Hydromorphone

Guildford Advanced Courses

September 2022

Declarations of interest

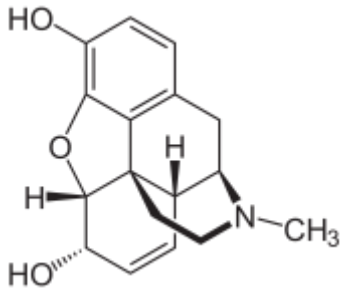
- President-elect, British Pain Society
- Council member and Technical Committee chair, Advisory Council on the Misuse of Drugs

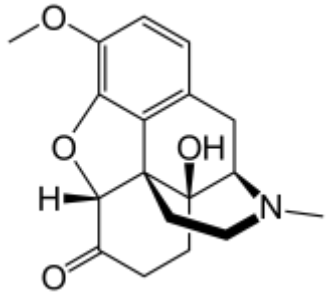
Overview

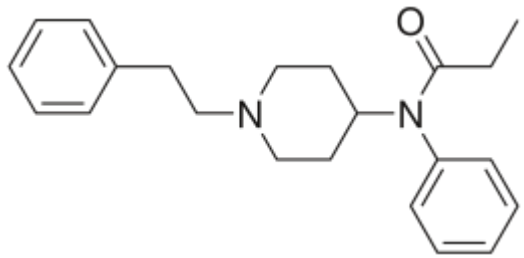
- Chemistry and formulations
- Pharmacodynamics
- Pharmacokinetics
- Opioid equivalence
- CSCI compatibility

