TramaDO or TramaDON'T?
Re-evaluating the role of tramadol in pain management

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Pharmacy Grand Rounds
March 24th, 2020

The Opioid Crisis

400,000 deaths due to opioid overdose from 1999-2017

Three waves:
Prescription → Heroin → Synthetic

Each day ~130 Americans die from an opioid overdose

MAYO CLINIC

WONDER. CDC, National Center for Health Statistics; 2017.
Drug and Opioid-Involved Overdose Deaths, US. M&M Weekly Report; Dec 2018.

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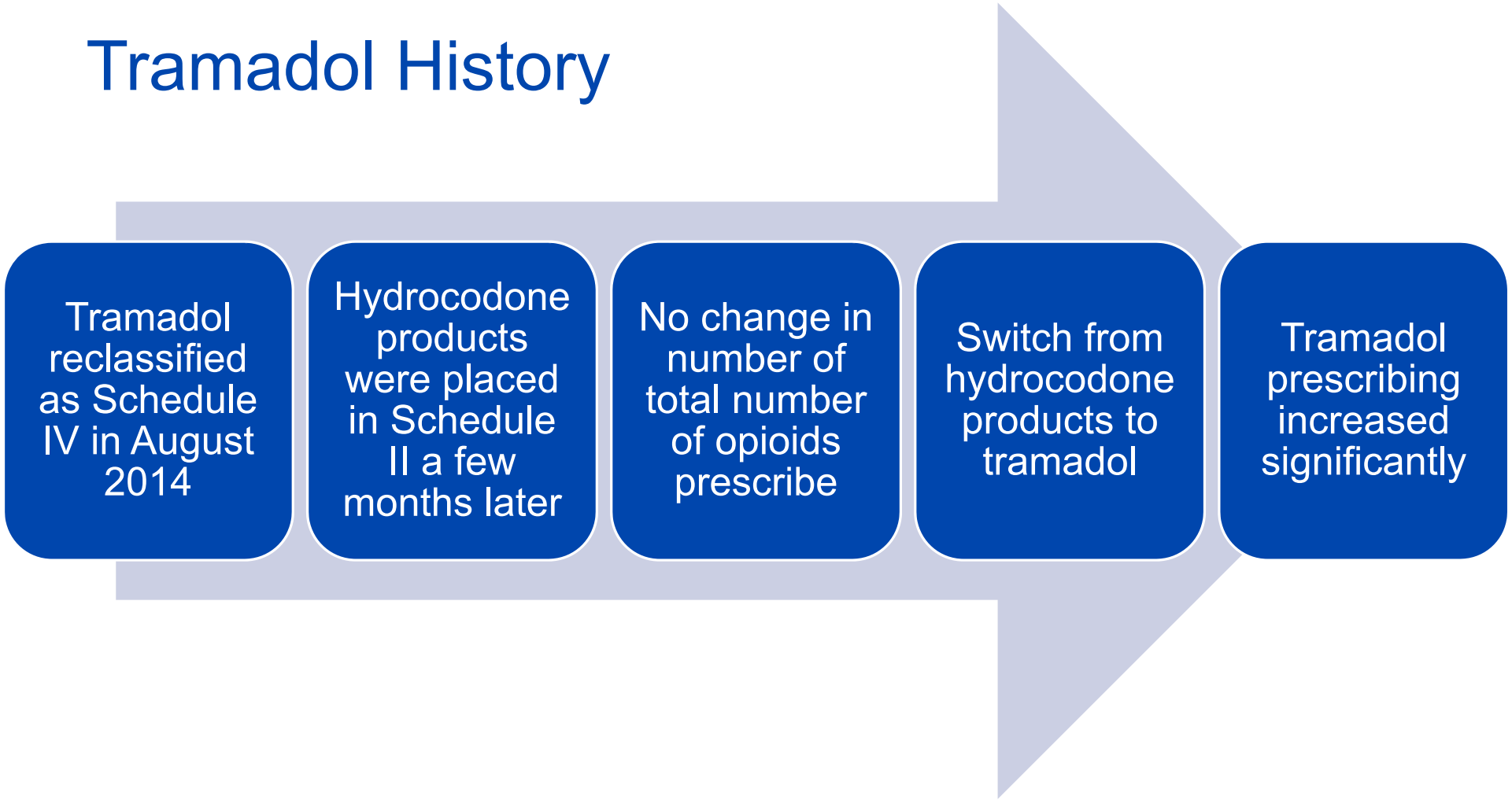
Objectives

