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Alexis Diane Snyder
nyalih@gmail.com

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Alexis Diane Snyder

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Craig Nuttall, Chair

College of Nursing

Brigham Young University

ABSTRACT

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Alexis Diane Snyder
College of Nursing, BYU
Master of Science

Opioid use disorder (OUD) is increasing in incidence in the United States. Buprenorphine is the mainstay of medication-assisted treatment for OUD. Nurse practitioners play an essential role in solving the opioid epidemic and are increasingly relied on to prescribe buprenorphine. Even though buprenorphine is considered a long-term therapy, many patients request to taper off the drug. Evidence suggests that tapering from buprenorphine is frequently unsuccessful and remains as a challenge. The purpose of this article is to provide the best available evidence regarding the taper of buprenorphine in patients with OUD. Considering a buprenorphine taper should begin by evaluating if the patient is a good candidate, specifically if their maintenance dose of buprenorphine is less than 8 mg/day. This evaluation should also include assessment of the patient's withdrawal expectation. Evidence suggests that a longer buprenorphine taper duration combined with naltrexone leads to better results compared to shorter tapers without naltrexone. Ancillary medications and counseling should be made available to patients as a component of the tapering protocol. Tapering from buprenorphine is difficult but following current evidence gives patients the best likelihood of success.

Keywords: buprenorphine, taper, opioid use disorder

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Opioid Use Disorder (OUD) is an epidemic, affecting every state in the United States (U.S.). The opioid epidemic is primarily due to the over-prescription of opioids for chronic pain (National Institute on Drug Abuse, 2020). Recent evidence is now challenging the long-term use of opioids. Despite this evidence, many patients are still dependent on opioids to manage long-term pain. Over 21% of patients taking opioids long-term will end up misusing the medications (National Institute on Drug Abuse, 2020). This misuse often leads to OUD with or without the introduction of heroin. Overdose deaths from illicit opioid use sharply increased 38.4% in the first half of 2020 (Centers for Disease Control and Prevention, 2020). The effects of the opioid crisis are far-reaching, not only measured by lives lost but also a considerable burden on the criminal justice system and the economy through loss of productivity and associated healthcare costs.

Evidence-based treatment for OUD is a multifaceted approach involving counseling and medication-assisted treatment, specifically buprenorphine, to help patients discontinue the use of opioids. Buprenorphine is a partial agonist on the mu-opioid receptor, therefore having less respiratory depression and euphoria than other narcotic drugs. It is frequently combined with naloxone to prevent intoxicating effects and has been a leading treatment for OUD since its approval by the Food and Drug Administration (FDA) in 2002 (Drug Enforcement Administration, 2019). Buprenorphine is relied on by the OUD community to provide a safe, effective, and accessible means to abstinence. The role of buprenorphine is so pivotal that there is a direct correlation between opioid overdose deaths and the lack of buprenorphine providers in the U.S. (C. W. Jones et al., 2018). Nurse practitioners fill this void; they are more likely to serve

underserved populations and prescribe buprenorphine at the upper end of legal limits compared with physician (Jackson & Lopez, 2018; C. M. Jones & McCance-Katz, 2019).

Nurse practitioners were not legally permitted to prescribe buprenorphine for addiction treatment until 2016, and as a result, they are still frequently overlooked in the fight against the opioid epidemic. However, since the law change in 2016, nurse practitioners' roles in solving the epidemic has rapidly grown. Despite needing to become specially certified to prescribe buprenorphine through 24-hours of supplementary training, over 3,500 nurse practitioners, or 1.7% of those eligible, received the certification just 1 year after the law allowed (Andrilla, 2018). In 2018, only 2 years after the law passed, there were nearly 7,000 nurse practitioners certified to treat OUD with buprenorphine (Moore, 2019). This number is likely much higher in 2021 though these data are not currently available.

Because the current evidence regarding OUD recommends treatment with long-term buprenorphine, there is little guidance on buprenorphine cessation. Even the 24-hour buprenorphine certification courses only teach providers the evidence-based prescribing guidelines of buprenorphine, offering no information on discontinuing the treatment. Despite the recommendation to prescribe buprenorphine long-term for OUD, many patients decide to terminate buprenorphine therapy within the first 6 months of treatment (Bentzley, Barth, Back, & Book, 2015; Fiellin et al., 2014). Although it is difficult to predict all patients' reasoning, many patients will taper off buprenorphine due to lack of access, (Bentzley et al., 2015; Dunn, Saulsgiver, Miller, Nuzzo, & Sigmon, 2015) the stigma involved with medication-assisted treatment, (Dunn et al., 2015; Truong et al., 2019) or the patients' preferences. Since tapering patients off buprenorphine is not an evidence-based treatment, providers do not have a standardized treatment approach and, as a result, most patients will relapse to illicit opioid use

within 1 month of buprenorphine cessation (Bentzley et al., 2015; Weinstein et al., 2018). Therefore, the purpose of this paper is to review the available evidence regarding tapering buprenorphine to aid nurse practitioners as they assist patients with the cessation process.

