

Utilizing buprenorphine–naloxone to treat illicit and prescription-opioid dependence

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Objectives: To review current evidence on buprenorphine–naloxone (bup/nx) for the treatment of opioid-use disorders, with a focus on strategies for clinical management and office-based patient care.

Quality of evidence: Medline and the Cochrane Database of Systematic Reviews were searched. Consensus reports, guidelines published, and other authoritative sources were also included in this review. Apart from expert guidelines, data included in this review constitute level 1 evidence.

Findings: Bup/nx is a partial μ -opioid agonist combined with the opioid antagonist naloxone in a 4:1 ratio. It has a lower abuse potential, carries less stigma, and allows for more flexibility than methadone. Bup/nx is indicated for both inpatient and ambulatory medically assisted withdrawal (acute detoxification) and long-term substitution treatment (maintenance) of patients who have a mild-to-moderate physical dependence. A stepwise long-term substitution treatment with regular monitoring and follow-up assessment is usually preferred, as it has better outcomes in reducing illicit opioid use, minimizing concomitant risks such as human immunodeficiency virus and hepatitis C transmission, retaining patients in treatment and improving global functioning.

Conclusion: Bup/nx is safe and effective for opioid detoxification and substitution treatment. Its unique pharmaceutical properties make it particularly suitable for office-based maintenance treatment of opioid-use disorder.

Keywords: Zubsolv, Suboxone, methadone, opiate detoxification, opiate substitution, clinical management

Introduction

Dependence on opioids is a major health issue worldwide. The costs associated with opioid dependence are extensive, exacting an enormous toll in terms of health care, mental illness, quality of life, unemployment, and crime. Concomitant risks include the transmission of the human immunodeficiency virus (HIV), hepatitis B virus, hepatitis C virus (HCV), and tuberculosis, as well as a high incidence of death due to respiratory depression and overdose.^{1–6} It is well recognized that the abuse of prescription opioids is on the rise in North America as well as Australia and New Zealand.^{6–9} In numerous street-drug populations in both the US and Canada, prescription opioids have replaced heroin as the main opioid of choice.^{2,10} Moreover, US medical emergencies related to opioid misuse increased by 183% between 2004 and 2011.¹¹

Given the high medical and psychiatric comorbidities associated with opioid abuse, both primary care physicians and mental health specialists are regularly confronted with the sequelae of prescription and illicit opioid dependence.^{12,13} Pharmacological

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substitution therapies, including buprenorphine and methadone, have been shown to be more effective than any other type of treatment for opioid dependence, particularly when used in combination with psychosocial interventions.¹⁴ Methadone, which is often administered through specialized licensed opioid-treatment programs, has been the standard of care for illicit opioid dependence for the past 40 years, particularly in the US. However, the lack of global access to specialized methadone clinics, strict regulations, long waiting lists, and stigma often discourage patients from enrolling in substitution treatment.^{15–17} In Europe, buprenorphine (Subutex) was introduced widely in primary care facilities as an alternative to methadone for the treatment of opioid dependence, with demonstrated success.^{18,19} Prescription opioid-dependent patients in particular may be amenable to treatment in primary care or office-based practice rather than specialized addiction-treatment centers. They appear to be younger and of higher socioeconomic status, with a lower prevalence of HCV infection, fewer years of opioid use, and fewer prior addiction-treatment episodes compared to patients receiving treatment for illicit opioid dependence.²⁰

In the US, buprenorphine and buprenorphine–naloxone (bup/nx) were approved by the US Food and Drug Administration (FDA) in 2002, offering an office-based maintenance treatment for opioid dependence.^{21–23} Like methadone, buprenorphine and bup/nx substitution treatment have been shown to decrease hospital admissions, morbidity, and mortality.^{24–26} Moreover, buprenorphine is associated with lower risk of overdose and diversion, thereby offering more flexibility to both physicians and patients.^{12,27} The combination of buprenorphine with the opiate antagonist naloxone (bup/nx) demonstrates the same benefits as buprenorphine alone, with the added benefit of further reducing potential misuse.

Considering its safety profile, as well as its diminished abuse potential, bup/nx constitutes a promising alternative therapy for opioid dependence that could be used by general medical and mental health practitioners, thereby increasing access to substitution treatment. However, evidence is accumulating at a rapid pace, making it challenging for physicians unfamiliar with this topic to obtain the appropriate knowledge. In order to counteract barriers to the drug's clinical use, this article was designed as a comprehensive review of the literature surrounding the use of bup/nx in the treatment of illicit and prescription-opioid dependence.

