

# **PinneyAssociates' Response to the Physicians for Responsible Opioid Prescribing Citizen Petition**

Federal Docket: FDA-2012-P-0818

1/16/2013

## 1 Introduction

These comments are submitted in response to the Physicians for Responsible Opioid Prescribing (PROP) Citizen Petition [**Federal Register Meeting Notice: Docket No. FDA-2012-P-0818**].

**Pinney**Associates appreciates the opportunity to provide input directly to the Food and Drug Administration (FDA) regarding the actions the Physicians for Responsible Opioid Prescribing (PROP) has requested the FDA undertake with respect to opioid analgesics. **Pinney**Associates' scientists and health policy experts provide science and public health-based strategic solutions to support decision making by pharmaceutical companies, including premarketing risk assessments, human abuse liability assessments, assessment of tamper-resistant medications, data collection and analysis, and the development and implementation of risk management programs and Risk Evaluation and Mitigation Strategies (REMS). Although **Pinney**Associates provides advice and guidance to companies marketing products that would be impacted by the recommendations in this Petition, we are not representing nor speaking on behalf of any client with this comment. The views reflected here are solely our own and have not been vetted or shared with any potentially affected company.

The purpose of these comments is to:

1. Provide commentary on the potential public health impact of:
  - a. the removal of "moderate" from the indication for non-cancer pain
  - b. adding a maximum daily dose, equivalent to 100 mg of morphine for non-cancer pain
  - c. adding a maximum duration of 90-days for continuous (daily) use for non-cancer pain
2. Assess the scientific points made by PROP in their Citizen Petition

We understand and we share the petitioners' goal to address the issues of nonmedical use (NMU) of opioids and opioid-related overdose deaths. **Pinney**Associates staff members have worked in drug addiction science, prevention and treatment for decades and much of our work is with the intent of reducing nonmedical drug use and opioid-related overdose deaths. However, we strongly believe that eliminating the term "moderate" from the indication, adding a maximum daily dose, and adding a maximum duration of use for non-cancer pain to the prescription opioids' label will do little if anything to address the problem. Conversely, it could be harmful to people with pain. Specifically, we are concerned that such actions could have a profound impact on the treatment of pain and eliminate a treatment option available to approximately 100 million adults living with chronic pain conditions.<sup>1</sup> This will lead to the development of debilitating pain and a substantially reduced quality of life for many pain patients resulting in lost productivity in job, school and family life. It may also result in the inappropriate use of other medications or illicit drugs for the treatment of pain. The measures proposed by PROP, since they are not based on a strong scientific

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<sup>1</sup> Institute of Medicine. 2011. *Relieving Pain in America: a blueprint for transforming prevention, care, education and research*. Washington, DC: National Academies Press. 2011. p 62

foundation, will not appropriately address prescription opioid NMU and opioid-related overdose deaths. We believe that more effective risk management approaches including prescriber and patient education, along with increasing the number of extended-release (ER) opioids in tamper and abuse-deterrent formulations as are supported by the FDA are affirmative actions that can make a difference (REF FDA Draft abuse deterrence guidance. But the challenges are complex and thus we also believe that more targeted research is needed to address the issues. These efforts are a better approach for addressing NMU and overdose deaths than what PROP has proposed.

## **2 The Public Health Challenge**

Both the treatment of pain and the curbing of prescription opioid abuse are public health challenges for which significant knowledge gaps remain. The FDA recently held a public workshop to discuss what is known about the treatment of chronic non-cancer pain (CNCP) using opioid analgesics. The FDA concluded there are many unknowns regarding the effectiveness of opioids when used for more than 12 weeks to treat CNCP and that tools are needed to help better identify people who will be helped and those who will be harmed by opioids.<sup>2</sup>

The recommendations of the 2011 Institute of Medicine (IOM) report on pain and care should be heeded. That report, which was commissioned by the U.S. Department of Health and Human Services, clearly stated that a “population-level prevention and management strategy” is needed to address pain treatment and mitigate the risks of NMU of prescription opioids<sup>3</sup>. Ensuring the appropriate use, storage, and disposal of prescription opioids is not the purview of the regulatory agencies alone. These challenges must and should be addressed by the FDA, industry, healthcare providers, patients who suffer from CNCP, law enforcement and the public together. Only by working together can we truly begin to ensure the safety of the public while maintaining patients’ access to these needed and life-changing medications.

The three actions proposed by PROP will not solve the problems they are intended to address. They may also lead to unintended consequences that would be deleterious to the patients who are most in need of these medications. Together, the three actions could lead to a balloon effect; that is, some pain patients might seek illicit drugs and/or other medications in an effort to adequately treat their pain. It is critical that pain patients have legitimate treatment options, specifically, medications that have demonstrated efficacy for the indication.

Removing the word “moderate” from the indication for non-cancer pain will not have the intended effect. While it is true that clinicians may prescribe prescription opioids off-label to patients with moderate non-cancer pain if the indication is modified, it is

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<sup>2</sup> Food and Drug Administration. FDA scientific workshop on analgesics highlights the critical need for evidence of the long-term effectiveness of opioids for chronic pain.

