PAINWEEK®

The Road Less Traveled: Appropriate Use of Atypical Opioids for Individualized Care

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Titles & Affiliations

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Dr. Atkinson Disclosures

Affiliation	Role/Activities
Axial Healthcare Inc	Consultant – Design, review, and implement opioid metrics and peer review utilizing claims data
ASHP	Opioid REMS virtual CE design, presentation
Auburn University/AL Dept of MH	Speaker – Opioid Crisis CE Programs
Rockpointe, Inc	REMS opioid presentation/lecture, OUD Program (a continuing education company)
Purdue Pharma LP	Epidemiology Advisory Board – Category 4 Post-Marketing Studies for OxyContin

Dr. Fudin Disclosures

Affiliation	Role/Activities
Abbott Laboratories	Speaking, non-speakers bureau
AcelRx Pharmaceuticals	Acute perioperative pain (speakers bureau, consulting, advisory boards)
BioDelivery Sciences International	Collaborative publications, consulting, advisory boards
Firstox Laboratories	Micro serum testing for substances of abuse (consulting)
GlaxoSmithKline (GSK)	Collaborative non-paid poster presentations)
Medscape/WebMD	Presentations / webinars on medication assisted treatment (MAT) for opioid-use disorder
Pharmacy Times	Webinars, writing/publishing
Practical Pain Management	Co-Editor-At-Large, writing, and editing
Rockpointe, Inc	REMS opioid presentation/lecture (a continuing education company)
Scilex Pharmaceuticals	Collaborative non-paid publications
Salix Pharmaceuticals	Speakers bureau, consultant, advisory boards
Trinity Health, Inc.	Direct patient care, virtual consultations for pain management akin to a virtual private medical practice

Learning Objectives

- Review pharmacokinetics and pharmacodynamics of atypical opioids
- Explain clinical rationale for atypical opioid use and multimechanistic effects
- Emphasize specific patient cases where an atypical opioid was utilized to leverage its unique properties for successful management
- Describe clinical pearls related to effective clinical application of atypical opioids

Pre-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)

Pretest 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

Pretest 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

Pretest 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

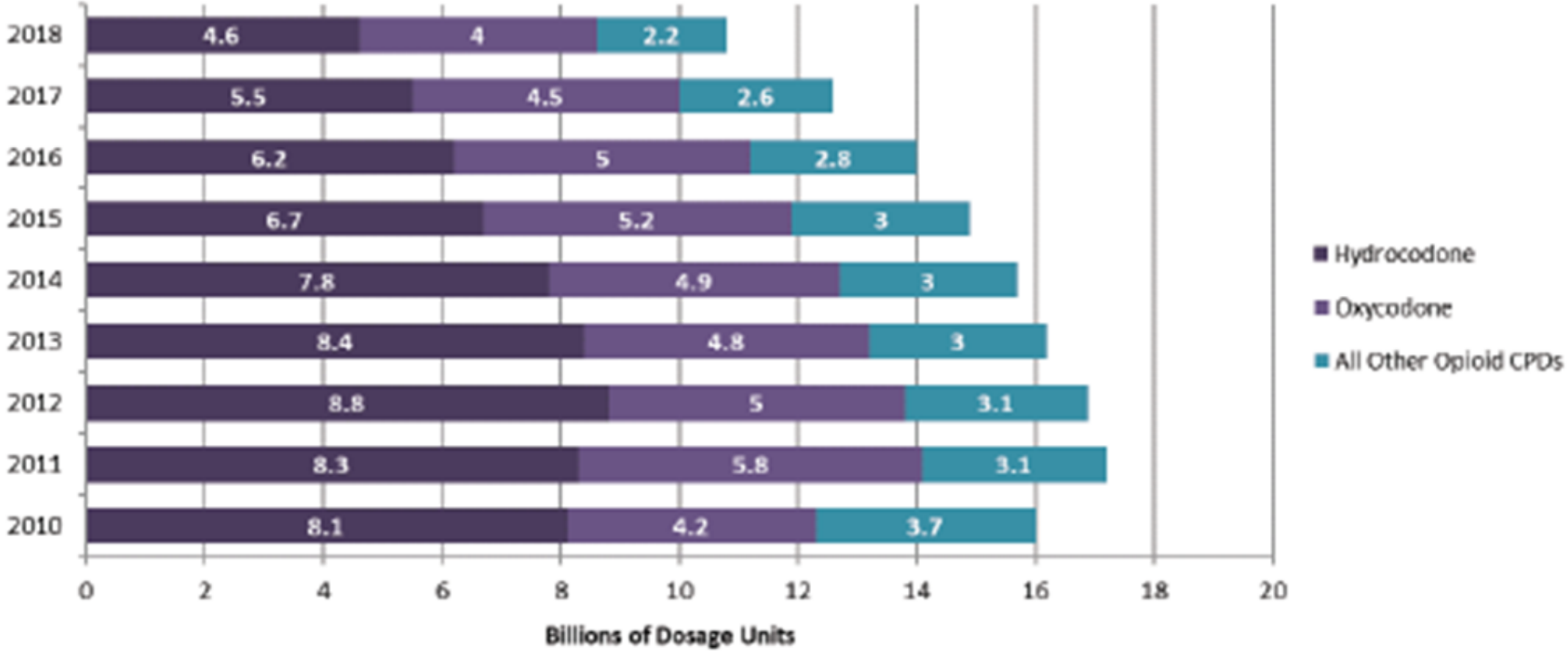
US Prescription Opioid Prescribing Trends

