

# Twelve Reasons for Considering Buprenorphine as a Frontline Analgesic in the Management of Pain

Mellar P. Davis, MD, FCCP, FAAHPM

**B**uprenorphine was originally developed as an analgesic, and is a semisynthetic thebaine derivative that has a unique cyclopropylmethyl group also classified as an oriparvine derivative of morphine.<sup>1,2</sup> It has been available in a parenteral formulation since 1981 in the United States. Sublingual tablets are now available in certain countries and are licensed for analgesia. However, in the United States, sublingual buprenorphine is licensed only for addiction maintenance therapy.<sup>3</sup> Buprenorphine in a transdermal delivery system preparation (TDS buprenorphine) is available in the United States and Europe for moderate pain; it is available only in Europe for severe pain. The transdermal formulation has buprenorphine embedded in an acylated benzyl acetate polymer matrix that prevents dose dumping.<sup>4,5</sup>

Buprenorphine has a unique and complex pharmacology. It is classified as a partial agonist in vitro by activation of the pertussis toxin-sensitive G protein, and as a full analgesic agonist clinically. The published conversion ratio between oral morphine and TDS buprenorphine ranges from 75:1 to 115:1.<sup>6,7</sup> Buprenorphine is nearly as potent as fentanyl.<sup>7-10</sup>

Buprenorphine activates a distinct subset of the G protein, different from what is activated by morphine, fentanyl, and methadone.<sup>11-14</sup> Downstream from receptor activation, buprenorphine interacts with adenylyl cyclase in a timeframe that differs from methadone. (Activation of the adenylyl cyclase is associated with analgesic tolerance

**ABSTRACT** Buprenorphine is an opioid that has a complex and unique pharmacology which provides some advantages over other potent mu agonists. We review 12 reasons for considering buprenorphine as a frontline analgesic for moderate to severe pain: (1) Buprenorphine is effective in cancer pain; (2) buprenorphine is effective in treating neuropathic pain; (3) buprenorphine treats a broader array of pain phenotypes than do certain potent mu agonists, is associated with less analgesic tolerance, and can be combined with other mu agonists; (4) buprenorphine produces less constipation than do certain other potent mu agonists, and does not adversely affect the sphincter of Oddi; (5) buprenorphine has a ceiling effect on respiratory depression but not analgesia; (6) buprenorphine causes less cognitive impairment than do certain other opioids; (7) buprenorphine is not immunosuppressive like morphine and fentanyl; (8) buprenorphine does not adversely affect the hypothalamic-pituitary-adrenal axis or cause hypogonadism; (9) buprenorphine does not significantly prolong the QTc interval, and is associated with less sudden death than is methadone; (10) buprenorphine is a safe and effective analgesic for the elderly; (11) buprenorphine is one of the safest opioids to use in patients in renal failure and those on dialysis; and (12) withdrawal symptoms are milder and drug dependence is less with buprenorphine. In light of evidence for efficacy, safety, versatility, and cost, buprenorphine should be considered as a first-line analgesic.

and withdrawal.)<sup>15</sup> Buprenorphine is a kappa receptor antagonist; unlike morphine and fentanyl, it acts as a "chaperone" ligand, which means that buprenorphine increases mu receptor expression on membrane surfaces.<sup>10,16,17</sup> Buprenorphine is also an opioid receptor-like 1 (ORL1) agonist that has a unique interaction with pain processing. Activation of the ORL1 receptor in the dorsal horn is analgesic, but cerebral ORL1 activation blunts antinociception as seen in animal models. Paradoxically, ORL1 also blocks analgesic tolerance.<sup>1,18</sup> ORL1 blunts the rewarding effects of potent opioids as seen in morphine-tolerant animals; ORL1 agonists block conditioned place preference.<sup>19-21</sup>

Dr Davis is at the Cleveland Clinic Lerner School of Medicine at Case Western University, and the Palliative Medicine and Supportive Oncology Services in the Division of Solid Tumor Oncology at the Taussig Cancer Institute of the Cleveland Clinic, Cleveland, Ohio.

Submitted for Publication: February 15, 2012; final revision received May 14, 2012; accepted May 18, 2012.

