

ALSDAC MEETING

Thursday, September 13, 2001
Morning Session

Opiate Analgesic Development and Use

***Opiate Analgesic Development and Use:
The Role of Patient Populations in Clinical Trials***

One challenge to the study and treatment of pain is the heterogeneity of pain syndromes. The Agency is committed to insuring that patient populations entered into clinical trials of opioid analgesics are representative of the large number of patients who can potentially benefit from these agents. In view of the potentially severe side effects of these agents, however, the Agency is also interested in insuring that clinical trial entry criteria do not include patients who can be successfully treated with other, better-tolerated agents and who are therefore not candidates for opioid therapy. The Agency recognizes that the distinction between a medically appropriate use of an opioid and a medically inappropriate use of an opioid is not always clear, and is seeking input from the Advisory Committee on this issue as it applies to clinical trial design and interpretation.

Patient populations with chronic pain for clinical trials can be defined in a variety of ways. One way is to define entry criteria based on intensity of pain, without regard to etiology. For example, the study could enroll “patients with chronic pain of cancer or non-cancer origin”. A second way is to define pain with some restriction on the etiology. For example, the entry criteria could include “patients with chronic pain due to cancer”, but not further specify the type of pain (ie, bone pain, plexopathy pain, visceral pain, etc.). A third option is to include pain due to a specific condition. For example, the entry criteria could be limited to “patients with osteoarthritis of the hip or knee not responsive to non-opioid analgesics.”

A review of recent NDA submissions for opioid analgesics designed for treatment of chronic pain reveals that a variety of patient populations have been used:

Drug*	Patient Populations^
Drug 1	<ul style="list-style-type: none"> • Chronic low-back pain • Osteoarthritis of the hip or knee
Drug 2	<ul style="list-style-type: none"> • Chronic malignant or non-malignant pain • Moderate to severe osteoarthritis of the hip or knee
Drug 3	<ul style="list-style-type: none"> • Cancer or other chronic pain • Pain of malignant or non-malignant origin
Drug 4	<ul style="list-style-type: none"> • Cancer pain • Chronic pain of cancer or non-cancer origin
Drug 5	<ul style="list-style-type: none"> • Chronic pain of malignant or non-malignant origin, suitable for Step 3 of the WHO ladder
Drug 6	<ul style="list-style-type: none"> • Osteoarthritis • Cancer-related or chronic non-malignant pain

*Each drug is an opioid analgesic
^Each bullet represents a single study or set of studies

In light of the above table, consider the following scenarios:

- Drug 1 is a mu-agonist opiate analgesic designed to treat chronic pain. If the studies in chronic low back pain and in osteoarthritis are successful and the drug is approved,

would data from these studies provide a sufficient rationale to use this drug to treat another type of chronic pain, such as chronic bone pain due to metastatic cancer?

- Drug 3 is a mu-agonist being tested in studies using broadly defined populations of patients with chronic pain. If these studies are successful and the drug is approved, would there be sufficient rationale to treat patients with a chronic musculoskeletal condition such as chronic low back pain, even if patients with chronic low back pain were not represented in the studies?

Clinical trials in narrowly-defined patient populations, such as those used in the clinical development of Drug 1, may afford a better chance to demonstrate a clinically beneficial effect of the drug by reducing patient heterogeneity. On the other hand, trials that enroll patients with a broad spectrum of pain conditions, such as those used in the development of Drug 3, may better reflect actual practice. In these situations patient heterogeneity may limit the ability to detect a true treatment effect of the study drug. However, careful design and sample size considerations may overcome this problem. If the study drug is shown to be effective, it is not clear from the data that this result applies to all pain conditions included in the entry criteria, or if there are some pain conditions that do not respond to the study drug. While sub-group analysis may shed some light on this issue, the relatively small number of patients included in these analyses often make the results difficult to interpret.

Defining the appropriate patient population for entry into clinical trials of opioid analgesics is thus of critical importance in the clinical development of opioid analgesics.
