BRIEF REPORT

Buprenorphine Microdose Induction for the Management of Prescription Opioid Dependence

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Prescription opioid dependence remains a major source of morbidity and mortality in the United States. Patients previously on high-dose opioids may poorly tolerate opioid tapers. Current guidelines support the use of buprenorphine therapy in opioid-tapering protocols, even among patients without a diagnosis of opioid use disorder. Buprenorphine microinduction protocols can be used to transition patients to buprenorphine therapy without opioid withdrawal. From November 2019 to April 2020, we transitioned 8 patients on high-dose prescribed opioids for pain to sublingual buprenorphine-naloxone using a microdose protocol without any evidence of precipitated withdrawal. Six of these patients remain on buprenorphine-naloxone and report improved analgesia. Because of its simplicity, the buprenorphine microinduction protocol can be easily adapted for telemedicine and may help to prevent unnecessary clinic visits and opioid-related admissions in the setting of social distancing regulations during the coronavirus 2019 pandemic. (J Am Board Fam Med 2021;34:S141–S146.)

Keywords: Buprenorphine Naloxone, COVID-19, Opioid Addiction, Pain, Pandemics, Telemedicine

Background

Prescription opioid dependence remains a significant source of morbidity and mortality, with nearly 15,000 deaths attributable to prescription opioid overdose in 2018.1–3 Shared decision making regarding the risks and benefits of chronic opioid therapy and voluntary opioid tapering can help to mitigate opioid side effects.4,5 However, rapid or forced opioid tapering can destabilize patients and lead to opioid withdrawal and a loss of function, and some patients struggle with slow tapers.6,7

In the Centers for Disease Control and Prevention’s Guideline for Prescribing Opioids for Chronic Pain, Dowell et al.8 advocate for sublingual (SL) buprenorphine products for patients on prescription opioids who develop an opioid use disorder (OUD), but the authors did not explicitly recommend SLbuprenorphine as an alternative to tapering in patients with opioid dependence. Opioid dependence is the physiologic adaptation to chronic opioid use through the development of tolerance and withdrawal; OUD is characterized by craving, use despite consequences, loss of control, and compulsive use and is diagnosed using the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5).9 In 2019 Chou, Ballantyne, and Lembke10 argued for widespread use of SL buprenorphine as a complement to opioid tapering and to treat prescription opioid dependence, even in the absence of an OUD. Their rationale was that SL buprenorphine has important safety advantages, particularly in minimizing unintentional overdose and improved quality of life.10 This recommendation was further codified in the 2019 US Health and Human Services guidelines on opioid tapering and discontinuation.11

Buprenorphine is a partial agonist at the μ opioid receptor with high binding affinity and slow dissociation from the receptor.12 Low-dose transdermal and buccal buprenorphine products...
are Food and Drug Administration (FDA)
approved for chronic pain and are typically used
in opioid-naïve patients, whereas higher-dose SL
buprenorphine is FDA approved for OUD only
and considered off label for opioid dependence or
pain.\textsuperscript{10} The partial agonist effect has significant
safety benefits when compared with full agonist
opioids; buprenorphine products are unlikely to
cause respiratory arrest unless combined with
other central nervous system depressants.\textsuperscript{13}
Furthermore, buprenorphine has been hypothe-
sized to reverse opioid hyperalgesia, a common
and frustrating complication of long-term opioid
therapy.\textsuperscript{14}

Because buprenorphine has a higher binding af-
finity for the µ receptor than full agonist opioids,
immediately starting buprenorphine in a patient
taking full agonist will abruptly displace the full
agonist from the µ receptor, leading to precipitated
withdrawal. To avoid precipitated withdrawal,
during conventional buprenorphine inductions,
patients abstain from full agonist opioids until they
experience moderate to severe opioid withdrawal.
The conventional buprenorphine induction pro-
cess is a barrier to treatment for both patients and
providers.\textsuperscript{15} This is particularly true in patients
with chronic pain, who fear both withdrawal and
an increase in pain.\textsuperscript{16}

Buprenorphine microdose inductions were first
described by Hämmig in 2016 (the Bernese protocol)
and involve repetitive, low-dose exposure to bupre-
norphine over several days, such that partial and full
opioid agonists can be continued concurrently with-
out precipitated withdrawal.\textsuperscript{17} Buprenorphine micro-
induction can improve care of patients with OUD by
minimizing opioid withdrawal symptoms, reducing
the dropout rate during induction, and decreasing
fear of withdrawal.\textsuperscript{17} Microinductions have been
shown to be safe and effective in inpatient and outpa-
tient settings for patients with OUD.\textsuperscript{17–26} Less is
known about SL buprenorphine microinductions for
opioid-dependent patients on long-term opioid ther-
apy (LTOT) for chronic, noncancer pain.\textsuperscript{27} Here we
describe our experience using microdose buprenor-
phine inductions for patients with prescription opioid
dependence in an urban, academic general internal
medicine practice.