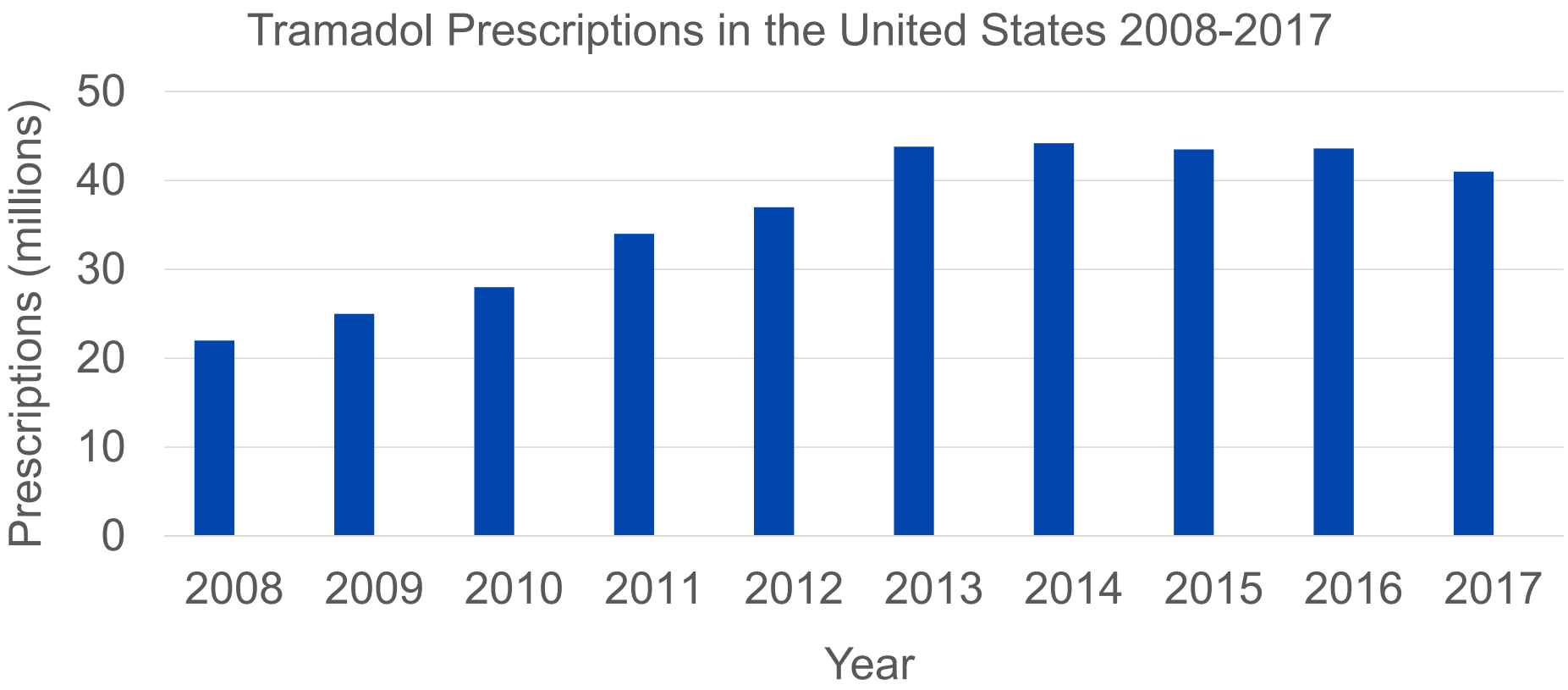
- Discuss evidence for efficacy of tramadol for indications of acute or chronic pain in adults
- Describe major safety and pharmacokinetic considerations for the utilization of tramadol
- Assess the current misuse and abuse potential of tramadol

Tramadol History



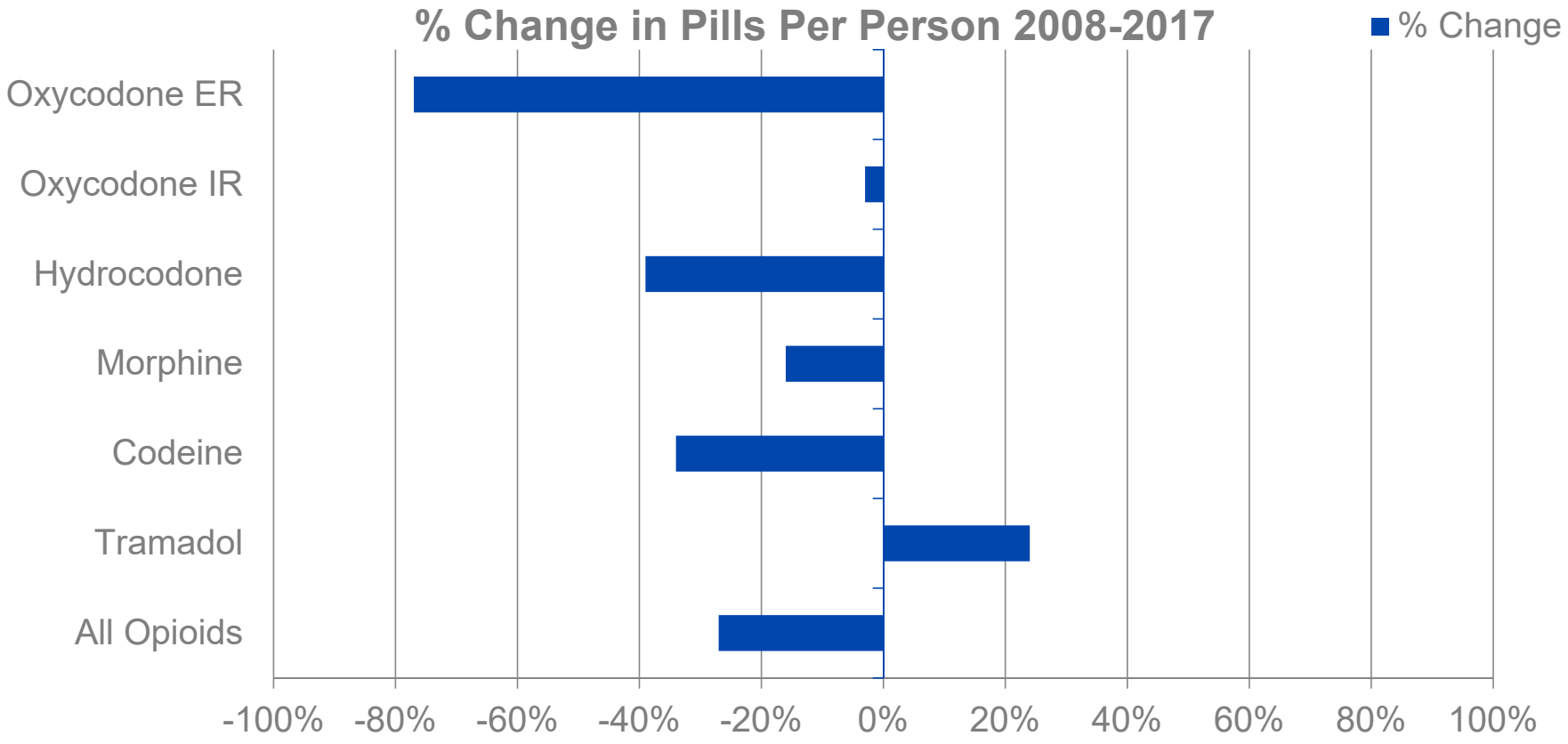
J Neurosci Rural Pract. 2018, 9(3):397-403.
Clin Toxicol. 2019;57(11):1064-1072..