Methods

A search of the CINAHL, MEDLINE, and PsychInfo databases was conducted. Inclusionary criteria included '"buprenorphine OR Suboxone' AND 'taper*."' Different keywords were attempted, but "taper*" was found to have the most relevant results. Limits were set to filter results 2014 to present. Articles written in the English language were included. With these criteria, 232 articles were found. These results were further restricted to research articles whose main focus was tapering, and only six articles met these standards. The lack of information is assumed to be due to the widely accepted view that buprenorphine is a long-term therapy and the fact that buprenorphine is a relatively new treatment, with less than 20 years since FDA approval (Drug Enforcement Administration, 2019).

As the body of literature on this topic is not large, the search was continued using a reverse snowball strategy, or ascendancy approach. Articles that were cited frequently by key studies were used for this paper, even if outside the established date range.

Tapering Buprenorphine Evidence

While buprenorphine is a long-term treatment therapy for OUD, many patients will choose to terminate their buprenorphine treatment at some point. It is, therefore, the provider's responsibility to guide the patient through the tapering process and set proper expectations for discontinuing buprenorphine with realistic outcomes. Since buprenorphine for OUD is used in place of opioids, a failed taper is classified as a relapse to illicit opioid use.

Patient Considerations

The highest predictor of a successful taper is the maintenance dose after buprenorphine induction (Bentzley et al., 2015). There is a direct correlation between the patient's dose and the likelihood of relapse; with a lower dose, there is a smaller chance of relapse (Bentzley et al., 2015; Sigmon et al., 2013). Patients with a maintenance dose of less than 8 mg of buprenorphine per day are more likely to successfully taper off the medication. The strong association between buprenorphine dose and successful taper is likely due to the dose being directly linked to the level of dependence, with a higher dose indicating a higher level of dependence (Bentzley et al., 2015). Nurse practitioners should educate patients on their likelihood of successfully discontinuing the use of buprenorphine by weighing the probability of success against the patient's maintenance dose.

Additionally, the "Expected Withdrawal Scale" (EWS) is a valuable predictor of a buprenorphine taper's withdrawal severity and helps predict patient readiness and the probability of success (Dunn et al., 2015). With the EWS, patients rate how severe they expect withdrawal symptoms to be on a 100-point scale. The scale is simple: on a scale of 0-100, patients give the provider the number they feel most closely correlates with their expectation of withdrawal symptom severity. The number 100 indicates the expectation of the worst possible withdrawal symptoms, while the number 0 signifies no expected withdrawal symptoms. Patients' EWS score is a great predictor of how well they will manage withdrawal symptoms; those who give lower ratings and therefore have a better presumption of withdrawal have a better chance of a successful taper (Dunn et al., 2015). Alternatively, patients who begin a buprenorphine taper against their will in the inpatient setting have low success rates (Cushman, Liebschutz, Anderson, Moreau, & Stein, 2016). Patients are considerably more likely to successfully taper

off buprenorphine if they expect withdrawal will not be too difficult and if the choice to taper is patient initiated (Cushman et al., 2016; Dunn et al., 2015).

Naltrexone

Naltrexone is an opioid antagonist, acting on the mu-opioid receptor. Supplementing buprenorphine treatment with naltrexone reduces withdrawal cravings, with less likelihood of relapse (Bentzley et al., 2015; Dunn et al., 2015; Sigmon et al., 2013). Patients with naltrexone introduction midway through the buprenorphine taper had better success than patients who received naltrexone after the buprenorphine was discontinued (Bentzley et al., 2015; Fiellin et al., 2014; Sigmon et al., 2013). In fact, initiation of naltrexone after the patient had discontinued buprenorphine was futile, as most participants had already relapsed to opioid or illicit drug use. Additionally, when comparing treatment of extended-release naltrexone as a monotherapy against naltrexone combined with buprenorphine, participants with the buprenorphine-naltrexone treatment experienced fewer withdrawal symptoms and were also less likely to use opioids or illicit drugs during the tapering process (Bisaga et al., 2018).

