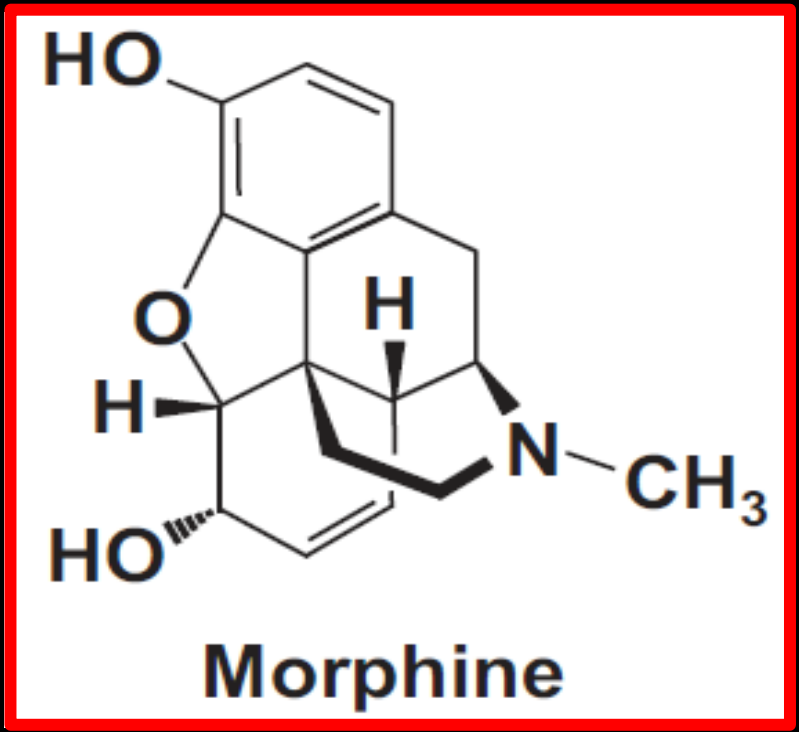
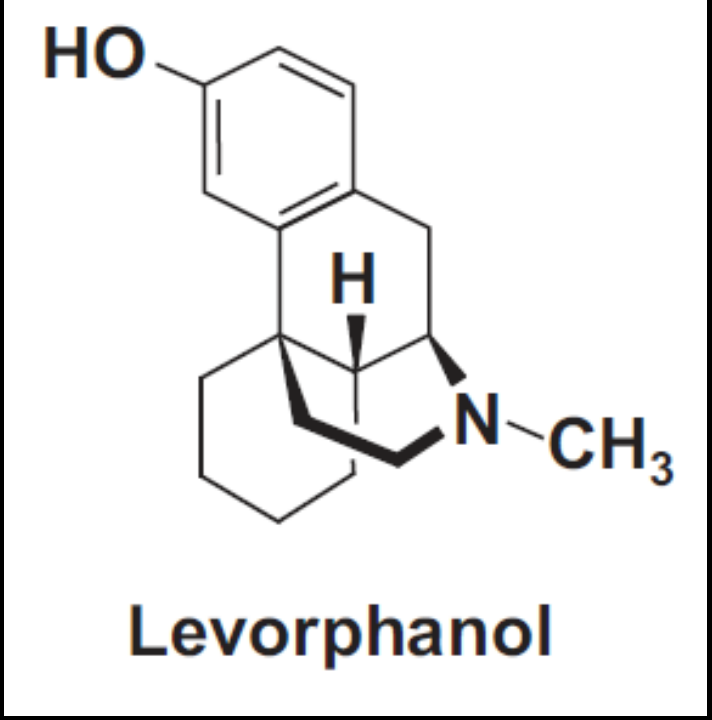
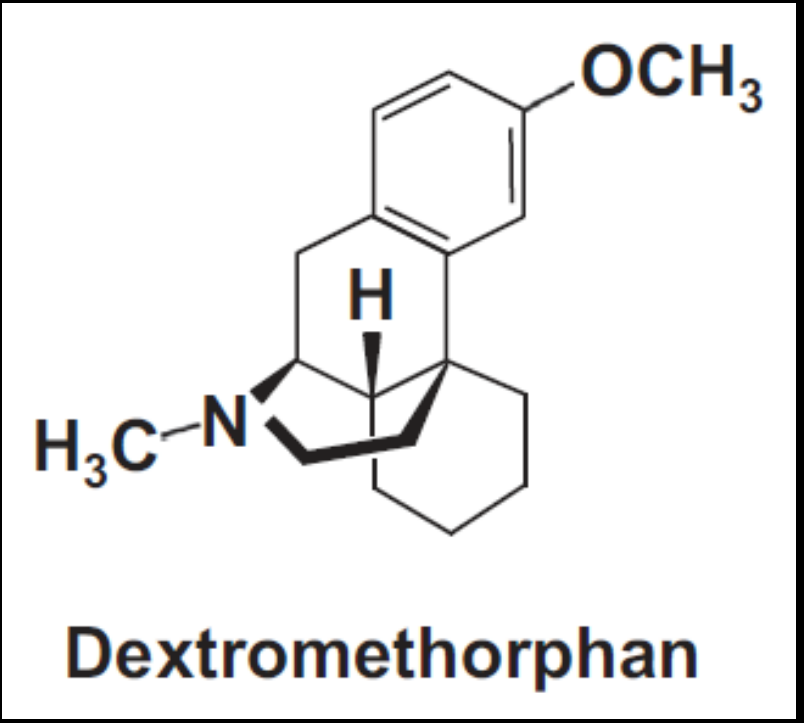
Jeffrey Fudin, PharmD, DAIPM, FCCP, FASHP

