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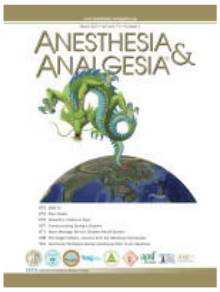

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The Development of New Analgesics Over the Past 50 Years: A Lack of Real Breakthrough Drugs

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Abstract

Fifty-nine drugs identified as analgesics were introduced from 1960 to 2009 and remain in use. Seven can be regarded as having novel molecular targets; however, only one, sumatriptan, was sufficiently effective to motivate the introduction of many similar drugs acting at the same target (triptans). Publication productivity in the area of pain grew exponentially during this period. Pain-related publications on morphine were dominant among other analgesics. Very intensive research efforts directed at diverse molecular targets related to pain mechanisms produced thousands of publications, but those efforts have not yet yielded new analgesics with sufficient effectiveness to change the share of publications on opioids or nonsteroidal antiinflammatory drugs. Morphine and aspirin, introduced for the treatment of pain more than a century ago, continue to dominate biomedical publications despite their limited effectiveness in many areas (e.g., neuropathic pain) and multiple serious adverse effects. The present assessment reveals the lack of real breakthroughs in analgesic drug development despite intense research efforts. Possible factors contributing to the apparent drought of novel analgesics are discussed.

Opioids and nonsteroidal antiinflammatory drugs (NSAIDs) have been the mainstay of pain treatment for a very long time. Their adverse effects and insufficient effectiveness in many types of pain were the main driving forces in the development of new analgesics. Over the past 50 years, many new drugs have been introduced for the relief and prevention of pain. Presently, there is a feeling that success in the development of new analgesic drugs is quite limited. This feeling is accentuated by the lack of real breakthrough analgesics despite improvements in our understanding of pain mechanisms.[1]

The aim of this article is to provide some quantitative assessment of the status quo of analgesic drug development over the past 50 years. The assessment is based on 4 criteria. First is the ability of a new analgesic to stay in medical practice. As a result, only drugs that are presently in use are considered. Second, the drugs are assessed according to the degree of novelty characterizing molecular targets of their analgesic action. This was done using the approach suggested by Hill.2 He described 3 types of advancement in the development of new analgesics: (1) an incremental improvement on an existing drug mechanism; (2) novel selective mechanism arising from a better understanding of the mechanism of an existing analgesic drug; and (3) a completely novel mechanism. Accordingly, the element of novelty is included in the analgesic assessment. The third criterion is the therapeutic success of a breakthrough drug as indicated by the existence of similar drugs acting at the same molecular target (which are introduced in response to the success of a breakthrough drug). Finally, drug assessment includes the analysis of its impact on publications in biomedical journals. The publication impact indirectly reflects the intensity of research efforts related to drug development and its appropriate use in medical practice.

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METHODS

The Food and Drug Administration (FDA) Web site for approved drug products (http://www.fda.gov/Drugs) was used to obtain information on analgesics approved as New Molecular Entities and also on drugs developed for nonpain indications with subsequent approval for the treatment of pain as an additional indication. The analgesic potential of drugs without FDA-approved indications for the treatment of pain was assessed by reviewing publications with a meta -analysis (Cochrane Review, Systematic Review). The year of the first positive meta-analysis was considered confirmation of the drug's analgesic value.

The National Library of Medicine's PubMed Web site (www.ncbi.nlm.nih.gov/PubMed) was used to count the number of articles in English published during time intervals within the period from January 1960 until July 2009. The search included the following types of publications: all articles, human study articles, animal study articles, clinical trial articles (including all types and phases of clinical trials), randomized controlled trial (RCT) articles, and meta-analysis articles. Specific keywords were selected according to the name of a group of analgesics or a single drug in addition to using PubMed Medical Subject Heading (MeSH) terms. Terms added to the name of a drug, group of drugs, or molecular target were “pain” OR “headache disorder” [MeSH], OR “migraine.” Boolean operations were used in which variables were the selected keywords, years of publications, and type of publications.

The publication metrics, especially those related to animal study articles and clinical trial articles, should indirectly reflect the intensity of research efforts for the development of analgesics and their appropriate use in medical practice. The number of publications on a drug before the approval for market entry reflects only research on the development of this analgesic (related to both its efficacy and adverse effects). Publications on an old analgesic reflect research associated with appropriate use of the drug in medical practice, mostly relative to other analgesics.

