EDITORIAL

DOI:10.5055/jom.2021.0619

Buprenorphine not a silver bullet but an opioid of choice for chronic pain

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I want to thank Dr. Potru for his thoughtful letter and would like to respond in kind. I agree that chronic pain should be treated with a multi-disciplinary approach and not treated solely with opioids as a single modality.[1] I also agree that opioid therapy should be a trial and only considered when other non-opioid medications and modalities have failed to improve patient function.[2,3] We also agree that universal precautions should be used for all opioids used to treat chronic noncancer pain. We also agree that the long-term results of opioid therapy is not established.[4,5] There are a large number of patients who discontinue opioid therapy due to side effects. Iatrogenic addiction is a risk as well as other long-term and even short-term adverse effects.[6] However, there are a subset of patients who do benefit from opioid therapy in the long-term.[7]

Buprenorphine was originally developed by Alan Cowan, PhD as a safer (not absolutely safe) analgesic and is a schedule III opioid as a result rather than schedule II. Buprenorphine was originally developed as an analgesic and it was only later that it was used as an opioid maintenance therapy. Heit and Covington, published a letter addressing the issue to the DEA regarding the use of buprenorphine-naloxone for analgesia. The response was though buprenorphine-naloxone is licensed for opioid maintenance therapy, its use is not limited to maintenance therapy and it can be used as an analgesic.[8]

Dr. Potru mentioned that buprenorphine is metabolized by a the cytochrome CYP3A4 but the rate limiting metabolism is through the glucuronidases UGT1A1, UGT1A3 and UGT2B7.[9-11] Norbuprenorphine is an active metabolite as a "full" agonist at MOR but is excluded from the CNS by P-glycoprotein. Its analgesic potential is ¼-1/50th that of buprenorphine. Norbuprenorphine is responsible for the respiratory depression associated with buprenorphine.[12-14] Buprenorphine does not but norbuprenorphine does activate beta-arrestin and beta-arrestin activation appears to be responsible, at least in part, for constipation and respiratory depression observed with buprenorphine. Blocking norbuprenorphine production as a result of blocking CYP3A4 may increase buprenorphine utility and safety.[15,16] The affinity of buprenorphine and metabolites for various receptors is outlined on Table 1. What is evident from this table is that buprenorphine is not a nociceptin agonist and that only buprenorphine-3-glucuronide of the glucuronides has MOR activity.

We can summarize buprenorphine pharmacodynamics in the following way:

- Norbuprenorphine has mu activity and is a potent full agonist
- Buprenorphine is a partial agonist at mu-1 and a kappa antagonist
- Buprenorphine-3-glucuronide has partial mu and delta, but not kappa activity
- Norbuprenorphine-3-glucuronide has kappa activity and nociception, but no mu or delta activity

It is generally accepted, but not carefully studied that partial agonists cause less constipation; presumably, only the parent compound, and presumably the 3-glucuronide metabolite (passage back into gut from circulation) are present in the gut, but not norbuprenorphine. Standard buprenorphine sublingual doses of 8mg will produce peak concentrations of

Table1. Buprenorphine and metabolite affinity (IC50)[41]				
Opioid	**MOP ng/ml**	**DOP ng/ml**	**KOP ng/ml**	**NOP ng/ml**
Buprenorphine	0.00013	15	0.00098	11,675
Norbuprenorphine	0.00084	607	0.0006	16,812
Buprenorphine-3-Glucuronide	0.0023	126	NB	16,812
Norbuprenorphine-3-Glucuronide	NB	NB	140,000	8,406

buprenorphine of 10-12 nanograms/ml(ng/ml), norbuprenorphine 1 ng/ml, buprenorphine-3-glucuronide 3ng/ml and norbuprenorphine-3-glucuronide of 3.5ng/ml.[17]

Another unique pharmacodynamic mechanism to buprenorphine which is shared with nalbuphine, butorphanol and levorphanol involves interactions with the exon 11 6-transmembrane MOR receptors. Analgesics which are partial agonists at this receptor have a ceiling on respiratory depression.[18-24]

Buprenorphine is as effective in managing acute pain at all timeframes (from less than 1 hour to 48 hours) as is morphine.[25] Pain relief is no different between transdermal buprenorphine and sublingual buprenorphine.[26] Transdermal fentanyl has a greater risk for respiratory depression per does-concentration ratio than fentanyl.[27-37] Buprenorphine is a better analgesic and is less constipating than morphine though buprenorphine may have greater nausea.[27,28,38] The analgesia of buprenorphine is greater in patients with chronic pain without an opioid use disorder (OUD) than those with pain and an OUD. This may reflect the psychological milieu of addiction and not the opioid.[39] The anesthesiology literature contains reviews which are favorable towards buprenorphine as an analgesic.[40]

The United States Department of Health And Humans Services monograph entitled "Pain Management Best Practices Inter Agency Task Force Report: Updates, Gaps, Inconsistencies and Recommendations" (May 2019) (*https://www.hhs. gov/ash/advisory committees/pain/reports/index.html;* accessed 2/24/2021) has the following recommendations (page 29):

> "Recommendation 4A: Buprenorphine treatment for chronic pain available for specific groups of patients and include buprenorphine in third-party payer and hospital formularies."

> "Recommendation 4B: Encourage CMS and private payers to provide coverage and reimbursement for buprenorphine treatment, both for OUD and for chronic pain. Encourage primary use of buprenorphine rather than use only after failure of standard me you agonist opioids such as hydrocodone or fentanyl, if clinically indicated."

> "Recommendation for CV: Encourage clinical trials using buprenorphine for chronic pain to better understand indications, usage and dosage."

The reasons for such a recommendation are described on page 25 of the committee report and are quoted here: "Buprenorphine, an opioid medication that the FDA has approved for clinical use, is a partial agonist at the mu opioid receptor and therefore has a reduced potential for respiratory depression; it is thus safer than full agonists such as morphine, hydrocodone, and oxycodone. Buprenorphine also acts as an antagonist at the kappa receptor, an effect shown in experimental studies to reduce anxiety, depression, and the unpleasantness of opioid withdrawal. Buprenorphine is widely used and encouraged for treating patients with OUD and is approved for the treatment of pain. In some states, there is a significant challenge, however, for prescribing clinicians to get authorization for using buprenorphine for chronic pain management (Section 2.2: Medication, Gap 4 and Recommendations)."

In regard to other comments, I would agree that naltrexone is a reasonable and perhaps safer choice for maintenance therapy than buprenorphine. I would agree that the addition of *any* benzodiazepine to *any* opioid is a hazardous practice. Buprenorphine can be abused, and universal precautions should be used if prescribed for pain.

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