Quality of evidence

A Cochrane Database of Systematic Reviews and Medline search on Ovid of all published articles identified with the

keyword “buprenorphine” was conducted as of June 2013, limiting the search to human studies published in English. It yielded a total of 2,160 potential articles. Studies related to pain control were eliminated. Subsequently, all other abstracts were reviewed, and relevant studies with adequate methodology, including randomized controlled trials, meta-analyses, and systematic reviews, were selected and reviewed in depth. Consensus reports and guidelines published by the Center for Substance Abuse Treatment, the Royal Australian College of Physicians, the Centre for Addiction and Mental Health, the Community Care Behavioral Health Organization, the American Society of Addiction Medicine, and the World Health Organization were also included in this review. Apart from expert guidelines, data included in this review constitute level 1 evidence.

Pharmacology/pharmacokinetics Buprenorphine

Originally developed for pain treatment, buprenorphine is a semi-synthetic derivative of the opioid thebaine. Buprenorphine has a mixed agonist–antagonist action on opioid receptors: it acts as a partial agonist at the μ -receptor and as an antagonist at the κ -receptor.^{28,29} As a partial agonist with low intrinsic activity, it produces milder and less euphoric and sedating opioid effects while still occupying opioid receptors, thus preventing withdrawal in dependent patients.³⁰ There is also a “ceiling effect,” in which the agonist properties increase linearly up to a maximum of 16–32 mg daily, followed by a plateau, in which further increases in dosage produce no pharmacological effects.^{29,31} As a result, the intensity of the rewarding effects is milder than other full μ -opioid agonists at higher doses, and the risk of abuse as well as respiratory depression is lower.^{30,32}

Buprenorphine has a higher affinity for the μ -receptor than other opioids, such as heroin, so it reduces the effects of full agonists and can in fact precipitate withdrawal symptoms in those actively using other opioids.^{33–35} This high affinity combined with a slow dissociation from the μ -receptor also results in milder withdrawal symptoms upon discontinuation compared to methadone and other opioids.^{36–38}

Sublingual buprenorphine has a long half-life (24–60 hours, mean 37 hours), and it is highly bound to plasma proteins (96%). It has poor oral bioavailability, because it is inactivated by gastric acid and undergoes significant first-pass metabolism in the liver. It is metabolized by cytochrome P450 (CYP) 3A4 to various metabolites, including the active norbuprenorphine.^{28,32} Peak plasma concentrations are achieved in 90–150 minutes following

administration, and the μ -receptor blockade can last for 3–5 days due to the slow dissociation from the receptor, allowing for the possibility of alternate-day dosing.³⁹

Buprenorphine–naloxone (Suboxone)

Suboxone® (Reckitt Benckiser Pharmaceuticals Inc., Richmond, VA, USA) is formulated as a combination of buprenorphine with the opiate antagonist naloxone in a 4:1 ratio. Naloxone binds tightly to the opioid receptor without producing a euphoric effect, thereby blocking or reversing the psychoactive effects of partial- or full-opioid agonists.⁴⁰ Naloxone has poor bioavailability in the sublingual form; therefore, it does not alter buprenorphine's properties when the medication is taken as prescribed.^{28,41} If bup/nx is injected, however, sufficient naloxone is absorbed to precipitate acute withdrawal in opiate-dependent users, thus discouraging further abuse via the intravenous route of administration.^{40,42,43}

Dosing and formulation

Bup/nx is available sublingually in tablet (Zubsolv® [Orexo AB with AAIPharma, Wilmington, NC, USA] and generic)

or film formulation (Suboxone). The Suboxone film is offered in bup/nx doses of 2/0.5 mg, 4/1 mg, 8/2 mg, and 12/3 mg, while the generic tablet only exists in doses of 2/0.5 mg and 8/2 mg. Zubsolv, a new sublingual tablet with higher bioavailability, received FDA approval in July 2013, and is distributed in 1.4/0.36 mg and 5.7/1.4 dosages.⁴⁴ All formulations and dosage strengths can be dispensed in the US for take-home use by prescription. Bup/nx is formulated as a combination of buprenorphine with the opiate antagonist naloxone in a 4:1 ratio. Bup/nx doses will be stated in terms of mg buprenorphine in the text below, as well as in the figures.

The target dose for maintenance therapy is usually 16 mg buprenorphine per day, although most recent guidelines favor an individualized approach with no specific dose or range recommendations. In both inpatient and outpatient settings, the therapeutic goal is to find the lowest dose to eliminate illicit opioid use, reduce withdrawal symptoms, and improve treatment retention.³⁴ The final maintenance dose is likely to be in the range of 4–24 mg buprenorphine per day.⁴⁵ Due to the ceiling effect, there is no added benefit of increasing the daily dose above 32 mg per day.^{29,31}

