PAIN® 152 (2011) 1705–1708

PAIN®

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Topical review

Considerations for extrapolating evidence of acute and chronic pain analgesic efficacy

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1. Introduction

Evidence of the efficacy of analgesic treatments is typically based on double-blind randomized clinical trials (RCTs) conducted in patients with a specific pain diagnosis, disease, or condition [1,2,9–11,40]. The results of these RCTs provide evidence of efficacy in the specific condition investigated, especially when there is replication of the results. However, little attention has been devoted to considering whether evidence of efficacy in one particular condition can be extrapolated to others with a reasonable degree of confidence that the treatment will be efficacious. For example, can it be assumed that the results of RCTs demonstrating that a medication is efficacious for knee osteoarthritis (OA) pain indicate that this medication would also be efficacious for hip OA pain, or that efficacy in postherpetic neuralgia (PHN) predicts efficacy in painful diabetic peripheral neuropathy (DPN)? In considering such generalization of efficacy, it would be important to specify the boundaries of extrapolation, especially between pain conditions with different neurobiological mechanisms, for example, neuropathic and musculoskeletal pain.

The extrapolation of analgesic treatment efficacy to unstudied conditions has broad implications. Most importantly, if efficacy is extrapolated to conditions in which treatments are truly not effective, patients will be exposed to ineffective treatments that may be associated with undesirable side effects, safety risks, and financial costs. Conversely, if efficacy is *not* extrapolated to conditions in which treatments are truly efficacious but have not yet been studied, patients may be denied effective treatments that could provide meaningful relief. This is an important concern because many efficacious analgesics have been studied in relatively few conditions, and there are numerous acute and chronic pain conditions for which effective treatments have not been identified.

The United States Food and Drug Administration convened a workshop to initiate discussion of the issues involved in considering the extrapolation of analgesic efficacy. The meeting included 16 pain specialists representing diverse disciplines and medical specialties, all of whom are authors of this article. Participants were asked to discuss the types of evidence that could provide the basis for extrapolating efficacy to pain conditions in which the treatment has not been studied. These discussions did not address the extrapolation of safety, and also did not consider migraine headache given distinct regulatory and research design issues involving its prevention and acute treatment [25].

This article summarizes the conclusions from the workshop—which was held on December 2, 2009—and subsequent discussions among the participants. The considerations contained in this article are not intended to serve as "consensus recommendations" or to represent the views of the Food and Drug Administration or any other public or private agency or organization. Most importantly, given the major limitations of the evidence base for considering the extrapolation of analgesic efficacy, the material

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0304-3959/$36.00
doi:10.1016/j.pain.2011.02.026

in this article should *not* be used as a basis for determining the eligibility of patients for treatment and reimbursement or coverage of treatment costs. Our objective in presenting the following considerations is to stimulate further discussion and research on important issues that have received very limited attention in the literature on pain treatments [18].

2. General considerations

Regulatory agencies have approved pharmacologic treatments for: (1) specific conditions (eg, "knee OA pain," "painful DPN"); (2) groups of related conditions that are relatively specific (eg, "chronic musculoskeletal pain," "neuropathic pain"); (3) groups of relatively broadly related conditions (eg, "acute pain," "chronic pain"); and (4) pain in general, often with a specification of severity (eg, "moderate to severe pain"). In approving treatments for groups of pain conditions—whether these groups are relatively specific or broad—regulatory agencies must consider the validity of extrapolating treatment efficacy among the different conditions. The generalizability of treatment efficacy can also be relevant to clinicians treating patients with pain conditions for which available interventions have unknown efficacy. This situation is very common in clinical practice, and requires that clinical judgment be used to inform treatment decisions for which there is limited or no evidence base.

At least 3 different types of data are potentially relevant when considering extrapolation of analgesic efficacy: (1) evidence from RCTs showing that a treatment is efficacious in several pain conditions with different etiologies; (2) evidence that pathophysiologic mechanisms are shared by the conditions and that the treatment mechanism of action targets these mechanisms; and (3) evidence that different conditions share similar patterns of symptoms and signs (ie, the "pain phenotype" [32,33]). Unfortunately, all 3 of these types of data have significant limitations in providing a basis for extrapolating efficacy. For example, the results of RCTs have suggested that pharmacologic treatments approved by regulatory agencies and generally considered first- or second-line for the treatment of neuropathic pain [2,11]—largely on the basis of RCTs in painful DPN or PHN—might not have efficacy in all neuropathic pain conditions. In patients with painful human immunodeficiency virus neuropathy, 2 RCTs failed to show efficacy for amitriptyline [23,34], and recent trials of topical lidocaine [13] and pregabalin [35] were also negative. Similarly, there have been failures to show efficacy for nortriptyline [17], gabapentin [29], and amitriptyline [21] in chemotherapy-induced peripheral neuropathy, and pregabalin [5] and nortriptyline, morphine, and their combination [22] in lumbosacral radiculopathy.

