programs developed and financed by the U.S. National Institutes of Health (NIH), and pain research is one such field. Approximately one in five articles on molecular pain targets covered by the PubMed Database are supported by the U.S. Public Health Service (PHS), which overwhelmingly (95%-98%) represents NIH funding.[13] An additional aim of this study was to use scientometric methods to determine whether NIH-supported studies have specific features that distinguish them from the general pool of scientific studies. Such features, if they exist, might be associated with the specific mechanisms of NIH grant support. These mechanisms might have especially high

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value for insufficiently effective areas of research, including the development of new analgesics.

Methods

The assessment of pain research efforts based on the discovery of new analgesics analyzed two outcomes: evaluation of the success of a new analgesic as well as the analysis of the intensity of efforts associated with its discovery and development. The degree of success was determined using three criteria. First, a drug's status with the FDA: either approval for the treatment of pain, or positive outcomes in Phase II-III Clinical Trials. A positive Cochrane meta-analysis was also acceptable. Second, a drug's commercial perspective as indicated by the development of similar drugs acting on the same molecular target (which are predictably introduced in response to the success of a first-in-class drug). Third, the degree of novelty of the molecular target of the drug's action: either a novel selective mechanism arising from a better understanding of the action of an existing analgesic drug or a completely novel mechanism.

The intensity of efforts related to the discovery of an analgesic was assessed using scientometric indices based on the number of articles published in biomedical journals on specific molecular targets. Pain mechanisms and their molecular drivers described in previous publications on new analgesics[9–12] were used to collect appropriate pain targets. They were assessed and divided into specific topics presented in Table 1. These topics represent popular directions in analgesic discovery efforts during 1982-2016. A number of new drugs approved by the FDA during this period belong to "old" pharmacological groups of analgesics, e.g., opioids, nonsteroidal anti-inflammatory drugs, anticonvulsants, and antidepressants. With few exceptions, they represent, at best, only incremental improvements on well-known mechanisms. Therefore, most molecular targets related to new drugs in these groups were not included in the searches. The PubMed database, i.e., the National Library of Medicine's Website (http://www.ncbi.nlm.nih.gov/pubmed), was used as the source of information on articles published in biomedical journals. Articles were assessed in two ways: total number of all articles without regard to the funding support category, and the number of articles with funding support from the PHS. PHS-supported articles constitute approximately $^1/_5$ of the total number of articles with very wide variation in the number depending on the topic. PHS research support information has been included in PubMed since 1975.[13]

Information on each of 13 topics (Table 1) was obtained via searches by entering the names of various molecular targets in combination with the keywords "Pain" and "Migraine Disorders" (MeSH term) into the search box. For example, for the topic "Neurotrophins" the following keywords were used: "(Nerve Growth Factors OR NGF OR Neurotrophins OR TrkA) AND (Pain OR Migraine Disorders)." If possible, keywords indicated by the National Library of Medicine as "MeSH terms" were used. As a rule, a keyword was included if its addition increased the total number of articles on a topic by ≥2% (above the number already present for this topic from the previously included keywords). Articles during certain time intervals were counted with the use of the custom range for publication dates; only articles with abstracts were included.

Two additional scientometric parameters were used. The first was **Popularity Index** (PI),[5,6] the percentage of all types of articles on a specific topic among all articles on pain and migraine disorders published over the same 5-year period. It allows the assessment of a topic's comparative popularity among authors. The second was **Top Journal Selectivity Index** (TJSI),[5,8] the ratio of the number of all types of articles on a particular topic in the top 20 journals relative to the number of articles in all (>5000) biomedical journals on the same topic covered by PubMed over 5 years. The top 20 journals were selected on the basis of their rank sorted by impact factor (as indicated by journal citation report for 2016) and the journal specialty area. They included journals related to pharmacology, pain medicine, and general biomedical journals as follows: *Anesthesiology; Ann Intern Med; Br J Anaesth; J Med Chem; Annu Rev Pharmacol Toxicol; Clin Pharmacol Ther; J Pain; Expert Opin Ther Target; J Clin Invest; J Pharmacol Exp Ther; JAMA; Lancet, Nat Rev Drug Discov; Nature; Neuropharmacology; New Engl J Med; Pain; Pharmacol Rev; Science; Trends Pharmacol Sci.*

Results

General scientometric data on 13 topics related to analgesic discovery efforts for the period 1982-2016 are presented in Table 2. It compares the initial 5-year period with the 5-year period of maximal growth of publication using three main criteria: (1) the PI, indicating a topic's frequency among all articles on pain and migraine disorders, (2) the total number of articles covered by PubMed (counted without regard to the category of support) on each topic, and (3) the number of PHS-supported articles. In addition, the last column shows the degree of success for each of the 13 topics, presenting the FDA-approved drugs, or investigational drugs with positive Phase II Clinical Trials.

The PI index shows that the most active topics in the general field of pain were "Serotonin" and "Glutamate," ie, the number of articles on these topics exceeds 1 % of all articles in the field of pain—1.2 with "Serotonin", and 1.1 with "Glutamate". The important difference

Table 1
Topics and keywords used for searches related to analgesic discovery efforts, 1982-2016.