- Efficacy and tolerability in cancer pain

Types of opioid

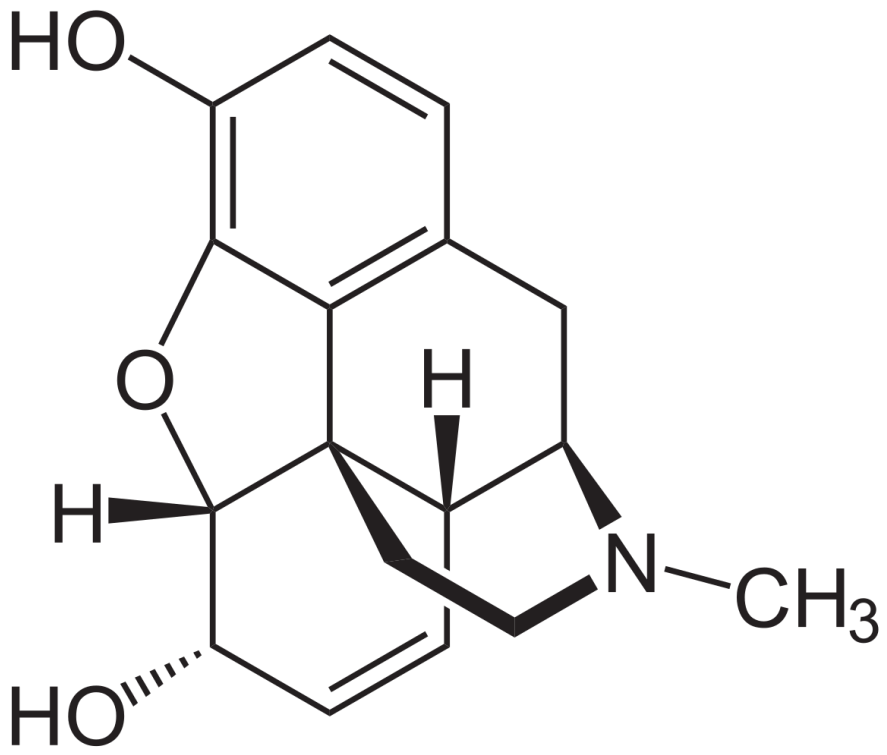




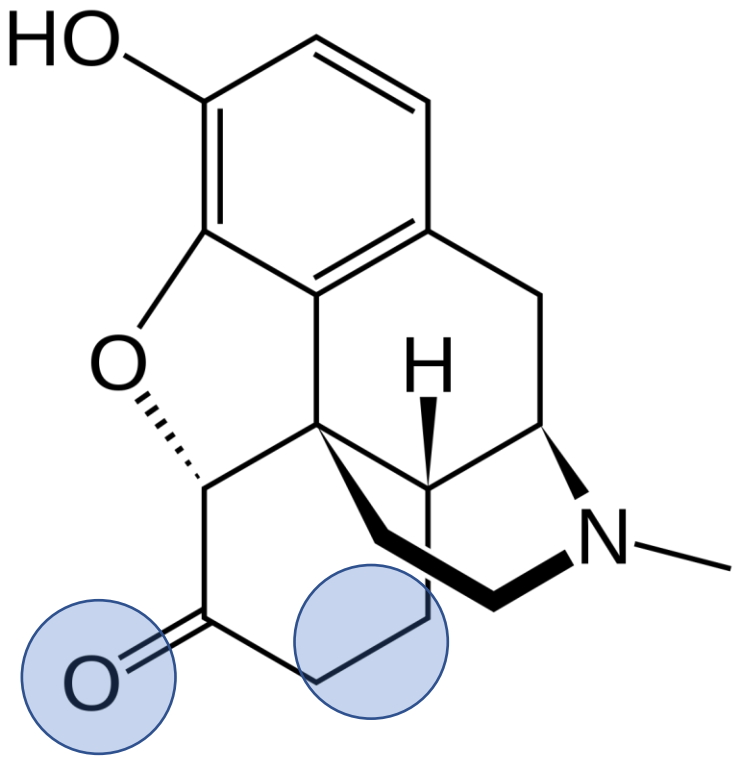


Naturally occurring	Semi-synthetic	Synthetic
Morphine	Oxycodone	Tramadol
Codeine	Diamorphine	Pethidine
Thebaine	Buprenorphine	Fentanyl
Papaverine	**Hydromorphone**	Alfentanil

Morphine



Hydromorphone



Formulations in the UK

- Oral
  - Immediate release (capsule) 1.3mg, 2.6mg
  - Modified release (capsule) 2mg, 4mg, 8mg, 16mg, 24 mg

- Injection
  - 2mg/ml, 10mg/ml, 20mg/ml and 50mg/ml (1ml amps)
  - Unlicensed formulation from specials manufacturers

Pharmacodynamics

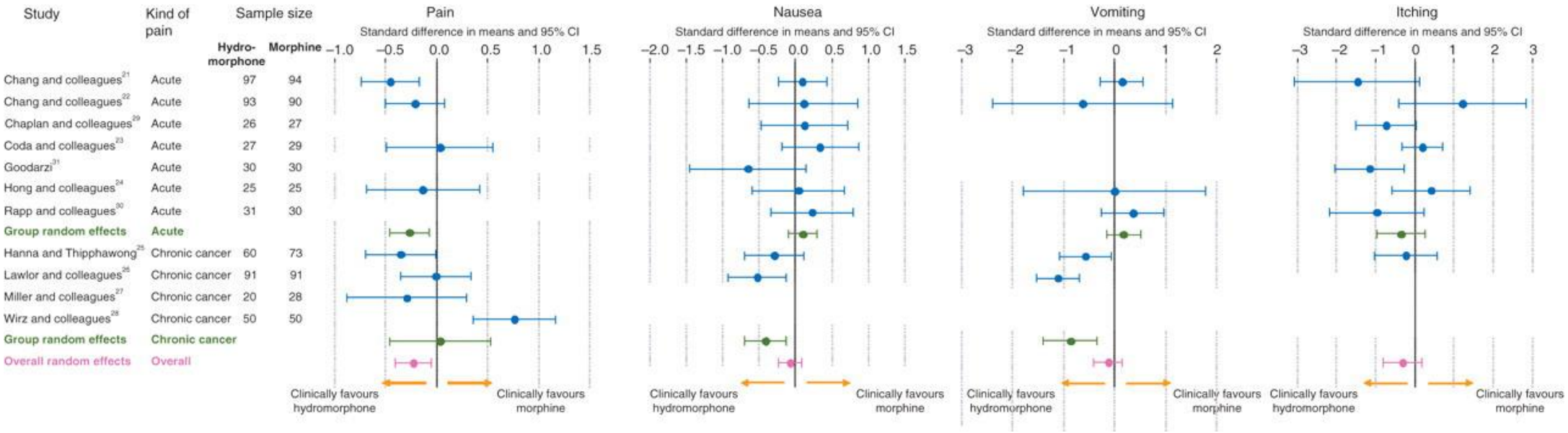
- Agonist at the mu opioid peptide receptor
- Much weaker affinity at the delta and kappa opioid peptide receptors
- No intrinsic limit to the analgesic effect of hydromorphone

