

Supplemental Table 1. Centrally acting opioid antagonists

	Clinical Use(s)	Year Approved	Brand Name(s)	Formulation(s)	Oral Bioavailability, %	Parenteral/ Other Bioavailability, %	Receptor Profile	Half-life, hours	Common AE(s)	Special Considerations
Nalmefene ¹⁻⁵	Opioid agonist overdose	1995	Revex	IM, IV, or SC injection	NA	102 (IM) 100 (SC)	MOR and DOR antagonist, partial KOR agonist	11	Nausea, vomiting, tachycardia, hypertension	None
			Opvee	IN	NA	NA			Nasal discomfort, headache, nausea, dizziness	
Naloxone ⁶⁻¹⁰	Opioid agonist overdose	1971	Narcan	IN	NA	44–54	MOR antagonist, affinity for KORs and DORs	1–2	In healthy volunteers: increased blood pressure, musculoskeletal pain, headache	None
			Zimhi	IM or SC injection	NA	98			In healthy volunteers: nausea, dizziness, lightheadedness, elevated bilirubin	
Naloxone + buprenorphine ^{8,11-16}	OUD	2002	Suboxone	Sublingual tablet/film	Naloxone: 3 Buprenorphine: 51	NA	Naloxone: MOR antagonist, affinity for KORs and DORs Buprenorphine: partial MOR and KOR agonist, DOR antagonist	Naloxone: 2–12 Buprenorphine: 24–42	Oral hypoesthesia, glossodynia, oral mucosal erythema, headache, nausea, vomiting	Buprenorphine has abuse potential; life-threatening respiratory depression may occur if used with another respiratory depressant drug(s)
		2013	Zubsolv	Sublingual tablet	Similar exposure at an ≈ 30% lower dosage than Suboxone	NA			Headache, nausea, vomiting	

Naltrexone ¹⁷⁻²⁰	OUD/AUD	1984 (OUD) 1994 (AUD)	Revia	Oral	5–40	NA	MOR and KOR antagonist, lower affinity for DORs	4–240	In patients with OUD: difficulty sleeping, anxiety, nervousness, abdominal pain, nausea, vomiting In patients with AUD: nausea, headache, dizziness, nervousness, fatigue	None
		2006 (AUD) 2010 (OUD)	Vivitrol	IM injection	NA	Undetermined				
Naltrexone + bupropion ^{17,21}	Body weight reduction	2014	Contrave	Oral	5–40	Undetermined	Naltrexone: MOR and KOR antagonist, lower affinity for DORs	Naltrexone: 5	Nausea, constipation, headache, vomiting	Adjunct to reduced-calorie diet and increased physical activity
Samidorphan + olanzapine ²²	Body weight reduction	2021	Lybalvi	Oral	69	Undetermined	Samidorphan: MOR antagonist, partial KOR and DOR agonist	Samidorphan: 7–11	In patients with SZ: weight gain, somnolence, dry mouth, headache In patients with BD-I (derived from olanzapine studies): somnolence, dry mouth, dizziness, asthenia, constipation, dyspepsia, increased appetite, tremor	Significantly reduces olanzapine-associated weight gain

AE, adverse event; AUD, alcohol use disorder; BD-I, bipolar I disorder; DOR, delta opioid receptor; IM, intramuscular; IN, intranasal; IV, intravenous; KOR, kappa opioid receptor; MOR, mu opioid receptor; NA, not applicable; OUD, opioid use disorder; SC, subcutaneous; SZ, schizophrenia.

REFERENCES

1. *Revex [package insert]*. Deerfield, IL: Baxter Healthcare; 2006.
2. *Selincro [summary of product characteristics]*. Valby, Denmark: H. Lundbeck; 2022.
3. *Nalmefene hydrochloride [package insert]*. Stamford, CT: Purdue Pharma; 2021.
4. US Food and Drug Administration. FDA approves prescription nasal spray to reverse opioid overdose [press release]. 2023. Available at: <https://www.fda.gov/news-events/press-announcements/fda-approves-prescription-nasal-spray-reverse-opioid-overdose>. Accessed: October 26, 2023.
5. *Opvee nasal spray [package insert]*. Santa Monica, CA: Opiant Pharmaceuticals; 2023.
6. *Narcan [package insert]*. Radnor, PA: Adapt Pharma; 2015.
7. *Zimhi [package insert]*. San Diego, CA: Adamis Pharmaceuticals; 2021.
8. Miller RD, Eriksson LI, Fleisher LA, Wiener-Kronish JP, Young WL. *Miller's Anesthesia*. 7th ed. Philadelphia, PA: Churchill Livingstone; 2009.

9. Choi YS, Billings JA. Opioid antagonists: a review of their role in palliative care, focusing on use in opioid-related constipation. *J Pain Symptom Manage.* 2002;24(1):71-90.
10. Ryan SA, Dunne RB. Pharmacokinetic properties of intranasal and injectable formulations of naloxone for community use: a systematic review. *Pain Manag.* 2018;8(3):231-245.
11. *Suboxone [package insert]*. North Chesterfield, VA: Indivior, Inc; 2023.
12. *Zubsolv [package insert]*. Morristown, NJ, USA: Orexo US, Inc; 2016.
13. Coe MA, Lofwall MR, Walsh SL. Buprenorphine pharmacology review: update on transmucosal and long-acting formulations. *J Addict Med.* 2019;13(2):93-103.
14. Katzung BG, Masters SB, Trevor AJ. *Basic and Clinical Pharmacology*. 12th ed. New York, NY: McGraw Hill Lange; 2012.
15. Kuhlman JJ, Jr., Lalani S, Magluito J, Jr., Levine B, Darwin WD. Human pharmacokinetics of intravenous, sublingual, and buccal buprenorphine. *J Anal Toxicol.* 1996;20(6):369-378.
16. Wentland MP, Lou R, Lu Q, et al. Syntheses and opioid receptor binding properties of carboxamido-substituted opioids. *Bioorg Med Chem Lett.* 2009;19(1):203-208.
17. McIntyre RS, Citrome L, Cummings H, et al. Opioid antagonism mitigates antipsychotic-associated weight gain: focus on olanzapine. *CNS Spectr.* 2022;28(3):288-299.
18. *Revia [package insert]*. Pomona, NY: Duramed Pharmaceuticals, Inc; 2013.
19. Wentland MP, Lu Q, Lou R, Bu Y, Knapp BI, Bidlack JM. Synthesis and opioid receptor binding properties of a highly potent 4-hydroxy analogue of naltrexone. *Bioorg Med Chem Lett.* 2005;15(8):2107-2110.
20. *Vivitrol [package insert]*. Waltham, MA: Alkermes, Inc; 2022.
21. *Contrave [package insert]*. Morristown, NJ: Currax Pharmaceuticals LLC; 2020.
22. *Lybalvi [package insert]*. Waltham, MA: Alkermes, Inc.; 2024.