It is difficult to determine whether the results of these negative RCTs have identified specific neuropathic pain conditions to which evidence of treatment efficacy in related conditions cannot be generalized (ie, "true negative" results) or whether these are "false negative" results for treatments that are actually efficacious in these conditions [12]. The results of negative trials can be challenging to interpret, and even treatments with well-established efficacy can fail to show efficacy in well-designed RCTs [20,28,39]. There are many possible reasons for false-negative results, including inadequate power and other methodologic features that potentially compromise assay sensitivity [12]. It is also important to recognize that poor study quality can lead to "false positive" results or exaggerated treatment effects [36,37], which makes replication from well-controlled confirmatory trials especially important [15].

Evidence from animal models and studies of human conditions suggests that the same mechanisms can be involved in different pain conditions and that a single pain condition may have multiple pain mechanisms [7,14,24,27]. To the extent that partially overlapping patterns of multiple mechanisms provide the pathophysiologic basis for acute and chronic pain [4,38], pain mechanisms might provide a basis for extrapolating analgesic efficacy [18]. It should be noted, however, that attention has recently been called to the need for uniform standards in reporting the results of animal studies of analgesics [31], which would make it possible to assess the rigor of these studies in much the same way that the quality of RCTs in humans is evaluated [15,36,37].

The results of several studies suggest that the "pain phenotype" of patients with PHN appears to differ from other neuropathic pain conditions [3,6,8,16,26]. In a recent study of diverse neuropathic pain conditions, the patterns of sensory gain and loss found in PHN and painful polyneuropathies differed the most [26]. If these sensory profiles reflect multiple pain mechanisms [7,14,27], showing efficacy in *both* PHN and a painful polyneuropathy could provide a more valid basis for extrapolating efficacy to other peripheral neuropathic pain conditions than showing efficacy in only one condition or in 2 conditions with similar patterns of symptoms and signs.

Existing research on treatment efficacy, pathophysiologic mechanisms, and pain phenotypes provides a limited basis for considering the extrapolation of efficacy between different pain conditions. To encourage further discussion and additional studies, we present several *suggested* patterns of findings from clinical trials that could serve as a basis for considering the extrapolation of efficacy for acute and chronic pain conditions. Extrapolation of efficacy should be as evidence based as possible, and will typically be conducted by considering all available data on patterns of treatment response, disease pathophysiology, and analgesic mechanisms of action. To the extent possible, our suggestions are consistent with such evidence. However, because of the very limited evidence base directly relevant to the extrapolation of analgesic efficacy, it must be emphasized that the following considerations and suggestions represent consensus opinions of the authors and are presented to encourage continued debate and research.

3. Acute pain (⩽30 days)

Several types of acute pain can be distinguished: (1) acute postoperative pain; (2) acute pain associated with nonsurgical trauma; (3) acute disease-associated visceral pain; and (4) other types of acute pain (eg, procedural pain, pain in herpes zoster, and inflammatory pain in conditions such as gout or tonsillitis). Evidence of efficacy in the first 3 of these types of pain is suggested as a basis for considering the extrapolation of treatment efficacy to acute pain conditions in general (Table 1), with other types of acute pain potentially substituting for acute pain associated with nonsurgical trauma or acute disease-associated visceral pain. Replicated evidence of efficacy in 2 different acute postoperative pain conditions could serve as an "anchor" in considering extrapolation because acute postoperative pain is a very well-established model for testing analgesic efficacy.

Table 1
Acute pain (⩽30 days): suggested basis for considering the extrapolation of efficacy.

2 positive trials in acute postoperative pain, each in a different type of surgery For example, amputation, herniorraphy, mastectomy, orthopedic surgery (eg, bunionectomy), thoracotomy, or visceral surgery (eg, hysterectomy)
1 positive trial in acute pain associated with nonsurgical trauma For example, sprains, strains, and/or fractures
1 positive trial in acute disease-associated visceral pain For example, renal colic, acute pancreatitis, or diverticulitis

Note. The phrase "positive trial" refers to a double-blind randomized clinical trial in which the investigational treatment has shown statistically significant superiority to placebo or, in certain circumstances, to an active comparator (eg, a lower dosage of the same treatment).