- Comparable in analgesic efficacy to other potent opioids, including morphine and oxycodone, although differing potencies

- Side effects similar to other opioids, but can vary in severity between individuals

Lee KA et al. J Pall Med 2016; 19: 1179. Wright AW et al. Life Sci 2001; 69: 409.

Side effects



Felden L et al. Br J Anaeth 2011; 107: 319.

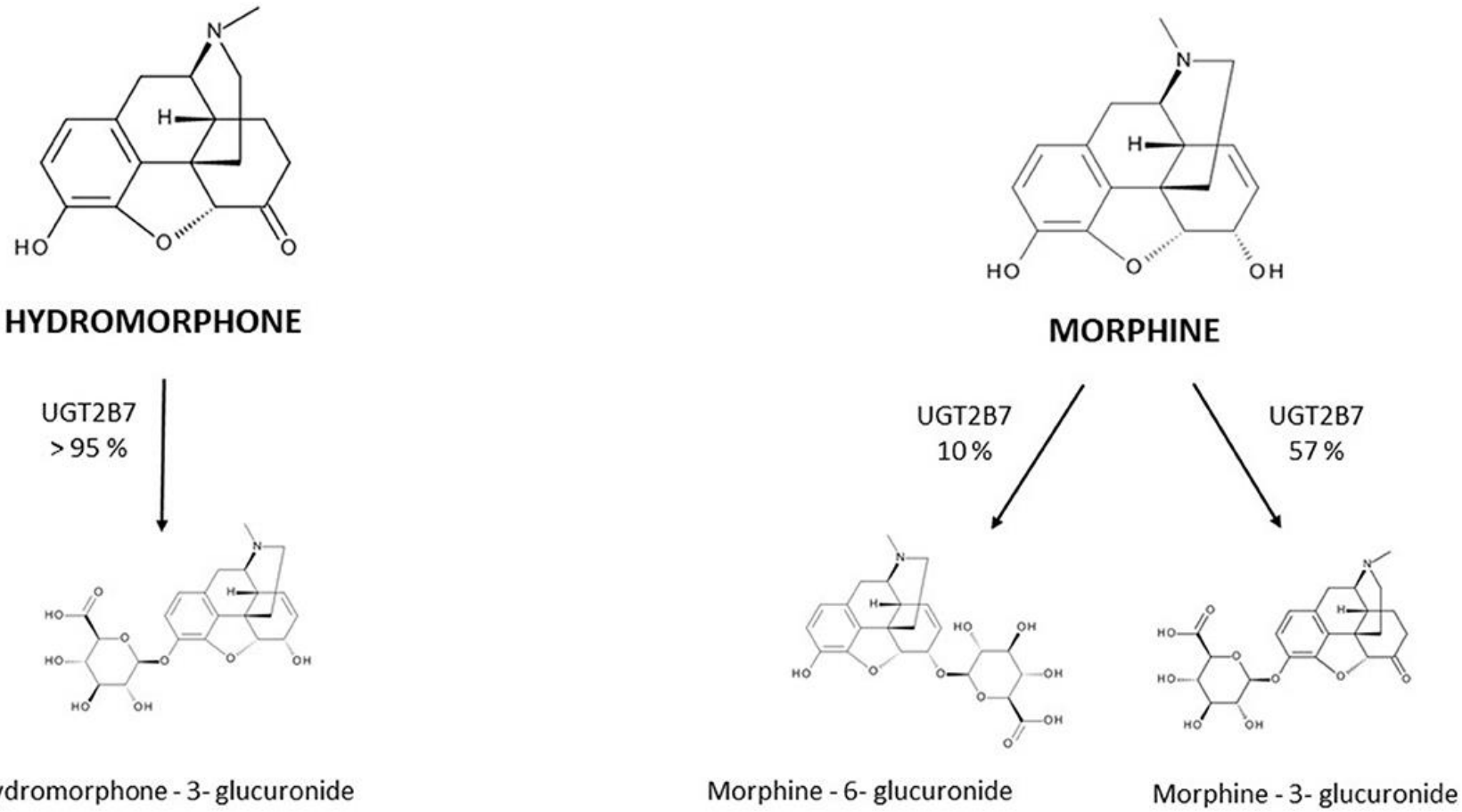
Absorption & distribution

Bioavailability	Oral	37 – 62%
Onset of action	IV	< 5 mins
	SC / IM	15 mins
	Oral (IR)	30 mins
T_{max}	Oral (IR)	45 mins
Duration of action	Oral (IR)	4-5 hours
	Oral (MR)	12 hours

- Absorbed in small intestine
- Wide inter-individual variation in bioavailability

Vallner J et al. J Clin Pharmacol 1981; 21: 152,

Metabolism



Rodieux F et al. Front. Pediatr 2022; 10: 842454. doi: 10.3389/fped.2022.842454

Active metabolites

- Hydomorphone 3-glucuronide
  - No analgesic activity (cf M3G)

  - CNS excitation (agitation, myoclonus, seizures) in animal models