Published Online:

Correspondence: Mellar P. Davis, MD, Cleveland Clinic Main Campus, Mail Code R35, 9500 Euclid Avenue, Cleveland, OH 44195; e-mail: davism6@ccf.org

J Support Oncol 2012;20:2000-2002. © 2012 Elsevier Inc. All rights reserved. <http://dx.doi.org/10.1016/j.suponc.2012.05.002>

The availability of sublingual buprenorphine is 30%–50% and the availability of buccal buprenorphine is 28%, relative to parenteral buprenorphine. Terminal half-life of sublingual buprenorphine is long, relative to parenteral administration, because of the sequestration of the drug in oral mucosa and buccal fat.<sup>22–24</sup> Sublingual buprenorphine blood levels peak at 2 hours, then rapidly decline for 6 hours, and finally slowly decline over 24 hours.<sup>25</sup> The prolonged terminal half-life is in part due to enterohepatic recirculation. Buprenorphine is largely excreted in the stool.<sup>26,27</sup> The main metabolite of buprenorphine, norbuprenorphine, is generated through the cytochrome CYP3A4. Buprenorphine and its metabolites do not inhibit cytochromes at therapeutic doses, and as a result have few drug interactions.<sup>28,29</sup> Buprenorphine and norbuprenorphine are rapidly conjugated by UGT2B7 and UGT1A1 in the liver. Although both conjugations are rate limiting to buprenorphine metabolism, they are relatively spared in liver disease; as a result, buprenorphine is relatively safe in mild to moderate liver failure.<sup>30–34</sup> Buprenorphine-3-glucuronide and norbuprenorphine-3-glucuronide blood levels can exceed the parent drug levels. Buprenorphine-3-glucuronide in vitro is a  $\mu$ ,  $\delta$ , and ORL1 agonist, whereas norbuprenorphine-3-glucuronide is a  $\kappa$  and ORL1 ligand. Neither buprenorphine nor the glucuronide metabolites reduce respiratory rates, although norbuprenorphine-3-glucuronide has been demonstrated to reduce tidal volume in animal models.<sup>35,36</sup>

Norbuprenorphine is a weak  $\mu$  agonist. Pharmacokinetic/pharmacodynamic studies performed in rats have found norbuprenorphine to be responsible for respiratory depression. However, norbuprenorphine rarely exceeds 10% of buprenorphine blood concentrations, well below levels associated with respiratory depression in normal human volunteers.<sup>37</sup> Norbuprenorphine activation of  $\mu$  receptors appears to be responsible for respiratory depression.<sup>38</sup>

The usual parenteral/TDS buprenorphine dosage for cancer pain ranges from 35 mcg/hour to 70 mcg/hour, but dosages greater than 210 mcg/hour have been used without a ceiling effect on analgesia. Equivalent sublingual doses are 1.6 mg to 3.2 mg daily if a 50% bioavailability is assumed.<sup>39</sup>

There are limitations to the present opioids commonly used for pain (fentanyl, oxycodone, morphine, hydromorphone, and methadone). Opioid-related side effects limit titration; common titration-limiting side effects include nausea, vomiting, and cognitive dysfunction. Physicians greatly fear respiratory depression and often fail to titrate doses for that reason.<sup>40</sup> Individuals often do not respond to the first opioid, and require a second opioid that is non-cross-analgesic tolerant.<sup>41</sup> Potent opioids can have unusual adverse effects, such as hypogonadism, which can lead to loss of libido; long-term effects include osteoporosis and loss of muscle mass.<sup>42</sup> Opioids that are metabolized through cytochromes will have altered pharmacokinetics resulting in liver failure.<sup>43</sup> Accumulation will lead to delayed toxicity; certain opioids that are conjugated will accumulate in renal failure.<sup>44</sup> When swallowing is no longer possible, having transdermal and

sublingual routes of administration improves patient compliance and facilitates continued analgesia.<sup>45</sup> Having both routes as options will reduce the need for computerized activated delivery devices (CADD pumps) and syringe drivers for parenteral opioid delivery, as well as their associated technical problems.<sup>46–48</sup> Buprenorphine has the potential to address many of these problems.

## REASONS FOR CONSIDERING BUPRENORPHINE AS A FRONTLINE ANALGESIC FOR CANCER PAIN

### 1. Buprenorphine Is Effective in Pain

Large numbers of cancer and noncancer patients with pain have been treated with buprenorphine.<sup>49–55</sup> Starting doses for severe pain have ranged from 35 mcg/hour (74%) to 52.5 mcg/hour (21%) to 70 mcg/hour (5%). Pain severity on average decreases from 62 mm on the visual analogue scale to 16 mm (range, 0 = no pain, 100 mm = severe pain) over a 2-week period. On average, 85% of patients experience pain relief in the range of good to very good. Sleep quality improves in 48% of individuals, and only 3% discontinue buprenorphine.<sup>50,51</sup> The great majority of patients like the convenience of a transdermal patch. Sublingual and parenteral formulations have also been effectively used for chronic cancer pain with the same benefits as transdermal buprenorphine.<sup>49,52–59</sup> Based upon the number of studies and individuals treated with buprenorphine, the evidence of benefit is equivalent to that of morphine, hydromorphone, oxycodone, fentanyl, and methadone.<sup>46–51</sup>

