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MANITOBA OPIOID AGONIST THERAPY RECOMMENDED PRACTICE MANUAL

2.1 Introduction: The Pharmacology of Buprenorphine, Precipitated Withdrawal & Management of Adverse Effects

PHARMACOLOGY

Buprenorphine is a long-acting semi-synthetic opioid that is a partial agonist and has a high affinity at the mu-opioid receptor. This unique pharmacology allows it to be utilized as an effective tool in the treatment of opioid use disorder.

Buprenorphine – The Partial Agonist

The partial agonist activity of buprenorphine at the mu-opioid receptor helps reduce cravings and alleviate opioid withdrawal, in a patient experiencing withdrawal. Buprenorphine has a relatively high affinity for the mu-opioid receptor and will displace and block most of the full agonist effects of other opioids (e.g., morphine, oxycodone, or heroin). A long duration of action allows buprenorphine to be dosed once daily, providing a convenient method for health professionals to witness and monitor ingestion. Since buprenorphine is a partial agonist, the intrinsic activity (e.g., respiratory depression effect) plateaus when the dose increases, essentially producing a "ceiling effect" at higher doses[1]. This differs from the response produced by a full agonist (e.g., methadone) in that the intrinsic activity continues to increase linearly with the dose (see FIGURE 1). The partial agonist property of buprenorphine may reduce its potential for abuse and makes it a safer choice in terms of overdose risk, especially when compared to methadone.

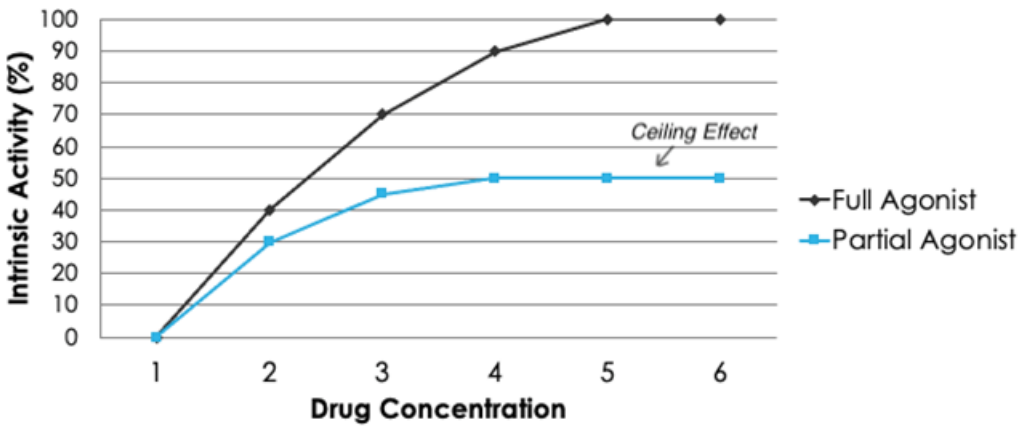

FIGURE 1: FULL AGONIST VS. PARTIAL AGONIST

Sublingual Administration

Buprenorphine has poor oral bioavailability due to a high first-pass hepatic metabolism and generally requires alternative routes of administration to be effective. Sublingual administration of buprenorphine produces an efficacious bioavailability of approximately 30%[2]. Other effective methods of administration include subcutaneous (e.g., Sublocade®) and subdermal implant (e.g., Probuphine®) methods. Sublingual administration produces an onset of action in 30 to 60 minutes, and the peak effects occur between 1 and 4 hours. The mean elimination half-life is 37 hours, and most of the dose is excreted in the feces with approximately 10-30% excreted in the urine[1].

Naloxone – The Antagonist

The sublingual formulation of buprenorphine used most commonly in opioid agonist therapy (OAT) contains naloxone in a ratio of 4:1 (buprenorphine:naloxone). Naloxone, an antagonist at the mu-opioid receptor, has poor oral and sublingual bioavailability. In the doses used in the sublingual formulation this component has not been found to affect the pharmacokinetics of buprenorphine when used sublingually[1]. **The naloxone component is helpful in discouraging intravenous and intranasal use of the sublingual tablet since the resultant plasma levels can precipitate opioid withdrawal**[3].

ADVERSE EFFECTS & MANAGEMENT

A patient may experience adverse effects immediately after switching to buprenorphine which are most consistent with opioid withdrawal symptoms (precipitated withdrawal). This is fortunately a rare occurrence and is discussed in greater detail later in this document.

If precipitated withdrawal is successfully avoided, then the patient may still experience mild to moderate opioid withdrawal symptoms until they reach a therapeutic dose.

Comparatively, opioid agonist effects are more common. These adverse effects are generally milder than full agonists (e.g., methadone) due to the partial agonist activity of buprenorphine. Some adverse effects will dissipate with continued use, such as nausea, sedation, headache, and insomnia. Other adverse effects may persist and require some management, such as constipation, hyperhidrosis, and sexual dysfunction.