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RESULTS

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Drugs Developed During 1960 to 2009

Drugs developed during the period 1960 to 2009 and presently in use for the treatment of pain are presented in Table 1.3-12 Of these 59 drugs, 39 were specifically developed as analgesics, and the remaining 20 were developed for nonpain indications, but their effectiveness in pain was later confirmed by a meta-analysis or by an FDA review. NSAIDs (20), opioids (9), and triptans (7) are the largest groups of analgesics. Among drugs developed for indications other than pain but effective in the treatment of pain, anticonvulsants and antidepressants are the most numerous. The rate at which new analgesics were approved by the FDA (Table 2) was low from 1960 to 1969 (4), but increased from 1970 to 1979 (6) and 1980 to 1989 (10). However, during the last 3 decades (1980-2009), the rate at which FDA has approved new analgesics has remained unchanged (10, 11, and 8). The effectiveness of drugs developed for nonpain indications in the treatment of pain was established during either the 1990 to 1999 or the 2000 to 2009 period. Most of these drugs were known to be effective in the treatment of pain for several decades before confirmation by meta-analysis or FDA-approved addition to the drug indications.

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Drugs with Novel Molecular Targets

Assessment according to the degree of a real therapeutic advance 2 showed that 52 of the 59 drugs belong to the category demonstrating only an incremental improvement on an existing drug mechanism. Three drugs fit the category of drugs with a novel selective mechanism arising from a better understanding of the mechanism of an existing drug. These 3 analgesics, developed on the basis of a modified (but previously known) molecular target, are pentazocine, sumatriptan, and celecoxib (Table 3). Although they demonstrate a lower degree of novelty than the drugs in Table 4 (which have completely novel molecular targets), their impact on clinical practice seems to be very pronounced; their development led to the introduction of similar drugs acting on the same molecular target(s). Additional information associated with the analgesics is presented in Table 3.

Graph Table 3

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Pentazocine

Pentazocine was synthesized as part of a deliberate effort to develop an effective analgesic with little or no abuse potential.13 It was the first opioid in the mixed agonist-antagonist group. The analgesic effect of pentazocine is produced by agonistic actions at [kappa] opioid receptors, but it is a weak μ receptor antagonist.14 Two other opioids from this group, nalbuphine and butorphanol, have a similar profile of actions. However, it was determined that the agonist-antagonists do have the potential for abuse, which is relatively low and probably corresponds to their lower analgesic efficacy. The clinical use of these compounds is limited.

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Sumatriptan

Sumatriptan was developed as a cranial vasoconstrictor to mimic the desirable effects of serotonin, while avoiding its adverse effects. This was achieved by using the serotonin 5-hydroxytryptamine 1B/1D receptor as its selective molecular target.15 Sumatriptan's therapeutic advantages over traditional drugs for acute migraine have led to the development of 6 other triptans with the same molecular target. Despite the unquestionable effectiveness of sumatriptan in migraine, it has shortcomings and in many situations may not be much better than NSAIDs. For example, according to a Cochrane review 16 based on 14 trials, the use of oral sumatriptan in acute migraine (maximal dose of 100 mg) resulted in an NNT (number needed to treat) of 3.4 for the decrease in pain intensity and of 5.1 for pain-free response. This means that only 1 of

5 patients achieves complete pain relief, not considering patients with a placebo response. According to another analysis,17 oral sumatriptan (100 mg) provided complete pain relief in 29% of patients and a decrease in pain intensity in 59%. Several publications 18,19 have indicated that the differences between the effectiveness of treatment based on NSAIDs and sumatriptan were not impressive. In addition, triptans cannot be used safely in patients with cardiovascular risk factors.

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Celecoxib

The development of celecoxib was based on reducing the risk of serious gastrointestinal complications from NSAIDs (i.e., perforations, obstructions, bleeding) by selectively inhibiting the cyclooxygenase (COX)-2 isoform of COX. This goal seems to be achieved, but only at the expense of increased risk of vascular events (i.e., heart attacks and strokes).20 As a result, in 2004, 2 of the compounds (rofecoxib and valdecoxib) with the same mechanism of action as celecoxib were withdrawn from the market.