Methadone vs Levorphanol

Enantiomers





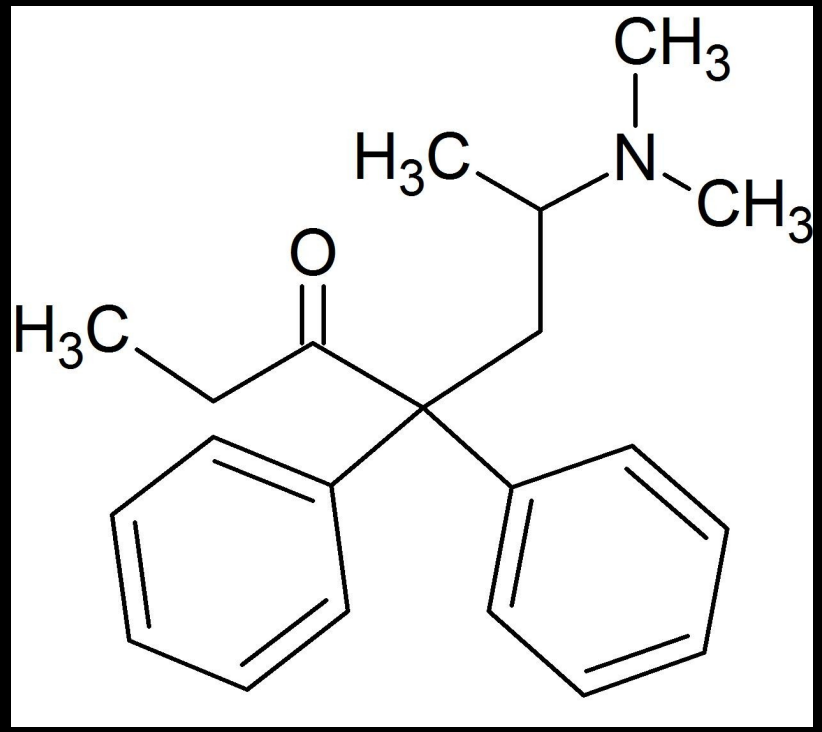


Chemically Dehydroxylated Phenanthrenes

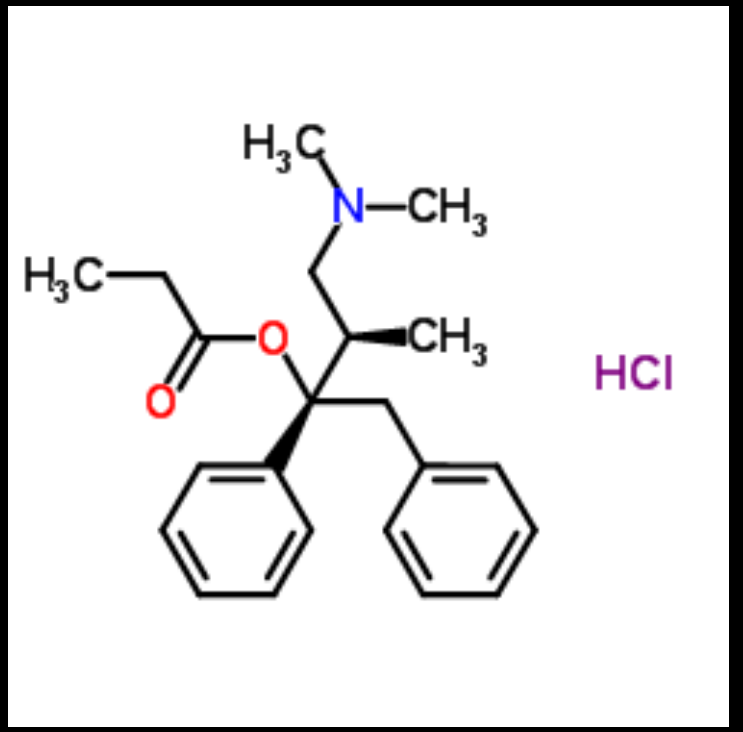
PAINWEEK

Gudin, J, Fudin J. and Nalamachu S. Levorphanol use: past, present and future. Postgraduate Medicine. 2016 January; 128(1): 46-53.

Methadone is a Diphenylheptane



Methadone



Propoxyphene HCl

https://paindr.com/wp-content/uploads/2018/10/Opioid-Structural-Classes-Figure_-updated-2018Oct.pdf

What do Methadone and Levorphanol have that other opioids don't offer?

- Complex Pharmacology
  - –Full opioid agonist activity
  - –Reuptake blockade of NE
  - –Reuptake blockade of 5-HT
  - –NMDA inhibition

Pham TC, Fudin J, Raffa RB. Is Levorphanol a Better Option Than Methadone? Pain Medicine. 2015 September; 16(9):1673-1679.

Practical Case Example of AB

- 78 year old Caucasian Patient with Severe Diabetic Neuropathy with typical comorbidities…
  - Multiple medications for pain have been tried
  - Current pain regimen includes:
    - Oxycodone CR 30mg P Q12H
    - Pregabalin 200mg Po Q12H
    - Duloxetine 40mg PO QAM
    - Desipramine 25mg PO QHS
    - Memantine 10mg PO QAM dementia, which is well-controlled
    - Quetiapine 50mg PO HS for PTSD nightmares
  - Let's review pharmacology and potential ADRs/toxicities from above…

AB has daily DPN pain rated 8/10 on current regimen

- Can we consolidate polypharmaceutical regimen?
- Is there an opioid that might be as or more useful than oxycodone?
  - –Tapentadol
  - –Tramadol
  - –Methadone
  - –Levorphanol

Provider decides on a slow methadone titration

- Change oxycodone CR 30mg to oxycodone IR 5mg PO QID PRN
- Start methadone 2.5mg PO BID
- Titrate slowly each week based on tolerability and response
- Consider reduction and/or elimination of duloxetine and desipramine due to overlapping pharmacology

AB 4-weeks later

- Methadone 5mg PO TID
- No oxycodone is being used
- Desipramine has been D/C'd
- Duloxetine is down to 20mg PO QAM
- Patient's pain is 1-2/10
- BUT…
  - Patient is talking to grandma
    - Grandma died 20 years ago
  - What do we do now?