Year	Total Number of Prescriptions	Prescribing Per 100 People
2006	215,917,663	72.4
2007	228,543,773	75.9
2008	237,860,213	78.2
2009	243,738,090	79.5
2010	251,088,904	81.2
2011	252,167,963	80.9
2012	255,207,954	81.3
2013	247,090,443	78.1
2014	240,993,021	75.6
2015	226,819,924	70.6
2016	214,881,622	66.5
2017	191,909,384	59.0
2018	168,168,611	51.4

CDC. Opioid Prescribing Rate Maps. https://www.cdc.gov/drugoverdose/maps/rxrate-maps.html

INDIVIDUALIZED CARE or ONE SIZE FITS ALL?

Figure 23. Hydrocodone and Oxycodone Prescription Drugs Sold to Retail Level Purchasers Compared to All Other Opioid CPDs in Billions of Dosage Units, 2010 – 2018



Source: Automation of Reports and Consolidated Orders System

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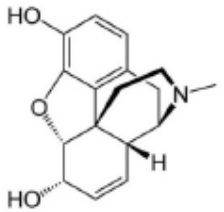
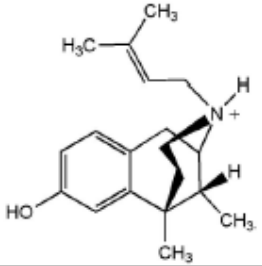
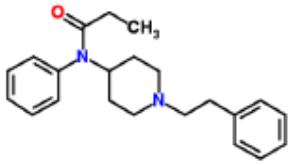
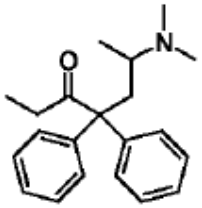
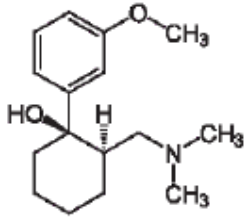
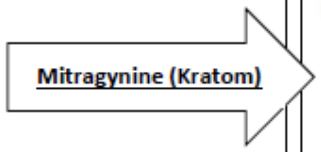
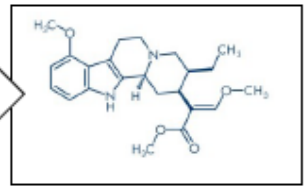
DEA. National Drug Threat Assessment 2019; page 32.