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Capsaicin, Ketamine, Dronabinol, and Ziconotide

Analgesic drugs with completely new mechanisms of action directed at the novel molecular targets belong to 4 types (Table 4). Each type is usually represented by 1 drug with an analgesic effect confirmed by FDA approval (ziconotide) or by meta-analysis (capsaicin, ketamine, and dronabinol). Three of these subgroups were identified some time ago in plants (chili peppers for capsaicin and cannabis for dronabinol) or snail venom (*Conus magus* for ziconotide), but novel molecular targets that determine their analgesic actions were discovered relatively recently (TRPV1 ion channel for capsaicin, CB1 and CB2 receptors for dronabinol, and *N*-type voltage-sensitive calcium channel for ziconotide). The analgesic action of the *N*-methyl-d-aspartate antagonist ketamine (developed as a general anesthetic) was known for almost 50 years, but its therapeutic effect in postoperative pain was convincingly confirmed only recently.21 The therapeutic advantages of these 4 drugs are probably not impressive enough to cause the development of a number of effective analgesic drugs with the same mechanism of action (as happened with sumatriptan).

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Publication Output

As presented in Figure 1, there has been an exponential increase in the number of articles related to pain in biomedical journals over the past 50 years. The number almost tripled during the first decade (1960–1969) and again during the second decade; then it doubled during each of the next 3 decades, reaching 171,400 for the 2000 to 2009 period. Pain publications related to different categories of articles (animal studies, clinical trials, and RCTs) underwent exponential growth similar to that for all publications (inset in Fig. 1).

Figure 1

The number of articles on major groups of drugs used for the treatment of pain from 1960 through 2009 is presented in Table 5. Publications on opioids and NSAIDs are more numerous than on any other group of drugs used for the treatment of pain, 3 to 5 times more for all articles and 5 to 8 times more for RCT articles. Figure 2A illustrates changes in output of pain-related publications concerning opioids and NSAIDs during the 1960 to 2009 period. The figure reflects the dramatic growth; however, if the output is calculated as a percentage of all pain publications (inset), the changes are smaller. A share of pain publications on NSAIDs stabilized starting from the 1980 to 1984 period. As a result, during the 2005 to 2009 period, the share of opioids is at approximately 6% and that of NSAIDs is close to 3%. Figure 2B demonstrates that the

Table 5

Figure 2

number of RCT pain articles (well reflected by PubMed only since 1990) on opioids and NSAIDs expressed as a share of all RCT pain articles is very high. In 2005 to 2009, it is 15% with opioids and 10% with NSAIDs, much higher than the share of all types of publications on these 2 classes of drugs (inset in Fig. 2A).

The publication impact of analgesics classified as novel is presented in Table 6. It demonstrates that the highest number of all publications among these drugs belongs to triptans: 1160 articles on sumatriptan plus 791 articles on 6 other triptans. Figure 3A illustrates how the modification of serotonin receptor agonists (the development of sumatriptan and other triptans) changed (starting in 1990-1994) the share of pain publications focused on serotonin. This increase was especially pronounced with RCTs. The publications related only to triptans are presented in Figure 3, B and C (all articles and RCT articles, respectively). The figures demonstrate that the publications on sumatriptan appeared 5 to 7 years earlier than on other triptans. It is interesting that RCT publications on sumatriptan only (excluding other triptans) profoundly decreased after 2006 (Fig. 3C). The other group of drugs in this category, COX-2 selective inhibitors, has significantly fewer publications than triptans (306 articles on celecoxib plus 570 on 2 other drugs from this group) (Table 6). The increase of the publications on the cardiovascular risk of COX-2 inhibitors and the related withdrawal of rofecoxib and valdecoxib from the market are presented in Figure 4. Opioid agonist-antagonists have a number of all publications close to that of COX-2 inhibitors, although the period of publication is much longer with the former (45 vs 12 years).

Graph
Table 6

Graph
Figure 3

Graph
Figure 4

Among the drugs with novel molecular targets (Table 6), ketamine has the highest number of publications: 1195 for all articles and 330 for RCT articles. These numbers are several times higher than those of 3 other drugs in this category of novelty. Ketamine has a very large time span of publications from 1968 to 2009; however, the reliable confirmation of its effectiveness in pain relief came relatively recently and is related to the treatment of postoperative pain.[21] It is obvious that the publication impact of drugs with the real novelty of a defined molecular target is less than that of many other drugs characterized only by incremental improvement on existing drug mechanisms. Table 7 presents the publication impact of analgesics only for the 2000 to 2009 period and it is limited to drugs with the highest levels of the impact (a share of 0.02% or higher for all articles or 1% or higher for RCT articles determined by using total number of pain-related publications in these categories). It is interesting that among drugs with novel molecular targets of action, only ketamine, sumatriptan, and celecoxib reached the level we set for inclusion in this table; however, they were not with the most significant impact. For example, sumatriptan had fewer publications than fentanyl or indomethacin.