<http://www.fda.gov/downloads/Drugs/NewsEvents/UCM308363.pdf>

<sup>3</sup> Institute of Medicine. 2011. *Relieving Pain in America: a blueprint for transforming prevention, care, education and research*. Washington, DC: National Academies Press. 2011.

possible that health insurers will not cover the medications for the treatment of moderate pain for chronic non-cancer pain conditions. This may well mean that a cancer patient, who may have been able to receive pain medications to treat their cancer pain, may be unable to treat the pain that has resulted from the cancer treatment because they are in remission. Moreover, for patients with severe CNCP who are adequately treated with opioids, the opioid may well reduce the pain to a moderate or lesser level. Since the pain is no longer categorized as severe, insurance providers may refuse to reimburse for what might now be considered off-label use. The ensuing lack of effective treatment would result in a resumption of severe pain, which would cause the patient unnecessary suffering. Since we are addressing a chronic condition, where the symptoms may wax and wane over time, it is critical to be able to maintain consistent therapy to patient.

Inadequate pain relief may also occur if the maximum daily dose of opioid analgesics is limited to an equivalent of 100 mg of morphine. The scientific evidence cited by the petitioners does not support this proposed restriction (see Section 3 Scientific Evidence for more details). Moreover, the petitioners do not indicate why they believe 100 mg is the appropriate dose for all patients, regardless of the variations in patients' needs to achieve pain relief and participate in daily life activities. A dose ceiling hinders clinicians from managing their patients' pain appropriately. Both the treatment of pain and the condition of pain evolve over time. As the intensity of pain and patient's health status change over time, the clinician has a responsibility to modify the patient's treatment plan, including the dose level and opioid formulation prescribed.

Furthermore, the proposed dosing limit would not "reinforce" the recommendations made by the Centers for Disease Control and Prevention (CDC), Washington State, and the New York City Department of Health and Mental Hygiene as the petitioners argue. The CDC's recommendations unambiguously state they "are not founded in evidence-based research but are based on promising interventions and expert opinion." In addition, the CDC's proposed dosing limit is not absolute. The CDC recommends that a pain specialist be consulted when a dose of  $\geq 120$  mg morphine equivalent does not provide substantial improvement in pain and function.<sup>4</sup> The Washington State guidelines make the same recommendations. Although the New York City Department of Health and Mental Hygiene uses a threshold of a 100 mg morphine equivalent dose, it recommends that clinicians "thoroughly reassess the patient's pain status and treatment plan and reconsider other approaches to pain management."<sup>5</sup> These recommendations recognize the fundamental reality that people in pain differ widely in their response to a given dosing regimen and that prescribers need to be flexible in addressing their needs. Labeling such as that recommended by PROP would likely have a chilling effect on the best medical practices by responsible practitioners while doing little to deter the unethical and those who distribute drugs illicitly or those who abuse them.

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<sup>4</sup> Centers for Disease Control (CDC). Poison Issue Brief: Unintentional Drug Poisoning in the United States, 2007. <http://www.cdc.gov/HomeandRecreationalSafety/pdf/poison-issuebrief.pdf>

<sup>5</sup> Paone D, Dowell D, Heller D. Preventing misuse of prescription opioid drugs. *City Health Information*. 2011;30:23-30. <http://www.nyc.gov/html/doh/downloads/pdf/chi/chi30-4.pdf>

The dosing limit sought by the petitioners also implies that a dose lower than a morphine-equivalent dose of 100 mg poses less risk. As discussed below in Section 3 Scientific Evidence, dose alone is not the cause of nor associated with opioid-related overdose deaths. There have been a substantial number of opioid-related overdose deaths in recent years<sup>6</sup>. However, these deaths often involve patients using other drugs that, when taken in combination with prescription opioids, can cause death. This suggests that better prescriber education is needed to ensure clinicians appropriately prescribe opioids at all dosing levels and monitor their patients, including what other medications those patients are taking. Since most of the deaths involve multiple drugs, the petitioners do not consider whether these patients may have taken the additional medications to moderate still unrelieved pain.

Finally, adding a maximum duration of 90-days for continuous (daily) use for non-cancer pain to opioid analgesic labels would not only effectively eliminate the use of opioids for CNCP, but could also have a spill-over effect on patients with cancer, limiting their use of opioids. This could effectively leave some proportion of the more than 100 million U.S. adults living with chronic pain with inadequate pain relief and a reduced quality of life because their ongoing pain condition cannot be treated beyond 90 days. Moreover, there is no conclusive evidence to show that use of prescription opioids for more than 90 days is unsafe or ineffective. The FDA has required the industry to conduct 12-week clinical trials to assess the safety and effectiveness of prescription opioids and has approved their use based on these trials' results. Significant research is needed to determine the best practices for treating CNCP and the appropriate use of opioid analgesics as a tool in a comprehensive treatment plan.