Critical Concepts of Opioid Medication Selection

Not All Opioids are Created Equally

PHENANTHRENES	BENZOMORPHANS	PHENYLPIPERIDINES	DIPHENYLHEPTANES	PHENYLPROPYL AMINES
				
MORPHINE	PENTAZOCINE	FENTANYL	METHADONE	TRAMADOL
Buprenorphine* Butorphanol* Codeine Dextromethorphan* Dihydrocodeine Heroin (diacetyl-morphine) Hydrocodone* Hydromorphone* Levorphanol* Methylnaltrexone** Morphine (Opium, conc) Nalbuphine* Naloxone* Naloxegol* Naltrexone** Oxycodone* Oxymorphone*	Pentazocine	Alfentanil Fentanyl Remifentanil Sufentanil Meperidine Diphenoxylate[a] Loperamide[a] **Illicit Fentanyl** Furanyl fentanyl Acetyl fentanyl Fluoro-fentanyl Carfentanil Others[b]	Methadone Propoxyphene Mitragynine (Kratom) 	Tapentadol Tramadol 
CROSS-SENSITIVITY RISK				
PROBABLE	POSSIBLE	LOW RISK	LOW RISK	LOW RISK

*Agents lacking the 6-OH group of morphine, possibly decreases cross-tolerability within the phenanthrene group
**6-position is substituted with a ketone group and tolerability is similar to hydroxylation

Jeffrey Fudin, BSPharm, PharmD, DAIPM, FCCP, FASHP, FFSMB
http://paindr.com/resources/quick-references/ (See "Opioid Chemistry")

a. Previously incorrectly listed as "Benzomorphans"
b. Bettinger JJ, Trotta ND, Fudin J. Wegrzyn EL, Schatman ME. Understanding the differences between pharmaceutical and illicit fentanyl and their analogues could save the opioid crisis. Practical Pain Management. 2018. July/August 18(5):59-67.

See separate slide for tapentadol & tramadol

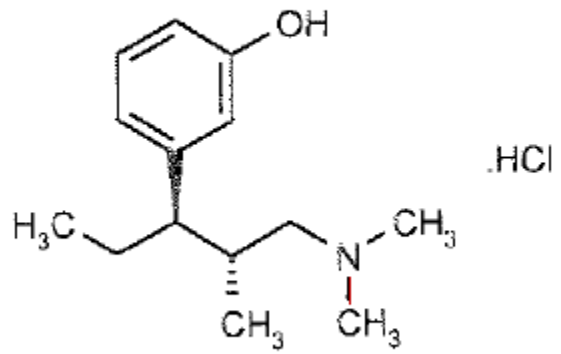
https://paindr.com/wp-content/uploads/2018/10/Opioid-Structural-Classes-Figure_-updated-2018Oct.pdf

Chemical Classes of Opioids (continued)

Dimethyl-amino hydrochlorides

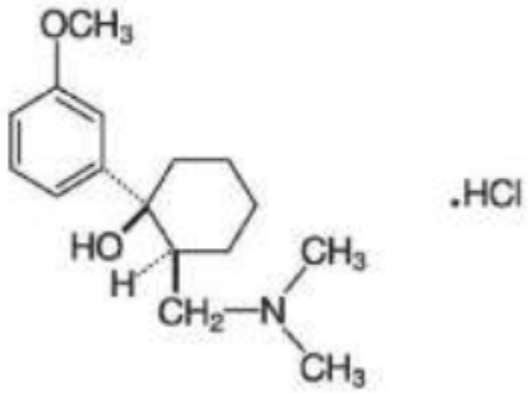
Tapentadol

Tapentadol is a 3-[(1*R*,2*R*)-3-(dimethylamino)-1-ethyl-2-methylpropyl]phenol monohydrochloride.



Tramadol

Tramadol is a (±)cis-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl cyclohexanol hydrochloride.