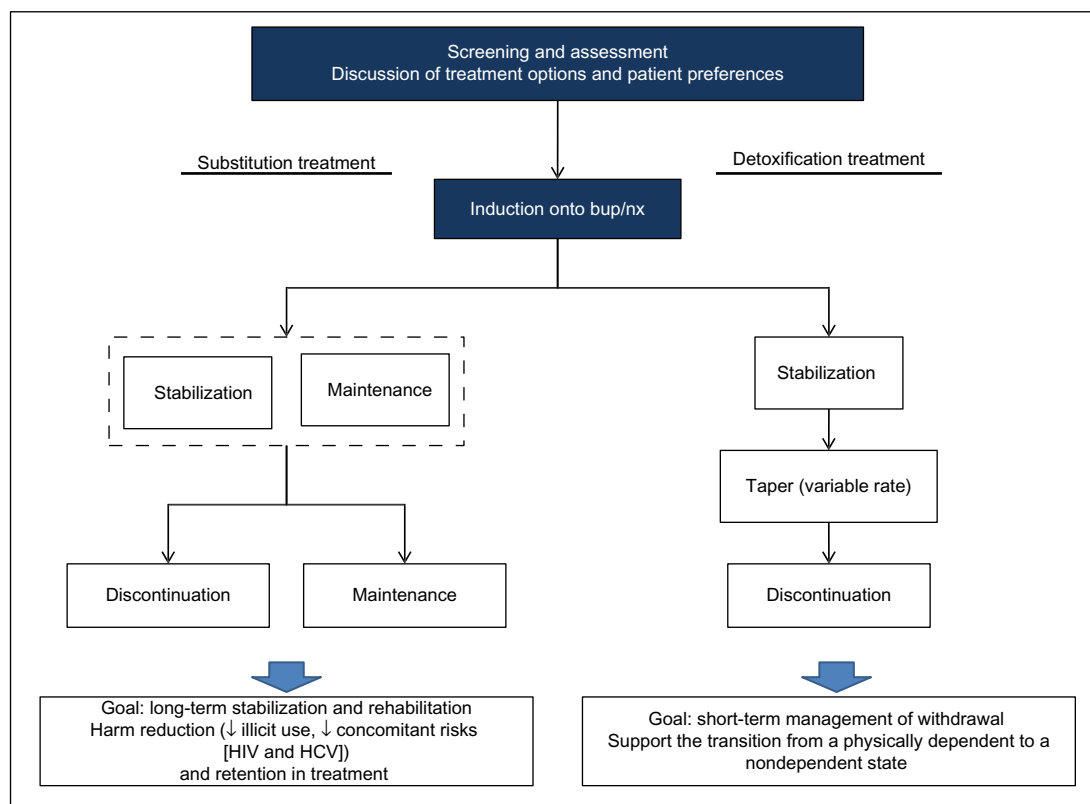


Figure 1 Clinical management: opioid substitution versus acute detoxification.

Abbreviations: Bup/nx, buprenorphine–naloxone; HIV, human immunodeficiency virus; HCV, hepatitis C virus.

Strategy for clinical management

There are two general approaches to the medical treatment of opioid addiction: medically supervised detoxification and opioid-substitution treatment (Figure 1). Bup/nx is indicated for both acute detoxification and long-term substitution among patients who have a mild-to-moderate physical dependence on opioids.⁴⁵ All treatment options can be carried out in an inpatient or ambulatory setting.³⁴ In medical detoxification, bup/nx is used as replacement therapy to help support the transition from a physically dependent to a nondependent state. Although it can sometimes lead to total abstinence, it has a low success rate and relapse rates are high.^{46–48} Younger patients who are only dependent on oral opioids, with a short history of dependence, a good support system, and no significant psychiatric comorbidities, have a better prognosis with this approach.³³

Among chronic intravenous drug users, opioid substitution is usually the preferred treatment approach. Substitution or maintenance treatment refers to the long-term use of a long-acting opioid (eg, bup/nx) with graduated take-home doses to manage opioid dependence. The goal is to reduce illicit opioid use and injection behavior, minimize concomitant risks such as HIV and HCV infection, and retain patients in treatment.^{34,49,50} Long-term substitution treatment has better outcomes than medically supervised detoxification, and should be considered within the context of a harm-reduction approach.⁵¹

As shown in Figure 1, treatment is initiated with a thorough screening and assessment of opioid dependence, including a discussion of available treatment options and patient preferences. This is followed by an induction phase, in which patients are transferred from their opioid of abuse to bup/nx. Details related to assessment, induction, stabilization, maintenance, and detoxification are provided in the following sections.

