

**ANALYZING THE RELATIONSHIP BETWEEN NONMEDICAL PRESCRIPTION-OPIOID USE AND HEROIN USE**

We read with interest the article by Compton and colleagues<sup>1</sup> entitled “Relationship between Non-medical Prescription-Opioid Use and Heroin Use,” published in the *New England Journal of Medicine* (*NEJM*). The authors highlight that nonmedical use of prescription opioids (NMUPO) is a major public health issue in the United States, both because of its overall high prevalence and because of marked increases in associated morbidity and mortality.<sup>1</sup>

Compton et al. cited that in 2014, a total of 10.3 million people reported using prescription opioids non-medically (ie, using medications which were not prescribed for them or were taken only for the experience or feeling associated with the medication).<sup>2</sup> There was a significant decrease in the total number of NMUPO compared to 2010 (estimated 12.2 million).<sup>3</sup> Surprisingly, this drop of 1.9 million (comparing 2012 with 2014) has not resulted into any improvement with regard to prescription opioid mortality, to prevalence of heroin abuse, or to heroin mortality. On the contrary, there has been a significant increase in opioid overdose related mortality, ie, 16,007 and 16,235 deaths in 2012 and 2013 respectively, compare to 18,893 deaths in 2014.<sup>4</sup> As concerning, the number of people who used heroin peaked to 914,000 in 2014<sup>2</sup> versus 373,000 in 2007.<sup>5</sup> Further, mortality related to heroin overdose has more than quintupled, from 1,842 in 2000 to 10,574 deaths in 2014.<sup>2</sup>

Though the data indicates a drop in the number of NMUPO by 1.9 million, there is a paradoxical dramatically increase in heroin abuse and associated mortality, along with significantly increased opioid mortality. These data contradict the assumption that NMUPO plays a key role in leading to the opioid epidemic in the US. Thus, a deeper look into the motivation of NMUPO may be helpful.

In 2012, in a systematic review and meta-analysis, Fischer and colleagues<sup>6</sup> demonstrated evidence of disproportionately increased mental health problems (pooled prevalence of 32 percent) and pain symptoms (48 percent) in the general population reporting NMUPO. Fischer et al. reasoned that the main pharmacotherapeutic purpose and medical use of prescription opioids is analgesic care or pain treatment. Therefore, on this basis, it appears that a

significant portion of individuals engaging in NMPOU are initially exposed to prescription opioids in the context of medical settings or procedures, for support of pain related pathogenesis.<sup>6</sup>

It is a well-known fact that there is a high prevalence of pain in the general population.<sup>7,8</sup> It is also well-established that there is complexity of chronic pain, with regard to its phenomenology, course of disease, psychosocial overlay, and mixed outcomes from standard treatment regimens. Therefore, it is quite possible that individuals with a previous history of prescription opioid supported pain care continue their prescription opioid use “nonmedically” when formal medical therapies involving prescription opioids are completed or terminated.<sup>6</sup> In other words, it appears a significant proportion of NMPOU might have used opioids for underlying pain rather than “getting high.” The basis for this theory is the fact that exogenous opioid delivery over weeks to months shuts down endogenous opioid production, making the body dependent on prescription opioids. Cessation of opioids after an extended use period is well-established to create a central nervous system hyperarousal state with a constellation of signs and symptoms that are largely unpleasant and painful. Further, though cessation may appear appropriate, pain may persist and the physician may, for a multitude of reasons, not wish to continue to prescribe prescription opioid medications.

Indeed, in a study to determine the prevalence of medical and nonmedical use of prescription opioids among high school seniors in the United States, McCabe and colleagues,<sup>9</sup> found that an estimated 80 percent of nonmedical users with an earlier history of medical use had obtained prescription opioids from a prescription they had previously. The odds of substance use behaviors were greater among individuals who reported any history of nonmedical use of prescription opioids relative to those who reported medical use only.