The inability to access a wide variety of naltrexone doses can be a limiting factor in successful naltrexone titration, as smaller doses of naltrexone are only available at compounding pharmacies. Due to the difficulty of access, the use of naltrexone should be addressed with patients before the initiation of a taper from buprenorphine. Naltrexone is formulated in a 50 mg tablet; however, many compounding pharmacies offer varying dosages as small as a 0.5 mg capsule dose. Additionally, Vivitrol is the intramuscular formulation and is available in a vial, which allows for incremental dosing in the clinic setting.

Buprenorphine Taper Length with Naltrexone Initiation

Buprenorphine taper lengths vary from provider to provider, as there are no clear guidelines that identify a best practice. The best treatment retention and lowest chance of relapse is found with longer tapers that also initiate naltrexone (Bentzley et al., 2015; Dunn et al., 2015; Marsch et al., 2016; Sigmon et al., 2013). A buprenorphine taper length of at least 1 month has better results than shorter, 1- or 2-week taper lengths (Bentzley et al., 2015; Dunn et al., 2015; Marsch et al., 2016; Sigmon et al., 2013). Even longer taper lengths that range from 30-56 days result in milder withdrawal symptoms, with fewer moments of severe withdrawal symptoms, and fewer sleep disruptions than with shorter buprenorphine tapers (Dunn et al., 2015).

Due to the difficulty of tapering buprenorphine and the limited evidence on the subject, Sigmon et al.'s study offers the best guidance on the issue. Most other studies conclude a buprenorphine taper is too risky due to the high chance of relapse and increased mortality, especially if the patient relapses to heroin (Cushman et al., 2016; Fiellin et al., 2014; Weiss et al., 2011). In the Sigmon et al. study, 64% of participants completed phase one's 4-week buprenorphine taper, and 50% completed the study’s second phase with initiation of naltrexone. Comparatively, only 3-5% of participants complete the process of tapering buprenorphine in other studies that did not utilize naltrexone (Dunn et al., 2015; Fiellin et al., 2014). Sigmon et al. first stabilized patients with an appropriate dose of buprenorphine, by using the Clinical Institute Narcotic Assessment (CINA) scale to determine the amount of buprenorphine necessary to prevent withdrawal symptoms without causing sedation (Peachey, 1988). This scale can be easily accessed on the website https://integrationacademy.ahrq.gov/resources/7551 (Agency for Healthcare Research and Quality). The average initiation time to become stabilized on

buprenorphine was 8-20 days (Sigmon et al., 2013). Once the patient is stabilized on ≤8 mg/day of buprenorphine, the taper has two phases (See Appendix A).

Phase One

For the first 5 weeks, the provider should slowly taper the patient's dose of buprenorphine. The dose is reduced by 2 mg each week until a 2 mg/day dose is reached. At that point, the patient's dose should decrease to a 1 mg/day dose of buprenorphine for 1 week, followed by the patient being completely tapered off buprenorphine the following week.

Oral naltrexone is also started on week 1, at the same time as the initiation of the buprenorphine taper, as long as the patient has one negative urine sample and self-reports no opioid use for the last 24 hours (Dunn et al., 2015). Naltrexone begins with 12.5 mg on day one, 25 mg on days two and three, and then 50 mg daily beginning on day four and continuing for the rest of phase one (week 1-5) (Sigmon et al., 2013). At the end of phase one, the patient is completely tapered off buprenorphine and titrated onto a 50 mg daily dose of naltrexone.

Phase Two

Phase two includes weeks 5-12 of treatment. During this phase, the naltrexone is transitioned to a three times per week dosing schedule with 100 mg on Mondays and Wednesdays and 150 mg on Fridays (Sigmon et al., 2013). Upon completion of phase two, naltrexone dosing can continue at the provider's discretion as these data were not included in this study.

Ancillary Medication

Ancillary medications further help reduce withdrawal symptoms during the taper from buprenorphine and are a valuable option for patients. These medications include clonidine, trazodone, clonazepam, hydroxyzine, ibuprofen, loperamide, and promethazine. The provider

should prescribe medications to alleviate the withdrawal symptoms specified on the CINA or as indicated by the patient's complaint (Bisaga et al., 2018; Dunn et al., 2015). Doses of these ancillary medications can be administered in the office or provided as prescriptions for the patient’s use at home (Dunn et al., 2015). While ancillary treatment should be available to manage withdrawal symptoms, these medications should not be prescribed long-term.