#	Topic	Keywords used in addition to "Pain OR Migraine Disorders"
1	Serotonin	Serotonin
2	Substance P	Substance P, NK-1
3	Bradykinin	Bradykinin
4	Glutamate	Excitatory Amino Acid Agonists, glutamate, AMPA, NMDA
5	GABA[1]	Gamma-Aminobutiric Acid, GABA, "Receptors GABA-A," "Receptors GABA-B"
6	CGRP[2]	Calcitonin Gene-Related Peptide, CGRP
7	Cholecystokinin	Cholecystokinin, CCK, "Receptors Cholecystokinin"
8	Neurotrophins	Nerve Growth Factors, NGF, neurotrophines, TrkA
9	Cannabinoids	Cannabinoids, CB1, CB2
10	Calcium Channels	"Calcium channels," T-type, N-type, CaV2.2, CaV3.2
11	VGSC[3]	"Voltage-Gated Sodium Channels," NAV1.3, NAV1.7, NAV1.8
12	TRP[4] Channels	"Transient Receptor Potential Channels," TRPA1, TRPV1, TRPC
13	Purinergic Receptors	"Purinergic receptors," P2X, P2Y, P2X3

[1] GABA, gamma aminobutyric acid.
[2] CGRP, calcitonin gene-related peptide.
[3] VGSC, voltage-gated sodium channels.
[4] TRP, transient receptor potential.

Table 2
General scientometric data related to analgesic discovery efforts, 1982-2016.

#	Topic	Data related to initial 5-year period				Data related to 5-year period with maximal number of articles				Drugs approved by FDA for pain relief (year) and investigational NME[4] or biologics with positive phase II trials[5]
		Years	PI[1]	Total number of all PubMed articles[2]	Number of PHS-supported articles[3]	Years	PI[1]	Total number of all PubMed articles[2]	Number of PHS-supported articles[3]	
1	Serotonin	82-86	1.1	340	28	07-11	1.2	1631	147	**Sumatriptan** (1992), and **6 other triptans**, **duloxetine** (2006), **milnacipran** (2009).
2	Substance P	82-86	0.6	176	23	02-06	0.5	516	123	None
3	Bradykinin	82-86	0.4	130	23	07-11	0.3	380	54	None
4	Glutamate	87-91	0.3	122	51	07-11	1.1	1509	346	Ketamine (CR-2006)[6]
5	GABA[7]	87-91	0.3	106	26	12-16	0.9	1765	202	Baclofen[8], **Gabapentin** (2002)[9], **Pregabalin** (2004)[10], Mirogabalin (DS-5565)
6	CGRP[11]	92-96	0.3	146	26	07-11	0.5	660	149	**Erenumab** (2018) and 3 other biologics blocking CGRP pathway. Ubrogepant (MK-1602) and 2 other small-molecule CGRP antagonists.
7	Cholecystokinin	92-96	0.2	108	22	92-96	0.2	108	22	None
8	Neurotrophins	97-01	0.4	270	55	12-16	0.5	1005	170	Tanezumab (RN624), Fasinumab (REGN-475), biologics against nerve growth factor.
9	Cannabinoids	97-01	0.2	178	51	07-11	0.5	685	152	Dronabinol (CR-2007)[8]
10	Calcium channels	97-01	0.3	238	26	07-11	0.4	545	101	**Ziconotide** (2004)
11	VGSC[12]	02-06	0.1	115	25	12-16	0.3	496	64	Raxatrigine (CNV1014802)
12	TRP[13] channels	02-06	0.3	355	101	07-11	0.7	994	256	**Capsaicin** (8% patch, 2009)
13	Purinergic receptors	02-06	0.2	165		12-16	0.2	379	46	None

Drug names in bold are those approved by the FDA for the treatment of pain; tanezumab and fasinumab are on the FDA fast track designation.
[1] Popularity Index—the percentage of articles on a specific topic among all articles on pain and migraine disorders over the same 5-year period.
[2] All types of articles on a topic in the PubMed database, the National Library of Medicine's website (http://www.ncbi.nlm.nih.gov/pubmed).
[3] Articles on studies which received research support from the US Public Health Service (includes both extramural and intramural NIH funding).
[4] NME—new molecular entity; investigational NMEs or biologics are presented with development code names (in brackets).
[5] Clinical trial phases, according to the FDA.
[6] (CR-2006)–positive Cochrane meta-analysis, (year).
[7] GABA—gamma aminobutyric acid.
[8] The analgesic effect of baclofen in trigeminal neuralgia and other pain conditions was not studied with Cochrane meta-analysis.
[9,10] Gabapentin and pregabalin are antiseizure drugs that consist of a modified GABA molecule; however, the exact mechanism underlying the analgesic effects of both drugs are not known (they may work through calcium channels and also modulate other analgesic targets).
[11] CGRP, calcitonin gene-related peptide.
[12] VGSC, voltage-gated sodium channels.
[13] TRP, transient receptor potential.

between them is that the PI of "Serotonin" was very high even in the initial period (1.1 in 1982-1986 vs. 1.2 in 2007-2011), whereas with "Glutamate" the PI increased dramatically (0.3 in 1987-1991 vs. 1.1 in 2007-2011). The total number of all articles covered by PubMed reflects the actual number of studies per topic. It shows that the increases in the number of articles were very profound even if the PI did not markedly increase, as was the case with "Serotonin." The maximal numbers of articles per 5-year period were especially high with Gamma-Aminobutyric Acid "GABA" (1765), "Serotonin" (1631),"Glutamate" (1509), and "Neurotrophins" (1005). The number of PHS-supported articles in PubMed varied depending on the topic and the time period. On average, PHS-supported articles on these 13 topics constituted approximately 1/5 of the total number of articles covered by PubMed.