### **3 Examination of the Scientific Evidence Presented by Petitioners**

#### **3.1 Is there a cause-and-effect relationship between opioid prescribing and overdoses and deaths?**

There has indeed been an increase in the use of opioid analgesics over the last several years,<sup>7</sup> and in the number of opioid-related overdose deaths. The increase in prescribing is the result of various factors including aging population, increased rates of chronic conditions, as well as an increased awareness about the undertreatment of pain. More than 100 million adults have been found to be living with chronic pain conditions such as low back pain, trauma, cancer, and postsurgical pain.<sup>8</sup> Among patients visiting the emergency department (ED) with acute painful conditions, 60% received analgesics (opioid and non-opioid) according to the 2011 IOM report. According to the 2007 National Hospital Ambulatory Medical Care Survey, significant

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<sup>6</sup> <http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6043a4.htm>

<sup>7</sup> FDA. *Outpatient Prescription Opioid Utilization in the US, Years 2000-2009*. Presented by Laura Governale on July 22, 2010.

<sup>8</sup> Institute of Medicine. 2011. *Relieving Pain in America: a blueprint for transforming prevention, care, education and research*. Washington, DC: National Academies Press. 2011. p 28

proportions of people presenting to the ED reported moderate (23%) or severe (22%) pain.<sup>9</sup>

The petitioners conflate this population of pain patients with individuals experiencing opioid-related overdose deaths and individuals seeking addiction treatment. The important term here is “opioid-related.” As stated above, these cases most often involve multiple drugs, making it impossible to attribute one drug as the cause of death. The patient population prescribed opioids for pain, however, is not necessarily the same population that is engaging in the nonmedical use (NMU) of prescription opioids (thus not necessarily the same as those experiencing opioid-related overdoses or seeking addiction treatment). For example, data from the 2009 National Survey on Drug Use and Health (NSDUH) show that more than two-thirds of the individuals engaging in NMU obtain their opioids from family or friends.<sup>10</sup> These NSDUH data demonstrated that among individuals who began engaging in NMU in the past year, 17% obtained the opioid medications from 1 or more doctors, while 68% obtained them from a friend or relative and 9% purchased them from a friend or relative, dealer, or the internet. About 66% of individuals involved in the NMU of prescription opioids less than once a week on average over the past year obtained the prescription opioids from a friend or relative, 13% purchased them from a friend or relative, dealer, or the internet, and 17% were prescribed the medicines by 1 or more doctors. Among chronic nonmedical users of opioid pain relievers, 41% obtained the pills from a friend or relative, 26% were prescribed the medication by one or more physicians, and 28% purchased it from a friend or relative, dealer or the Internet.<sup>11</sup>

The petitioners correctly describe the increased number of prescriptions for opioid analgesics, but fail to mention that the NSDUH data from 2002-2010 for NMU of opioid pain relievers are essentially flat and do not reflect a proportional increase. The NSDUH rates are population based. If the number of prescriptions was used as the denominator, the rate would be declining. These NSDUH data also lead to the question: whose medication is being diverted? In a survey of 275 adult patients who underwent surgery, Bates et al. (2011) found that 58% of patients consumed their prescription opioids and 12% requested refills.<sup>12</sup> About 67% had leftover medication from the first prescription and 92% (213 of 231) received no information regarding disposal of their surplus medication. Of the 8% (18 of 231) who did receive instructions, two identified nurses as providing instruction, while two others indicated pharmacists and one indicated a mail order pharmacy provided instructions. The remaining patients

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<sup>9</sup> Niska R, Bhuiya F, Xu J. *National Hospital Ambulatory Medical Care Survey: 2007 Emergency Department Summary*. National health statistics reports; no 26. Hyattsville, MD: National Center for Health Statistics. 2010. <http://www.cdc.gov/nchs/data/nhsr/nhsr026.pdf>

<sup>10</sup> Results from the 2009 National Survey on Drug Use and Health (NSDUH): National Findings, SAMHSA (2010)

<sup>11</sup> Office of the National Drug Control Policy. National Survey shows friends and family are primary sources of abused painkillers. White House Press Release. April 25, 2012. Accessed October 31, 2012. <http://www.whitehouse.gov/ondcp/news-releases-remarks/national-survey-shows-friends-and-family-are-primary-sources-of-abused-painkillers>

<sup>12</sup> Bates C, Laciak R, Southwick A, Bishoff J. Overprescription of postoperative narcotics: a look at postoperative pain medication delivery, consumption and disposal in urological practice. *Journal of Urology*. 2011; 185: 551-555.

were unable to specify the source of the instructions. Among the patients who had leftover medication, 91% kept the medication at home.

These data not only suggest that the majority of patients with surplus medication are a potential source for prescription opioids, but also that clinicians and patients are in need of additional education. Health care providers should be educated on prescribing an appropriate amount of prescription opioids based on the needs of the individual patient. In addition, they should inform patients regarding the appropriate disposal of their opioid medication to ensure these medications are used only as prescribed and unused medications are disposed of appropriately.