  - Hyperalgesia, cognitive impairment, delirium, tremor, myoclonus,

  - May accumulate in renal impairment

Elimination

- Renal excretion, primarily as HM3G
- Small amounts of unchanged hydromorphone
- Urinary HM3G:HM about 25:1

- Elimination $t_{1/2}$ 2.6 +/- 0.9 hr

Opioid equivalence

- Oral morphine to hydrocodone
  - SPC recommends 1.3 mg hydrocodone is equivalent to 10 mg morphine (1 : 7)
  - Most other sources use 1 : 5 conversion ratio

- Oral to Injection
  - SPC recommends a 3:1 conversion ratio (i.e. dividing the total daily oral dose by 3 to give the total daily parenteral dose)
  - Most other sources including PCF use traditional 2:1 dose conversion ratio

Renal and hepatic impairment

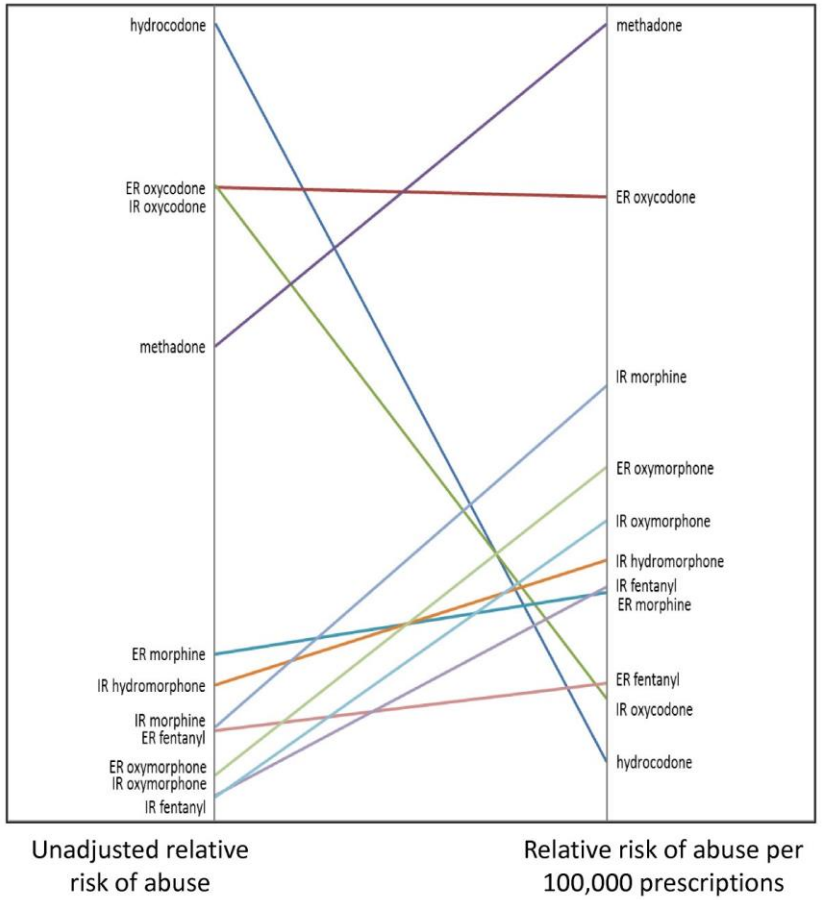
- Renal impairment
  - Use with caution
  - Lower starting doses in moderate – severe renal impairment
  - Has been used severe renal impairment and end stage renal failure