Graph
Table 7

Among non-opioid and non-NSAIDs, gabapentin (initially suggested as an anticonvulsant) has the largest number of pain-related publications. It is interesting to note that gabapentin has a publication impact feature common to a number of other new analgesics: at their introduction, the share of RCT articles devoted to them increased to a greater degree than the share of all types of articles (Fig. 5).

Graph
Figure 5

Table 8 presents publications on pharmacological modulators of pain in the period 2000 to 2009. New drugs for the treatment of pain may be expected to emerge from among compounds acting on the molecular targets related to these modulators. The number of all articles reflects the intensity of general research activity associated with a specific modulator(s). The number of RCT articles indicates

Graph
Table 8

activity quite close to the development of a specific drug (s). The highest level of activity is related to the following modulators: glutamate, cytokines, protein kinases, adenosine, and cholinergic modulators. It is interesting that during the same time period (2000–2009), pain publications on morphine alone were many times more numerous (Table 7) than publications on any of the pain modulators studied for the past decade.

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DISCUSSION

As stated above, of 59 drugs developed from 1960 to 2009 and presently in use for the treatment of pain, 39 were specifically developed for this purpose, and 20 were developed for nonpain indications, but their effectiveness in pain was later confirmed by meta-analysis or by FDA approval for the treatment of pain. With a few exceptions (7 of 59), the molecular targets of their actions underlying analgesia are not novel. Hill 2 suggested the division of new analgesics into 3 main classes according to the degree to which their development represents a real advance: (1) an incremental improvement on an existing drug mechanism; (2) novel selective mechanism arising from a better understanding of the mechanism of an existing analgesic; and (3) completely novel mechanism. Only drugs presented in Tables 3 and 4 can be regarded as having novel molecular targets that determine their analgesic effect. This review identifies only 3 drugs (Table 3)—pentazocine, sumatriptan, and celecoxib developed on the basis of a modified molecular target arising from existing analgesics but with an important modification. Capsaicin (topical), ziconotide, ketamine, and dronabinol were identified (Table 4) as drugs with completely novel molecular targets. With the exception of ziconotide, these drugs were known for a long period of time, although the novelty of their molecular targets was discovered relatively recently.

The novelty characterizing the molecular targets of the above drugs does not necessarily determine the degree to which their introduction represents a therapeutic advance. Clinical effectiveness is the final determining factor of a drug's success. For example, sumatriptan's effectiveness is superior to that of any of the 4 drugs in Table 4 with a higher degree of molecular target novelty. An effective novel drug usually has a drug “following.” The number of similar drugs acting on the same target that emerge after a breakthrough drug can indicate its clinical success. The introduction of sumatriptan was followed by the introduction of 6 other triptans. In contrast, so far, none of the drugs in Table 4 have an impressive “following” with the same molecular target. At the same time, the clinical effectiveness of sumatriptan is far from outstanding; it provided complete pain relief in only one-third of patients with acute migraine (and partial pain relief in two-thirds).17 There was no convincing evidence that the difference in effectiveness between the treatments based on NSAIDs and sumatriptan is statistically significant.18,19 This can be explained by the relatively small advantage of sumatriptan over NSAIDs (aspirin). According to McQuay and Moore,23 a close approximation to the true clinical impact of an analgesic therapy requires an extremely large number of patients per group, making it very difficult to establish even a moderate advantage of one analgesic over another.

Publication productivity in the area of pain for the 1960 to 2009 period grew exponentially. The number of articles almost tripled during the first and second decades then doubled during each of the next 3 decades for all categories of articles. Pain-related publications on opioids and NSAIDs were dominant among publications on analgesics. The dominance of publications on opioids is best illustrated by pain-related publications in the 2000 to

2009 period on morphine and fentanyl, 5786 and 2153, respectively. This can be compared with only 796 publications on sumatriptan and 817 on ketamine (2 drugs with the highest publication impact among analgesics with novel molecular targets). The dominance of publications on opioids and NSAIDs reflects their position as the mainstay in clinical practice.

One of the most important categories of articles reflecting clinical research is the RCT, because it provides a higher quality of evidence than other types of clinical articles. When a drug is in the process of introduction into clinical practice, the share of RCT articles about it usually increases to a greater degree than the combined share of all other types of articles about this analgesic. Figures 3A and 5 illustrate this feature of the publication impact of a new analgesic.