Screening and assessment

The initial screening and assessment should include comprehensive medical, psychiatric, and psychosocial evaluations in order to confirm a diagnosis of opioid dependence.⁴⁵ The decision to initiate either medical detoxification or long-term substitution treatment should be guided by the severity of dependence, prior treatment history, and the patient's preferences. Assessment of addiction severity is essential, as it will guide buprenorphine dosing and treatment needs, including potential risk of diversion. Consideration should be given to the time since the last opioid dose, the type of opioid used (long- versus short-acting), and the degree of physical dependence.⁵² Due to opioid dependence, comorbidities and potential side effects of bup/nx, a pregnancy test, baseline liver enzymes, and HCV, Hepatitis B virus (HBV), and HIV testing are recommended prior to induction.³³

Table I Induction onto bup/nx for short-, long-, and ultralong-acting opioids

	Short-acting (eg, heroin, oxycodone)	Long-acting (eg, morphine, OxyContin®)	Ultralong-acting (eg, methadone)
Stage I: Early withdrawal – Fear of withdrawal, anxiety, craving	4–6 hours	8–12 hours	12–24 hours
Stage II: Mid-withdrawal – Insomnia, restlessness, anxiety, yawning, stomach cramps, lacrimation, rhinorrhea, diaphoresis, mydriasis	8–12 hours	12–24 hours	36–72 hours
Stage III: Late withdrawal – Diarrhea, vomiting, fever, chills, piloerection, muscle spasms, tremor, tachycardia, and hypertension	24–72 hours	48–72 hours	72–96 hours
Induction onto bup/nx	<ol style="list-style-type: none"> Switch to bup/nx 12–24 hours from last dose when in moderate withdrawal (COWS >12) The goal is to reach a target dose of 12–16 mg buprenorphine during the first week 	<ol style="list-style-type: none"> Switch to bup/nx 18–36 hours from last dose, when in moderate withdrawal (COWS >12) OR <ol style="list-style-type: none"> Switch to equivalent dose of short-acting opiate Maintain dose × 3 days, Switch to bup/nx as per short-acting opiates 	<ol style="list-style-type: none"> Taper methadone dose to 30 mg/day Maintain 30 mg/day × 5–7 days Switch to bup/nx >24 hours after last dose, when in moderate withdrawal (COWS >12)

Note: Sources of data: Kosten and O'Connor,⁵⁵ Dijkstra et al,⁵⁶ and Farrell.⁵⁷

Abbreviations: Bup/nx, buprenorphine–naloxone; COWS, Clinical Opioid Withdrawal Scale.

Induction phase

Bup/nx induction entails titration over 1–3 days until a comfortable level is reached. Patients can be started on bup/nx 6–24 hours after the last opiate dose, when they develop objective signs of spontaneous withdrawal.^{28,45,53,54} As shown in Table 1, cravings usually begin 4–6 hours after the last dose of a short-acting opioid, and the withdrawal pattern is delayed with ultralong-acting opioids, such as methadone. The main features of opioid withdrawal are nausea, vomiting, diaphoresis, yawning, fatigue, aches and pain, diarrhea, mydriasis, and piloerection.⁵⁷ Subjective symptoms are much greater than objective signs, and weak withdrawal discomfort is usually experienced after 36–72 hours and decreases thereafter.^{57,58} In theory (and practice), administration of a partial opioid agonist (bup/nx) exerts the least antagonistic effect when the patient is experiencing mild-to-moderate withdrawal symptoms.³² If the patient is not in sufficient withdrawal when the first dose of bup/nx is administered, buprenorphine will displace the full-opioid agonist (eg, heroin) and intensify rather than relieve withdrawal symptoms (precipitated withdrawal). If precipitated withdrawal occurs, patients will experience intensified withdrawal symptoms after the first induction dose.^{32–35} Validated assessment tools, such as the Clinical Opioid Withdrawal Scale (scores >12) and the Clinical Institute Narcotic Assessment can be used to ensure that patients are in moderate withdrawal prior to bup/nx induction.⁵⁹

The initial dose is 2–4 mg buprenorphine, which is increased based on clinical symptoms up to a total first-day

dose of 8 mg.²⁸ The goal is to reach the target dose of 12–16 mg buprenorphine during the first week.³⁴ A recent retrospective chart-review study (n=40) suggested that more rapid buprenorphine initiation up to 16 mg on the first day was well tolerated.⁶⁰ As indicated in Table 1, prior to induction onto bup/nx, it is possible to substitute long-acting opioids with an equivalent dose of a short-acting medication. Table 2 provides an approximate equivalency among the various opioids and routes of administration.⁶¹ However, clinicians must be aware that equivalency tables have not been developed for chronic (tolerant) opioid-dependent populations, and the information in Table 2 must therefore be employed with clinical judgment. Extrapolating from Mattick et al, 6–12 mg buprenorphine would correspond roughly to 35–60 mg of methadone.⁶²