Tramadol Prescribing Trends



DEA. Tramadol Drug & Chemical Evaluation Section. 2018.
Curr Pain Headache Rep. 2019;23(10):76.

Opioid Prescribing Trends



ER= extended release
IR= immediate release

Health Care Cost Institute. Opioids Prescriptions 2008 to 2017. July 2019.

Tramadol Pros & Cons

- Schedule IV
- Proven efficacy
-Safer opioid
-Lower risk of abuse

?

Pharmacology of Tramadol

Metabolized primarily via CYP2D6

Metabolite M1 responsible for most of its opioid activity

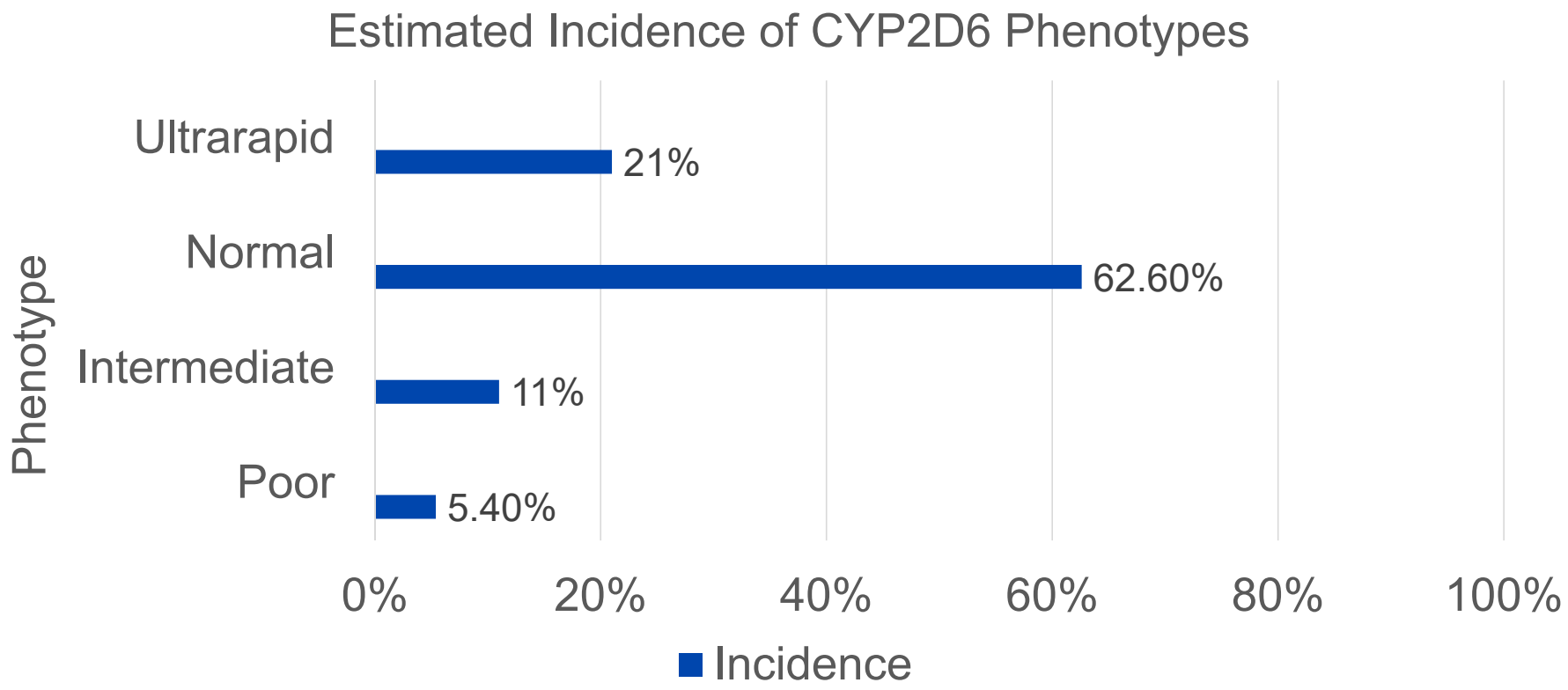
Inhibits the reuptake of norepinephrine and serotonin

Metabolites are renally eliminated

CYP= cytochrome P450

BJA. 2019;122(6):e136-e145.