The CDC's 2011 Morbidity and Mortality Weekly Report (MMWR)<sup>13</sup> included deaths of any intent, including unintentional, suicide, homicide, and undetermined. The report did not specify how many of these deaths were unintentional. In addition, data were not provided as to how many of the deaths also involved alcohol and/or other prescription and/or illicit drugs. The fact that these deaths are called opioid-related implies they may have been the result of different factors, such as drug-drug interactions. For example, it is well known that the co-administration of benzodiazepines and opioids can potentially lead to death. Cone et al. (2003) reported that among 1,014 oxycodone-related deaths (919 of them drug abuse related), only 3.3% (n=30) of these death cases included only oxycodone as a single drug.<sup>14</sup> Approximately 96.7% (n=889) of the drug abuse deaths (n=919) involved at least one other drug that may have contributed to the death. The most common substances found with oxycodone in these death cases were benzodiazepines, alcohol, cocaine, other narcotics, marijuana, and antidepressants.

Finally, the 2011 MMWR report includes methadone in the number of opioid-related overdose deaths between 1999 and 2008. Methadone has two distinct indications: 1) treatment of pain and 2) detoxification and maintenance treatment for opioid addiction. A subsequent 2012 MMWR report focusing on methadone's use for the treatment of pain showed that the drug was involved in more than 31% of the opioid-related deaths in 13 states and about 40% of single-drug opioid-related overdose deaths.<sup>15</sup> While we do not disagree that there has been an increase in the number of overdose deaths involving methadone, we strongly believe that this 2012 MMWR report should have taken into account that the lower cost of methadone relative to other opioids has led some states and insurance companies to list methadone as its preferred opioid medication, although, generally methadone is not considered a first-line pain medication.

Methadone has unique pharmacological properties, including a highly variable terminal half-life (that can lead to drug accumulation in patients) and different pharmacokinetic and pharmacodynamic half-lives, which necessitate that prescribers and dispensers are

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<sup>13</sup> <http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6043a4.htm>

<sup>14</sup> Cone EJ, Fant RV, Rohay JM, et al. Oxycodone involvement in drug abuse deaths: a DAWN-based classification scheme applied to an oxycodone postmortem database containing over 1000 cases. *Journal of Analytical Toxicology*. 2003; 27: 59-67.

<sup>15</sup> Centers for Disease Control and Prevention. Vital signs: risk for overdose from methadone used for pain relief – United States, 1999-2010. *Morbidity and Mortality Weekly Report*. July 6, 2012; 61: 493-497.

well educated about the medicine to prevent serious adverse events. Greater prescriber education regarding methadone's indications, titration, and appropriate patient selection and dosing could potentially curtail the number of methadone-related overdose deaths. While states and insurance companies have encouraged the use of methadone as a cost reduction measure, there has not been a parallel increase in prescriber education. The increase in methadone-related deaths may be related to these developments.

Additionally, Webster and Fine's 2012 literature review showed that opioid rotation strategy, which is commonly used by clinicians, can be a cause of opioid-related deaths due to prescriber error, inconsistent guidelines, and inconsistent dose conversion tables.<sup>16</sup> All of these data, along with the increasing number of individuals seeking opioid addiction treatment, suggest that greater awareness of, and consistent information regarding, appropriate prescribing, use, and disposal of prescription opioids are greatly needed. They do not suggest that dose or duration of treatment are factors in mitigating opioid-related overdose deaths.

### **3.2 Does the lack of data establishing long-term safety and effectiveness of opioids for CNCP mean that these drugs should not be prescribed for longer than 90 days? Long-term safety and effectiveness of managing CNCP with opioids has not been established.**

Pre-approval studies to assess long-term (greater than 12 weeks) use of most medications are costly to conduct and therefore have not been conducted (nor required by FDA) pre-approval, but observational data can be relevant and informative. As Chou et al. (2009) and Nobel et al. (2010) have noted, studies conducted to assess the long-term benefit of managing CNCP with opioids are "limited" and "the evidence regarding the effectiveness of long-term opioid therapy in CNCP is too sparse to draw firm conclusions, including quantity of pain relief."<sup>17</sup> Clinical experience in patients treated with opioids for extended periods of time have shown substantial benefit, suggesting that further research would provide additional information on which patients will benefit most from long-term opioid therapy.

### **3.3 Do recent surveys demonstrate high rates of addiction among CNCP patients receiving opioids?**

The petitioners state that recent surveys using DSM criteria found high rates of addiction in CNCP patients receiving chronic opioid therapy (COT). Although the two Boscarino et al. (2010<sup>18</sup> and 2011<sup>19</sup>) studies cited by PROP use the same data, the criteria the two papers used to determine the rates of addiction are not comparable. The

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<sup>16</sup> Webster LR, Fine PG. Review and critique of opioid rotation practices and associated risks of toxicity. *Pain Medicine*. 2012; 13: 562-570.

<sup>17</sup> Noble M, Readwell JR, Tregear SJ, et al. Long-term opioid management for chronic noncancer pain. *Cochrane Database Syst Rev*. 2010; (1): CD006605. Review.

<sup>18</sup> Boscarino JA, Rutstalis M, Hoffman SN, Han JJ, Erlich PM, Gerhard GS, Stewart WF. Risk factors for drug dependence among out-patients on opioid therapy in a large US health-care system. *Addiction* 2010; 105:1776-1782.

