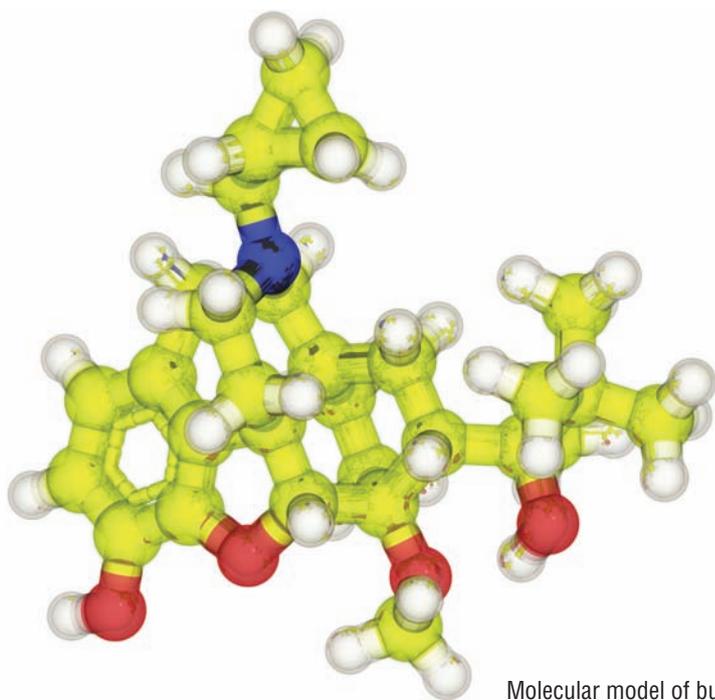


# The Interface



Molecular model of buprenorphine

## BUPRENORPHINE TREATMENT FOR NARCOTIC ADDICTION: Not Without Risks

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This ongoing column is dedicated to the challenging clinical interface between psychiatry and primary care—two fields that are inexorably linked.

### ABSTRACT

While most clinicians will never prescribe buprenorphine or combined buprenorphine/naloxone, familiarity with the risks of these pharmacological approaches to the treatment of narcotic addiction remains relevant. Overall, medication-assisted treatment has clearly resulted in meaningful gains for a number of individuals who are addicted to narcotics (i.e., opiates and

opioids). However, a certain level of risk is inherent with these approaches. For example, both buprenorphine and buprenorphine/naloxone may be diverted and misused (e.g., intravenously injected, intranasally administered), particularly buprenorphine. Likewise, when illicitly injected, both can cause infectious complications as well as result in death from overdose. The risk of death with

buprenorphine overdose appears to be heightened with the coadministration of either benzodiazepines or sedative/hypnotics. To conclude, as with all interventions in medicine, buprenorphine treatment for narcotic addiction has a clinically fluctuating risk/benefit equation that must be continually monitored.

### KEY WORDS

Buprenorphine, buprenorphine/naloxone, naloxone, narcotics, opiates, opiate addiction, opioids, opioid addiction

### INTRODUCTION

The growing epidemic of narcotic addiction (both naturally occurring opiates and synthetically derived opioids) remains a public health concern. This epidemic serves as an impetus for finding better treatments. Medication-assisted treatment for narcotic addiction originated with methadone and has now progressed to treatment with buprenorphine and the combination drug buprenorphine/naloxone. While medication-assisted treatment has culminated in meaningful gains for a significant proportion of narcotic-addicted individuals, it continues to pose risks as well. In this edition of *The Interface*, we examine some of these risks, including diversion and misuse, medical complications of illicit injections, and death through overdose. While the majority of readers will never prescribe these medications, some familiarity with this clinical terrain is useful for clinicians, both in psychiatry and in primary care.

### A PRIMER ON BUPRENORPHINE

Buprenorphine became available as a treatment for narcotic addiction through the United States Food and Drug Administration (FDA) in 2002. According to the *Clinical Guidelines for the Use of Buprenorphine in the*

*Treatment of Opioid Addiction*, which is published by the United States Department of Health and Human Services, “Buprenorphine has unique pharmacological properties that make it an effective and well-tolerated addition to the available pharmacological treatments for opioid addiction.”<sup>1</sup> In terms of pharmacology, buprenorphine is a mixed agonist/antagonist that affects various opioid receptor sites, including mu opioid receptors (the classic morphine receptor).<sup>2</sup> However, rather than being an unequivocal opioid agonist at mu-opioid receptors like heroin and methadone, it is believed that buprenorphine is less active.<sup>2,3</sup> Because of this distinct pharmacological feature, buprenorphine has been perceived as, “a safe and effective treatment option for the treatment of opioid addiction.”<sup>1</sup>

Many clinicians may not be familiar with buprenorphine or its prescription, as it can only be prescribed by “qualifying” physicians.<sup>4</sup> Qualifying physicians must 1) complete a training course of at least eight hours or possess a certification in addiction medicine, 2) have access to psychosocial support services, and 3) comply with established limits regarding patient volumes (i.e., no more than 30 patients during the first year of prescribing, then up to 100 patients per year thereafter).<sup>4</sup>

