Pain Management in Patients Taking Suboxone® / Subutex®

This letter is in response to your inquiry regarding pain management in patients maintained on Suboxone® (buprenorphine HCl and naloxone HCl dihydrate) or Subutex® (buprenorphine HCl). Subutex and Suboxone are indicated for the treatment of opioid dependence. Suboxone and Subutex are not approved for the treatment of pain. The information presented here is intended to aid in your assessment of the appropriate use of Suboxone or Subutex for your specific patient. This information should not be used to replace sound medical judgment, nor does it represent a recommendation or endorsement by Indivior.

Available Evidence
As buprenorphine is a partial agonist at the mu opioid receptor with a high affinity for this same receptor, pain management for patients who are maintained on Suboxone/Subutex may be perceived as problematic. While there are limited published data from case reports or formal clinical trials in this area, current recommendations from both the medical literature and clinical practice suggest that pain can be adequately managed if addressed pragmatically. A literature search on MEDLINE produced few results of clinical papers that offer practical solutions or guidance for the management of pain in patients maintained on buprenorphine for the treatment of opioid dependence. This letter focuses on a review of three papers; two of these focus specifically on patients taking buprenorphine and one on opioid dependent patients in general. These three papers provide clinical guidance for patients maintained on buprenorphine or other opioid agonists based on the authors clinical experience and theoretical considerations.

General principles Pain Management in Buprenorphine-maintenance Patients

There is a common assumption that doses of opioid analgesics used in the treatment of opioid dependence also provide analgesia. However due to the differing pharmacodynamic profiles of opioids for either analgesia or the treatment of opioid dependence, coupled with the fact that many patients develop tolerance to opioid effects and hyperalgesia, opioid analgesics used during dependency often do not achieve analgesic effects at their recommended doses.

The central concern regarding buprenorphine-maintained patients who require treatment for acute pain is the high affinity of buprenorphine for the mu-opioid receptor; higher than most
other clinically used opioids including morphine, methadone, and heroin. This means that not only will buprenorphine block the reinforcing effects of illicit opioids in a dose-dependent manner; \textit{theoretically} it may block the analgesic effect of opioids used for the management of pain. To achieve an analgesic effect in patients taking buprenorphine, it may be necessary to prescribe higher than usual doses of an opioid in order to achieve analgesia in opioid dependent patients.\textsuperscript{4} Such dosing practices can raise health safety risks not described in the approved labeling.

\textbf{Chronic pain}
Management of chronic pain in the patient maintained on Suboxone/Subutex should include consultation with a specialist in pain medicine when possible and appropriate. Patients with chronic pain disorders and opioid addiction may be best managed by multidisciplinary teams that include pain and addiction medicine specialists. Note that Suboxone and Subutex are only indicated for the treatment of opioid dependence (i.e., addiction); Suboxone and Subutex are not approved to treat pain.

\textbf{Acute pain}
The general principles for the management of acute pain for the patient maintained on Suboxone/Subutex include:

- Provision of adequate analgesia – taking into account the patient’s level of tolerance to opioids, and the increased risk of adverse events, such as respiratory depression, sedation and / or nausea at higher doses.
- Minimal disruption of opioid-dependence treatment to reduce the potential for withdrawal symptoms, craving, and ultimately relapse to illicit opioid use. In order to decrease anxiety, Alford et al (2006) suggest that patients be reassured that opioid addiction treatment will continue and pain will be aggressively treated.\textsuperscript{3}

The following pages contain a review of suggested strategies for the management of both anticipated and unanticipated pain as suggested in the featured clinical papers.

Sincerely,

Lars Petersen, MD,
External Medical Consultant, Indivior,

September 2016.
### Suggested pain management strategies as evidenced in the featured Literature