<sup>19</sup> Boscarino JA, Rukstalis MR, Hoffman SN, et al. Prevalence of prescription opioid-use disorder among chronic pain patients: comparison of the DSM-5 vs. DSM-4 diagnostic criteria. *J Addict Dis*. 2011; 30:185-194.



2010 study uses the Diagnostic and Statistical Manual of Mental Disorders (DSM) - IV diagnostic criteria for opioid dependence whereas the DSM-V criteria are used in the 2011 study. In DSM-V, the opioid abuse and dependence categories are subsumed under the new diagnosis of 'opioid-use disorder.' Furthermore, the terms 'abuse', 'misuse', and 'overdose' are not used in the proposed criteria for 'opioid-use disorder' and neither DSM-IV nor DSM-V have diagnostic criteria for 'addiction'. Therefore, Boscarino et al. are essentially equating 'addiction' to 'opioid dependence' and 'opioid-use disorder', which would overestimate the rate of addiction in CNCP patients receiving COT.

The use of the term 'opioid-use disorder' is new in DSM-V, which has recently been finalized. As previously stated, there are two different populations using prescription opioids, although there may be some degree of overlap: patients using the medications as prescribed to treat pain, and those engaging in NMU. Boscarino et al. (2011), using the DSM-V criteria, reported that 22% of COT patients met the criteria for moderate 'opioid-use disorder' while 13% met the criteria for 'severe opioid-use disorder'. In the 2010 Boscarino et al. study, the rate of 'opioid dependence' is 26% using the DSM-IV criteria. No 'opioid-use disorder' rates were included in the 2010 study because that term was not used in DSM-IV. Using the criteria in DSM-IV, it is easy to misdiagnose a chronic pain patient as meeting the criteria for dependence.<sup>20</sup>

It is important to emphasize that one should not simply add up diagnostic criteria to declare individuals as having a specific drug-use disorder. One must also recognize that, although the behaviors of pain patients and nonmedical users of pain medications may appear similar, their motives for use of the medication are often very different. Pain patients are taking medication to treat their continuing pain whereas nonmedical users are often motivated by other factors including the desire to get high and as well as other "benefits" they attribute to the drug. Despite the different motivations, it is possible for both populations to experience symptoms that fit the criteria for the diagnosis of opioid dependence. For example, pain patients may experience clinically significant impairment or distress as a result of an increase in pain intensity when they attempt to reduce the amount of pain medication they take rather than as a result of dependence or withdrawal. In contrast, nonmedical users may experience similar symptoms when unable to access the medication. In addition, it is well known that patients taking pain medication appropriately over prolonged periods may experience both tolerance and withdrawal—two of the three criteria used to make diagnosis of opioid dependence—although few would suggest that the use of these medications by patients in pain is inappropriate.

### **3.4 Does chronic pain stop after 90 days of treatment?**

Chronic pain is not a static condition. Chronic pain can last more than several months, be ongoing or recurring, and impact an individual's quality of life. It is a complex condition that may result from a medical condition, an injury, medical treatment,

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<sup>20</sup> Sees KL, Clark HW. Opioid use in the treatment of chronic pain: assessment of addiction. *J Pain Symptom Manage.* 1993; 8:257-64

inflammation, neuropathic pain, and unknown causes.<sup>21</sup> When prescribers treat people living with chronic pain they are attempting to manage the patient's pain to improve the person's quality of life and enable the individual to partake in daily activities. Opioids may be one among a number of instruments employed to address pain, as opioids are not indicated to cure pain. As with the treatment of other chronic conditions such as diabetes, heart disease, arthritis, and asthma, the treatment plan may evolve over time as the person's health status may change requiring different doses opioid formulations (e.g. immediate-release, extended-release) or the cessation of opioid treatment. Setting arbitrary limits on dose and duration of treatment that are not supported by science is not in the best interest of the patient, who should be our ultimate concern. In addition, prescribers may also need to use a multidisciplinary (e.g., physiological, cognitive, psychological, and/or self-care) approach along with opioids to manage an individual's chronic pain. It is of concern that insurance providers often do not reimburse patients for attendance at a multidisciplinary pain clinic which could induce an increased reliance on medication.

The patients in the Martin et al. (2011) study cited by the petitioners are using opioids to treat a chronic pain condition.<sup>22</sup> Therefore, it is not surprising or unusual that they are still using opioids years later because the medications are necessary to achieve pain relief and optimize their quality of life. The authors of this study provide no data on the severity of the conditions being treated, which would be important in understanding why they may still be on the medication. The fact that some patients with chronic pain are continuing to use opioids to manage their pain over the long term is not in and of itself an issue.

### **3.5 Where are the data in support of adverse patient selection?**

If adverse patient selection is occurring, the petitioners have not presented adequate data in support of that conclusion. This argument, along with the other arguments put forward by the petitioners, further demonstrate that value of better prescriber education for selecting appropriate patients for COT, monitoring their treatment, and instructing them on the appropriate use, storage, and disposal of their medications. These data do not provide evidence to support a change in indication or limits on dose or duration of use of opioids for CNCP.