Keys to Effective Use of Atypical Opioids

Knowledge in KEY areas:

- Mechanism – Improved targeting of pain generators
- Metabolism – Challenges or drug interactions with metabolic pathway
- Titration to Steady State – When will they receive the full effect of the medication
- Counseling points – Explain what to expect with initiation and titration

Phase I Metabolism

Oxidative reactions – CYP450

- Age decreases number of isoenzymes
  - Increases sensitivity to medications and drug interactions
- CYP3A4 metabolizes 50% of all drugs
- CYP 2D6, 2C9, 2C19 are most polymorphic
  - CYP2D6 most of all
- Hepatic dysfunction may result in 50-100% decrease in number of isoenzymes

Cayot A et al. Clin Rheumatol. 2014; 33(9):1231-1238.
Lynch T et al. Am Fam Physician. 2007; 76(3):391-396.

CYP450 Polymorphisms

- CYP3A4: influenced by gender
  - Inducible by a variety of substances
- CYP2C9: increased risk for bleeding with NSAIDs
- CYP2D6: predominantly influenced by genetic polymorphisms
  - Metabolizes 20-30% of all drugs, many of which are in pain management
  - Impacts antidepressant and opioid metabolism

Cayot A et al. Clin Rheumatol. 2014; 33(9):1231-1238.
Lynch T et al. Am Fam Physician. 2007; 76(3):391-396.

Phase II Metabolism

Glucuronidation (UGT)

- High capacity/low affinity pathway
- Less affected than CYP450 in mild to moderate hepatic dysfunction
- Decreased risk of drug interactions
  - Compared to CYP450

Verbeek R. Eur J Clin Pharmacol. 2008; 64:1147-1161.

Soars M et al. Drug Metabol Disp. 2004; 32:140-148.

Phase II Metabolism

Some drugs are actually active metabolites and have already undergone Phase I Metabolism

- Rare for drugs to repeat Phase I
  - Examples: Hydromorphone, Oxymorphone, Oxazepam, Temazepam
- Decreased risk of drug interactions
  - Often preferred in hepatic dysfunction
- Accumulation occurs in moderate to severe hepatic dysfunction
  - Regardless of Phase I or Phase II
  - Phase II is more predictable

Verbeek R. Eur J Clin Pharmacol. 2008; 64:1147-1161.

Soars M et al. Drug Metabol Disp. 2004; 32:140-148.

Metabolic Pathway for RX Elimination

DRUG	OPIOID CLASS	MAJOR METABOLIC PATHWAY
Morphine	Phenanthrene (w/-OH)	Glucuronidation
Hydrocodone	Phenanthrene	Glucuronidation, minor 2D6
Hydromorphone	Phenanthrene	Glucuronidation
Codeine	Phenanthrene (w/ -OH)	Demthylation, glucuronidation, 2D6
Levorphanol	Phenanthrene	Glucuronidation
Oxycodone	Phenanthrene	Demethylation 3A4, glucuronidation, keto-reduction, minor 2D6
Oxymorphine	Phenanthrene	Glucuronidation
Meperidine	Phenylpiperidine	Oxidation, hydrolysis, demethylation, glucuronidation
Fentanyl	Phenylpiperidine	Oxidation, hydrolysis, minor 3A4
Alfentanil	Phenylpiperidine	Oxidation
Sufentanil	Phenylpiperidine	Dealkylation, demethylation
Methadone	Diphenylheptane	Demethylation, 3A4 substrate (significant) and other P450 iso-enzymes

Volles DF, McGory R. Pharmacokinetc considerations, 15:5:Jan 1999.

Tramadol vs Tapentadol

Clinical Case Question

You have a patient with severe uncontrolled pain described as throbbing, burning, and stinging pain. Available non-opioid therapies have been optimized or failed. She has used low dose hydrocodone for years but pain is severe and it's not working, what would be your suggestion?