A low dose of buprenorphine has been used in the opioid-naïve individual who has moderate pain. The starting dose was 17.5 mcg/hour (that is, one-half of a 35-mcg/hour patch) or 0.8 mg of sublingual buprenorphine. Pain intensity was reduced by 1 week. Dose adjustments occurred over 4 weeks, with dose increases up to 41%, on average. Pain control could be achieved as early as 1.5 days after starting a low dose of TDS buprenorphine. In addition, improvement in patients' quality of life has been reported.<sup>60</sup> An expert consensus panel concluded that buprenorphine is a valuable treatment for chronic cancer pain and its neuropathic component.<sup>39</sup> In a systematic review of the efficacy and safety of buprenorphine, fentanyl, and morphine in pain management, transdermal fentanyl was associated with greater nausea (odds ratio [OR], 4.66), a significant higher rate of discontinuation because of adverse events (OR, 5.94), and a nonsignificant difference in analgesia. In comparison with morphine, transdermal buprenorphine reduced pain intensity to a greater degree (mean difference, –16.20 by visual analogue scale) whereas morphine caused more constipation (OR, 5.63), nausea (OR, 4.23), vomiting (OR, 15.85), and increased treatment discontinuation because of adverse effects (OR, 4.26).<sup>61</sup>

### 2. Buprenorphine Is Effective in Treating Neuropathic Pain

Both central sensitization and peripheral neuropathy activate rostral ventromedial medulla "on" cells, which facilitates pain through the dorsal lamina funicularis.<sup>62</sup> There is a close

association between peripheral neuropathy and loss of conditioned pain modulation known as diffuse noxious inhibitory control (DNIC).<sup>63</sup> When ORL1 receptors are activated, "on" cells and pain-facilitation pathways are blocked.<sup>64,65</sup> In animal models, buprenorphine is fully effective in producing antinociception for neuropathic pain.<sup>9,66,67</sup>

In human experimental pain, buprenorphine – unlike other potent mu agonists – blocks secondary hyperalgesia from central sensitization.<sup>65–68</sup> There is some evidence that certain potent mu agonists actually increase secondary hyperalgesia.<sup>69</sup> Morphine has been known to inhibit diffuse noxious inhibitory control (DNIC) as has buprenorphine. Interference with DNIC may contribute to the analgesia in neuropathic pain or be a mechanism of hyperalgesia. The issue is controversial.<sup>70–74</sup> Neuropathic pain is associated with loss of pertussis toxin-sensitive G-protein activity.<sup>75</sup> Morphine analgesia is highly dependent on pertussis toxin-sensitive G protein, whereas buprenorphine analgesia is not highly dependent on pertussis toxin-sensitive G proteins.<sup>11,76,77</sup> Buprenorphine has successfully treated neuropathic pain.<sup>52,66,67,78–80</sup> In 2 case series, buprenorphine has produced responses where transdermal fentanyl failed to do so.<sup>52,81</sup> In this small group of patients, buprenorphine potency was greater than anticipated, with an oral morphine-to-transdermal equianalgesia of 110:1 to 115:1. In addition, 40% of individuals with various central neuropathic syndromes (usually considered refractory to opioid analgesia) responded to buprenorphine. Starting doses were low (8.75 mcg/hour) and were titrated.<sup>82</sup> In a double-blind, randomized study involving patients with post-thoracotomy pain, intravenous (IV) buprenorphine was effective in reducing pain.<sup>83</sup> Response rates are as high as 69% with doses from 35 mcg/hour to 70 mcg/hour. A consensus panel stated that although there are no randomized control trials comparing buprenorphine with other opioids, there is significant evidence that buprenorphine effectively relieves neuropathic pain.<sup>16,67</sup> More studies are needed to identify neuropathic syndromes that are responsive to buprenorphine, and randomized studies are needed to compare those responses to buprenorphine vs responses to other opioids.<sup>67</sup>

### 3. Buprenorphine Treats a Broader Array of Pain Phenotypes Than Do Certain Potent Mu Agonists, Is Associated With Less Analgesic Tolerance, and Can Be Combined With Other Mu Agonists

Animal models have demonstrated that buprenorphine reduces pain from a variety of mechanisms, including formalin injection, cold temperature tail flick, and DNIC tests.<sup>97</sup> A comparison of buprenorphine vs. fentanyl with human volunteers and different pain phenotypes found that buprenorphine was effective in a larger number of pain phenotypes than was fentanyl. Buprenorphine attenuated experimental bone pain, heat pain, pain related to nerve growth-factor injections, and cold pressor pain, whereas fentanyl at equal analgesic doses was effective only in attenuating cold pressor pain.<sup>84</sup> A similar but less dramatic finding has also been

reported by another researcher but with less differences between fentanyl and buprenorphine.<sup>85</sup> The differences between the studies may be related to design and outcome measures. However, there is evidence of a distinctively different tissue-differentiating effect and pain-phenotype response between buprenorphine and fentanyl.