- Hepatic impairment
  - Lower starting dose in moderate hepatic impairment
  - Avoid if possible in severe hepatic impairment

Drug – Drug Interactions

- Sedatives
  - particularly benzodiazepines, gabapentinoids and other opioids
- MAOIs
  - During treatment and for 2 weeks after discontinuation
- Little metabolism by CYP450

Misuse and addiction potential



- Like all opioids risk for dependence, misuse and addiction
- Regular monitoring to assess efficacy, side effects and harms

Butler SF *et al.* Harm Reduct J 2011; **8**, 29.

CSCI compatibility considerations

- 50x greater aqueous solubility than morphine
- Dilute with WFI, sodium chloride 0.9% or glucose 5%
- Most compatibility data are with sodium chloride 0.9%

- 2-drug compatibility in WFI
  - Glycopyrronium
  - Hyoscine butylbromide
  - Hyoscine hydrobromide
  - Ketamine
  - Levomepromazine
  - Metoclopramide
  - Midazolam

- Concentration dependent incompatibility
  - Cyclizine
  - Dexametasone
  - Haloperidol
  - Ketorolac

Efficacy in cancer pain

- Compared to oxycodone
  - Patient reported pain intensity were similar in hydromorphone and oxycodone groups (n = 462 participants; GRADE: very low)

- Compared to morphine
  - For pain intensity measured by VAS from weeks 1–12, both morphine and hydromorphone groups had mean pain levels of 'no worse than mild pain. (n = 433 participants; GRADE: very low)

- Compared to fentanyl
  - Mean decrease from pain score at randomisation showed no clear difference between the 2 groups after 60 mins (n = 88 participants; GRADE very low)

Li et al. Hydromorphone for cancer pain. Cochrane Database of Systematic Reviews 2021, Issue 8. Art. No.: CD011108.

Tolerability compared with other opioids

	Oxycodone	Morphine	Fentanyl
Nausea	**1.13** (0.74 to 1.73)	**0.94** (0.66 to 1.30)	-
Vomiting	**1.18** (0.72 to 1.94)	**0.87** (0.58 to 1.31)	-
Dizziness	**0.91** (0.58 to 1.44)	**1.15** (0.71 to 1.88)	-
Constipation	**0.92** (0.72 to 1.19)	Higher incidence of constipation of hydromorphone occurred at a shorter treatment (24 days t), but not longer treatment periods (12 weeks)	-

Li et al. Hydromorphone for cancer pain. Cochrane Database of Systematic Reviews 2021, Issue 8. Art. No.: CD011108.

Cost

£££

Summary

- Similar efficacy to other opioids when used in similar doses
- Side effect profile similar, although may vary for individuals

- Morphine likely to remain first-line opioid for cancer pain

- Consider as an alternative when other opioids result in excessive adverse events such as sedation and respiratory depression, and in renal impairment

- Requires clinicians to balance potential benefits against potential adverse events on the merit of each individual case when recommending treatment in clinical practice