**Case Series**

From November 2019 to April 2020, providers com-
pleted 8 microdose buprenorphine inductions in
opioid dependent patients on LTOT using a modi-
fied Bernese protocol\textsuperscript{17} (Table 1). We adapted a
more gradual approach than the Bernese protocol,
and taper rather than abruptly stop full agonist
opioids, to improve patient acceptance of SL bupre-
norphine therapy\textsuperscript{27} (Table 2). Our protocol served as
a general guide for the microinduction process, with
minor variations in SL buprenorphine dosing and
speed of full agonist taper, depending on clinical cir-
cumstances. We used the SL buprenorphine-nalox-
one combination product unless otherwise stated.

The average patient age was 63 years, all were
white, and half were women. The insurance break-
down was 1 privately insured, 2 on Medicaid, 3
Medicare-Medicaid, and 2 Medicare only. The av-
erage morphine equivalent daily dose at the time of
microinduction was 127 mg, although many
patients had previously tapered from higher full
agonist doses. Physical and mental comorbidities
were common (Table 1). Two of the 8 patients met
the DSM-5 criteria for mild OUD at the time of
microinduction; the remaining 6 had opioid de-
pendence without an OUD.

All 8 patients tolerated SL buprenorphine
microinduction without precipitated withdrawal. Two patients were unable to remain on buprenor-
phine-naloxone because of side effects that per-
sisted after the induction phase and after tapering
full agonist opioids. These included oversedation
for 1 patient and persistent nausea for another. The
side effects did not abate despite dose reduction or
a trial of SL buprenorphine monoprodut. The 6
patients who successfully transitioned to SL bupre-
norphine reported stable to improved pain.

**Discussion**

Our institution has adopted a general dose limit for
LTOT of 90 morphine equivalent daily dose for
noncancer pain. Many patients are unable to taper
to this dose because of profound disruption of the
endogenous opioid system caused by years of exog-
enous high-dose opioids.\textsuperscript{28} For these patients with
opioid dependence, transition to SL buprenorphine
therapy is increasingly supported by federal guide-
lines and considered best practice.\textsuperscript{11} Patients and
providers in our primary care practice have readily
adopted the practice of SL buprenorphine microin-
ductions. The microinduction protocol has elimi-
nated concerns for precipitating opioid withdrawal.
<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (y)</th>
<th>Gender</th>
<th>Full Agonist Opioid at Time of Induction</th>
<th>MEDD (mg)</th>
<th>Substance Use Disorder (by DSM-V)</th>
<th>Psychological/Medical Comorbidity</th>
<th>Pain Generators</th>
<th>Maintenance SL Buprenorphine Dosage at 30 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>53</td>
<td>Female</td>
<td>Fentanyl 100 µg</td>
<td>240</td>
<td>None</td>
<td>Rheumatoid arthritis; paroxysmal atrial fibrillation, major depressive disorder</td>
<td>Rheumatoid arthritis</td>
<td>4 mg – 8 mg – 8 mg</td>
</tr>
<tr>
<td>2</td>
<td>67</td>
<td>Male</td>
<td>Hydrocodone/acetaminophen 10–325 mg 8 per day</td>
<td>80</td>
<td>None</td>
<td>None</td>
<td>Shoulder, knee, cervical, lumbar osteoarthritis</td>
<td>Not applicable; unable to tolerate buprenorphine 2 mg due to oversedation; back on full agonist at previous dose</td>
</tr>
<tr>
<td>3</td>
<td>69</td>
<td>Male</td>
<td>Oxycodone 30 mg 5 times per day</td>
<td>225</td>
<td>Benzodiazepine use disorder, mild</td>
<td>Major depressive disorder, hypogonadism, paroxysmal atrial fibrillation</td>
<td>Failed back surgery syndrome</td>
<td>8 mg 3 times daily and continues on oxycodone 15 mg 3 times daily on slow taper</td>
</tr>
<tr>
<td>4</td>
<td>62</td>
<td>Female</td>
<td>Oxycodone 10 mg 5 times per day</td>
<td>75</td>
<td>Alcohol use disorder, moderate</td>
<td>Bipolar 2 disorder</td>
<td>Chronic pancreatitis, chronic abdominal pain</td>
<td>Not applicable; unable to tolerate buprenorphine due to nausea; switched back to full agonist, slowly tapering</td>
</tr>
<tr>
<td>5</td>
<td>63</td>
<td>Female</td>
<td>Methadone 10 mg twice daily; hydromorphone 2 mg 4 times daily</td>
<td>92</td>
<td>Opioid use disorder, mild</td>
<td>Major depressive disorder, adrenal insufficiency, benzodiazepine dependence</td>
<td>Fibromyalgia, knee osteoarthritis</td>
<td>4 mg 4 times daily</td>
</tr>
<tr>
<td>6</td>
<td>67</td>
<td>Male</td>
<td>Hydromorphone 4 mg 5 times daily; morphine extended release 15 mg daily</td>
<td>95</td>
<td>Opioid use disorder, mild</td>
<td>Parkinson’s disease, severe odynophagia</td>
<td>Multiple orthopedic surgeries, Parkinson’s disease</td>
<td>8 mg 3 times daily</td>
</tr>
<tr>
<td>7</td>
<td>70</td>
<td>Female</td>
<td>Morphine extended release 30 mg twice daily; morphine immediate release 15 mg 3 times daily</td>
<td>105</td>
<td>None</td>
<td>Major depressive disorder</td>
<td>Neuropathy, fibromyalgia, knee osteoarthritis</td>
<td>8 mg 3 times daily</td>
</tr>
<tr>
<td>8</td>
<td>53</td>
<td>Male</td>
<td>Oxycodone 10 mg 7 times daily</td>
<td>105</td>
<td>None</td>
<td>Ischemic heart failure, uncontrolled type 2 diabetes mellitus</td>
<td>Chronic leg wounds, lumbar spine osteoarthritis</td>
<td>8 mg twice daily</td>
</tr>
</tbody>
</table>