Analgesic tolerance to opioids seems to be related to a number of mechanisms. Dynorphin, an endogenous kappa agonist, is upregulated by morphine, and paradoxically promotes central sensitization.<sup>86</sup> Buprenorphine reduces opioid tolerance by blocking kappa receptors. Morphine impairs DNIC in a naloxone-reversible manner and thus facilitates pain via bulbospinal pathways.<sup>70,71,74,87</sup> Buprenorphine blocks secondary hyperalgesia and central sensitization to a greater extent than do other mu agonists, possibly through ORL1 receptors.<sup>65</sup> Chronic opioids (morphine and methadone) cause a selective increased sensitivity to cold pressor pain, which is less so with buprenorphine.<sup>88</sup>

Buprenorphine produces less analgesic tolerance than does fentanyl, as measured by an opioid escalation index in a retrospective study involving nearly 900 cancer and noncancer patients.<sup>7</sup> Non-cross-tolerance between opioids is seen with rotations between fentanyl and buprenorphine.<sup>89</sup> Buprenorphine has been successfully combined with morphine and tramadol without loss of analgesia.<sup>90–93</sup> Supra-additive analgesia is reported with the combination of buprenorphine plus oxycodone or hydromorphone; additive analgesia has been reported with morphine.<sup>10,94–96</sup> Despite its high affinity for the mu receptor, buprenorphine occupies fewer receptors for analgesia, which leads to a significant receptor reserve for other mu agonists.<sup>97</sup> Buprenorphine increases mu receptor expression, which allows other mu agonists to interact with receptors.<sup>97</sup> Future studies will need to confirm combination therapy and the role of buprenorphine in opioid rotation.

### 4. Buprenorphine Produces Less Constipation Than Do Certain Other Potent Mu Agonists, and Does Not Adversely Affect the Sphincter of Oddi

Buprenorphine-related constipation in large longitudinal or pooled randomized trials has ranged from 1% to 5%.<sup>98–100</sup> Other studies have not verified the relatively low rate of constipation associated with buprenorphine, but conversion ratios were different from what are usually reported in the literature.<sup>101</sup> Cancer patients often have a variety of causes for constipation other than opioids, which may falsely increase the reported frequency of constipation with buprenorphine. In a meta-analysis of randomized, controlled trials, TDS buprenorphine and fentanyl were each associated with significantly less constipation than were equianalgesic doses of sustained-release morphine (OR, 0.38).<sup>102</sup>

Spasm of the sphincter of Oddi may be one of the causes of colic associated with opioids. Unlike other opioids, buprenorphine does not cause spasm of the sphincter of Oddi.<sup>103,104</sup> Therefore, in addition to NSAIDs (nonsteroidal anti-inflammatory drugs), buprenorphine should be considered in the management of biliary colic and/or pancreatitis.

## 5. Buprenorphine Has a Ceiling Effect on Respiratory Depression

Respiratory depression occurs in approximately 1% to 11% of individuals receiving systemic or spinal opioids. The frequency is dependent upon the definition of respiratory depression (which varies, depending on whether it is defined in terms of respiratory rate, carbon dioxide levels, or hypoxia).<sup>105</sup> For most opioids, the risk is greater for patients who receive a background infusion with demand patient-controlled analgesia and in those receiving high doses of opioids except for buprenorphine. Populations who are at risk for respiratory depression include the morbidly obese, those with sleep apnea (central rather than obstructive), those with neuromuscular diseases, the very old, the very young, and the very ill.<sup>105</sup>