Induction is one of the most critical phases of bup/nx treatment. A detailed chart indicating the procedures and decision points during the first day of bup/nx induction is provided in Figure 2. An association has been established between difficult induction (strong withdrawal symptoms and cravings) and poorer treatment retention and outcome.^{63–65} Evidence also suggests that increasing the induction dose more rapidly is associated with better treatment outcome.⁶⁶ Therefore, patients should be observed regularly during the induction period to exclude precipitated withdrawal, signs of overmedication (eg, sedation) or unwanted side effects, and to confirm the effectiveness of the dose at suppressing withdrawal symptoms.^{34,58} Current guidelines recommend direct observation of initial dosage of bup/nx for 2–4 hours, with a series of subsequent visits for dose adjustments.^{34,45,67,68} Observed induction can, however, present significant challenges to many office-based practitioners, and as an alternative, “home” or unobserved induction has been proposed. Evidence supporting this practice is accumulating, but further research is still needed to confirm the feasibility and safety of this innovative treatment approach.^{13,68–71} To favor compliance, initial prescription of bup/nx can be written daily in order to provide supervised medication dispensing.⁷²

Note that a bup/nx combination can be used for induction treatment in most patients. However, pregnant women and patients who are on ultralong-acting opioids (eg, methadone) should be induced using buprenorphine monotherapy^{45,73} instead of bup/nx. The transition from methadone to buprenorphine is gaining popularity, due to a more flexible outpatient setting, safer side-effect profile, and lower potential for misuse and abuse.^{74–77} However, concerns about the possibility of inducing significant withdrawal during the

Table 2 Approximate opioid equivalencies compared with 10 mg of IV morphine

Generic name	Potency ratio (in IV morphine equivalent)	Equivalent doses (mg) ^a
Fentanyl	100–200	0.05–0.1
Hydromorphone IV	5	1.5
Heroin	1–2	5–10
Hydromorphone PO	1.3	7.5
Morphine IV	1	10
Methadone PO	0.5	20
Oxycodone PO	0.5	20
Morphine PO	0.5	20–30
Meperidine IM	0.13	75
Codeine PO	0.05	200
Meperidine PO	0.03	300

Notes: ^aEquivalencies are approximate, and should be used with clinical judgment; clinicians must be particularly careful when the total equivalent opioid dose is more than 100 mg of methadone. Data source: Ducharme et al.⁶¹ Table originally published in *Canadian Family Physician* and reprinted with permission. Copyright © 2012.

Abbreviations: IM, intramuscular; IV, intravenous; PO, per os.

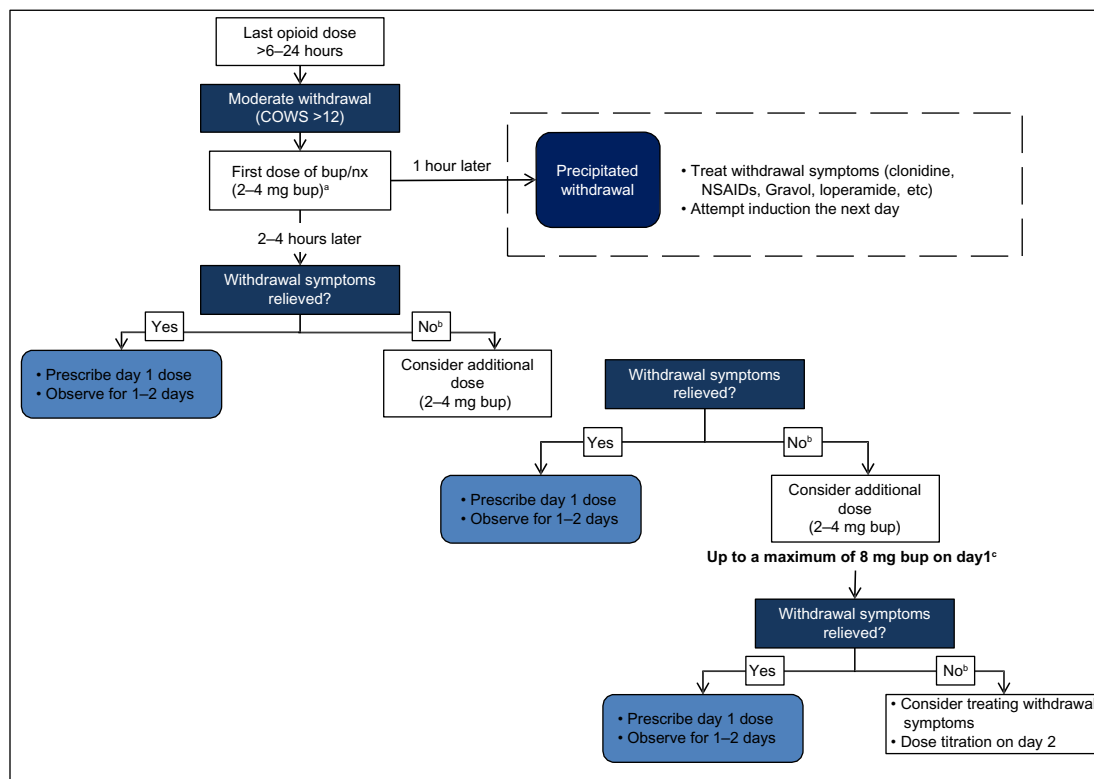


Figure 2 Bup/nx induction (day 1).