DSM-5, *Diagnostic and Statistical Manual of Mental Disorders*, fifth edition; MEDD, morphine equivalent daily dose.
during standard induction, which is a well-documented barrier to the use of buprenorphine.29

In our practice, patients on LTOT are often older with significant medical and psychiatric comorbidities and can be resistant to medication changes. Unlike other SL buprenorphine microinduction protocols for patients on LTOT, we choose to taper full agonist opioids by no faster than 25% a week after buprenorphine is initiated, rather than abruptly stopping opioids.27 A tad of SL buprenorphine, 90% of the μ receptors are occupied, and it is unlikely that discontinuing full agonist opioids after microinduction would lead to significant opioid withdrawal.30 Our approach recognizes the emotional distress and emotional pain that can accompany changes to opioid homeostasis, a concept referred to as hyperkatifeia.31 We found that engaging in shared decision making about the speed of the full agonist opioid taper after initiating SL buprenorphine has increased acceptance of therapy and makes this transition more tolerable.

In the setting of the coronavirus 2019 (COVID-19) pandemic, our practice minimized in-person visits and shifted clinical care to telephone or video visits, and some staff and providers have been redeployed to respiratory clinics. Conventional SL buprenorphine inductions can involve significant time commitments from providers and ancillary staff, including the active management of opioid withdrawal and daily titration of SL buprenorphine after home or office induction.29 Buprenorphine microinduction is well suited for telemedicine; in-person follow-up needs are minimal and can be addressed via phone or video visits. Opioid overdoses have increased during COVID-19,32 and there is an increasing call for low-barrier SL telebuprenorphine that has been facilitated by temporary changes in regulatory standards, which allow initiation of SL buprenorphine telephonically without an initial in-person visit.33–35

Table 2. Outpatient Microinduction Protocol Using Sublingual 2 mg Buprenorphine/Naloxone Tablets or Films

<table>
<thead>
<tr>
<th>Day</th>
<th>Bup/Nlx Dose and Frequency</th>
<th>Full Agonist Opioid</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.5 mg daily (1/4 tablet or film)</td>
<td>No change</td>
</tr>
<tr>
<td>2</td>
<td>0.5 mg BID</td>
<td>No change</td>
</tr>
<tr>
<td>3</td>
<td>1 mg BID (half-tablet or film)</td>
<td>No change</td>
</tr>
<tr>
<td>4</td>
<td>2 mg BID</td>
<td>No change</td>
</tr>
<tr>
<td>5</td>
<td>2 mg TID</td>
<td>No change</td>
</tr>
<tr>
<td>6</td>
<td>4 mg TID</td>
<td>No change</td>
</tr>
<tr>
<td>7 and beyond</td>
<td>Per provider discretion</td>
<td>Taper by 25% weekly</td>
</tr>
</tbody>
</table>

Bup, Buprenorphine; Nlx, naloxone; BID, twice a day; TID, twice a day.

Conclusions

Microdose buprenorphine inductions have been well tolerated in opioid-dependent patients in a general internal medicine outpatient practice. Our case series adds to a growing body of evidence that SL buprenorphine microinduction is safe and feasible in diverse practice settings and populations. Despite the absence of randomized or case-controlled trials, we believe that microdose buprenorphine inductions should be offered to patients on LTOT who meet clinical criteria for a transition to SL buprenorphine therapy. This technique is low risk and can greatly reduce unnecessary suffering in the form of opioid withdrawal. Importantly, the FDA indication for high-dose SL buprenorphine products should expand to opioid dependence to reflect current guidelines. Buprenorphine microinductions are well suited for telemedicine and virtual care, which has important applications during the COVID-19 pandemic.

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References