The last column of Table 2 shows two categories indicating success in drug development. One category is new drugs approved by the FDA for the treatment of pain (presented in bold). Multiple drugs were developed with two topics: "Serotonin"—nine drugs (sumatriptan, six other triptans, duloxetine, and milnacipran) and "GABA"—two drugs (gabapentin and pregabalin, also see calcium channels—$\alpha 2\delta$ ligands below). Two other topics, "Calcium Channels" and "TRP Channels," were associated with one drug each, with very limited applications (ziconitide and capsaicin 8% patch, respectively). The second category suggesting success in drug development is investigational drugs with positive Phase II Clinical Trials, indicating a probability of FDA approval for the treatment of pain. Multiple investigational drugs in this category belong to "CGRP" and "Neurotrophins." With "CGRP," erenumab and three other biologics were developed to block the CGRP pathway. Erenumab was approved by the FDA for preventive treatment of migraine in 2018 (outside the 1982-2016 study period). In addition, "CGRP" encompasses three small-molecule CGRP antagonists including ubrogepant. "Neurotrophins" covers two investigational biologics, tanezumab and fasinumab, both against nerve growth factors and well on the way to FDA approval for the treatment of pain. Outside of these two pre-defined "successful" categories (ie, without present or pending FDA approval for the treatment of pain), there are drugs for which there is still good evidence for pain relief, as confirmed by Cochrane meta-analysis: ketamine ("Glutamate" topic) and dronabinol ("Cannabinoid" topic).

Table 3 presents the time course of change in the number of articles on each of the topics related to analgesic discovery efforts. It reflects a common increase in publishing activity in almost every 5-year period compared to the previous one, both in PubMed articles counted without regard to the category of support, and in PHS-supported articles. The clear exception is the topic "Cholecystokinin": after the first two 5-year periods the number of articles began to decline, and this decline continued over several 5-year periods. With the remainder of the topics, decreases in the number of articles were rare exceptions. With the total number of PubMed articles in 12 of 13 topics, there were no decreases in publication activity in any 5-year period. With PHS-supported articles, there was a decline in the number of articles in seven of the topics, usually during the last 5-year period (marked by arrows, Table 3).

Table 4 shows the topics with >25 years of intensive research efforts (covering five to seven 5-year periods) grouped according to

Table 3
Time course of change in number of articles on topics related to analgesic discovery efforts, 1982-2016.

#	Topic	Years of 1st Period	Number[1] of articles during consecutive 5-year periods						
			1st	2nd	3rd	4th	5th	6th	7th
1	Serotonin	82-86	**251** 28	**363** 71	**581** 55	**1116** 78	**1574** 116	**1512** 147	**1491** 139 ↓
2	Substance P	82-86	**135** 23	**240** 47	**354** 67	**447** 98	**516** 123	**506** 103 ⇊	**571** 73 ⇊
3	Bradykinin	82-86	**106** 23	**160** 26	**204** 37	**276** 40	**337** 51	**380** 54	**428** 34 ⇊
4	Glutamate	87-91	**117** 51	**367** 122	**779** 198	**1139** 270	**1484** 346	**1629** 280 ⇊	–
5	GABA	87-91	**99** 26	**192** 40	**453** 69	**825** 121	**1355** 160	**1640** 202	–
6	CGRP	92-96	**138** 26	**254** 40	**434** 111	**626** 149	**792** 108 ⇊	–	–
7	Cholecystokinin	92-96	**106** 22	**136** 18 ⇊	**129** ↓ 16 ↓	**110**⇊↓ 14 ↓	**80** ⇊↓ 10 ⇊	–	–
8	Neurotrophins	97-01	**252** 55	**395** 112	**621** 138	**977** 170	–	–	–
9	Cannabinoids	97-01	**154** 51	**419** 91	**650** 152	**822** 147	–	–	–
10	Calcium channels	97-01	**221** 26	**367** 61	**511** 101	**595** 97	–	–	–
11	VGSC	02-06	**109** 25	**265** 47	**472** 64	–	–	–	–
12	TRP channels	02-06	**320** 101	**947** 256	**1198** 243 ↓	–	–	–	–
13	Purinergic receptors	02-06	**162** 26	**299** 44	**371** 46	–	–	–	–

Arrows indicate the degree of decline in the number of articles: one arrow—a decline in the number of articles ≥5% compared to a previous 5-year period, two arrows—a decline ≥15%.
[1] Number of all PubMed articles, counted without regard to the category of support, are in bold font; number of PHS-supported articles are in normal font.

the type of outcome in development of new analgesics. In one group of three topics, there were new approved analgesics or drug candidates with at least one positive Phase II Clinical Trial: "Serotonin"(sumatriptan and six other triptans, duloxetine, and milnacipran); "GABA"(gabapentin and pregabalin); and "CGRP"(erenumab with three other biologics blocking the CGRP pathway, and ubrogepant with two other small-molecular CGRP antagonists). In another three topics there were no new drugs: "Substance P", "Bradykinin", and "Cholecystokinin." Table 4 indicates that PHS-supported studies diverged very little from a common trend for all studies: the changes in the number of PHS-supported articles were in the same direction and, more or less, of the same degree as the changes in number of all articles without regard to the source of support.

