

BUPRENORPHINE

for Opioid Use Disorder

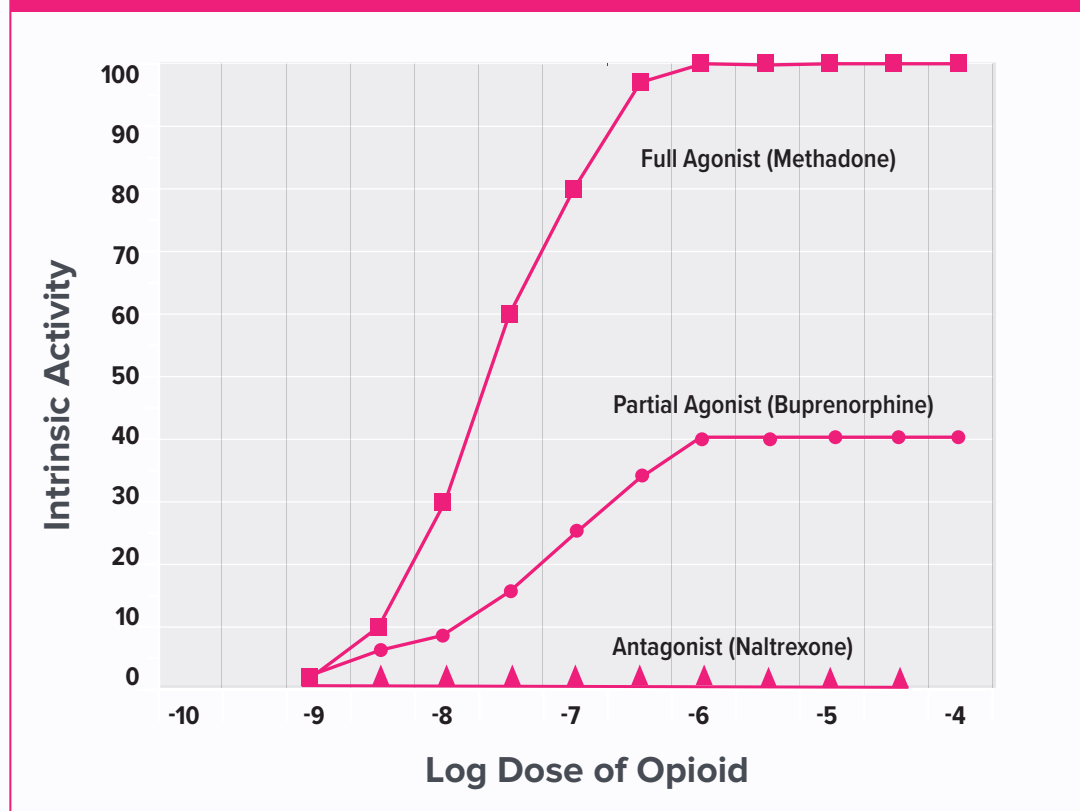
Module 2: Pharmacology and Administration



Buprenorphine for Opioid Use Disorder
Pharmacology and Administration

- Buprenorphine is a **partial agonist at the mu-opioid receptor**, (among other pharmacologic actions).¹
 - Buprenorphine binds with high affinity and **activates opioid receptors, but not to the same extent as full agonists.**^{2,3}
 - **Buprenorphine relieves drug cravings without producing the euphoric effects of full opioid agonists⁴ and with a lower risk of overdose compared to full agonists.**^{5,6}
- Partial agonist properties give buprenorphine a **“ceiling effect”**. Increasing the dose of buprenorphine does not produce the same subjective or physiologic effect as increasing the dose of a full agonist.^{7,8}
 - In spite of the “ceiling effect”, exposure to buprenorphine in pediatric patients may result in fatal respiratory depression.⁹ Appropriate storage should be ensured to avoid unintentional exposure to children.¹⁰
 - Individuals who are not opioid dependent may experience euphoric effects with buprenorphine use.^{11,12}

Exhibit 3A.4. Intrinsic Activity of OUD Medications



SAMSHA ¹³

Potential for Misuse and Diversion of Buprenorphine Products

Buprenorphine products for sublingual (SL) or buccal administration containing naloxone (an opioid antagonist) have been developed to decrease potential for misuse via injection or intranasal routes of administration^{14, 15, 16}

- Naloxone will block the pharmacologic action of buprenorphine when administered by injection or intranasally, but has limited bioavailability when taken transmucosally (SL or buccally) and thus has little-to-no pharmacologic action when these products are administered as directed.¹⁷

Buprenorphine products are diverted¹⁸ for purposes of self-medication of opioid dependence, self-medication of withdrawal, to decrease use of other opioids, to decrease injection use, and to relieve pain and to produce euphoria.¹⁹

- Naloxone lowers the desirability of buprenorphine/naloxone combination products for misuse.⁴
- Data have shown a significant decrease in heroin overdoses once buprenorphine has been implemented into specific treatment systems in the US.²⁰

Buprenorphine Method of Administration

SL or buccal administration of buprenorphine is used due to poor oral bioavailability.²¹ Patients should be instructed to leave the medication on the inside of the cheek or under their tongue until dissolved.

An implantable intramuscular depot formulation of buprenorphine lasting 6 months is also available. This product is recommended for use in patients needing 8 mg or less of buprenorphine per day, a low to moderate dose.²²

Care must be taken when switching between buprenorphine products as dosage can vary based on different bioavailability between products.

Patient preference, insurance coverage of formulations and out-of-pocket expenses for the patient are considerations in selection of formulation.

An extended release injection is available for subcutaneous administration. It is given monthly and started only after initiation of a transmucosal buprenorphine product.²⁴

Buprenorphine Drug Interactions

Buprenorphine should be used cautiously with other **Central Nervous System (CNS)** depressants, including benzodiazepines, alcohol and other sedative drugs.^{24,25}

- Excessive sedation, respiratory depression, impaired cognition, and death can occur.^{26, 27, 28, 29, 30, 31, 32}
- Buprenorphine's "ceiling effect" may be overcome when administered with other CNS depressants, particularly benzodiazepines; this can potentially increase the risk of overdose and fatalities.³⁷
- **Concomitant treatment with benzodiazepines and buprenorphine can be accomplished with careful monitoring. If deemed medically necessary, treatment with benzodiazepines or other CNS depressants is not a reason to withhold buprenorphine treatment.**³⁴

Buprenorphine is metabolized to norbuprenorphine and other metabolites by CYP 450 3A4 and has the potential to interact with other inhibitors, or inducers of this pathway.^{35,36} These includeazole antifungals such as ketoconazole, macrolide antibiotics such as erythromycin, and protease inhibitors.

Opioid antagonists can block the effects of buprenorphine, and buprenorphine has the potential to **displace and block other opioids** from the opioid receptor due to its high affinity for and slow dissociation from the opioid receptor.^{37,38,39} At higher doses, buprenorphine can precipitate withdrawal in individuals dependent on full opioid agonists.

- Opioid antagonists, such as naltrexone, can block the effects of buprenorphine.
- Use of naltrexone in a patient with buprenorphine in their system will precipitate withdrawal.⁴⁰
- If emergency treatment with full opioid agonists is required, careful titration of dose and close monitoring for safety and effectiveness is required (see Module 4: Special Populations - Patients with Pain).

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