March 26, 2013

Re: Impact of Approved Drug Labeling on Chronic Opioid Therapy; Public Hearing; Request for Comments [Docket No. FDA–2012–N–1172]

To Whom It May Concern:

The New York City Department of Health and Mental Hygiene appreciates the opportunity to submit comments regarding impact of approved drug labeling on chronic opioid therapy. Our comments in support of label changes are based on our review of the literature, and on New York City population and prescription data. We recommend opioid labeling that indicates a maximum duration of 90 days of continuous (daily) use and an upper dose limit of 100 morphine milligram equivalents (MME) for non-cancer pain outside the setting of end-of-life palliative care.

**Systematic reviews do not support long-term opioid use for pain relief or function**

No systematic review of available research has found good evidence for long-term control of chronic non-cancer pain with opioids.

- Manchikanti et al.¹ found that among the few randomized controlled trials of opioids lasting longer than 12 weeks, there was “fair evidence for Tramadol in managing osteoarthritis with poor evidence for all other drugs and conditions.”

- A meta-analysis of randomized trials for opioids for chronic non-cancer pain found that “Other drugs produced better functional outcomes than non-opioid drugs, whereas for pain relief they were outperformed only by strong opioids. Despite the relative shortness of the trials, more than one-third of the participants abandoned treatment.”²

- A systematic review of opioid treatment for chronic back pain³ found “The evidence in favor of opioids is not always consistent and when supportive, only supports this treatment for short periods (for example, <4 months).”
• A Cochrane Review published in 2010\(^4\) reporting on studies (randomized controlled trials and pre-post case series) that collected data on patients receiving at least 6 months of opioids for chronic non-cancer pain concluded that “many patients discontinue long-term opioid therapy (especially oral opioids) due to adverse events or insufficient pain relief; however, weak evidence suggests that patients who were able to continue opioids experience clinically significant pain relief. Whether quality of life or functioning improves is inconclusive.”

• A 2008 review of the literature on opioids in the treatment of chronic non-cancer pain\(^5\) found that “many patients in the included studies were dissatisfied with adverse events or insufficient pain relief from opioids and withdrew from the studies. For patients able to continue on opioids, evidence was weak suggesting that their pain scores were lower than before therapy and that this relief could be maintained long term (>6 months)….for long-term opioid therapy of 6 months or longer in managing chronic non-cancer pain, with improvement in function and reduction in pain, there is weak evidence for morphine and transdermal fentanyl. However, there is limited or lack of evidence for all other controlled substances, including the most commonly used drugs, oxycodone and hydrocodone.”

In summary, there is not good evidence for long-term pain control or improved function from opioid analgesics for chronic non-cancer pain.

While very few randomized, controlled trials have evaluated opioid analgesic efficacy beyond 90 days, those that have do not provide good evidence of efficacy

The few trials that have evaluated opioid analgesic efficacy beyond 90 days have not provided persuasive evidence that pain is substantially improved, and they suggest that pain control may diminish over time. Manchikanti et al. undertook a systematic review of randomized, controlled trials published from 1966 through September 2010 on opioid treatment for chronic non-cancer pain with at least 12 weeks of follow-up.\(^1\) Of the trials they found with longer than 90 days of follow-up,\(^5,7,8,9\) all had very large drop-out rates (range 49% – 56%), making it impossible to draw conclusions about long-term safety and difficult to assess long-term efficacy. However, the results suggest that long-term efficacy was relatively poor. For example, one study that prospectively defined “clinically meaningful” change as a 2-point improvement in pain score (on a 0 to 10 scale) found neither extended-release morphine sulfate nor controlled-release oxycodone exceeded this standard at 24 weeks. Pain scores were reported as decreasing from 7.2 to 5.3 and from 7.4 to 6.0, respectively.\(^8\) Moreover, these improvements were only among patients who remained in the trial at week 24; 54% of those initially randomized to treatment had discontinued. If intent-to-treat outcomes were known and reported, including pain scores at week 24 for all patients initially assigned to treatment, these improvements would most likely have been even smaller.

None of these studies report the absolute number of patients who were able to tolerate opioids and obtain relief, despite the fact that these papers all describe “intent-to treat” populations. It may seem reasonable to report proportion with pain relief at last measurement before the patient dropped out of the study. However, it is important to keep in mind that the most common reasons for discontinuation were
adverse events and insufficient pain relief. Reporting pain relief only among those who have not dropped out inflates efficacy compared to reporting pain relief among all those who were assigned to study medication. A more recent study did report absolute numbers with pain relief and found that just 14 of 46 patients initially randomized to treatment (30%) had significant reduction in pain level on treatment at 3 months. Efficacy decreased to less than 13% after 6 months. The authors noted that tolerance could explain this dramatic decrease in efficacy, “as prolonged use can induce changes that reduce the efficacy of the drug over time.”

**Observational studies demonstrate increased overdose risk with higher doses of opioids**

Randomized trials have been relatively small and short-term, so they cannot accurately assess long-term safety. The best available safety evidence is from observational studies, including at least 4 well-designed cohort studies with longer follow-up periods. Among patients with chronic non-cancer pain, Dunn found 1 in 195 experienced overdoses, and 1 in 1657 died from overdose. Bohnert found 1 in 2500 Veterans Health Administration patients receiving opioids for pain died from overdose, and Gomes found 1 in 415 Canadians eligible for publically funded prescription coverage and with at least one opioid prescription for chronic non-cancer pain died from an overdose. Considering that an estimated 9 million Americans take opioids long-term for chronic pain, it is easy to see how these drugs could account for thousands of deaths among these patients.