Constipation

Constipation is a common persistent adverse effect that has been found to be prevalent in 8-12% of individuals, compared to 3% in placebo, after 4 weeks of treatment with buprenorphine[4].

An effective treatment regimen for opioid-induced constipation can include:

- Daily administration of an osmotic laxative (e.g., polyethylene glycol 3350),
- Use of a stimulant laxative, as needed (e.g., senna or bisacodyl),
- The above can be used with or without a stool softener (e.g., docusate), and
- Non-pharmacological methods such as increased fiber intake and fluid consumption should always be endorsed for the prevention of opioid-induced constipation[5].
- While most laxatives can be helpful, bulk-forming laxatives (e.g., psyllium) are typically not effective for opioid-induced constipation and should be avoided.

Constipation often goes unrecognized in this patient population and may adversely affect quality of life. OAT prescribers are encouraged to ask about and treat constipation aggressively. This approach may improve long-term adherence to agonist therapy.

Hyperhidrosis

Hyperhidrosis has been shown to occur in approximately 15% of patients taking buprenorphine/naloxone[1]. While most cases of hyperhidrosis are mild and do not require pharmacological intervention, there are instances where the severity can be enough to affect the patient's quality of life. Clonidine, an inhibitor of sympathetic stimulation, has been used off-label with some success to treat excessive sweating[6], although it should be noted that research analyzing its use in this patient population is lacking. Misuse of clonidine has been reported[7], and consideration should be made to control the dispensing frequency. **Clonidine should, in most patients, be dispensed on the same schedule as buprenorphine.** Oxybutynin has been shown to have some success off-label as well[8], however the evidence is very limited.

Most patients with hyperhidrosis, who benefit from treatment with clonidine, will experience effective relief with no more than clonidine 0.1 mg po BID.

In cases where a trial of clonidine is not effective in reducing sweating, it should be discontinued to avoid unwanted side-effects and prevent diversion. Clonidine has sedating properties and may cause fatigue that not all patients tolerate. Clonidine is also centrally acting and reduces blood pressure. A baseline blood pressure check, repeated after starting clonidine, may be warranted. The use of clonidine can also exacerbate postural hypotension, especially is older patients. Educating patients about this risk is important, especially if they are already at risk of falls.

Sexual Dysfunction

There is some research showing that buprenorphine/naloxone may cause sexual dysfunction in some patients. Hypoactive sexual desire, intercourse dissatisfaction, and erectile dysfunction (ED) were shown to be the most common sexual dysfunctions in men[9]. There is robust evidence to suggest that chronic opioid use can lead to decreased testosterone levels in men, and it is speculated that this may be a contributing factor to sexual dysfunction[10]. The research on sexual dysfunction in women is much more limited. It is speculated that interference with the production of LH and FSH subsequentially interferes with certain sex hormones, which can lead to a depressed libido and oligomenorrhea or amenorrhea[10].

Sexual dysfunction may have a major impact on treatment adherence, so addressing this adverse effect may improve patient outcomes. Treating the specific symptoms, for example, by using PDE-5 inhibitors for ED, or managing low testosterone levels in men, can be a suitable approach to managing this condition.

PRECIPITATED WITHDRAWAL

The unique pharmacology of buprenorphine can lead to a risk of precipitated withdrawal during the induction phase. Precipitated withdrawal can occur when a partial agonist with a higher affinity for the mu-opioid receptor (e.g., buprenorphine) replaces a full agonist with a lesser affinity for the receptor (e.g., morphine, heroin, fentanyl). If precipitated withdrawal occurs, withdrawal symptoms will appear as early as 15 to 60 minutes after taking buprenorphine and can sometimes be very distressing. This may discourage a patient who is new to buprenorphine from continuing with treatment. It is imperative to take preventative measures to avoid this situation when switching from a full agonist to buprenorphine. If precipitated withdrawal does occur, supportive therapy is indicated. This is discussed in more detail in the Conventional Buprenorphine Induction and initial monitoring section of this manual (see *Management of Precipitated Withdrawal*).

To avoid precipitated withdrawal, ensure that the patient is in adequate withdrawal before initiating treatment. The timing of the last reported use of opioids can be useful in determining whether it is safe to proceed. Initiation of treatment can usually be considered 6 to 12 hours after the last use of a short-acting opioid (e.g., heroin, oxycodone, fentanyl), at least 24 hours after a long-acting opioid (e.g., oxycodone or morphine controlled-release), or at least 72 hours after the last use of methadone[11]. Additional strategies to avoid the risk of precipitated withdrawal are discussed elsewhere in this manual. See Ongoing Care for further guidance on rotating between OAT medications, specifically, *Patients Transitioning from Methadone to Buprenorphine*.

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