Buprenorphine is unique in that it has a dose-ceiling effect on respiratory depression, but not on analgesia. The relative safety increases with dose titration.<sup>106-109</sup> In an animal model that used 80% of the LD<sub>50</sub> dose (that is, the dose that would be lethal to half of the subjects); buprenorphine only slightly reduced arterial oxygen pressure (PaO<sub>2</sub>), whereas fentanyl, morphine, and methadone caused significant carbon dioxide (CO<sub>2</sub>) retention. Methadone, fentanyl, and morphine reduced the time in expiration, whereas buprenorphine did not.<sup>110</sup> Respiratory depression associated with buprenorphine is related to its metabolite, norbuprenorphine, and not to the parent drug; paradoxically, buprenorphine prevents and reverses respiratory depression in rats that are given lethal injections of norbuprenorphine.<sup>111</sup> In a study that compared the safety index of buprenorphine with fentanyl using pharmacokinetic/pharmacodynamic data, the OR of analgesia to respiratory depression was narrower (1.2) with fentanyl than with buprenorphine, which was 10-fold greater (14).<sup>112</sup> Buprenorphine's mild to minimal respiratory depression is adversely influenced by the addition of benzodiazepines or alcohol.<sup>36,113-115</sup> This interaction is both pharmacodynamic and pharmacokinetic.<sup>116,117</sup> However, the combination of buprenorphine plus benzodiazepine is safer than is the methadone-benzodiazepine combination.<sup>118</sup> Those with liver disease are at a particular risk for a respiratory depression with the combination of buprenorphine plus a benzodiazepine.<sup>119-121</sup>

Case reports found no respiratory depression in patients who had attempted suicide and were being treated with buprenorphine doses as high as 88 mg.<sup>122</sup> In human volunteers, fentanyl had a linear dose-related analgesia and respiratory depression without a ceiling effect on either outcome; buprenorphine had a linear analgesic effect and improved cutaneous pain 3-fold when doses were increased from 3 mcg/kg to 6 mcg/kg, but had no additional effect on respiration.<sup>108</sup> Similar results have been observed in other pharmacokinetic/pharmacodynamic studies of fentanyl and buprenorphine in normal human volunteers.<sup>37</sup> Doubling buprenorphine doses from 0.2 mg/70 kg to 0.4 mg/70 kg in healthy volunteers remarkably improved tolerance to transcutaneous electrical stimulation pain (from 29% to 160% above baseline) without changing minute ventilation.<sup>107</sup> Doses as high as 1,600 mcg/

hour or 32 mg of sublingual buprenorphine daily have not produced respiratory depression.<sup>123,124</sup>

Buprenorphine is one of the safest analgesics to use in individuals who are at risk for respiratory depression; however, it should not be combined with benzodiazepines, particularly in individuals with liver disease. In the rare circumstances in which respiratory depression does occur, 2 mg of naloxone should be given as a bolus, followed by 2 mg to 4 mg of naloxone infused over 90 minutes because of the high receptor affinity and the long half-life of buprenorphine.<sup>105</sup> Most of the data have been derived from the perioperative setting and from normal volunteers. Further studies are needed in cancer patients and in those with severe illness.

## 6. Buprenorphine Causes Less Cognitive Dysfunction Than Do Certain Other Opioids

Opioids can impair cognition and driving ability. Increased motor vehicle accidents have been reported in individuals on methadone or buprenorphine maintenance therapy (OR, 2). Other factors common to addiction (such as impaired reliability and risk-taking behaviors) can contribute to cognitive dysfunction and impair driving ability.<sup>125</sup> Patients on chronic opioids demonstrate an increased impulsiveness and reduced ability to comprehend instructions.<sup>126</sup> Several studies have demonstrated that opioids in stable doses do not necessarily impair complex activities such as driving ability; however, because of intraindividual variability in opioid responses and other confounding factors (eg, pain intensity, comorbidity), a judgment regarding driving ability must be made on an individual basis.<sup>127</sup> The addition of alcohol or a sedative to opioid maintenance therapy will impair driving ability.<sup>128,129</sup> Various tests have been performed to gauge driving ability. Individuals on buprenorphine (8 mg daily) have been compared with those on morphine (average dosage, 348 mg daily). Those on buprenorphine had better visual pursuit test results.<sup>130</sup> There was less impairment on certain portions of the driving-related psychomotor battery in individuals who were on buprenorphine, compared with those on methadone maintenance.<sup>131,132</sup> In 2 studies, it was shown that a group of patients who had chronic pain and received sustained treatment with transdermal fentanyl or buprenorphine performed significantly better in tests than did healthy persons with a legally relevant 0.05% concentration of blood alcohol.<sup>133</sup> Patients receiving a stable dosage of sublingual buprenorphine (7.3 mg +/- 3.9 mg daily) showed no significant impairment of complex psychomotor or cognitive performance, compared with healthy controls.<sup>134</sup> Compared with healthy opioid-naïve controls, individuals on TDS buprenorphine were noninferior when they were tested for attention, reaction time, visual orientation, motor coordination, and vigilance.<sup>135</sup> Buprenorphine has been reported to have lower psychomotor side effects than does fentanyl, and to have side effects similar to those of placebo.<sup>10,51,98,136</sup>