4. Chronic neuropathic pain (⩾90 days)

Peripheral and central neuropathic pain are typically distinguished on the basis of whether pain is associated with lesions of the peripheral or central nervous system. In considering the extrapolation of efficacy, positive trials are suggested for each of 3 different types of peripheral neuropathic pain (Table 2, first section), with replication for either PHN or a painful polyneuropathy because these are well-characterized models that have identified multiple efficacious treatments and that have different sensory profiles, as discussed above [26]. To ensure that different etiologies and mechanisms are represented, it is suggested that one of the 3 conditions should be chronic postoperative, posttraumatic, or entrapment nerve injury pain (eg, postthoracotomy pain, lumbosacral radiculopathy, complex regional pain syndrome, carpal tunnel syndrome). Once replicated evidence of efficacy is shown for one peripheral neuropathic pain condition, a single positive confirmatory trial in a second peripheral neuropathic pain condition could potentially serve as a basis for extrapolation to that specific condition.

For central neuropathic pain, single positive trials in spinal cord injury neuropathic pain and in central post-stroke pain—the most common central neuropathic pain conditions—could serve as a basis for considering the extrapolation of efficacy (Table 2, second section). For extrapolating efficacy to all chronic neuropathic pain, consideration can be given to reducing the combined suggestions for peripheral and central neuropathic pain by excluding the third peripheral neuropathic pain condition and by including a single positive trial in *either* spinal cord injury pain or central poststroke pain (Table 2, third section).

5. Chronic nonneuropathic pain (⩾90 days)

Chronic nonneuropathic pain includes musculoskeletal, inflammatory, visceral (eg, irritable bowel syndrome), and other pain conditions with mixed (eg, cancer pain) or uncertain (eg, fibromyalgia, temporomandibular joint disorder) etiology. Because OA is a well-established model for testing analgesic efficacy, and nonradicular (musculoskeletal, axial) low back pain is the most common chronic pain condition in the general population [19], replication in either of these conditions could serve as an "anchor" for considering the extrapolation of efficacy to other types of nonneuropathic pain (Table 2, fourth section). The category of chronic nonneuropathic pain is very broad, and extrapolation within more "homogeneous" groups of such conditions—for example, chronic musculoskeletal pain [30]—could also be considered.

Table 2
Chronic pain (⩾90 days): suggested basis for considering the extrapolation of efficacy.

Peripheral neuropathic pain
2 positive trials in a single painful polyneuropathy (eg, diabetic, human immunodeficiency virus, chemotherapy) and 1 positive trial in postherpetic neuralgia (PHN), *or* 2 positive trials in PHN and 1 positive trial in a single painful polyneuropathy
1 positive trial in chronic postoperative, posttraumatic, or entrapment nerve injury pain (eg, postthoracotomy pain, lumbosacral radiculopathy, complex regional pain syndrome, carpal tunnel syndrome)
Note: Once replication of efficacy has been shown in a single peripheral neuropathic pain condition, 1 positive trial in a second condition could potentially serve as a basis for extrapolating efficacy to that condition.
Central neuropathic pain
1 positive trial in spinal cord injury neuropathic pain
1 positive trial in central poststroke pain
Neuropathic pain
2 positive trials in either a single painful polyneuropathy or in PHN
1 positive trial in chronic postoperative, posttraumatic, or entrapment nerve injury pain
1 positive trial in either spinal cord injury pain or central poststroke pain
Nonneuropathic pain
2 positive trials in either osteoarthritis or nonradicular low back pain
1 positive trial in a second nonneuropathic pain condition
1 positive trial in a third nonneuropathic pain condition

Note. The phrase "positive trial" refers to a double-blind randomized clinical trial in which the investigational treatment has shown statistically significant superiority to placebo or, in certain circumstances, to an active comparator (eg, a lower dosage of the same treatment).

6. Chronic pain (⩾90 days)

Combining the suggestions for neuropathic and nonneuropathic pain presented in the third and fourth sections of Table 2 could provide a basis for considering extrapolating efficacy to patients with chronic pain in general. This would comprise 3 neuropathic and 3 nonneuropathic pain conditions and a total of 8 positive trials. Although this could be considered an overly conservative basis for the extrapolation of efficacy, chronic pain includes numerous different conditions with diverse etiologies and mechanisms.

7. Conclusions

The major objective of this article is to promote further discussion and research and thereby facilitate the development of an evidence-based approach to the extrapolation of analgesic efficacy. In pursuing this objective, clinical trials designed to test the hypothesis that pain phenotypes can serve as a basis for extrapolating treatment efficacy within and between specific pain conditions will be especially important.

Conflict of interest statement

The workshop on which this article is based was convened and funded by the United States Food and Drug Administration. Other than reimbursement of travel expenses to attend the workshop, none of the authors received any compensation for their participation in the workshop and in article preparation. None of the authors have financial conflicts of interest related to the material in this article. No official endorsement by the US Department of Veterans Affairs, US Food and Drug Administration, or US National Institutes of Health should be inferred.

Acknowledgement

The authors express their appreciation to Drs Bob Rappaport, Ellen Fields, Sharon Hertz, and Robert Shibuya for their support and encouragement.

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