Consider science, chemistry, and expertise

- AB tolerated oxycodone, a dehydroxylated phenanthrene
- AB tolerates memantine which is an NMDA inhibitor
- Oxycodone didn’t help the pain (mu agonist)
- Methadone did help the pain
  - multiple mechanisms, including NMDA blockade
- Levorphanol considerations and potential advantages
  - Dehydroxylated phenanthrene (like?)
  - Blocks NMDA (like?)
  - Blocks reuptake of NE (like?)
  - Won’t increase qTc interval (like?)

AB Plan and Outcome

- D/C methadone x 24 hours
- Start levorphanol 1mg (1/2 x 2mg tablet) PO Q8H after above
- Follow-up in one week…
  - No hallucinations
  - DPN pain: 1-2/10
  - Consider dose reduction and D/C of pregabalin

Methadone versus Levorphanol

PK, Safety, and Opioid Conversion Risks

Methadone vs Levorphanol Pharmacology Summary

Compound	MOR	DOR	KOR	NRI	SRI	NMDA*	nACh†	ED_{50}‡
Morphine	1	145	23	IA	IA	IA	—	2.4
Methadone (±)	2	435	405	—	—	≥850	—	0.9
L isomer	1	371	1,860	702	14	—	—	—
D isomer	20	960	1,370	12,700	992	—	2,500	—
Levorphanol	0.1–0.4	4–5	2–4	1,210	86	630	—	0.4
Dextromethorphan	1,280	11,500	7,000	240	23	1,720	—	—
Tramadol (±)	2,120	57,700	42,700	785	992	—	—	—
(+) enantiomer	1,330	62,400	54,000	2,510	528	—	—	—
(–) enantiomer	24,800	IA	53,500	432	2,350	—	—	—

MOR, DOR, KOR = μ, δ, κ opioid receptor type, respectively; NRI = neuronal norepinephrine reuptake inhibition; SRI = neuronal serotonin (5-HT) reuptake inhibition; nACHR = $\alpha 3\beta 4$ nicotinic acetylcholine receptor; ED_{50} = rat tail-flick test; IA = inactive (>100,000 nM); NT = not tested.

Pham TC, Fudin J, Raffa RB. Is Levorphanol a Better Option Than Methadone? Pain Medicine. 2015 September; 16(9):1673-1679.

Levorphanol Less Drug Interactions

- Levorphanol is metabolized via phase II glucuronidation
  - Lack of CYP450 interactions
  - Lack of p-glycoprotein (P-gp) interactions
- The metabolite is excreted renally

Prommer E. Levorphanol: the forgotten opioid. Supportive care in cancer. 2007 Mar 1;15(3):259-64.

Methadone More Drug Interactions

- Methadone is metabolized through multiple cytochrome (CYP) P450 enzymes
  - Major: CYP3A4 and CYP2B6
  - Minor: CYP2D6 and CYP2C19
- Recall methadone is a racemic mixture
- Genetic polymorphisms to CYP2B6 exist

Enantiomer	Characteristic	CYP Enzyme
R-methadone	Analgesic activity	CYP3A4
S-methadone	Adverse effects including QTc prolongation	CYP2B6