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Type of Pain &amp; Use</th>
<th>Details</th>
<th>Reported in</th>
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<tbody>
<tr>
<td>Non-opiate based analgesic medications (e.g., NSAIDs)</td>
<td>Anticipated Unanticipated</td>
<td>- If a patient is experiencing pain but it is not an emergency situation, pain may be treated with standard doses of a non-opioid medication such as non-steroidal anti-inflammatory drugs (NSAIDs) or acetaminophen. Non-pharmacologic methods of pain control, such as heat/cold therapy, acupuncture, massage, or meditation may also be suitable and of benefit for some patients.</td>
<td>Alford et al (2006) Rober ts</td>
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| Increase dose of buprenorphine                | Anticipated Unanticipated | - Depending on the dosage of buprenorphine an increase in the buprenorphine dose may produce an analgesic effect. A 25% increase in the total daily dose has been suggested.  
  - The addition of non-opioid medication may also provide supplemental analgesia CAUTION - The long-term safety of chronic administration of buprenorphine doses above 24 mg has not been established. Increased dosing may increase the risk of side effects such as respiratory depression, sedation and nausea. | Roberts et al (2005)             |
| Increase dosing frequency (split dosing)      | Anticipated Unanticipated | - Divide the daily buprenorphine dosage (as used for addiction treatment) and decrease the dosing interval (e.g., from once daily to every 6 hours or 4 times daily).  
  - Although buprenorphine is a potent analgesic, its analgesic profile is shorter (6-8 hours) than its profile for opioid-addiction treatment (24-48 hours).  
  - The addition of non-opioid medication to this regimen may also be of benefit. | Alford et al (2006)             |
| Titrate full-opioid agonist                   | Emergency Unanticipated | - In the case of unanticipated pain (e.g., secondary to trauma or medical emergency) full opioid agonists may be of use but require careful dose titration and close patient observation.  
  - Higher doses of a full agonist opioid may override the blockade caused by buprenorphine. Note - Currently there are no controlled studies to support that higher doses of a full opioid agonist will override buprenorphine blockade and produce an analgesic effect.  
  - The use of a rapidly acting opioid analgesic with a relatively short duration of action (to minimize the duration of potential respiratory depression) has been | Roberts et al (2005)             |
The dose of opioid medication should be titrated against the patient's analgesic and physiological (especially respiratory) responses.

**CAUTION** – Due to an individual's tolerance to opioids, the dose of the full opioid agonist required may be greater than usual. In order to ensure patient safety, close observation and monitoring by trained staff is essential.

- For a suggested dosing regimen, see Table 1, Roberts et al (2005) pg.22.

<table>
<thead>
<tr>
<th>Action</th>
<th>Anticipated/Unanticipated</th>
<th>Details</th>
<th>Source(s)</th>
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</table>
| Transfer to methadone or short acting opioid agonist | Anticipated               | - In anticipated or non-emergency situations where analgesia may be required (e.g., elective surgery, dental work) the buprenorphine dosage may be titrated down and supplemental full opioid agonists may be used for the duration of the analgesic need.  
  - Alternatively, completely withdraw the patient from buprenorphine and temporarily transfer to a full mu opioid agonist prior to the procedure.  
  - Some suggest that induction of a full opioid agonist can begin 24 hours after the last dose of buprenorphine.⁷ Commencing with a standard dose, the dosage of the full opioid agonist must first be titrated to suppress opioid withdrawal signs and symptoms and then titrated further to achieve the desired analgesic effect.  
  **CAUTION** - Care should be taken not to increase the dose of the full opioid agonist too quickly, as buprenorphine may diminish its effects for up to 72 hours after the last buprenorphine dose.⁸ Some recommend that any resulting opioid withdrawal symptoms occurring during this titration period should be managed symptomatically. | Alford et al (2006) |
| Regional anaesthesia / conscious sedation | Emergency Unanticipated   | - The use of regional anesthesia, conscious sedation, use of non-opioid analgesics, or general anesthesia until the opioid-blocking effects of buprenorphine have dissipated and typical opioid analgesia can be commenced. The use of regional anesthesia such as epidural blockade may also be considered in non-emergency situations. | Roberts et al (2005)  
<p>| AVOID use of mixed agonists-antagonist     | All                       | It is possible that those with mu-receptor antagonist may precipitate withdrawal in buprenorphine maintained individuals?                                                                                           | Alford et al (2006) |</p>
<table>
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<tr>
<th>Transfer back to SUBOXONE / SUBUTEX following resolution of pain</th>
<th>Roberts et al (2005)</th>
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| - After the need for analgesia subsides, some recommend that the buprenorphine dose may be titrated upwards until the desired clinical response is achieved.  
- The transition back to buprenorphine should be easier if a short-acting full opioid agonist is used.  
- In order to prevent precipitating an opioid withdrawal syndrome, ensure that observable signs of opioid withdrawal are present before re-induction onto buprenorphine. |
References:

1 Suboxone® (buprenorphine hydrochloride and naloxone hydrochloride dihydrate) and Subutex® (buprenorphine hydrochloride) product information, December 2015.


5 Mehta V & Langford RM. Acute pain management for opioid dependent patients. Anaesthesia. 2006; 61:269-276