Pharmacogenetic Considerations for Efficacy



CYP= cytochrome P450

Genetics in Medicine. 2017,19(69-76).

Pharmacogenetic Considerations for Efficacy

Effect of CYP2D6 polymorphisms on metabolism of tramadol:

Phenotype	Genotype	Implications	Therapeutic Recommendations
Ultrarapid	More than two copies of functional alleles	High concentrations of M1 metabolite	 by 50%
Normal	Two copies of functional alleles	Normal metabolism and M1 concentrations	
Intermediate	One active allele and one inactive allele or one decreased activity allele and one inactive allele	Potential for slightly decreased concentrations of active M1 metabolite	 Or use alternative
Poor	Two inactive alleles	Low concentrations of active M1 metabolite	

CYP= cytochrome P450

Clin Pharmacol Ther. 2011;89(5):662-673

ADE=adverse drug events

Tramadol Pros & Cons

- Schedule IV
- Proven efficacy
-Safer opioid
-Lower risk of abuse

-CYP2D6 variation

Assessment Question #1

Which of the following medications has tramadol shown superiority to in regard to the treatment of acute or chronic pain?

- Ibuprofen
- Acetaminophen
- Hydrocodone-Acetaminophen
- None of the above

Efficacy in Treating Chronic Pain

Double-blind, randomized cross-over study

55 patients with refractory chronic low back pain

Interventions (q8h)

- Tramadol 100 mg
- APAP-codeine two 500-30 mg tablets

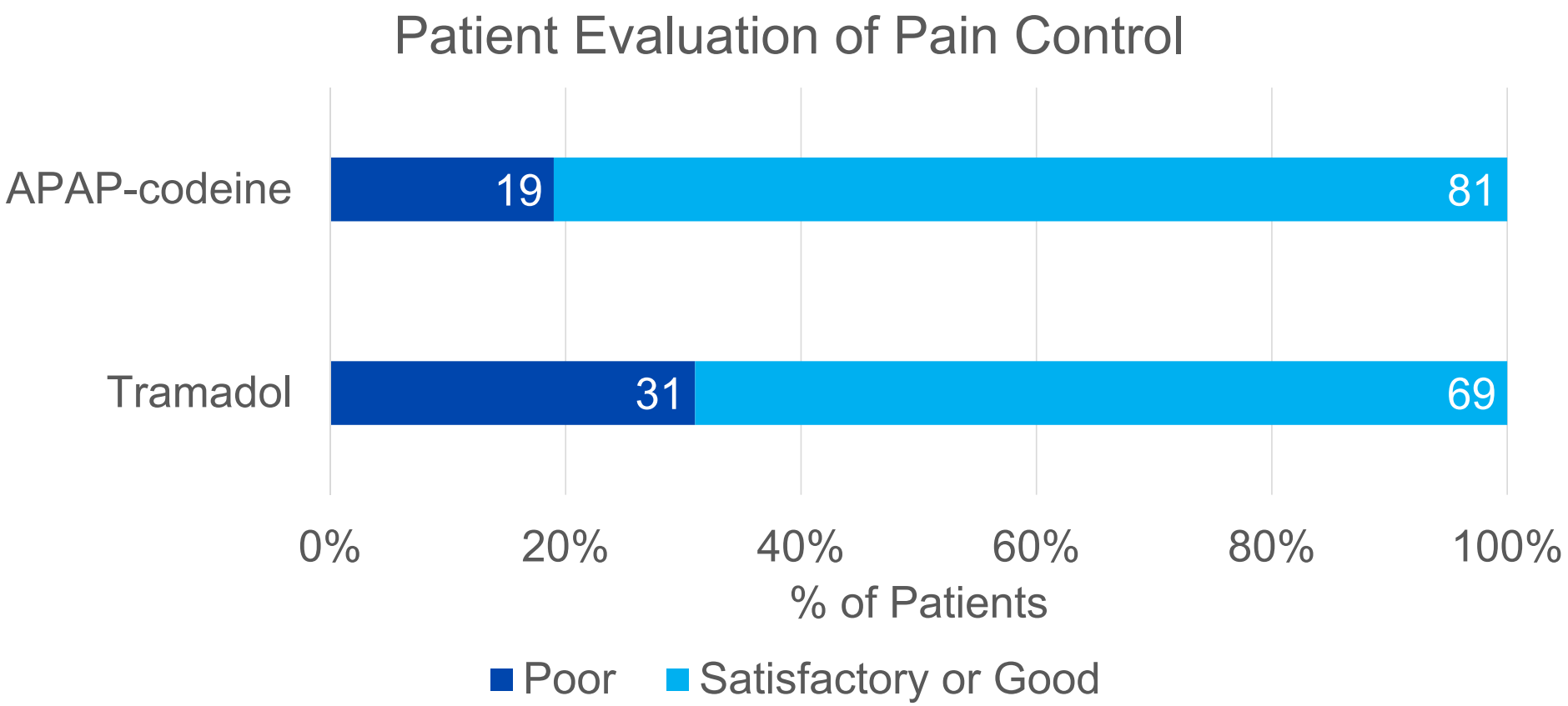
Utilized each drug for 7 days

Pain improvement measured subjectively

APAP = acetaminophen

Arzneimittelforschung. 1998;48(6):657-679.