### **3.6 Is there evidence for dose-related overdose risk?**

We believe the studies (Dunn et al, 2010; Bohnert et al, 2011<sup>23</sup>; Gomes et al., 2011<sup>24</sup>) cited by the petitioners to support the assertion of a dose-related overdose risk strongly support the need for more and better prescriber education on opioid and psychotropic drug co-prescribing rather than the need for a change in indication or limits on dose or

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<sup>21</sup> Institute of Medicine. 2011. *Relieving Pain in America: a blueprint for transforming prevention, care, education and research*. Washington, DC: National Academies Press. 2011. p 33-34

<sup>22</sup> Martin BC, Fan MY, Edlund MJ, Devries A, Braden JB, Sullivan MD. Long-term chronic opioid therapy discontinuation rates from the TROUP study. *J Gen Intern Med*. 2011; 26:1450-1457.

<sup>23</sup> Bohnert ASB, Valenstrein M, Bair MJ, et al. Association Between Opioid Prescribing Patterns and Opioid Overdose-Related Deaths. *JAMA*. 2011;305(13):1315-1321.

<sup>24</sup> Gomes T, Mamdani MM, Dhalla IA, et al. Opioid dose and drug-related mortality in patients with Nonmalignant Pain. *Arch Intern Med*. 2011;171(7):686-691

duration of use. These studies' findings should be considered with caution as they do not demonstrate that dose alone caused the overdoses. Dunn et al. (2010) assessed the rates of opioid overdose including overdose deaths and their association with an average prescribed daily opioid dose among patients who received 3 or more opioid prescriptions within 90 days. Among the 9,940 individuals on long-term opioid therapy, about 27% had been diagnosed with depression and 6.2% with a substance abuse disorder. In addition, their pain diagnoses included back pain (38%) and extremity pain (30%). Of the 51 (.005% of the cohort) patients Dunn et al. identified as having had 1 or more overdose events, 78% (n=40) had experienced a fatal or serious overdose and 22% (11) had nonserious overdose events. Among these overdose patients, 8 had accidentally ingested an excess of opioids, 6 were suicide attempts, 4 had drug abuse noted in their medical records, 4 either applied additional fentanyl patches or sucked on the patch, and 3 obtained opioids from nonmedical sources. Patients receiving 100 mg per day had a 9.9-fold increase in overdose risk and a 1.8% annual overdose rate compared to patients receiving lower doses of opioids. Dunn et al. also noted that there were more than 7 nonfatal overdoses for each fatal overdose. As noted, the .005% rate is very low and should be compared with patients taking other chronic medications to determine if this rate is consistent with medication overdoses in those with other chronic medical conditions.

The high rates of sedative hypnotic use (75%), muscle relaxants (52%), and benzodiazepines (43%) among the subjects in this study are of concern because the interactions of these drugs with opioids may lead to serious adverse events including death. Furthermore, the number of patients in this study engaging in nonmedical use (e.g., obtaining opioids other than from a prescriber, applying additional patches, and drug abuse) is of particular concern as these overdoses may well be associated with these patient behaviors rather than the opioid dose being taken. This may also be true for the individuals in the study with depression or substance abuse diagnoses. Studies have indicated there may be an association between mental health disorders and nonmedical use of prescription drugs and vice versa.<sup>25,26,27</sup> It is unknown if the patients in this study took all of their medications as prescribed. Finally, the opioid tolerance level of these patients is unknown. Knowledge of an individual's opioid tolerance is necessary to determine if the blood level of opioid in that individual is toxic and likely to be a cause of the overdose.

The issue of whether patients took their medication as prescribed also emerges in the study by Bohnert et al. (2011). While methadone and buprenorphine were excluded from this study, codeine, morphine, oxycodone, hydrocodone, oxymorphone, and

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<sup>25</sup> Martin SS, Keyes KM, Strr CL et al. Pathways between nonmedical use/dependence and psychiatric disorders: results from the national epidemiologic survey on alcohol and related conditions. *Drug Alcohol Depend.* 2009; 103: 16-24.

<sup>26</sup> Schepis TS, Hakes JK. Nonmedical prescription use increases the risk for the onset and recurrence of psychopathology: results from the national epidemiological survey on alcohol and related conditions. *Addiction.* 2011; 106: 2146-55.

<sup>27</sup> Schepis TS, McCabe SE. Exploring age of onset as a causal link between major depression and nonmedical use of prescription medications. *Drug Alcohol Depend.* 2012; 120: 99-104.

hydromorphone were included. Among a random sample of close to 155,000 patients using the Veterans Health Administration between 2004 and 2008 and being treated with opioids for CNCP, cancer, and acute pain, the estimated overall risk of opioid overdose was 0.04%. The authors also noted that “opioid overdose death represents a particularly important outcome, but a rare one, and the findings should be interpreted accordingly.” Furthermore, the study found that 43.5% (326 of 750 cases) of opioid overdose deaths occurred when the maximum prescribed dose was equal to zero (0 mg), suggesting that these individuals may have obtained the opioids from another medical setting or illicitly.