## 7. Buprenorphine Is Not Immunosuppressive

There is a bidirectional communication between the brain and the immune system that is modulated by opioids.<sup>137</sup> Exogenous opioids are immunosuppressive, whereas endogenous opioids stimulate the immune system. In the late 19th century, morphine was used to suppress cellular immunity and to lower resistance in guinea pigs, which were used as an experimental model for infection.<sup>138</sup> Most potent opioids reduce antibody production, reduce natural killer cell activity, and impair the cytokine expression and phagocytic activity of white cells.<sup>138-140</sup> Both morphine and fentanyl are examples of immunosuppressive analgesics.<sup>141,142</sup> Immunosuppression is potentiated by exogenous corticosteroids, the coadministration of other immunosuppressive medications, and chemotherapy.<sup>2,143</sup> The cause of immunosuppression is through activation of the mu receptor within the central nervous system, which activates the sympathetic system and increases cortisol.<sup>117,144-149</sup> Tolerance develops over time to the immunosuppression associated with morphine and fentanyl.<sup>150,151</sup> Immunosuppression is also generated independent of mu receptor activation, and is not reversed by naltrexone or standard doses of methylnaltrexone.<sup>146,152</sup>

Pain, cancer, and surgery reduce and impair natural killer cell activity, and are associated with poorer outcomes in multiple common cancers.<sup>153-158</sup> In animal models, morphine is associated with increased morbidity and mortality from infection and cancer.<sup>140</sup> Paradoxically, the use of opioids after surgical injury in experimental animals reduces metastatic spread of cancer and reduces the adverse effect of surgery on natural killer cell function.<sup>159-164</sup> However, in 2 retrospective studies, the use of patient-controlled analgesia with morphine was associated with increased relapse rates in breast cancer patients post mastectomy and in prostate cancer patients post radical prostatectomy, compared with spinal local anesthetics.<sup>165,166</sup>

Unlike morphine, when buprenorphine is injected into the periaqueductal gray it does not reduce natural killer-cell function, increase cortisol, reduce adrenocorticotropic hormone levels, or alter norepinephrine or serotonin levels.<sup>148,167</sup> Unlike morphine and fentanyl, buprenorphine does not increase metastases in natural killer-cell-sensitive tumors when it is injected into animals.<sup>147</sup> Chronic buprenorphine does not adversely influence antimicrobial responses or tumor surveillance, in contradistinction to fentanyl.<sup>140,151</sup> Buprenorphine maintenance therapy also restores immune function in heroin addicts.<sup>168,169</sup> Recovery of immune function may be, in part, related to morphine abstinence.

Most of the studies regarding buprenorphine and the lack of immunosuppression have been conducted in animal. It is unclear whether the immunosuppression of most opioids is clinically relevant. Future studies will be needed to demonstrate either reduced infection or altered course of cancer with buprenorphine. However, it is good practice to avoid such opioids in patients who are already immunosuppressed by disease or therapy. Buprenorphine should be a consideration in this group of patients.<sup>143,170</sup>

## 8. Buprenorphine Does Not Adversely Affect the Hypothalamic-Pituitary-Adrenal Pathway or Cause Hypogonadism

Chronic use of most potent mu agonists is associated with hypogonadotropic hypogonadism, loss of libido, and fatigue.<sup>171</sup> Over time, hypogonadism can lead to osteopenia and loss of muscle mass. Medication exposures associated with osteoporosis risk include opioids, glucocorticoids, and antidepressants.<sup>172</sup> In animals, morphine and fentanyl rapidly reduces diencephalon testosterone levels, which does not occur with buprenorphine.<sup>173</sup> Because morphine and fentanyl reduce testosterone levels, testosterone replacement is frequently required to improve sexual function and quality of life.<sup>174,175</sup> When men on buprenorphine maintenance therapy are compared with those on methadone, those on buprenorphine have higher testosterone levels and less sexual dysfunction.<sup>176-178</sup> Lower testosterone levels were associated with a higher body mass index (calculated as the weight in kilograms divided by height in meters squared) and greater depression as reported in 2 studies.<sup>177,178</sup> TDS buprenorphine in women relieves pain without inducing hypogonadism, lowering testosterone levels, or influencing menstrual cycles or follicle-stimulating hormone, luteinizing hormone, or estrogen levels.<sup>179</sup>

Even in high doses, buprenorphine will minimally influence sexual hormone levels. As a result, it will have less of an adverse effect than will other potent mu agonists (such as morphine and fentanyl) on psychological function, libido, muscle mass, and bone mineral density. There are 3 nonrandomized studies that have provided data about buprenorphine and gonadal function<sup>177-179</sup>. More prospective data are needed.