Notes: ^aUse higher dose (4 mg bup) in patients in severe withdrawal; ^bno improvement in withdrawal symptoms or persisting signs of mild-to-moderate withdrawal (COWS >4); ^cGunderson et al⁶⁰ suggests going up to 16 mg on the first day. Data sources: Center of Addiction and Mental Health,³³ Substance Abuse and Mental Health Services Administration,³⁴ Community Care Behavioral Health Organization,⁴⁵ Tompkins et al,⁵⁹ Gunderson et al,⁶⁰ and Kraus et al.⁷³

Abbreviations: Bup/nx, buprenorphine–naloxone; COWS, Clinical Opioid Withdrawal Scale; NSAIDs, nonsteroidal anti-inflammatory drugs; bup, buprenorphine.

induction procedure limit the practice.^{78,79} Prior to the transition to buprenorphine, methadone dose should be gradually tapered to 30–40 mg per day and maintained at this dose or lower for at least 5–7 days. The patient should then discontinue methadone for 48–72 hours prior to receiving the first dose of buprenorphine.⁴⁵

Stabilization and maintenance

Stabilization begins when the patient is no longer having withdrawal symptoms or cravings and there are minimal side effects from bup/nx. The goal is to find the minimum dose that eliminates withdrawal symptoms, prevents other opioid use, decreases cravings, and improves psychosocial functioning (the maintenance dose).^{80,81} As each patient must be dosed individually, medication adjustment can take up to 1–2 months (7–14 days in acute detoxification), with slow increments/decrements every 5–7 days achieved through weekly contact with the patient during early stabilization. The Suboxone manufacturer recommends that dosing be observed for the first 2 months, even though this treatment protocol is not always possible in clinical practice. Relapse should be ruled out when a stable patient's dosing requirements change suddenly.^{45,54}

During the maintenance phase, moderate-to-high doses (8–16 mg buprenorphine) have been shown to be significantly more efficacious than low doses (1–4 mg buprenorphine).^{62,82,83} Although the maximum recommended dose by the Suboxone manufacturer is 24 mg, doses of up to 32 mg have been used in some trials.⁸⁴ A recent observational retrospective chart-review study showed that using a flexible dosing schedule with the option of titrating the dose up to 32 mg offered better treatment outcomes, especially for patients who did not respond to lower doses.⁸⁵

The optimum duration of maintenance is unclear, but it may involve long-term or even lifetime medication use.⁸⁶ Patients who were induced with buprenorphine for the transition from methadone to bup/nx should be switched to bup/nx for maintenance once transition is complete.³⁴ An alternate-day dosing schedule of bup/nx is possible, and this may be preferred or better tolerated by some patients.^{34,45} The weekly dose can then be divided by the number of days of dosing (eg, double dose for alternate days). Routine urine toxicology screens can be utilized to assess bup/nx compliance and detect the use of other prescribed, undisclosed, or illicit substances (eg, alcohol, benzodiazepines, morphine, oxycodone, etc), although evidence for the cost-effectiveness of urine testing is weak.⁷² On-site dispensing

or observed taking of bup/nx is indicated until the patient has a negative urine screen or is compliant with treatment.⁴⁵

Discontinuation (detoxification)

In medically supervised withdrawal, reaching an opioid-free state is the ultimate goal of treatment, and discontinuation can also be considered for patients on long-term maintenance treatment. However, tapering off or cessation of bup/nx should only be considered for patients who are motivated to discontinue, have a stable income and housing arrangements, and have adequate psychosocial support.³⁴ Dose-reduction protocols range from 3 days (short), 10–14 days (moderate), to months (long).^{34,45,73} Initial studies yielded conflicting results about the optimal duration of the taper.^{87–89} A recent large randomized trial demonstrated that after a month of stabilization on Suboxone treatment, a 7-day taper was equivalent to a 28-day taper in terms of the number of opioid-free urine samples.⁹⁰ Conversely, another comparative study suggested that a 30-day taper enhanced participation in longer-term treatment compared with a 5-day taper.⁹¹ Recent guidelines suggest a gradual bup/nx discontinuation with a taper of no more than 2 mg every 5–7 days.^{33,34,73} It is important to assess

the patient regularly during the discontinuation process. If withdrawal symptoms emerge as the dose is decreased, the taper can be temporarily suspended.³⁴ Medications commonly used to alleviate withdrawal symptoms are presented in Table 3. Following completion of the taper, naltrexone, an opioid-receptor antagonist that blocks the euphoric effects of opioids, can also be used to minimize the risk of relapse to opioid abuse.⁹²

Integrated multidisciplinary approach

A purely pharmacological approach to medication-assisted recovery is rarely sufficient.⁹³ The goals of psychosocial interventions (counseling, self-help groups, and rehabilitation programs) are to engage patients in the process of change and retain them in treatment long enough to improve global functioning and quality of life. Contingency-management techniques that use motivational incentives to condition or influence behaviors (eg, receiving a “voucher” with monetary value for negative urine-toxicology screening), have been found to help in initiating and maintaining abstinence among addiction patients.⁹⁴ These resources are available in structured treatment programs as well as in the community.