Table 5 presents a time course of the PHS-related ratio, ie, the ratio of the number of PHS-supported articles to the total number of all PubMed articles. The highest value of the PHS-related ratio is usually reached during one of the initial 5-year periods and gradually declines to its lowest value by the final 5-year period. Three of the 13 topics had an exceptionally high PHS-related ratio during the first 5-year period—above 30.0: "Glutamate", "Cannabinoids", and "TRP Channels." In the last of the 5-year periods, the PHS-related ratios of these three topics were much lower than in the beginning (17.2, 17.9, and 20.3, respectively), but were still among the highest of all 13 topics in the last 5-year period. High PHS-related ratios indicate greater participation of authors supported by the PHS. It is of interest that even topics without positive outcomes (no new analgesics or drug candidates with positive Phase II Clinical Trials—see Table 2) still had PHS-related ratios above 10.0 during the last 5-year period: "Substance P"—14.3, "Cholecystokinin"—12.5, and "Purinergic Receptors"—12.4. This indicates extremely persistent interest in these three topics among authors with PHS support. Table 5 also demonstrates a certain trend in the PHS-related ratio that could indicate the important contribution of PHS-supported studies to the discovery of new analgesics. There is a very distinctive increase in the PHS-related ratio (indicated by the exclamation mark in Table 5) immediately before the 5-year period covering the initial articles on the clinical trials of a successful drug (marked in Table 5 by a circle with the first letter

Table 4
Growth of publications with two types of outcomes in development of new analgesics.

Type of outcome	Topic[1]	Initial 5-year period	Number of 5-year periods	Increase in number of articles from first to last period	
				All PubMed[2] (%)	PHS-supported[3] (%)
New drugs[4]	Serotonin	82-86	7	+ 379	+ 425
	GABA	87-91	6	+ 1556	+ 677
	CGRP	92-96	5	+ 352	+ 473
No new drugs[5]	Substance P	82-86	7	+ 193	+ 435
	Bradykinin	82-86	7	+ 192	+ 135
	Cholecystokinin	92-96	5	- 24	- 54

[1] Topics with period of publications ≥25 years.
[2] Total number of all articles covered by the PubMed counted without regard to the category of support.
[3] Articles with support from the US Public Health Service (PHS); 85%-90% of it is from the National Institute of Health (NIH).
[4] Drugs approved by the FDA (since 1982) for the treatment of pain.
[5] No drugs or candidate drugs with a positive Phase II Clinical Trial for pain relief (1982-2017).

Table 5
PHS-related ratios[1] for articles on analgesic discovery efforts.

#	Topic	Initial drug or drug candidate[2]	Year of 1st period	PHS ratios for consecutive 5-year periods						
				1st	2nd	3rd	4th	5th	6th	7th
1	Serotonin	Sumatriptan	82-86	**11.2**	**19.6**!	ⓢ **9.5**	**7.0**	**7.4**	**9.7**	**9.3**
2	Substance P	None	82-86	**17.0**	**19.6**	**18.9**	**20.5**	**23.8**	**20.4**	**14.3**
3	Bradykinin	None	82-86	**21.7**	**16.2**	**18.1**	**14.5**	**15.1**	**14.2**	**7.9**
4	Glutamate	Ketamine	87-91	ⓚ **43.6**	**33.2**	**25.4**	**23.7**	**23.3**	**17.2**	-
5	GABA	Baclofen (?)[3]	87-91	ⓑ **26.3**	**20.8**	**15.2**	**14.7**	**11.8**	**12.3**	-
6	CGRP	Ubrogepant (MK-1602)	92-96	**18.8**	**15.7**	**25.6**!	ⓤ **23.8**	**13.6**	–	–
7	Cholecystokinin	None	92-96	**20.8**	**13.3**	**12.4**	**12.7**	**12.5**	–	–
8	Neurotrophins	Tanezumab (RN624)	97-01	**21.8**	**28.3**!	ⓣ **22.2**	**17.4**	–	–	–
9	Cannabinoids	Dronabinol	97-01	**33.1**	ⓓ **21.7**	**23.4**	**17.9**	–	–	–
10	Calcium channels	Ziconotide	97-01	**11.8**	ⓩ **16.6**	**19.8**	**16.3**	–	–	–
11	VGSC	Raxatrigine (CNV1014802)	02-06	**22.9**	**17.7**	ⓡ **13.6**	–	–	–	–
12	TRP channels	Capsaicin (8% patch)	02-06	**31.6**	ⓒ **27.0**	**20.3**	–	–	–	–
13	Purinergic receptors	None	02-06	**16.0**	**14.7**	**12.4**	–	–	–	–

Circle with letter (name of drug) is placed in time period when the initial clinical studies on this drug were published.
Exclamation mark indicates a change in the PHS-related ratio that was specifically discussed in the text.
[1] The ratio between the number of PHS-supported articles and the total number of all articles in the biomedical journals (>5000) covered by the PubMed over the period of 5 years.
[2] Name of the first new drug approved by the FDA for the treatment of pain, the first investigational drug (new molecular entity [NME] or biologic) with positive phase II clinical trials (development code name in brackets), or drug with positive Cochrane meta-analysis.
[3] The analgesic effect of baclofen in trigeminal neuralgia and other painful conditions was not assessed with a Cochrane meta-analysis.

of the drug's name). Five-year periods fitting this pattern were associated with the discoveries of sumatriptan, ubrogepant, and tanezumab. Marked reductions in PHS-related ratios were most common during the last 5-year periods; for the following topics: "Substance P"—from 20.4 to 14.3, "Bradykinin"—from 14.2 to 7.2, and "Glutamate"—from 23.3 to 17.2.