Also like Dunn et al.’s study, a large proportion of the overdose decedents in the study by Bohnert et al. also had substance use (40%) and other psychiatric disorders (66%). As discussed above, there is an association between mental health disorders and nonmedical use of medications. As Bohnert et al. aptly conclude, prescribers should continually evaluate the risk of opioid overdose relative to the need to reduce pain and suffering and the risk should be considered along with other factors. This conclusion strongly supports that additional prescriber education is needed to ensure providers know how to appropriately prescribe opioids and educate their patients regarding appropriate use and disposal.

Gomes et al.’s (2011) study also strongly indicates that more prescriber and patient education is needed. The Gomes et al. study is a retrospective, observational study of more than 607,000 Canadian patients aged 15 to 64 years old who were eligible for publicly funded prescription drug coverage who had been prescribed at least one opioid (including codeine phosphate, morphine sulfate, oxycodone hydrochloride, hydromorphone hydrochloride, meperidine hydrochloride, or transdermal fentanyl) for nonmalignant pain between 1997 and 2006. In this population, there were 498 (0.08%) deaths that were identified as opioid-related. Toxicology screenings found that 38.8% (193) of these deaths involved more than 1 opioid type, 60.4% (301) involved benzodiazepines, and 18.5% (92) involved ethanol. Gomes et al. selected 1,714 controls based on a disease risk index developed by the authors and on gender, age, index year, and Charlson comorbidity index. The comparison found that, while those who experienced an opioid-related death were more likely than controls to have had a history of alcoholism and to have obtained prescription opioids from multiple doctors and pharmacies, they were similar to controls in terms of demographics and comorbidities.

These results should be considered with caution, however. Since this is a correlational study, one cannot conclude that the presence of drugs in a toxicology screen means that drug caused the death. Furthermore, the presence of a high dose of opioids does not necessarily mean that the dose was (in)appropriate. Although Gomes et al. indicated that the decedent’s opioid tolerance was determined using the coroner’s individual judgment, information regarding a person’s opioid tolerance is critical for determining whether the patient’s dose was high or whether it was appropriate given the patient’s level of tolerance. Furthermore, the high rates of co-administration with opioids of other medications such as benzodiazepines should also be noted since the use of

opioids and benzodiazepines can lead to death. Finally, the patients enrolled in the public assistance program, Ontario Drug Benefit Program, are individuals that are living in long-term care homes or homes for special care, receiving home health care, or disabled and either unemployed or economically disadvantaged.<sup>28</sup> This population may not generalize to the Canadian population.

### **3.7 Do the data support the conclusion that COT at high doses is associated with increased risks of overdose death, emergency room visits, and fractures in the elderly?**

Due to various confounding factors, the studies cited by the petitioners, Gomes et al., 2011; Braden et al., 2010; and Saunders et al., 2010 do not support the conclusion that dose alone is related to increased risks of overdose death, emergency department (ED) visits, or fractures in the elderly. As discussed above, a large proportion of the subjects in the Gomes et al. study were receiving opioids and benzodiazepines, which, when combined with opioids, can potentially cause death. Moreover, it is not known if the high dose of opioids the patients in the study were consuming was appropriate because their opioid tolerance was determined at the discretion of the medical examiner.

Unlike the Gomes et al. study where a high dose was defined as 200 mg or more morphine equivalent dose (MED), the Braden et al. study considered 120 mg MED to be a high dose. Braden et al. examined administrative claim records of Arkansas Medicaid (n=10,159) and Health Core (n=38,491) commercially insured enrollees with no cancer diagnosis who used prescription opioids for at least 90 continuous days within a 6-month period between 2000 and 2005. Like in the Gomes et al. study, about 43% of both the Arkansas Medicaid and Health Core enrollees used a sedative and/or hypnotic, including benzodiazepines, in addition to opioids during the study period. Among both populations, an increased risk in ED visits was found to be associated with using Schedule II short-acting opioids and sedatives and/or hypnotics. Additionally, opioid doses greater than 120 mg were not reported to be significantly associated with ED visits in either sample, although there was a doubling of risk of alcohol or drug-related encounters at these doses (i.e., alcohol intoxication, withdrawal, or overdose; drug intoxication or withdrawal; nonopioid drug overdose; or opioid drug overdose). Opioid dose over the median but below 120 mg was significantly associated with ED visits among Health Core enrollees, but not among Arkansas Medicaid enrollees. Furthermore, any use of short-acting Schedule II opioids was associated with more ED visits. These findings demonstrate the complex association of opioid medication use and ED visits.

Although the PROP petition cites Braden et al. as indicating the need for a dose limit on opioids for CNCP, the paper's authors clearly state, "we did not observe a clear dose response effect for the health services outcomes we examined" and ED visits may be "prompted by adverse effects occurring in the context of dose adjustment." The authors' conclusions provide additional support for the need for improved prescriber education regarding titrating patients appropriately. Clinicians need to be educated that

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<sup>2828</sup> Ontario Ministry of Health and Long-Term Care. *Ontario Public Drug Programs Questions and Answers*. Accessed October 29, 2012 <http://www.health.gov.on.ca/en/public/programs/drugs/faq.aspx#2>

appropriate administration of opioids is critical to curtailing opioid-related adverse events.