1. Increase hydrocodone/APAP
2. Rotate to transdermal fentanyl
3. Rotate to tramadol
4. Rotate to oxycodone

Tramadol vs. Tapentadol

Properties	Tramadol	Tapentadol
Mu Binding Affinity	6000x less than morphine	18x less than morphine
Metabolism	Significant CYP 450 2D6, 3A4	Conjugation, O-Glucuronide
Drug Interactions	Many	Few
Neuroamine Activity	5-HT / NE	NE, almost no 5-HT

- Combined mechanism delays development of tolerance
  - –Morphine develops tolerance 2.5 times faster than tapentadol

Tapentadol Clinical Trials

Compared Adverse Effects Profiles for Tapentadol and Oxycodone in Phase III Clinical Trials

Phase III Clinical Trials	Study Population	Gastrointestinal (GI)						Central Nervous System (CNS)					
		Nausea		Vomiting		Constipation		Dizziness		Somnolence		Headache	
Immediate-Release (IR)		Tap	Oxy	Tap	Oxy	Tap	Oxy	Tap	Oxy	Tap	Oxy	Tap	Oxy
Hartrick et al.	End-stage Joint Disease	18%	41%	7%	34%	4%	26%	18%	23%	6%	12%	6%	3%
Daniels et al.	Bunionectomy	49%	67%	32%	42%	10%	15%	31%	30%	21%	10%	12%	14%
Hale et al.	Lower Back Pain & Osteoarthritis	18%	29%	17%	30%	13%	27%	18%	17%	10%	9%	N/A	N/A
Extended-Release (ER)													
Buynak et al.	Lower Back Pain	20%	35%	9%	19%	14%	27%	12%	17%	13%	16%	20%	17%
Afilalo et al.	Knee Osteoarthritis	22%	37%	5%	18%	19%	37%	18%	19%	11%	20%	15%	15%
Schwartz et al.	Diabetic Peripheral Neuropathy	14%	-	7%	-	6%	-	8%	-	N/A	-	5%	-
Wild et al.	LBP & OA; LT Safety & Efficacy	18%	33%	7%	14%	23%	39%	15%	19%	15%	11%	13%	8%

Tap = Tapentadol; Oxy = Oxycodone; N/A = Not Available due to lack of reporting

Understanding Street Value

Predictors of abuse potential

- Cmax (higher peak)
- Tmax (faster onset)
- Mu-receptor affinity
- Dopamine release

Low← Street Value →High

Rank order opioid street value

- Hydromorphone IR
- Buprenorphine
- Oxymorphone IR (ER generic)
- Methadone
- Oxycodone IR

Dasgupta N et al. *J Med Internet Res*. 2013; 15:e178.
Lebin JA et al. *Pharmacoepidemiol Drug Saf*. 2019; 28:15-20.

Measuring Abuse Liability

Tables show rates of intentional abuse reports to Poison Control Centers

Drug	Event Rate	Rate Ratio
Tapentadol	.015	1
Oxymorphone	.114	7.414
Hydromorphone	.137	8.851
Morphine	.275	17.816
Tramadol	.521	33.736
Hydrocodone	1.255	81.276
Oxycodone	1.302	84.322

Event Rate per 1,000,000 population

Drug	Event Rate	Rate Ratio
Hydrocodone	.131	.632
Tramadol	.159	.766
Tapentadol	.207	1
Oxycodone	.280	1.098
Morphine	.374	1.459
Hydromorphone	.534	2.071
Oxymorphone	1.168	4.517

Event Rate per 10,000 prescriptions

Vosburg et al. Pain. 2018; 19(4):439-453.

Clinical Pearls

Tramadol

- Partial agonist & Prodrug
- Roughly equivalent to codeine
- Targets neuropathic pain
- Susceptible to 2D6 polymorphisms
- Caution with other serotonergic agents
- Seizure more likely than overdose

Tapentadol

- Parent molecule is the active drug
- Potency relies on NE reuptake
- Targets neuropathic pain
- Low risk of drug interactions
- Decreased GI symptoms
- Minimal serotonergic activation
- Headache and BP complicate abuse

Clinical Case Revisited

You have a patient with severe uncontrolled pain described as throbbing, burning, and stinging pain. Available non-opioid therapies have been optimized or failed. She has used low dose hydrocodone for years but pain is severe and it's not working, what would be your suggestion?

1. Increase hydrocodone/APAP
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