Tramadol vs APAP-Codeine



APAP = acetaminophen

Arzneimittelforschung. 1998;48(6):657-679.

Efficacy in Treating Acute Pain in the ED

Single center, randomized, prospective, double-blind trial

68 patients in the ED with acute musculoskeletal pain due to minor trauma

Excluded: patients who took any analgesic 4 hours prior
patients presenting for back pain

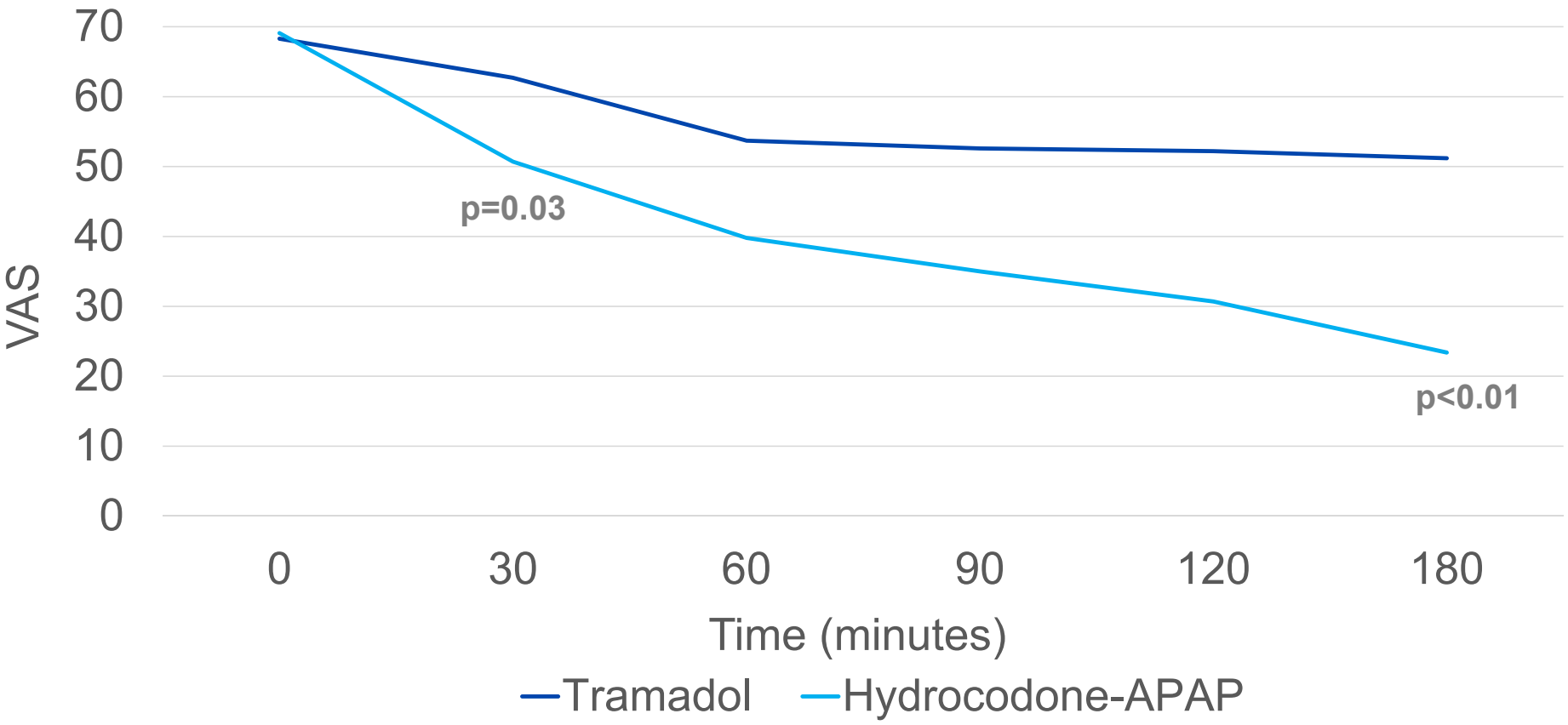
Interventions (single dose)

- 100 mg tramadol
- 5-500 mg hydrocodone-APAP
- Evaluated pain every thirty minutes for 180 minutes using VAS

APAP=acetaminophen
VAS= visual analog scale
MSK=musculoskeletal pain
ED= emergency department

Ann Emergency Med. 1998,32(2):139-143.

Hydrocodone-Acetaminophen vs Tramadol



APAP = acetaminophen
VAS = visual analog scale

Ann Emergency Med. 1998,32(2):139-143.