At the outset of treatment for narcotic addiction, sublingual buprenorphine (Subutex™) alone is traditionally recommended to avoid precipitous withdrawal reactions from current illicit narcotics.<sup>2</sup> However, during the maintenance phase of treatment for narcotic addiction, the combined sublingual tablet buprenorphine and naloxone (Suboxone™) is typically undertaken. Why is the combination sublingual tablet recommended at this juncture? While buprenorphine, itself, can be

readily abused through intravenous injection, it is believed that the combination drug tablet reduces this risk by precipitating an opioid withdrawal reaction when injected (via naloxone).<sup>3</sup>

In theory, this proposed deterrent to the abuse of the combined sublingual tablet is appealing. However, the pharmacology of these drugs suggests a more concerning profile. At the outset, the fundamental pharmacology appears straight forward. For the combined tablet, the mean half-life of sublingual buprenorphine is 37 hours, whereas the mean half-life of sublingual naloxone is 1.1 hours, with a buprenorphine/naloxone ratio of 4:1.<sup>2</sup> In keeping with the preceding theory, the oral bioavailability of naloxone is poor, whereas the bioavailability of injected naloxone is far greater (half-life of 30-81 minutes).<sup>2</sup> However, when the combination tablet is prepared by the user and injected, the functional blockade of buprenorphine by naloxone is apparently modest and short-lived, ultimately culminating in an overall subsequent agonist effect similar to buprenorphine alone.<sup>3</sup> The functional and clinical significance of this interaction is that buprenorphine either alone or in combination with naloxone is theoretically prone to misuse, and therefore, diversion. Is there any evidence to support these findings?

### CONCERNS ABOUT BUPRENORPHINE AND BUPRENORPHINE/NALOXONE DIVERSION AND MISUSE

Over the years, a number of authors have expressed clinical concerns about the abuse risks of buprenorphine and buprenorphine/naloxone. For example, in a commentary from France, the authors stated that, “buprenorphine users appear more likely to self-inject...compared to methadone

users.”<sup>5</sup> Ling affirmed the potential for buprenorphine misuse, including the combined formulation.<sup>6</sup> Mammen and Bell clarified that there were many circumstances, “...where injecting of buprenorphine-naloxone is reinforcing rather than aversive.”<sup>7</sup> Comer et al<sup>8</sup> confirmed the intravenous abuse of the buprenorphine/naloxone combination, but believed it to be less than buprenorphine alone. Middleton et al<sup>9</sup> broached their concerns about the intranasal misuse of buprenorphine due to the effects of greater bioavailability and faster onset. Yokell affirmed that buprenorphine and buprenorphine/naloxone diversion is well documented.<sup>10</sup> Wish et al<sup>11</sup> reinforced this latter conclusion by indicating that buprenorphine has wide-scale availability on the street and in prisons. Finally, Pauly et al<sup>12</sup> proffered their impression that buprenorphine has become a keen prescription drug for diversion and misuse in France. Clearly, a number of professionals have pulled the clinical fire alarm on buprenorphine and buprenorphine/naloxone. However, do existing empirical data support these clinical concerns?

### EMPIRICAL STUDIES OF BUPRENORPHINE AND BUPRENORPHINE/NALOXONE MISUSE

**Studies in Europe.** The largest number of studies in this area originates from Europe, particularly from France. In 1997, Lapeyre-Mestre et al<sup>13</sup> examined forged prescriptions that were submitted to several pharmacies in France and found that buprenorphine was among the top four medications requested. In a sample of 270 inmates entering into a French prison, Claudon-Charpentier et al<sup>14</sup> found that 97 individuals were addicted to narcotics; of these, 55 percent used buprenorphine. In a study of French intravenous drug

users, Obadia et al<sup>15</sup> found that one-third were poly-drug users who occasionally injected buprenorphine. Among 404 French participants in a buprenorphine maintenance program, 46.5 percent reported previously injecting buprenorphine and of these, two-thirds had injected buprenorphine since their entry into the program.<sup>16</sup> In a study of 111 stabilized French patients receiving buprenorphine treatment, Roux et al<sup>17</sup> found that nearly one-third reported injecting the drug after starting treatment.

In addition to these studies, in 2007, Aalto et al<sup>18</sup> examined 30 patients entering a Finnish treatment program for narcotic addiction and reported that at admission, buprenorphine was the preferred opioid of misuse. In a Swedish survey of 350 individuals obtaining sterile needles, Hakansson et al<sup>19</sup> found that 89 percent of heroin users acknowledged the misuse of buprenorphine at some time during the previous year. In a survey of addiction counseling centers in Germany, Kufner and Rosner<sup>20</sup> confirmed a pattern of increasing misuse of buprenorphine. In a study of 307 patients admitted to an Italian addiction treatment center, Moratti et al<sup>21</sup> reported that 23 percent acknowledged the intravenous misuse of buprenorphine; the authors concluded that such abuse is “a widespread problem.” Through a systematic review of the literature, Casati et al<sup>22</sup> reported in 2012 that the main groups of misused medications in the European Union were opioid analgesics, methadone, non-benzodiazepine benzodiazepine-receptor-site sedative/hypnotics, and buprenorphine. Clearly, the misuse of buprenorphine in Europe, which propels diversion, is sufficiently confirmed.