Prescriber education is also particularly important when treating specific populations such as the elderly. The petitioners cite Saunders et al. (2010) as evidence that high doses of opioids are associated with an increased risk for fractures.<sup>29</sup> However, Saunders et al. state their “finding of a 28% increased risk of fracture associated with opioid use did not reach statistical significance ( $p=0.06$ )” despite a trend showing an increase in fractures. The cohort study assessed the risk of fracture among 2,341 individuals aged 60 years and older who received three or more opioid prescriptions within a 90-day period for CNCP and had not used opioid in the previous 6 months between 2000 and 2005. The mean daily dose of opioids was 12.8 mg morphine equivalents. The most commonly prescribed opioids were hydrocodone (42%;  $n=976$ ), oxycodone (24%;  $n=552$ ), codeine combination (14%;  $n=328$ ), and long-acting morphine (8.3%  $n=194$ ). Saunders et al. did not reveal which opioids the remaining 12% of patients were receiving.

Among the cohort, 2.6% ( $n=61$ ) had had a prior fracture, which is known to be a risk factor for future fractures.<sup>30</sup> About 22% ( $n=524$ ) had been diagnosed with depression, 3.8% ( $n=89$ ) with substance abuse, and 4.8% ( $n=112$ ) with dementia. In addition, 60% were taking a sedative hypnotic and 57% were taking antidepressants during the follow-up period. While the authors adjusted for depression, substance abuse, dementia, comorbidity, prior fracture, antidepressant use, sedative use and other variables, they did not adjust for the patients’ diagnoses. Therefore, the patients that were more at risk of fracture could not be identified based on their diagnoses.

Individuals taking 50 mg/day or more of opioids had a 9.9% fracture rate, which was a two-fold increase over subjects not currently taking opioids. These individuals were consuming more opioids than the median of 12.8 mg per day. Differences at intermediate dosage levels were not statistically significant, and dose response was found to be of borderline significance. Saunders et al. also reported that “tests for interaction between opioids and sedatives and opioids and antidepressants were not significant.” Although this study raises an important question regarding risk of fracture and opioid use, it does not provide conclusive evidence of specific cause and effect for particular patients. The lack of a dose-response suggests that other factors may also be involved in the increased risk of fractures for some patients taking opioid medications.

## 4 Conclusions

The petitioners’ interpretation of the data is at times inconsistent with the statements made by the studies’ authors themselves. Some data are inconclusive and present methodological challenges. Overall, the scientific evidence provided by the signers of

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<sup>29</sup> Saunders KW, Dunn KM, Merrill JO, et al. Relationship of opioid use and dosage levels to fractures in older chronic pain patients. *J Gen Intern Med.* 2010;25:310-5.

<sup>30</sup> Cummings SR, Nevitt MC, Browner WS, et al. Risk factors for hip fracture in white women. *N Engl J Med.* 1995;332:767–73.

the PROP Citizen's Petition does not support their argument for the changes to opioid analgesic labels that they propose (i.e., removing the term 'moderate' from the indication, and adding a maximum dose and duration of use for non-cancer pain). The cited studies do emphasize the need for additional research to assess the safety and effectiveness of prescription opioids for all patient populations in order to identify the best practices for treating pain. Moreover, the studies strongly underscore the need for additional prescriber and patient education on the safe and effective use of opioid analgesic medications.

Understanding the need for further education, the FDA has already taken appropriate steps to address many of the issues related to the use of the long-acting and extended-release opioids in the treatment of CNCP by initiating a REMS that stresses the education of prescribers. Monitoring the effect of this REMS and making appropriate adjustments to it based on the data collected is the correct approach as it balances the need for pain treatment and mitigating the risks of NMU of opioids. Additionally, sponsors are marketing and continuing to develop new tamper-deterrent opioid formulations to reduce inappropriate use.

Enacting the measures proposed by PROP will inevitably lead to a significant increase in suffering and a reduced quality of life for patients with CNCP. These actions will not protect public health. They would effectively reduce and may eliminate the use of prescription opioids for the treatment of pain. Cognitive, behavioral, and interventional techniques alone may not be sufficient to treat moderate CNCP. Clinicians need the latitude to develop individual treatment plans using any combination of tools to manage their patients' pain based on their patients' health. Prescribers, patients, caregivers, and the public must understand that opioid analgesics, like other prescription drugs, are potent medications that can cause harm when inappropriately prescribed, used, stored, and disposed of. This information is most effectively communicated via patient and prescriber education, which plays an important role in ensuring the safe use of prescription opioids and curbing prescription drug abuse.

Finally, we propose that in addition to the education of prescribers as part of the ER/LA REMS, the FDA should foster more education of other healthcare providers and patients, continue to encourage the development of tamper-deterrent formulations of opioids and work with the National Institutes of Health and Agency for Healthcare Research and Quality to fund research that will help us better understand some of the issues raised in the PROP petition. To make decisions that are not based on solid research can and will lead to unintended consequences for the patients we are trying to help.

Sincerely,

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