Table 6 compares the PHS-related ratio with the TJSI, a scientometric index based on publication of articles in the top

Table 6
Comparisons of PHS-related ratio[1] with TJSI index[2].

#	Topic	Year of 1st period	Consecutive 5-year periods						
			1st	2nd	3rd	4th	5th	6th	7th
1	Serotonin	82-86	**11.2** 7.6	**19.6** 11.5	**9.5** 8.1	**7.0** 5.1	**7.4** 5.7	**9.7** 5.6	**9.3** 5.5
2	Substance P	82-86	**17.0** 5.1	**19.6** 11.6	**18.9** 12.1	**20.5** 12.7	**23.8** 10.1 ↓↓	**20.4** ↓ 9.3 ↓	**14.3** ⇊ 6.7 ↓↓
3	Bradykinin	82-86	**21.7** 6.1	**16.2** 4.5	**18.1** 6.6	**14.5** 10.5	**15.1** 13.1	**14.2** ↓ 9.0 ↓↓	**7.9** ⇊ 16.6 ↓↓
4	Glutamate	87-91	**43.6** 23.0	**33.2** 23.1	**25.4** 17.2 ↓↓	**23.7** 14.6 ↓↓	**23.3** 12.8 ↓	**17.2** ⇊ 8.4 ↓↓	–
5	GABA	87-91	**26.3** 8.5	**20.8** 11.0	**15.2** ⇊ 15.6	**14.7** 12.8 ↓↓	**11.8** ⇊ 10.4 ↓↓	**12.3** 7.4 ↓↓	–
6	CGRP	92-96	**18.8** 10.3	**15.7** 9.7	**25.6** 11.3	**23.8** 12.9	**13.6** ⇊ 9.1 ↓↓	–	–
7	Cholecystokinin	92-96	**20.8** 7.4	**13.3** ⇊ 11.3	**12.4** ↓ 7.6 ↓↓	**12.7** 6.2 ↓↓	**12.5** 4.9 ↓↓	–	–
8	Neurotrophins	97-01	**21.8** 11.5	**28.3** 12.2	**22.2** 10.3	**17.4** ⇊ 7.5 ↓↓	–	–	–
9	Cannabinoids	97-01	**33.1** 14.6	**21.7** 14.3	**23.4** 11.1 ↓↓	**17.9** ⇊ 8.0 ↓↓	–	–	–
10	Calcium Channels	97-01	**11.8** 11.3	**16.6** 10.7	**19.8** 11.9	**16.3** ⇊ 8.0 ↓↓	–	–	–
11	VCSC	02-06	**22.9** 17.4	**17.7** 13.7	**13.6** ⇊ 12.3 ↓	–	–	–	–
12	TRP channels	02-06	**31.6** 14.6	**27.0** 15.3	**20.3** ⇊ 8.1 ↓↓	–	–	–	–
13	Purinergeric receptors	02-06	**16.0** 17.0	**14.7** ↓ 10.0 ↓↓	**12.4** ⇊ 3.7 ↓↓	–	–	–	–

Arrows indicate the degree of decline in the number of articles, bold arrows—for PHS-supported articles, dashed arrows—for the total number of all articles. One arrow—a decline in the number of articles ≥5% compared to a pervious 5-year period, two arrows—a decline ≥15%.
[1] The ratio between the number of PHS-supported articles on a particular topic and the total number of articles on the same topic in all (>5000) biomedical journals covered by the PubMed over the period of 5 years (bold).
[2] The ratio of the articles on a particular topic in the top 20 journals relative to the number of articles in all (>5000) biomedical journals covered by the PubMed over 5 years.

biomedical journals—TJSI, is regarded as an indicator of a promising development. A comparison of these two indices for each of the 13 topics shows that they change in a relatively similar fashion. In eight topics, maximal increases in both indices occurred during the same 5-year period. Decline in the indices also often started simultaneously. However, in six of the 13 topics the decline of TJSI began earlier (or was greater) than that of the PHS-related ratio; and the decline of the PHS-related ratio began before that of the TJSI in two topics: "GABA Receptors" and "Cholecystokinin" (see arrows in Table 6).

Discussion

The 13 specific topics included in this study were evaluated by measuring research efforts via a scientometric approach on one hand, and by assessing successful outcomes as indicated by development of FDA-approved analgesics, on the other. Basic scientometric parameters used to characterize each of the topics were the number of articles on a topic and the topic's Popularity Index. The assessment of the outcomes for analgesics was based on the number of new drugs approved by the FDA for the treatment of pain as well as investigational drugs with positive outcomes in Phase II-III Clinical Trials. This assessment also took into account the degree of novelty of the molecular target of a new analgesic, and the extent of its commercial success as indicated by the development of similar drugs acting on the same molecular target.