The outcome of bup/nx treatment is best when combined with psychosocial counseling, prevention education, and recovery-support services.^{67,95–97} The best evidence to support the value of a multidisciplinary approach in the treatment of opioid addiction comes from a Cochrane review by Amato et al.¹⁴ This meta-analysis included eleven studies and evaluated five different psychosocial interventions and two pharmaceutical treatments (buprenorphine and methadone). The combination of pharmacological and psychosocial treatment was significantly superior in reducing dropout rates (relative risk [RR] 0.71), decreasing relapses or use of full agonist opioids (RR 0.82), and improving treatment compliance in terms of follow-up visits (RR 0.48). Currently, there are no data supporting a specific type of psychosocial approach. Despite limited evidence, most clinicians feel that bup/nx treatment should be accompanied by voluntary psychosocial counseling, participation in formal treatment programs and/or attendance at mutual aid groups, such as Narcotics Anonymous.^{14,86}

Patient-focused perspectives

Bup/nx is usually well tolerated. It is a safe pharmacological treatment, with expected side effects of sedation, constipation, headache, nausea/vomiting, and dizziness. It has a lower risk of respiratory depression than full agonists, and

Table 3 Symptomatic treatment of opioid withdrawal

Withdrawal symptoms	Somatic treatment	Dosing
Nausea and vomiting	→ Dimenhydrinate (Gravol®)	50–100 mg PO/IM q4h prn
	→ Prochlorperazine (Stemetil®)	5–10 mg PO q4h prn
Diarrhea	→ Loperamide (Imodium®)	4 mg PO for diarrhea, then 2 mg PO prn (max: 16 mg/24 hr)
Myalgia	→ Acetaminophen (Tylenol®)	325–650 mg PO q4h prn (max: 4,000 g/24 hr)
	→ Naproxen (Naprosyn®)	500 mg PO bid × 4 days, then prn
Anxiety, dysphoria, lacrimation, rhinorrhea	→ Hydroxyzine (Atarax®)	25–50 mg PO tid prn
Insomnia	→ Trazodone (Trazorel®)	50–100 mg PO qhs × 4 days, then prn
↓ Sympathetic drive (tachycardia, hypertension), diaphoresis, restlessness	→ Clonidine (Nexiclon®) ^a	0.1 mg PO qid × 4 days, then ^b 0.05 mg PO qid × 2 days, then 0.025 mg PO qid, then stop

Notes: ^aMonitor blood pressure prior to each dose, as clonidine may cause hypotension; ^bif <91 kg (200 lb) (doses need to be higher if >91 kg). Data source: Kosten and O'Connor⁵⁵ and Kleber et al.⁹²

Abbreviations: PO, per os; IM, intramuscular; q4h, quaque 4 hora (every 4 hours); prn, pro re nata (as needed); bid, bis in die (twice a day); tid, ter in die (three times a day); qhs, quaque hora somni (every night at bedtime); qid, quater in die (four times a day); max, maximum; hr, hours.

is associated with less QTc prolongation than methadone.^{98,99} Liver-function tests should be periodically monitored.^{28,100}

Many of the randomized trials on buprenorphine did not examine tolerability. In a 4-week randomized double-blind phase of a 52-week study comparing the efficacy of bup/nx with placebo, the most frequently reported adverse events were headache, withdrawal symptoms, pain, nausea, insomnia, and sweating. No serious treatment-related adverse events have been reported, except increases in hepatic alanine aminotransferase and aspartate aminotransferase.¹⁰¹ These are all expected side effects of bup/nx.

Bup/nx is sometimes favored because it carries less stigma than methadone. Patients also appear to prefer bup/nx due to its more flexible administration schedule, which enables office-based treatment and allows lower clinic-attendance requirements for medication dispensing and carry-outs.¹⁰² The main barrier to using bup/nx is its high cost, especially when compared to methadone.^{24,62,103} Moreover, buprenorphine programs tailored for marginalized populations with unstable lifestyles and greater risk of comorbidities and infectious disease transmission are currently limited.⁷³

Special populations

Hepatitis and liver disease

Buprenorphine is contraindicated in patients suffering from severe liver disease only, with liver-function tests three to five times above the upper limit of normal.⁷³ It can be used safely in patients with hepatitis whose liver-function tests are below that range.