**Studies in New Zealand and Australia.** Studies have been undertaken in New Zealand and Australia, as well. For example, in a

1993 study from New Zealand, Robinson et al<sup>23</sup> surveyed new patients presenting to a substance abuse treatment center. In this study, 57 percent of participants reported the misuse of the buprenorphine/naloxone in the four weeks prior to presentation and 43 percent had detectable levels of these drugs in their urine. In a study of Australian intravenous drug users, Jenkinson et al<sup>24</sup> reported that 37 percent had injected buprenorphine at some point in their lifetimes. In a 2007 study from Australia, Nielsen et al<sup>25</sup> surveyed 282 pharmacies that dispensed buprenorphine and found that the participants (pharmacists) believed that a significant level of diversion was occurring. Winstock and Lea<sup>26</sup> examined 448 clients in several narcotic-addiction treatment clinics in Australia and found that 1) rates of diversion for buprenorphine were three times higher than for methadone and 2) 25 percent of participants currently prescribed buprenorphine had previously injected the drug. Finally, in an Australian study of clients obtaining sterile needles, researchers found that buprenorphine/naloxone was abused, but at a lower rate than buprenorphine alone.<sup>27</sup>

**Studies in the United States.** Studies in the United States generally support the findings of studies from Europe, New Zealand, and Australia. For example, Cicero et al<sup>28</sup> recruited 1,000 participants who were seeking treatment for prescription narcotic abuse. During surveys in 2006 and 2007, 20 to 35 percent of participants acknowledged the misuse of buprenorphine. Monte et al<sup>29</sup> queried 51 individuals entering opioid addiction programs and found that 100 percent had diverted buprenorphine/naloxone. Schuman-Olivier et al<sup>30</sup> examined 129 admissions to an outpatient-based narcotics treatment program and found that 49 percent of participants had illicitly used buprenorphine in the

past 90 days. Bazazi et al<sup>31</sup> surveyed 51 opioid users and reported that 76 percent had illicitly obtained buprenorphine/naloxone and 41 percent had done so in the past month. Finally, Daniulaityte et al<sup>32</sup> interviewed 396 illicit users of prescription narcotics and found that 7.8 percent had illicitly used buprenorphine in their lifetimes.

As an exception to the impressive rates reported in previous studies, in a study of new admissions to a methadone treatment center as well as street users of narcotic drugs, Gwin Mitchell et al<sup>33</sup> reported in 2009 that only 5 of 515 participants used diverted buprenorphine. This surprising finding may relate to the methodology of the study.

## RISKS BEYOND DIVERSION AND MISUSE

In addition to diversion and misuse, buprenorphine and buprenorphine/naloxone may culminate in various medical complications. With injection, misusing individuals may develop various serious infections, including infectious endocarditis, cutaneous abscesses, osteoarticular infections, meningitis, and retinitis.<sup>34</sup>

In addition to the risks related to infections, lethal overdose is an ever-present threat. In this regard, between 2003 and 2007, one group of poison control centers received 1,117 calls about buprenorphine.<sup>35</sup> Likewise, a single poison control center in Utah received 462 calls for buprenorphine between 2002 and 2011.<sup>36</sup> While the risk of overdose-death with buprenorphine is lower than that of methadone,<sup>37</sup> the risk is heightened with the concomitant use of benzodiazepines.<sup>38,39</sup> In support of this impression, in a study of autopsies from 97 cases of buprenorphine-related deaths, alprazolam was present in more than 40 percent of the reports

and sedative/hypnotics were present in 75 percent of the reports.<sup>40</sup> Moreover, an investigation of six deaths in France revealed the presence of buprenorphine and benzodiazepines in each victim.<sup>41</sup> The suspected mechanism of death is respiratory depression.<sup>39,42</sup>

**CONCLUSION**

Undoubtedly, the treatment of narcotic addiction is challenging and difficult. With the advent of buprenorphine and buprenorphine/naloxone, treatment has seemingly improved. In particular, the development of the buprenorphine/naloxone formulation has appeared to reduce diversion and misuse in medication-assisted therapies. However, buprenorphine remains an attractive substance of misuse, even when combined with naloxone. Therefore, the prescribers of these drugs and the clinicians who provide services to patients who participate in these treatments need to remain ever-mindful of the risks of diversion and misuse as well as the medical complications of intravenous misuse and death from overdose. As stated adroitly by Stimmel, "...this is not to cast aspersions on the use of buprenorphine as a maintenance drug for heroin dependency, but rather to serve as a reminder that any mood-altering drug can be abused."<sup>3</sup>

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