Specific Topics

Below we discuss seven topics, each of which is either associated with drugs approved by the FDA for the treatment of pain or has an extremely high PI (above 1.0).

Serotonin

This topic has the highest levels of both the scientometric indices and the number of developed analgesics (Table 2): nine new drugs approved by the FDA, the most popular of which was sumatriptan. Sumatriptan has a novel molecular target (5-hydroxytriptamine 1B/1D receptor) and a therapeutic advantage over previous traditional drugs for acute migraine, which precipitated the subsequent development of six FDA-approved triptans. Two of the other drugs, duloxetine and milnacipran, are serotonin-norepinephrine reuptake inhibitors; although in essence antidepressants, they were approved by the FDA for use in several pain syndromes (ie, fibromyalgia, diabetic neuropathy, and chronic musculoskeletal pain).

Glutamate

This excitatory neurotransmitter plays an important role in the modulation of pain. The analgesic effect of ketamine has been known since its introduction (1966) as a general anesthetic. Among ketamine's known mechanisms of action is its effect on a novel molecular target, specifically as a selective antagonist of the ionotropic glutamate receptor (N-methyl-D-aspartate receptor). Its effectiveness in the treatment of pain was confirmed by a Cochrane meta-analysis,[14] but the drug has never been approved for this indication by the FDA. Efforts in investigating the glutamate topic consistently increased, and in 2012-2016 they almost caught up with the serotonin topic: PI values of 1.1 vs. 1.2, respectively (Table 2). However, no new ketamine-like drugs for pain relief have been approved.

GABA Receptors

Because GABA's principal role is reducing neuronal excitability, it has been the focus of many efforts to create new analgesics. As shown in Table 2, research efforts related to this topic were among the most intensive. Initially these efforts led to the development of baclofen—a GABA-B receptor agonist used for the treatment of spasticity. The analgesic effects of baclofen in trigeminal neuralgia and other pain conditions were described in a number of clinical studies; however, without any meta-analysis. Two drugs related to this topic, gabapentin and pregabalin, were designed as anti-seizure drugs and consist of a modified GABA molecule but do not interact with GABA A or B receptors or influence GABA uptake. Similar to many other anticonvulsants (such as carbamazepine or valproate) they are effective in the treatment of pain, indications for which they are approved by the FDA. The exact mechanisms underlying their analgesic effects are not known; however, it appears they may work by reducing excitatory neurotransmitter release by acting on calcium channels, for which they are regarded as nonselective $\alpha 2_{\delta}$ protein subunit ligands. Another drug candidate from the same group, mirogabalin, was developed as a selective $\alpha 2_{\delta}$ protein subunit ligand.

Neurotrophins

The most important development under this topic was targeting nerve growth factor (NGF) with several monoclonal antibodies to develop analgesics with a wide spectrum of action: osteoarthritis pain, low back pain, neuropathic pain, etc. Two candidates, tanezumab and fasinumab, are presently well on their way to FDA approval for the treatment of pain. They represent an exciting new class of analgesics based on the completely novel molecular target – NGF. The total number of PubMed articles on "Neurotrophins" was the fourth highest among the 13 topics (Table 2), mostly due to these two analgesics. Tanezumab has had an unusually prolonged process with the FDA: from a Phase III Clinical Trial for knee pain due to osteoarthritis published in 2010[15] to FDA fast-track designation in July 2018. The most important factor in the delay is the level of analgesic effectiveness of tanezumab (and fasinumab): their pain relief in osteoarthritis is only 1 to 2 points on an 11-point pain scale.[16,17] The possible adverse effects and the potential costs, more than an order of magnitude higher than conventional pain treatments (without more impressive clinical effectiveness), is also probably making the FDA very careful with approval, despite the analgesic's novelty.

CGRP

Calcitonin gene-related peptide has very diverse biological functions, especially in peripheral and central neurons. The interest in its role in migraine pathophysiology has led to the development of various CGRP antagonists: small-molecule (non-peptide) antagonists, monoclonal antibodies targeting the CGRP receptor, and monoclonal antibodies targeting the CGRP molecule. Three monoclonal antibodies targeting CGRP (ie, eptinezumab, fremanesumab, galcanezumab) and one targeting its receptor (ie, erenumab) are currently under evaluation for the prevention of episodic and chronic migraine; erenumab has already been approved by the FDA for this purpose. Although the efficacy, in terms of migraine prevention, of all four monoclonal antibodies is modest compared with placebo and overall comparable with available oral preventive treatments, recent tolerability and safety data promise a step forward for migraine prevention.[18,19] In addition, small-molecule antagonists are under investigation for migraine treatment and prevention. Similar to NGF-based analgesics, all CGRP-based drugs for prevention of migraine are designed for activity at a completely novel molecular target.

Calcium Channels

One development in this topic culminated in the introduction of ziconotide, an analgesic with a novel mechanism of action—selective blockade of the CaV2.2 (N-type) calcium channels. It was derived

from the sea snail *Conus magnus* and developed into a synthetic form of a w-conotoxin peptide. Ziconotide is the only drug (with the definitely known mechanism of action under this topic) with FDA approval for the treatment of pain. However, its utility is very limited because it is used only as a continuous intrathecal infusion and has many serious adverse effects. As commented above, gabapentin and pregabalin may also be considered in this topic area.