Counseling

Comprehensive counseling is attributed to better treatment outcomes during buprenorphine tapers (Sigmon et al., 2013) but can also be a reason for treatment discontinuation if the counseling requirements are considered too strict (Bentzley et al., 2015). According to DATA 2000, providers of buprenorphine should offer case management services and counseling (U.S. Department of Health and Human Services, 2020). Types of counseling include psychoeducational, cognitive-behavioral, and family systems, with mindfulness of other concerns in the participants' life, such as legal or housing issues (Marsch et al., 2016). For best results, counseling should be offered twice a week, with a strong suggestion of patient participation but no requirement (Sigmon et al., 2013). Providers can educate patients to expect better treatment outcomes with increased counseling attendance (Sigmon et al., 2013).

Schedule Requirements

Planning the tapering schedule should be meticulous and purposeful. More patients relapse when they are required to attend the clinic daily for medication administration (Marsch et al., 2016). In fact, patients report that daily attendance for medication administration is too onerous and unsustainable (Marsch et al., 2016).

However, there may be circumstances when more frequent check-ins would be necessitated. For instance, more frequent appointments may help the provider more accurately

assess if the patient is having difficulty with the tapering course. The most withdrawal symptoms, per patient report, is not in the beginning as most would expect, but the week following the end of the taper (Dunn et al., 2015). Knowing that patients continue to struggle beyond the length of the taper course would be helpful when scheduling, counseling, and preparing patients for their taper. There are better outcomes for patients between the ages of 16 and 24 when patients received buprenorphine daily in the clinic instead of self-administration of buprenorphine at home (Marsch et al., 2016).

Implications for Clinical Practice

Evidence is clear that buprenorphine is best used as a long-term medication for OUD. However, there are several reasons that a patient may need or desire to be tapered off of the drug. In the case that a buprenorphine taper is warranted, the nurse practitioner can follow the buprenorphine taper algorithm noted in Appendix A.

Recommendations

Tapering buprenorphine should begin with a discussion about the process and challenges involved in buprenorphine cessation. Eligibility and future success are predicted based on the stable dose of buprenorphine ($\leq$8 mg/day) and a low EWS . Once the taper is initiated, the nurse practitioner may also prescribe ancillary medications to assist with withdrawal symptoms during the taper, keeping in mind that the withdrawal symptoms usually peak during week 5. Counseling services should also be offered as adjunct to the taper protocol. The nurse practitioner should decide with the patient how frequently the patient will follow-up in clinic. Following these recommendations gives patients the best opportunity for a successful taper from buprenorphine.