Efficacy in Treating Acute Dental Pain

Meta-analysis of five unpublished, randomized, double-blind trials

Included 1376 patients

Interventions given as a single dose

- APAP 650 mg
- Tramadol 75 mg
- APAP 650 mg + Tramadol 75 mg
- Ibuprofen 400 mg

Observed pain relief hourly over 6-8 hour period

- Poor, fair, good, very good, excellent

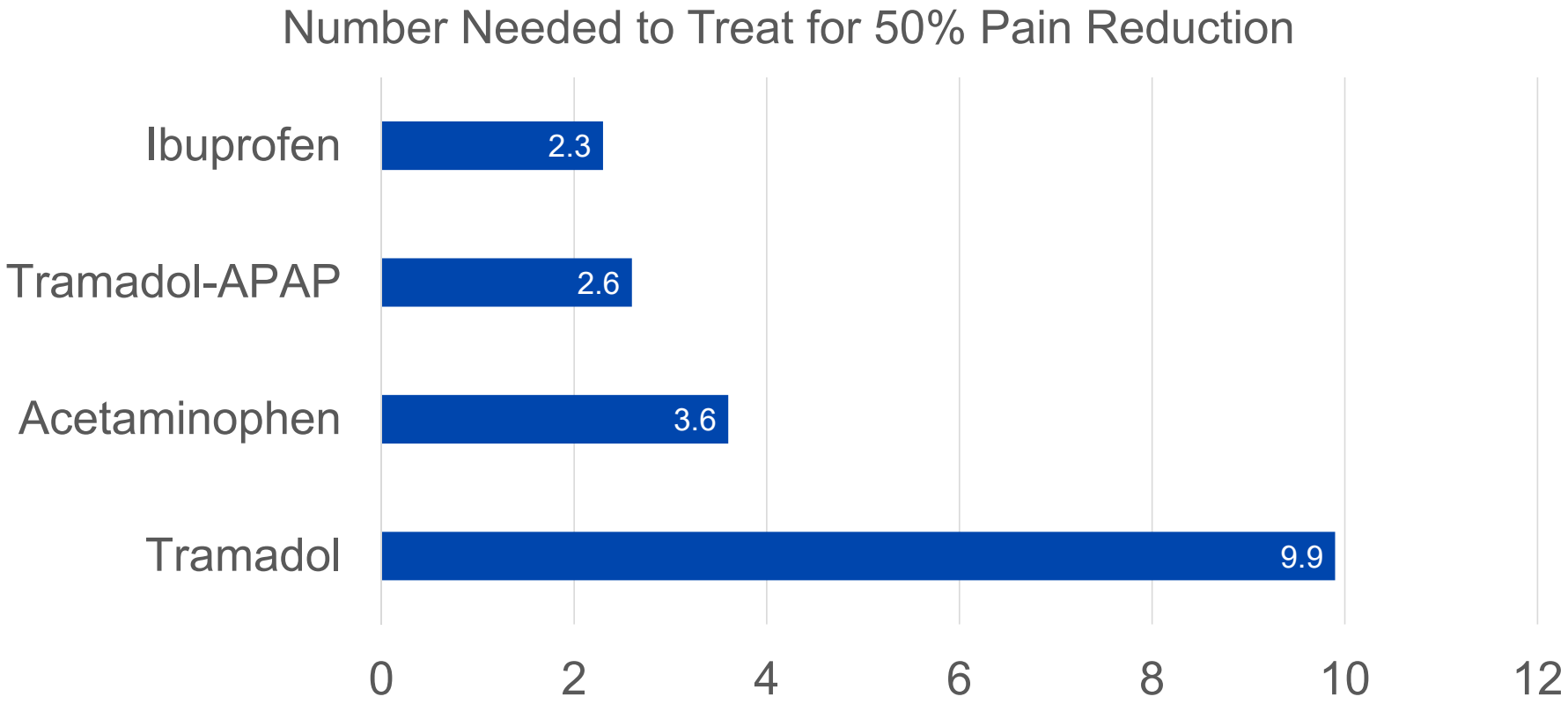
Also assessed overall pain intensity

- None, mild, moderate, severe

APAP=acetaminophen

J Pain Symptom Manage. 2002,23(2):121-130.