In 2013, Shield and colleagues<sup>10</sup> conducted a large scale survey (N = 13,032) and found that in Canada in 2009, the prevalence of prescription opioid use was 19.2 percent, NMPOU was 4.8 percent, and the use of pain relievers to get high was only 0.4 percent.<sup>10</sup> Their study was one of the few surveys which provided a clear distinction between using an opioid for pain relief versus for a recreational purpose (ie, to get

high). In their study, NMPOU included individuals who acknowledged using their pain relievers more than they were supposed to, obtaining the pain reliever from a family member or friend, obtaining the medication from the Internet, from a pharmacist without a prescription, or from any other source without a prescription, and using an opioid pain reliever to get high.<sup>10</sup>

Young and colleagues<sup>11</sup> conducted a web-based survey in 2,579 7th to 12th grade students to better understand nonmedical use of prescription medications by identifying distinguishing characteristics of two subtypes of adolescent nonmedical users of prescription opioids. They found that sensation seeking nonmedical users were best characterized by rule breaking and aggressive behaviors, and possible substance dependence. Medical users and nonmedical self treating users were best characterized by somatic complaints, anxiety/depressive symptoms, and history of sexual victimization.<sup>11</sup> Young et al. found that approximately 14 percent (n = 373) of the sample reported medical use of prescription opioids in the past 12 months, while 5 percent (n = 148) of the sample reported nonmedical use of prescription opioids in the past 12 months. The most common reason for nonmedical use was “to relieve pain” (n = 91, 62.8 percent), followed by “to get high” (n = 23, 15.9 percent) and “to experiment” (n = 16, 11.0 percent).<sup>11</sup>

Voon and Kerr<sup>12</sup> published a paper entitled, “‘Nonmedical’ prescription opioid use in North America: a call for priority action” and discussed their opinion on the findings of Shield et al., ie, 0.4 percent of NMPOU individuals reported using opioids to “get high.” Voon and Kerr reason that the term “nonmedical prescription opioid use” (NMPOU) is inaccurate and propose to redefine the term to “not-as-prescribed opioid use” (NAPOU), which recognizes that opiate use may not be “nonmedical” in nature, and includes opioid use not as indicated for the individual whether by use of someone else’s prescription or use of one’s own prescription.<sup>12</sup>

In a recent editorial entitled “Nonmedical use of prescription opioids: What is the real problem?” by Mary Lynch, MD, she opined, “It has also been determined that most of the individuals who are using opioids ‘nonmedically’ are actually using them for the treatment of pain and have obtained the medication from a friend or family member. There have been similar trends in the United States.”<sup>13</sup>

Based on the study of Fischer et al., those with a

label of “NMPOU” may suffer chronic, undertreated pain, and pain associated co-morbid conditions. These patients need co-treatment of both mental health and pain problems; however, the reality is they rarely can find providers who are willing to deliver the needed care to them.<sup>14</sup> These individuals are increasingly scrutinized or excluded from medical practices which prescribe opioids. The demand for prescription opioid treatment centers far outweighs the available resources. Adequate comorbidity diagnosis or care in the substance abuse field, especially associated with chronic pain and prescription opioid use, has long been recognized as a major challenge. Basically, we do not have a system that can accommodate the specific needs of this special population.<sup>6</sup> Many times, providers simply don’t even feel they want to be involved in taking care of these patients for extra liability concerns, or due to the lack of reimbursement for treating addiction, or when specialized mental health care is not available, accessible, or affordable. In the end, it is conceivable that these individuals will end up being victims of a presumed “vicious cycle,” and without other options but to continue their practice of NMPOU.<sup>14</sup>

Indeed, the disease burden of chronic pain is enormous, not only in the US, but at a global level, across the world. Recently, Vos and colleagues<sup>15</sup> published a titanic report entitled “Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990–2013: A systematic analysis for the Global Burden of Disease Study 2013, in the *Lancet*. This report is considered the most comprehensive and extensive assessment of the global burden of disease down to country level. What is striking, about the morbidity and disability burden data is the high prominence of pain and diseases associated with pain, as a global cause of disability in both the developed and developing world.<sup>16</sup>

Of 301 acute and chronic diseases and injuries in 188 countries, the top 10 disease/condition that caused people to live with disability, low back pain ranks first among the top 10 leading causes of years lived with disability (YLD), chronic neck pain and migraine were ranked numbers 4 and 6, respectively. Mental health conditions were also important causes of YLD, with major depressive disorder ranked number 2 while anxiety ranked number 9; both of these are important co-morbidities with chronic pain.<sup>15</sup> It is apparent that the overall burden

of disease of chronic pain and chronic pain associated comorbidities is unparalleled at the global level.