Limitations

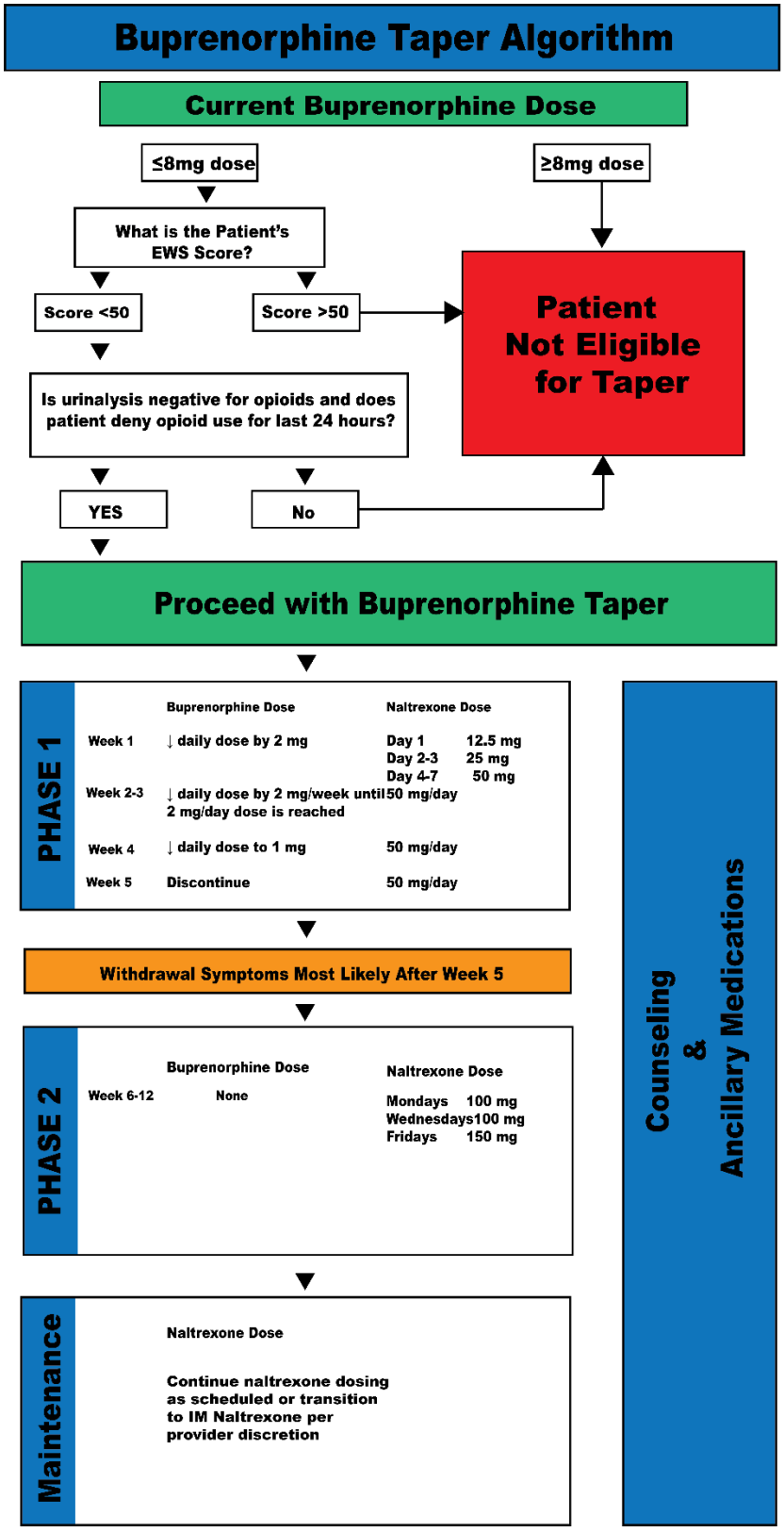
The data on tapering buprenorphine is limited. Only a few clinical trials focused on tapering buprenorphine. Most studies on buprenorphine cessation had high attrition rates. In fact, in some research studies nearly every participant in the taper group prematurely dropped out of the study (Fiellin et al., 2014). Many of the studies with the lowest rates of completion had the shortest buprenorphine taper periods, with some as short as 1-2 weeks (Dunn et al., 2015; Fiellin et al., 2014; Sigmon et al., 2013; Weiss et al., 2011). This finding indicates that tapering off of buprenorphine remains a significant clinical challenge. Due to the small number of available clinical trials regarding buprenorphine cessation, more high-quality research is needed in this area There is also a need for additional research with tapering buprenorphine across diverse patient demographics.

Conclusion

OUD is a rising problem, affecting many patients. Nurse practitioners need to prepare to care for patients with OUD, which includes prescribing buprenorphine. Although the gold standard of buprenorphine therapy is long-term treatment, many patients may choose to taper off buprenorphine. Information regarding successful buprenorphine tapering is limited; therefore, there is a need for more research in this area. The nurse practitioner should inform the patient seeking discontinuance of buprenorphine of the lack of evidence in how to successfully taper buprenorphine. If the patient wishes to continue, the nurse practitioner should determine the patient's likelihood of success by evaluating the patient's buprenorphine stabilization dose and their expectations of withdrawal severity. If buprenorphine cessation is still the patient's goal, the nurse practitioner should start the patient on a two-phase taper schedule with simultaneous naltrexone initiation. The nurse practitioner can and should prescribe ancillary medications as

indicated by CINA scores and can adjust counseling and schedule requirements on a per-patient basis. Tapering off buprenorphine is challenging but having a nurse practitioner who is equipped with the best available evidence is an invaluable tool to give patients the best possibility of success.

Appendix A


Buprenorphine Taper Algorithm
Current Buprenorphine Dose
≤8mg dose
≥8mg dose
What is the Patient's EWS Score?
Score <50
Score >50
Patient Not Eligible for Taper
Is urinalysis negative for opioids and does patient deny opioid use for last 24 hours?
YES
No
Proceed with Buprenorphine Taper
PHASE 1
Buprenorphine Dose
Naltrexone Dose
Week 1
↓ daily dose by 2 mg
Day 1 12.5 mg
Day 2-3 25 mg
Day 4-7 50 mg
Week 2-3
↓ daily dose by 2 mg/week until 2 mg/day dose is reached
50 mg/day
Week 4
↓ daily dose to 1 mg
50 mg/day
Week 5
Discontinue
50 mg/day
Withdrawal Symptoms Most Likely After Week 5
PHASE 2
Buprenorphine Dose
Naltrexone Dose
Week 6-12
None
Mondays 100 mg
Wednesdays 100 mg
Fridays 150 mg
Maintenance
Naltrexone Dose
Continue naltrexone dosing as scheduled or transition to IM Naltrexone per provider discretion
Counseling & Ancillary Medications

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