TRP Channels

Capsaicin, an active component of chili peppers, has long been used topically to relieve pain. However, only with an understanding of the mechanism underlying its effect as occurring via one of the TRP ion channels, TRPV1, did these channels become targets for development of new analgesics. The most intensive efforts were directed towards the development of TRPV1 antagonists. As a result, the total number of PubMed articles on TRP channels was very high (994) during 2007-2011, almost as high as that on neurotrophins (Table 2). However, many TRPV1 antagonists demonstrated prohibitive adverse effects, leading to their withdrawal from clinical trials. Though the development of new drugs aimed at TRPV1 targets continued in the area of agonists.[20] Lastly, a capsaicin 8% patch was approved by the FDA as a transdermal analgesic.

General Topics

On Success

Our assessment of the success of new analgesics (from 1982 through 2016) was based mainly on a drug's status with the FDA. Only two of 13 topics, "Serotonin" and "GABA", have garnered multiple drug approvals by the FDA for the treatment of pain—nine drugs from the serotonin group and two from the GABA group. Two other topics, "CGRP" and "Neurotrophins," have multiple analgesics with positive Phase II-III Clinical Trials, and thus are well on the way to FDA approval. Two additional topics, "Calcium Channels" and "TRP Channels", have a single approved drug each, but both with extremely limited use (Table 2).

Only four topics ("Serotonin", "GABA", "CGRP", and "Neurotrophins") fit our second criterion for therapeutic success: development of similar drugs acting on the same molecular target (ie, some of the analgesics in the group were introduced in response to the success of a first-in-class drug). Although this criterion for therapeutic success is reliable, since it is based on the assessments of potential competitors in the pharmaceutical industry, it does not indicate the degree of success. The ultimate measure of success is the outcome of a different type of competition: when a new drug takes the place of a drug that was previously commonly used for the same purpose—Index of Ultimate Success (IUS).[5,21] This process is very slow; for example, it took 15-20 years for sumatriptan to supplant ergotamine (and dihydroergotamine) for the treatment of acute migraine.[21]

The third criterion for success is the degree of novelty characterizing molecular target of analgesic action. This can be said to have three levels: incremental improvements on an existing drug's mechanism; a novel selective mechanism arising from a better understanding of an existing analgesic; and a completely novel mechanism. Of the drugs approved during 1982-2016, only ziconotide ("Calcium Channels") had a completely novel mechanism of action. Emerging analgesics from the topics "CGRP" and "Neurotrophins" also have completely novel targets of action. Sumatriptan ("Serotonin") has a lower level of novelty: being a modified molecular target arising from an existing analgesic—5-HT $_{1D/1B}$.

In the overall assessment of new analgesics, the following questions are extremely important: 1) is a new analgesic clearly more effective (with a favorable side effect profile) than the old one? And 2) if yes, how broad is the spectrum of its effectiveness in different types of pain (and pain syndromes)? Discoveries of new analgesics with satisfactory responses to these questions should help decrease the consumption of opioids and NSAIDs. Unfortunately, we are still waiting for such analgesics. Most likely they will be found among compounds acting on completely novel molecular targets.

On Growth of Efforts

Analgesic discovery efforts directed at a specific molecular target is usually a very prolonged process. It can last for more than 30 years and constantly increase in intensity even without clear success. For example, the total number of PubMed articles consistently increased over each of several consecutive 5-year periods in almost all 13 topics. In some of the topics (ie, "Substance P" and "Bradykinin") the number of articles increased more than threefold in 30 years without an investigational drug with at least one positive Phase II Clinical Trial resulting. The increases in the total number of articles on these two topics continued up to the last 5-year period (2012-2016). Only with one unsuccessful topic, "Cholecyctokinin", was there a decline of more than 5% in the number of publications in several 5-year periods. In all likelihood, 30 years is not long enough to see a profound decline in the number of articles on unsuccessful topics.

PI, indicating a topic's standing among all articles on pain (including migraine disorders), did not exceed 1.2 with any of the 13 target-related topics. It becomes especially important when the course of discovery efforts for a specific topic is analyzed at a time of rapidly increasing activity across the whole pain field. The highest PI was observed with the "Serotonin" topic (1.2), which has the most FDA-approved drugs (nine). However, the PI for" Glutamate" was almost the same (1.1) without any FDA-approved drug for pain treatment. This was probably due to the renewed interest in ketamine as an analgesic, given its action as noncompetitive NMDA-receptor antagonist.[22]

The number of PHS-supported articles constitutes approximately one fifth the total number of PubMed articles without regard to the category of support. PHS support, mostly in the form of NIH funding, reflects the specific mechanisms of NIH-grant award policies. The share of NIH-supported articles is large enough to justify exploring whether certain scientometric features distinguish NIH-supported studies from the general pool of studies. However, our scientometric analysis of PHS-supported studies demonstrated that PHS-related indices, in general, are not much better at predicting successes in the discovery of new analgesics than the indices related to all publications without regard to the category of support. This probably suggests that discovery efforts supported by the PHS are not more productive than the common efforts enabled by all possible sources of support.