## 9. Buprenorphine Does Not Significantly Prolong the QTc Interval, and Is Associated With Less Sudden Death Than Is Methadone

Methadone has been associated with a prolonged QTc interval and torsades de pointes, which are the assumed mechanism for sudden cardiac death. Recommendations for screening have been recently published.<sup>180</sup> Prolongation of the QTc interval greater than 500 ms increases the risk of torsades de pointes and sudden cardiac death. The prevalence of a prolonged QTc in methadone-maintained individuals is nearly 29%, with approximately 5% having a QTc interval greater than 500 ms. The risk of a prolonged QTc is particularly high when doses were greater than 120 mg daily. In contrast to methadone; buprenorphine at maintenance doses is not associated with a prolonged QTc interval.<sup>181-183</sup> Sudden cardiac deaths occur 4 times more frequently with methadone maintenance than with buprenorphine maintenance, which suggests less cardiac toxicity. All of these studies were done in individuals on maintenance therapy and not in those on buprenorphine for pain. Buprenorphine doses for maintenance therapy are usually higher than they are for analgesia; however, advanced cancer patients are on multiple medications, which may influence repolarization.<sup>184</sup> Such studies

need to be done in those with advanced cancer or serious illnesses.

#### 10. Buprenorphine Is a Safe and Effective Analgesic for the Elderly

The elderly (those aged 65 years and older) frequently suffer from pain syndromes related to arthritis, diabetes, and neurologic and cardiovascular diseases as well as cancer.<sup>185</sup> Chronic pain in the elderly is frequently undertreated, and analgesics have a narrower therapeutic index secondary to reduced organ function and alterations in drug pharmacodynamics.<sup>186-188</sup> Certain analgesics such as NSAIDs are not recommended for use in the elderly.<sup>189</sup> Drug-drug interactions are more common in the elderly because of polypharmacy.

Several retrospective studies have reported the use of buprenorphine in the elderly.<sup>16,52-54</sup> A prospective observational study found that buprenorphine was equally effective for those aged 65 years and younger, those between 65 and 75 years, and those aged 75 years or older.<sup>190</sup> Responses were from 64% to 68%. Sleep improved in 60% to 65% of respondents, as did quality of life. Adverse events did not increase with age. A similar study demonstrated the same benefits of buprenorphine in those aged 65 years and older.<sup>52</sup> In addition, this study found no difference in efficacy in those aged 65 years and older, compared with those aged 50 years and younger. Other studies found that there was no increased toxicity in the elderly<sup>99</sup> and no dose adjustment needed.<sup>191</sup> Buprenorphine pharmacokinetics are not altered with age.<sup>10</sup> For all opioids except buprenorphine, drug half-life and the half-life of active metabolites are increased in the elderly and those with reduced renal function.<sup>16</sup> Buprenorphine interacts differently with CYP3A4 than does methadone, and is also rapidly conjugated. Drugs that block CYP3A4 do not appear to significantly influence buprenorphine pharmacokinetics.<sup>1,192</sup> Drug-drug interactions through cytochrome P450 enzymes are common in elderly patients who are on multiple medications.<sup>193</sup> Buprenorphine and its active metabolite are rapidly conjugated, and glucuronidation is associated with few drug interactions.<sup>194</sup> Buprenorphine is the only potent opioid that is not associated with an increased fracture risk in elderly individuals.<sup>195</sup> By consensus, buprenorphine is recommended as a first-line opioid in the elderly.<sup>16</sup> However, more studies of buprenorphine in the elderly need to be done. Most of the experience has been retrospectively derived.

#### 11. Buprenorphine Is the Safest Opioid to Use in Patients With Renal Failure and in Those on Dialysis

Buprenorphine clearance is largely through the gastrointestinal tract; elimination is not influenced by renal function.<sup>26,27,100,191,196-198</sup> There is no change in pain rating or blood levels of buprenorphine or norbuprenorphine in individuals on hemodialysis.<sup>197</sup> Buprenorphine is one of the safest opioids to use in those whose renal function is worsening or unstable. Because buprenorphine has a ceiling effect on respiratory depression and is relatively safe in hepatic failure, it

is an excellent analgesic to use in the intensive care setting or in the face of multiple-organ failure.