In a recent Editorial entitled “The American chronic pain crisis and the media: About time to get it right?” by Michael Schatman,<sup>17</sup> the author opined “The media has happily published myriad stories regarding prescription opioid-related abuse, diversion, overdose, and deaths, yet is seemingly unwilling to write stories regarding the millions of Americans with chronic pain whose qualities of life are actually enhanced through their appropriate utilization of opioid analgesics. ‘If it bleeds, it leads’ has clearly become media’s mantra regarding pain management, resulting in the desire to sell print trumping its broader societal responsibility to disseminate accurate, unbiased, and balanced information.” “Today, with the Institute of Medicine report indicating that approximately 100 million Americans suffer from chronic pain, we are experiencing another type of crisis.”<sup>17</sup>

The drastic increase in heroin abuse and the resultant heroin mortality disclosed in the report of Compton et al. is shocking. A recent study published by the Centers for Disease Control and Prevention (CDC) in July 2015, *Morbidity and Mortality Weekly Report*.<sup>18</sup> revealed that heroin use has increased significantly across most demographics. It is very disturbing to see very significant increases in previously less affected subpopulations, ie, doubling among women and more than doubling among non-Hispanic whites.<sup>18</sup> Further, based on the CDC report, the heroin mortality rate is *underestimated* in the Multiple Cause of Death Files, because the specific drug or drugs involved in the overdose are not specified in approximately 25 percent of death certificates where the cause of death is drug overdose.<sup>18</sup>

Further, many heroin (illicit drug) users can be mistaken for morphine (prescription opioid) users. This is because heroin is a synthetic opiate made from morphine and is rarely detectable in body fluids. It has a half-life of a few minutes.<sup>19</sup> Heroin is metabolized to morphine. Heroin undergoes rapid deacetylation to 6-monoacetylmorphine (6-MAM). However, related to a short half-life of 6-MAM, it is only detectable in urine for about eight hours after administration,<sup>19</sup> which means in heroin users who have used heroin greater than eight hours prior, their urine test will only reveal morphine, the final metabolite of heroin, without any evidence of heroin use in standard urinary metabolite testing.

Finally, the recent increases in hepatitis C and HIV

infections associated with mounting heroin use, underscore the critical importance of improving access to addiction treatment.<sup>18</sup> Once again, the cruel reality is that in America finding addiction treatment has been difficult for decades.<sup>20</sup> In a recent article published in *JAMA*, Nelson and colleagues<sup>21</sup> stated “In 2013, more than three-fourths of adults aged 18 through 64 years who had prescription opioid use disorders did not receive any substance use treatment. Particularly, policy and societal barriers prevent broad dissemination, access, and adoption of highly effective medication-assisted therapies for people with prescription opioid use disorders.” Indeed, the problem of addiction will not be solved without all stakeholders working together to develop successful systems, including appropriate resources to enhance prevention, treatment, and abstinence.

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Xiulu Ruan, MD  
Adjunct Clinical Associate Professor of Anesthesia  
Department of Anesthesiology  
Louisiana State University Health Science Center  
New Orleans, Louisiana

Melville Q. Wyche, III, MD  
Assistant Professor of Anesthesiology  
Department of Anesthesiology  
Louisiana State University Health Science Center  
New Orleans, Louisiana

Alan David Kaye, MD, PhD  
Professor, Program Director, and Chairman of  
Anesthesia  
Department of Anesthesiology,  
Louisiana State University Health Science Center  
New Orleans, Louisiana

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