The distribution of publications among different analgesics demonstrating that the lion's share belongs to morphine could be interpreted as evidence of insufficient progress in the development of new analgesics. The number of articles about morphine expressed as a percent of all pain publications was approximately 4% both in the 1970 to 1989 and in the 1990 to 2009 period; a 20-year difference did not shift the interest from morphine to new developments. For all opioids, the percent of publications was 6.6% for 1970 to 1989 and 7.5% for 1990 to 2009; for NSAIDs it was 3.7% for 1970 to 1989 and 3.9% for 1990 to 2009. This does not indicate that the number of articles related to drugs for the treatment of pain is relatively stable in general. For comparison, the profound decrease in pain publications on [beta]-blockers can be considered. For the same time periods, it decreased from 3% to 0.5%. The dominance of publications on morphine is especially indicative of insufficient progress in the development of new analgesics, because it persists even in areas where the effectiveness of opioids is rather low, for example, in the treatment of neuropathic pain. The >=50% NNT index of opioid effectiveness in neuropathic pain is approximately 2.5.24 This means that only 1 of 2 or 3 patients will achieve pain relief and this relief will be only partial. The limited analgesic effectiveness demonstrates that the current clinical practice based on morphine leaves a great deal of room for more effective analgesics. Anticonvulsives and antidepressants frequently used for the treatment of neuropathic pain have NNT values similar to opioids.23,24 Nevertheless, there has been no major improvement in this area.

The major limitation of the publication metrics used is associated with uncertainty regarding the effect of extensiveness of drug use on the number of publications. Prevalence of analgesic prescribing for NSAIDs and opioids 25 seems to correlate with their dominance in research articles. However, it is possible that the publication volume of a new and very effective drug might cut significantly into the morphine and NSAID volume.

Research leading to the development of new analgesics and directed at various molecular targets related to pain mechanisms produced thousands of new publications (Table 8). Merely the diversity of molecular targets demonstrated by the table indicates that our understanding of clinical pain mechanisms is still limited; this is probably the main reason for the limited success in the development of new analgesics.

The demonstrated paucity of novel analgesics is difficult to explain. Pain mechanisms that are not yet discovered or mechanisms that are already known but not appropriately used for drug development could be the root of the problem. However, 3 factors contributing to the apparent drought of novel analgesics can be suggested: (1) insufficient mechanism-based approach to clinical pain

syndromes, (2) inadequate predictive validity of animal models for pain in humans, and (3) absence of the comparative benefit requirement for the approval of a new analgesic.

The need for a mechanism-based classification for clinical syndromes was stated by Woolf et al.[26] in the hope that it might generate testable hypotheses for the development of new treatments that act via specific mechanisms. Many attempts for the past 10 years demonstrated that associating particular clinical symptoms and signs with the underlying mechanisms that may reveal potential targets for pharmacological intervention is a very difficult task. A promising step in this regard was reported for low back pain.[27]

The other factor that hinders discovery of truly new analgesics is inadequate predictive validity of animal models for pain in humans. Failures in this regard have been related to both adverse effects and lack of efficacy of drugs in humans that seemed to be safe and effective in animal models.[1] This problem is so significant that some have called for abandonment of animal pain studies in favor of more extensive testing in humans.[28]

The third factor is related to the FDA requirements for the approval of a new analgesic. The FDA requires developers of new drugs to demonstrate the drug's safety and effectiveness to receive approval for market entry. Usually, drugs are approved on the basis of demonstrated superiority to placebo, not on the basis of superiority to an active comparator,[29] which contributes to the development of “me too drugs.” Placebo-controlled trials require smaller sample sizes than active-comparator trials and therefore are less expensive (they also present less risk of unanticipated adverse effects). Without the requirement for active-comparator superiority trials, it is possible to direct the development of new drugs to research providing a greater return on investment than research aimed at true clinical innovation.

In conclusion, 59 drugs identified as analgesics were introduced from 1960 to 2009 and remain in use. Seven can be regarded as having novel molecular targets; however, only one, sumatriptan, was sufficiently effective to motivate the introduction of many similar drugs acting at the same target (triptans). Publication productivity in the area of pain grew exponentially; the number of articles almost tripled during the first and second decades of the period 1960 to 2009 and then doubled during each of the next 3 decades. Pain-related publications on morphine were dominant among other analgesics even during the most recent years. Very intensive research efforts directed at diverse molecular targets related to pain mechanisms produced thousands of publications, but those efforts have not yet yielded new analgesics with sufficient effectiveness to significantly change the share of publications about opioids or NSAIDs. Morphine and aspirin, introduced for the treatment of pain more than a century ago, continue to dominate biomedical publications despite their limited effectiveness in many areas (e.g., neuropathic pain) and multiple serious adverse effects.

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