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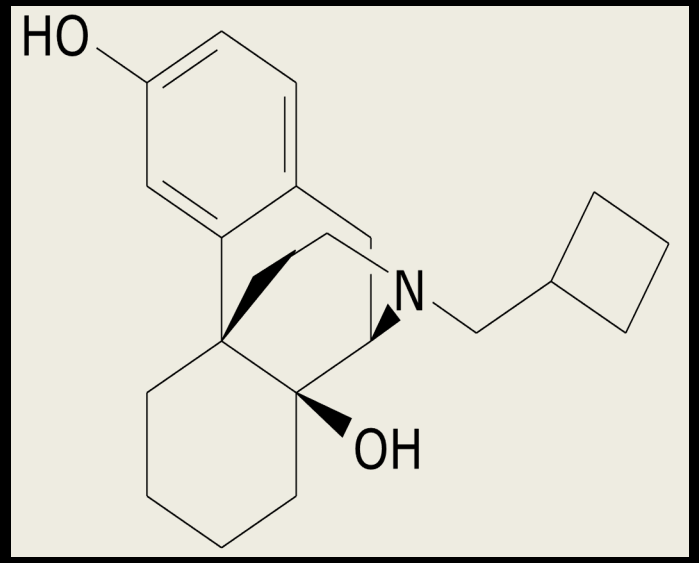
Butorphanol vs Pentazocine

Butorphanol



A Morphinan
Phenanthrene

Pharmacology

- Structurally similar to levorphanol except:
  - Hydroxy substitution at position 14
  - N-methyl group substitution for cyclopropyl
- Butorphanol is a partial agonist/antagonist
  - Mu 0.4 I Kappa 1.7 I Delta 25
  - Partial agonist at mu receptors
  - Agonist at kappa receptors
- 7 times more potent than morphine
- Butorphanol is a partial agonist/antagonist
  - Partial agonist at kappa opioid receptors
    - ✓ Dysphoria, dizziness, sedation, sensory disturbance
  - Ceiling opioid effect at 15mg/70kg

Chang K et al. Proc Natl Acad Sci. 1981; 78:4141-4145.
Kallos T et al. Anaesthesia. 1979; 34:633-637.
Reece P et al. J Clin Pharmacol. 1994; 34:1126-1132.

Butorphanol

Pharmacokinetics

- Bioavailability
  - Oral 17%
  - SL 19-29%
  - Nasal 48-70%
- Absorption: Tmax: 10 min
- Metabolism: Extensive Phase I metabolism → Phase II Glucuronidation
  - Both metabolites are inactive
- Excretion: t1/2 = 5.4 hrs
  - 70-80% urine
  - 15% feces

Shyu W et al. Biopharm Drug Dispos. 1993;14:371-379.
Wermeling D et al. Clin Ther. 2005; 27:430-440.
Gillis J et al. Drugs. 1995; 50:157-175.

Butorphanol Clinical Pearls

Pros

- Rapid onset
- Effective migraine termination
  - Guidelines endorse use
- Demonstrated Efficacy in Clinical Trials:
  - C-Section
  - Migraine
  - Dental Surgery
  - Fistulectomy
  - Musculoskeletal pain

Cons

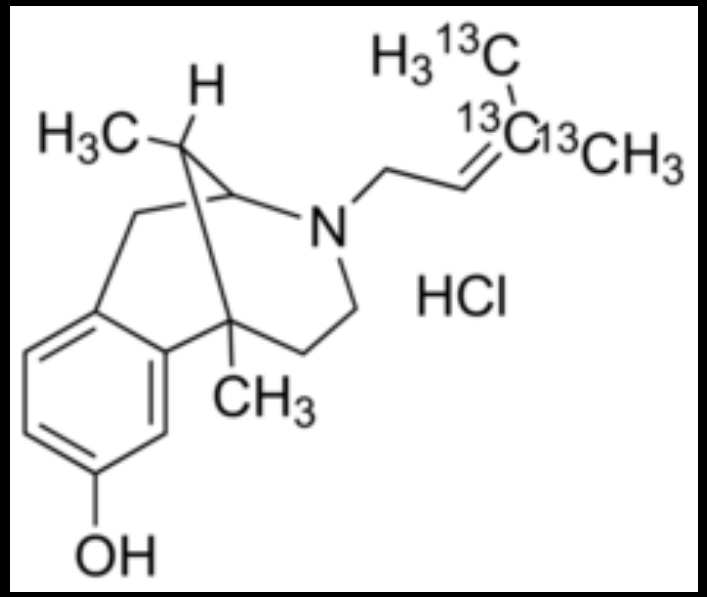
- Higher abuse potential than initially thought
- Limited doses per bottle
  - Multiple bottles per month
- Dysphoria
  - Yet high patient acceptance
- Study showed 22% patients overused (15 bottles per month)