Tramadol vs Ibuprofen



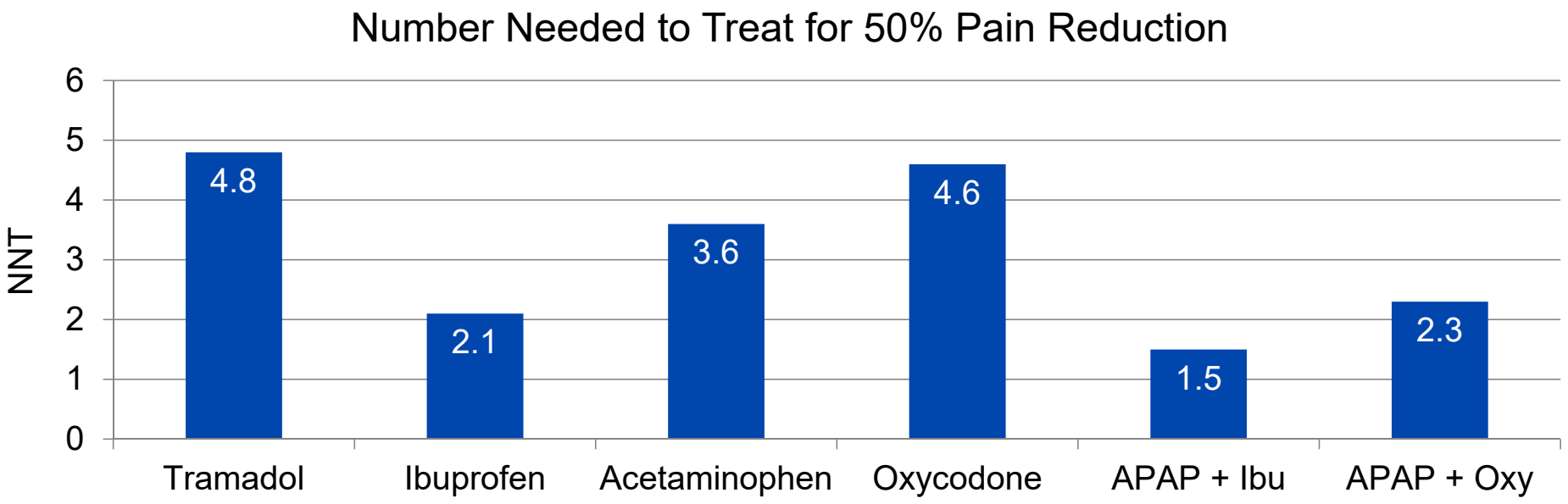
APAP=acetaminophen
NNT=number needed to treat

J Pain Symptom Manage. 2002,23(2):121-130.

Efficacy in Treating Acute Post-Operative Pain

Cochrane Review of 460 randomized, double-blind, placebo-controlled studies

Included over 50,000 post-operative patients



APAP=acetaminophen
Ibu=ibuprofen
Oxy=oxycodone

Cochrane Database of Systematic Reviews. 2015;9:CD008659.

Assessment Question #1

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- ~~Ibuprofen~~
- ~~Acetaminophen~~
- ~~Hydrocodone-Acetaminophen~~
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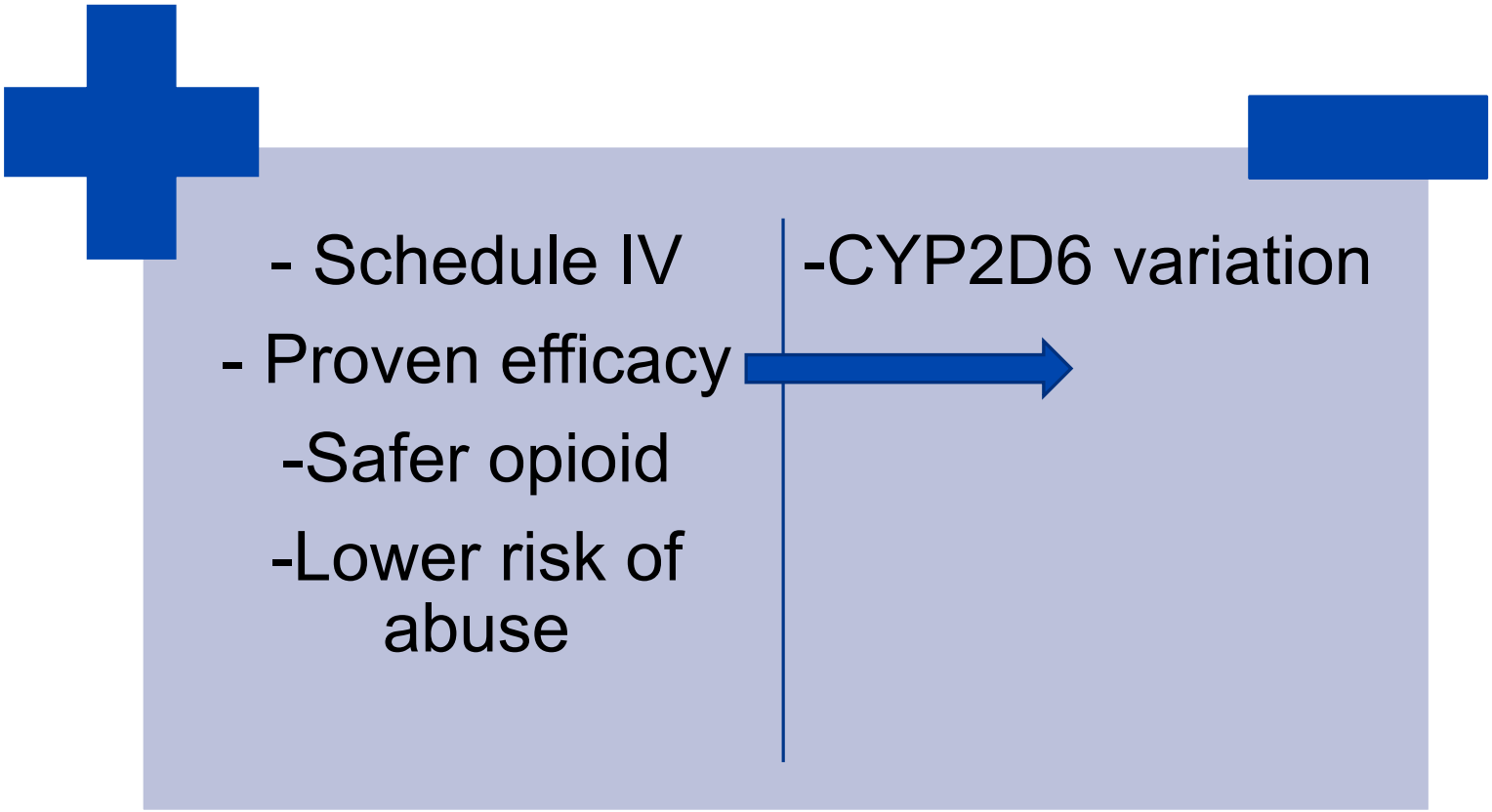
Tramadol Pros & Cons