However, there are two tendencies that might indicate some distinctions with PHS-supported studies. First, with the discoveries of three analgesics, sumatriptan ("Serotonin" topic), ubrogepant ("CGRP" topic), and tanezumab ("Neurotrophins" topic), there was a very distinctive rise in the PHS-related ratio (ie ratio between the number of PHS-supported studies and the total number of all PubMed articles) immediately before the 5-year period covering the initial clinical trials of a drug candidate (Table 5). Such a pattern of variation in the PHS-related ratio could indicate important contributions to these discoveries by PHS-supported studies.

The other tendency is related to the decline in the number of PHS-supported studies. Specifically, it usually takes place a bit more rapidly compared to articles without regard to the source of support. For example, with the topics "Substance P," "Bradykinin," and "Cholecystokinin", no new drugs (or drug candidates with at least one positive Phase II Clinical Trial) were developed. With the first two of these topics, despite this absence of success, the total number of all PubMed articles continued to increase even over the last 5-year

period (Table 3). At the same time, the number of PHS-supported articles for these two topics declined during the last 5-year period indicating a reversal of the direction of change (Table 3). As a result, the PSH-related ratio often began to decrease (Table 6) despite the absence of a decrease (or even the presence of an increase) in the number of all PubMed articles (Table 3). The PHS-related ratio changed its direction almost as early as the TJSI (Table 6), which is usually the first index to signify decline in interest among researchers.[5,8] Thus, the PHS-related ratio might be of value for the detection of the decline in interest in a topic.

On Causes of Failure

One can list multiple reasons for failure in the development of breakthrough analgesics. Three factors contributing to such failure were described previously[1]: (1) insufficient mechanism-based approaches to clinical pain syndromes,[23] (2) inadequate predictive validity of animal models for pain in humans,[24] and (3) absence of the comparative benefit requirement for the approval of a new analgesic.[25] However, the last point is more likely to be a consequence of the problem rather than a contributor to it: a drug may have clinical effectiveness sufficient to demonstrate a statistical difference from placebo, although not enough to prove superiority to an active comparator.

Pain mechanisms that are not known—or known but not yet used for drug development—will potentially be gateways to discoveries of breakthrough analgesics. Our data shows that the pace of research potentially related to such mechanisms is on the rise. The total number of all PubMed articles on all 13 topics of analgesic discovery efforts markedly increased in almost all the 5-year periods between 1982-2016 (Table 3). In addition, the number of PubMed articles related to "Drug Design" (MeSH term) for "Pain OR Migraine Disorders"(MeSH terms) increased over our study period by approximately 50% every 5 years. Thus, it is difficult to argue that the simple insufficiency of research efforts is a major obstacle to the breakthrough success of new analgesics. However, it is also possible to see that research efforts have been concentrated on well-accepted analgesic discovery topics for very long periods, with some of these topics for more than 30 years, without much success. Even PHS-supported studies showing a similar profile: as seen in Table 4, there is only a bit less continuance in research on conventional topics over several dozens of years compared with the total number of all PubMed articles. What is probably needed—is not so much a general increase in usual areas of pain research, but specific efforts concentrated in new, non-orthodox directions. One potential source of help in this regard might be "outsiders" to pain research, including scientists who are moving from one field of research to another. They are less likely to be influenced by "groupthink" and more likely to think in fundamentally new directions, making "outside-the-box" approaches more likely. How to stimulate an influx of outsiders is another question. Even the time-honored NIH funding system, based on the assessment of a scientific project, seems no longer to be working well. To make a research enterprise more attractive for bright creative individuals Germain[26] suggested switching NIH funding from a project-based to a person-based system. The current R01 grant system is centered on the project, describing in detail all future plans. The suggested "a person not project" -based scheme would be centered up to 90% on the previous creative contributions of a person and only 10% on general, not detailed, plans. Germain writes that the current project specific R01 funding system is too conservative. It requires a lot of "preliminary data" rather than having an emphasis on novel ideas. He states that often up to 50% or more of a faculty member's time can be spent in grant preparation. The MacArthur Award[27] might be a more appropriate model for attracting the "outsiders" to pain research. This is a no-strings-attached award to extraordinarily creative individuals as an investment in their potential. It provides $625,000 per year for 5 years. Nominations for the award are not solicited; nominees are chosen by a constantly changing pool of invited external nominators from a broad range of fields. In our scenario, in contrast to the MacArthur Award, there might be only one condition: a nominee must limit his/her efforts to the field of stagnation.

The economic input that drives progress in various areas of medical research consists mostly of public (government and charitable) investments and private (pharmaceutical) research and development (R&D) investments with pharmaceutical R&D expenditures mostly following public investments.[28,29] Increasing public spending for a specific field within biomedical research is always a topic of heated debate. In 1998, the Institute of Medicine recommended tracking National Institutes of Health (NIH) disease-specific funding allocations and developing a priority-setting process.[30] The most discussed approach in this regard was the comparison of the economic burden of a disease on society with its public funding.[31] This paradigm was used to justify a call to increase investment in R&D of novel therapies to treat mental disorders.[32] The pain-related burden on society has always been extremely high. The current opioid overdose death epidemic is one of the best illustrations of the need for better analgesics. The development of novel drugs for the treatment of pain should attract appropriate investments, both public and private.

Orthodox thinking—both in research and research funding—might be the root of the problem for the lack of breakthrough analgesics.

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