Pentazocine: An Interesting History

- 1967: Pentazocine single entity was approved by FDA
  - Sterling Drug Company, Rensselaer NY
- 1977 to 1981: “T's and Blues”
  - Street IV abuse of a pentazocine/tripelennamine
  - Sudden and violent deaths (62 homicides, 7 fatal intoxications)
  - Emergency room visits (137 in 1980)
  - Admissions to drug treatment programs (7.7% in 1978 up to 64% in 1981)
    - Police laboratory cases (100 in 1977 – 1978 / 700 in 1981
    - Initial popularity of the drugs was related to the decline in the quality of street heroin (2.5% in 1977 reduced to 0.5% by 1979)
  - Serious adverse reactions from IV Combo:
    - Clonic-tonic seizures and pulmonary foreign body granulomatosis
    - Ethanol and diazepam were present in several ME cases
- 1982: Combination of pentazocine with naloxone was FDA approved

Poklis A. Pentazocine/tripelennamine (T's and blues) abuse: a five year survey of St. Louis, Missouri. Drug and alcohol dependence. 1982 Oct 1;10(2-3):257-67.

Pentazocine



A Benzomorphan (enantiomers)

Pharmacology

- (-) pentazocine is a κ-opioid receptor agonist
- (+) pentazocine has 10-fold greater affinity for the sigma receptor.
- Pentazocine is a mixed agonist-antagonist
  - Agonist at the kappa opioid receptors
  - Weak antagonistic action at the mu opioid receptors
  - Agonist at sigma “opioid” receptors
    - ✓ Hallucinations, nightmares and delusions
  - Ceiling opioid effect

1. Hayashi T, Su TP. The sigma receptor: evolution of the concept in neuropsychopharmacology. Current neuropharmacology. 2005 Oct 1;3(4):267-80.
2. Sugai N. Recent developments in the pharmacology and clinical use of pentazocine. Masui. The Japanese journal of anesthesiology. 1991 Jul;40(7):1037.

Post-Test Question #1

Which of the following are true regarding tramadol and tapentadol?

A. Both are opioids that block reuptake of norepinephrine, serotonin, and have reduced GI adverse effects compared to traditional opioids

B. Tapentadol and tramadol have reduced street value and abuse potential compared to traditional opioids

C. Tapentadol is a prodrug susceptible to drug interactions and genetic polymorphisms

D. Tapentadol undergoes Phase I metabolism (CYP450), while tramadol undergoes Phase II metabolism (glucuronidation)

Post-Test Question #2

Which of the following are true regarding levorphanol and methadone?

A. Both are full agonist opioids that also block reuptake of norepinephrine, serotonin, inhibit GABA, and reduce glial cell activation

B. Both are partial agonists that affect kappa and mu opioid receptors, but also block NMDA, and NE reuptake

C. Levorphanol undergoes Phase I metabolism only, while methadone requires Phase II metabolism with high risk of polymorphic variability.

D. Methadone is less potent than levorphanol

Post-Test Question #3

Which of the following is NOT true regarding butorphanol?

A. 7 times more potent than morphine
B. Rapid onset
C. Ceiling effect on respiratory depression
D. Partial agonist at the kappa opioid receptors and full agonist at the mu opioid receptors

Post-Test Question #4

Pentazocine pharmacology is most consistent with which of the following?

A. Agonist at the kappa opioid receptors and weak antagonistic action at the mu opioid receptors

B. Antagonist at the kappa opioid receptors and significant agonist action at the mu opioid receptors

C. Full agonist at the mu opioid receptors

D. Increasing doses are infinitely linear and restricted only by toxicity

Thank you!