Concomitant drug dependence

The combination of bup/nx with sedative-hypnotics (eg, benzodiazepines, alcohol) has been associated with increased mortality, mainly due to respiratory depression.^{28,100} Sedative-hypnotic-dependent patients should be advised to reduce or discontinue their use prior to induction, and urine-toxicology testing should be performed regularly to assess concomitant use.⁴⁵ Active use of alcohol, benzodiazepines, and barbiturates is therefore a relative contraindication to buprenorphine outpatient treatment, and medically supervised withdrawal is suggested.^{104–106}

Pregnancy and children

Bup/nx is contraindicated for pregnant women, as naloxone has not been approved for use in pregnancy. Buprenorphine monotherapy, like methadone, which has been the standard of care in obstetric care since the 1970s, has been shown to reduce illicit opiate use, enhance compliance, and improve

neonatal outcomes, such as birth weight.^{107–110} Recently, the Maternal Opioid Treatment: Human Experimental Research (MOTHER) study confirmed these conclusions and suggested the superiority of buprenorphine in terms of fetal outcomes, with less frequent and severe neonatal abstinence syndrome compared to methadone.^{109,110}

The use of buprenorphine in women who are breastfeeding remains controversial. Both buprenorphine and its main metabolite (norbuprenorphine) appear at low concentrations in breast milk, levels that are unlikely to contribute to buprenorphine dependence in the infant. Due to limited data, the risks and benefits of buprenorphine exposure should be weighed before initiating or continuing substitution treatment among breastfeeding women.^{110,111}

Intoxication with bup/nx in children is relatively safe.⁸⁴ In a retrospective study, the main clinical effects were drowsiness or lethargy (55%), vomiting (21%), miosis (21%), respiratory depression (7%), agitation or irritability (5%), pallor (3%), and coma (2%), with no reports of death. None of these severe effects occurred in children who ingested less than 4 mg buprenorphine.¹¹² Children should be referred to emergency for all ingestions of over 2 mg buprenorphine or any type of ingestion in patients under 2 years old.³³

Adolescents and youth

Few studies have evaluated buprenorphine and bup/nx in the treatment of adolescents with opioid dependence. There is good evidence suggesting that youth are at higher risk of mortality and morbidity from opioid-use disorders (overdose, HIV and hepatitis transmission, concurrent disorders, suicide, and death).^{113–116} The risk–benefit ratio of bup/nx treatment should therefore be carefully evaluated prior to buprenorphine initiation. If substitution treatment with opioid agonists is considered, bup/nx may be preferred over methadone. Bup/nx prescribing in adolescents and young adults follows the same steps and dosages as in adults.^{33,113}

HIV patients

Bup/nx is associated with enhanced HIV outcomes, including increased antiretroviral therapy (ART) initiation, compliance and CD4⁺ count.¹¹⁷ However, it should be used with caution in patients with HIV on ART due to the potential for drug interactions. In theory, several nonnucleoside reverse-transcriptase inhibitors and protease inhibitors are CYP3A4 inducers (efavirenz, nevirapine, nelfinavir, lopinavir/ritonavir) or inhibitors (delavirdine, ritonavir, atazanavir/ritonavir), and thereby the combination has the potential to alter the metabolism of buprenorphine, ART, or both. Some studies

suggest that dose adjustments may be required, but no cases of opioid toxicity have been reported.¹¹⁸

Conclusion

Opioid addiction is a serious public health problem that results in significant individual and social costs, including increased disability, criminal activity, death from overdose, and risk of infectious and blood-borne disease transmission.^{1-4,6,34} Bup/nx, a partial-opioid agonist with unique pharmacological properties, is the only office-based maintenance treatment offered for opioid-use disorders. It is an attractive option for opioid-substitution therapy because of its favorable side-effect profile, flexible dosing schedules, and low diversion and abuse potential. It has demonstrated efficacy in reducing opiate cravings, ameliorating withdrawal discomfort, and increasing periods of abstinence from illicit drug use. In most cases, treatment is required for long periods or even throughout life.^{86,92} Rather than being considered a treatment failure, long-term treatment, which is common to many chronic medical conditions, should be envisaged as a cost-effective way to prolong longevity and improve quality of life.

Although bup/nx has shown multiple benefits, the cost of the medication hinders its widespread use, mainly for marginalized populations and street-heroin users. Members of these populations are at greater risk of comorbidities and infectious disease transmission, and thus it is crucial to increase access to efficacious treatments.

Physicians who wish to prescribe bup/nx in the US and Canada must complete a training program. More exhaustive continuing medical education programs are available for physicians with less experience in treating opioid dependence.

Disclosure

The authors report no conflicts of interest in this work.

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