These studies also examined overdose risk by dose. Risk increased with increased dose. Compared with <20 MME, the odds of overdose among patients prescribed opioids for chronic nonmalignant pain was between 1.2 and 1.9 for doses of 20 to less than 50 MME, between 1.9 and 4.6 for doses of 50 to less than 100 MME, and between 2.0 and 11.2 for doses of at least 100 MME. Using New Mexico state prescription monitoring program data, for patients prescribed opioids and dying of unintentional drug overdose between 2006 and 2008, Paulozzi et al. calculated opioid MME using three different ways: single peak dosage, total peak dosage, and average dosage. They provided a figure with curves showing odds ratios for overdose death plotted against MME for each method of calculating MME. The odds of fatal overdose increased above about 20 MME/day for single peak prescriptions and leveled off above 200 MME/day for all methods of calculation of daily dose.

Population-based data have also shown substantial and increasing opioid-associated adverse outcomes. Overdose deaths continue to increase. More than 16,000 people died of opioid analgesic-associated overdoses in 2010. In New York City, neighborhoods with high opioid analgesic-associated fatal overdose rates deaths are those where New Yorkers fill opioid prescriptions at high rates. Staten Island, a borough that has not had higher rates of illicit drug use compared to other boroughs, ranks highest in both prescriptions for opioids and overdose from opioids.

**Methods to establish a maximum daily dose of opioid drugs should weigh benefits of therapy against risks**

Doses associated with an unacceptably high risk for adverse events or that account for a large proportion of adverse events should be used to set a maximum daily dose. The indication for opioids should also be considered. Among Veterans prescribed opioids for pain, most opioid-associated overdose deaths (606/750) were among patients with chronic pain diagnoses. In addition, while a given risk of addiction and of overdose might be acceptable for pain control at the end of life, the same risk may not be acceptable.
when it could result in years of suffering from addiction or in years of life lost. As Mark Sullivan noted in the *Archives of Internal Medicine*, “death due to therapy for a nonprogressive, nonfatal condition must be taken very seriously.”

**Impact on patient care and pain control**

A maximum daily dose limit of 100 MME would likely affect a minority of patients. Using New York State Prescription Drug Monitoring Program data, we found only 7.2% of New York City residents filling opioid prescriptions (or less than 2% of New Yorkers) received doses of 100 MME or more. Although we did not have information on diagnosis, some portion of these prescriptions were likely for cancer or end-of-life care, so even fewer patients would be affected if limits were not applied to these conditions.

A 90-day limit would also affect a minority of New York City patients taking opioids. Only 6.8% of those who filled opioid prescriptions did so for more than 90 days consecutively. Substantial overlap exists between those using long term and high doses; 46.0% of patients who filled more than 90 days of consecutive opioid prescriptions took at least 100 MMEs/day.

Limits on dose and duration need not lead to reduced pain control. There is not convincing evidence that opioids are more effective than other therapies when used long term. In addition, if opioids are primarily reserved for acute pain and for end of life care, opioids are more likely to remain effective in these situations. Under revised labeling, prescribers could taper to labeled dosing. Based on information about tolerance and hyperalgesia, patients might derive analgesic benefits from dose reduction. Providers may also continue some patients on opioids long-term and/or on high doses (in an off-label fashion).

We are aware of concerns that FDA labeling may affect drug coverage. We believe this is unlikely. However, if it did occur, coverage for unusual situations in which benefits of long-term therapy outweigh risks could be addressed outside of FDA. FDA’s charge is to evaluate “the aggregate public health benefit of the product compared to its evolving risk profile” and not to set payment policy. Label limits would convey that, in general, benefits of high-dose or long-term opioid treatment do not outweigh risks.

A maximum dose can also provide important support to providers. As Dr. Mitchell Katz has observed in writing about his goals to alleviate suffering and provide patient-centered care, a maximum recommended opioid dose would not only reduce harm but “would also decrease the unhealthy patient physician negotiation that often occurs when patients seek higher doses… knowing that there is a firm ceiling on the dose saves [patients] from having to press for higher doses.”

**Public health benefits of label changes**

The primary effect of label changes would be to require that pharmaceutical company marketing of opioids is consistent with current scientific evidence regarding safety and efficacy. In particular, changes should discourage exaggeration of the benefits of long-term opioid therapy for chronic non-cancer pain and should bring attention to the risks of higher doses. Physicians would still have the ability to prescribe “off-label” in individual cases when they believe the benefits of long-term or high-dose therapy outweigh the risks.
Decreasing promotion of long-term and high-dose opioid use would achieve substantial public health benefits. We now know that opioid use disorder is common among chronic pain patients. Boscarino found it affected 35% of patients treated with opioids for chronic pain. 25 Decreasing the number of people started on long-term opioid therapy should decrease the number of new patients suffering from opioid use disorder. CDC has estimated that patients on at least 100 MME account for 80% of fatal overdoses. 15 A maximum daily dose is likely to reduce the number of patients exposed to risk for overdose and the number of opioid analgesic-associated overdose deaths.

Thank you for this opportunity to submit comments.

Sincerely,

[Signature]

Thomas Farley, MD, MPH
Commissioner


21 Angst MS, Clark JD. Opioid-induced hyperalgesia: a qualitative systematic review. *Anesthesiology* 2006 Mar;104(3):570-87.