#### 12. Patients Have Milder Withdrawal Symptoms and Less Drug Dependence With Buprenorphine

Buprenorphine selectively dampens central sensitization. Central sensitization is one of the mechanisms behind opioid withdrawal.<sup>9,65,199</sup> In addition, buprenorphine has a long half-life; its prolonged binding to the mu receptor dampens withdrawal mechanisms and delays withdrawal to more than 72 hours after discontinuation.<sup>27,200,201</sup> Buprenorphine produces fewer rewarding effects than do other potent mu agonists, and it blocks psychological dependence.<sup>124,201-203</sup> Buprenorphine can precipitate withdrawal in individuals on high doses of other potent mu agonists.<sup>201</sup> A single dose of buprenorphine can precipitate withdrawal in individuals on larger doses (100 mg) of methadone.<sup>204</sup> Splitting doses (ie, giving multiple small doses rather than a single large dose) minimized subjective withdrawal. Doses of a buprenorphine-naloxone combination (ranging from 1 mg:0.25 mg to 16 mg:4 mg, respectively) have been given to individuals who are also on hydromorphone (40 mg/day) as maintenance therapy without subjective withdrawal.<sup>205</sup> Heroin addicts can undergo rapid buprenorphine titration without withdrawal.<sup>206,207</sup> Individuals on lower doses of methadone (from 25 mg to 45 mg) who are switched to buprenorphine (2 mg to 4 mg) will not experience withdrawal.<sup>208</sup> With maintenance therapy, a gap (4 to 6 hours for short-acting opioids, 24 hours with high doses of methadone) is recommended between stopping the first opioid and starting buprenorphine to avoid inducing withdrawal. These conversion gaps are based on maintaining addiction therapy and managing withdrawal symptoms, rather than on providing analgesia.<sup>209-212</sup> Options when managing individuals might involve starting with a low-dose of buprenorphine and overlapping with the first opioid which is then weaned over several days, or provide a gap between opioids to allow the levels of the first opioid to fall before starting buprenorphine.<sup>213</sup> There are no clinical studies where buprenorphine was used as an analgesic to give guidance to the proper approach to converting to buprenorphine when individuals are on high doses of potent mu agonists such as morphine, hydromorphone, fentanyl or methadone. On the other hand, intravenous buprenorphine has been used to treat withdrawal in medically ill, hospitalized heroin addicts. Symptoms of withdrawal were decreased when buprenorphine was used to manage withdrawal; its use resulted in neither respiratory depression nor a psychological high.<sup>214</sup> Buprenorphine is better than clonidine in managing withdrawal symptoms; symptoms resolve more quickly when buprenorphine rather than methadone is used to manage withdrawal.<sup>215</sup>

#### CONCLUSION

In the past, morphine has been considered the opioid of choice for moderate to severe pain, largely based on efficacy. However, no objective criteria have been established as a reference for choosing opioids for pain. Additional criteria

include versatility, safety, tolerability, and cost.<sup>216</sup> Buprenorphine has several advantages over other potent mu agonists. Besides being effective, it is uniquely antihyperanalgesic, lacks respiratory depression, is not immunosuppressive, and does not produce hypogonadism. There is less cognitive impairment than with certain other opioids. It is not cardiotoxic, is safe to use in renal failure, and is relatively safe in hepatic failure. Buprenorphine has few drug interactions and is versatile in its routes of administration. Other than methadone, it is one of the few long-acting sublingual potent mu agonists, which is an advantage if patients are unable to swallow or suffer from nausea and vomiting. The average wholesale price for sublingual buprenorphine in the Cleveland area is approximately half that of sustained-release oxycodone, and is equal to that of the analgesic dose of the fentanyl transdermal patch. In the United States, commercial low-dose TDS buprenorphine is expensive, compared with the equivalent sublingual dose. In Germany, according to a Markov model, TDS buprenorphine was more cost effective per quality-adjusted life-year gained than were TDS fentanyl

and sustained-release oxycodone for chronic pain.<sup>217</sup> Buprenorphine is not a drug to be used for spinal analgesia, but this is also true for fentanyl and other lipophilic opioids because of their rapid redistribution and lack of regional confinement. It is therefore reasonable to consider buprenorphine as a first- or second-line potent analgesic based on clinical circumstances. More studies are needed to compare buprenorphine with other opioids that have not only analgesia as outcomes, but also various side effects including cognitive effects, immunosuppression, hypogonadism, substance abuse, and addiction. Buprenorphine needs to be tested in individuals with well-defined pain phenotypes, as most studies have included individuals with poorly defined phenotypes or with various pain syndromes.

**Conflict of Interest Disclosures:** The author has completed the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Davis's institution has received compensation in the form of a grant from Pfizer for a fatigue research project.

**Previous Presentation:** This review was presented in part at the Seventh Annual Chicago Supportive Oncology Conference; October 27-29, 2011; Illinois.

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