Major Safety Considerations

- Respiratory Depression
- Seizure Risk
- Serotonin Syndrome
- Drug Interactions

Tramadol [package insert]. Johnson & Johnson, 2014.

Respiratory Depression

Dose dependent effects verified in human & animal studies

- Attributed to action on mu opioid receptors
- Rare at clinically appropriate doses

High risk populations

- Morbidly obese
- CYP2D6 gene duplication
- Renal impairment

Drug interactions contribute to risk

- Other opioids
- Benzodiazepines
- CYP2D6 inducers
- Gabapentinoids

CYP = cytochrome P450

J Anaesth. 2001;87:860-865.
Anesthesia & Analgesia. 2008;107(3):969-929.
Pain. 1997;71(1):111-112.

Seizure Risk

Observed clinically at recommended and excess doses	• Case report of seizure seen in 51 year old male receiving 75 mg/day
Risk increases 6-fold when adjusting for concomitant drug use	• SSRIs, buproprion, neuroleptics
Highest risk populations	• Ages 25-54 • More than four dispenses of tramadol • History of alcohol abuse, stroke, head injury, seizure

SSRI=selective serotonin reuptake inhibitor

Anesth Essays Res. 2016;10(2):376-378.
Med J Aust. 2005;182:595-596.
Pharmacotherapy. 2000;20(12):1423-1431.

Serotonin Syndrome

Rarely reported in absence of interacting medications

Many documented case reports with other medications

- SSRIs
- Mirtazapine
- Venlafaxine

Risk may be HIGHER in the elderly

- Polypharmacy considerations
- Renal dysfunction

SSRI=selective serotonin reuptake inhibitor

Psychiatry. 2009;6(4):17-21.

Drug Interactions

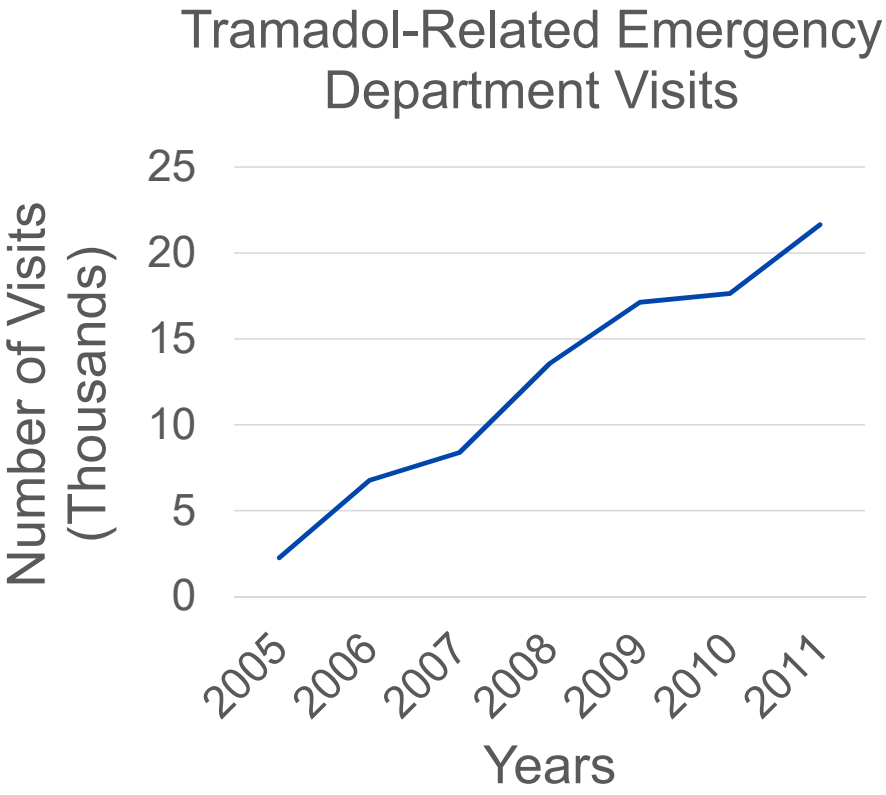
CYP2D6 Inhibitors	CNS Depressants	Serotonergic agents
• Quinidine • Cimetidine • SSRIs • Terbinafine • Mirabegron	• Benzodiazepines • Concomitant opioid use • Tizanidine • Cyclobenzaprine • Alcohol • Gabapentin • Pregabalin	• MAOIs • Selegiline • Buproprion • SSRIs • Venlafaxine • Mirtazapine • TCAs

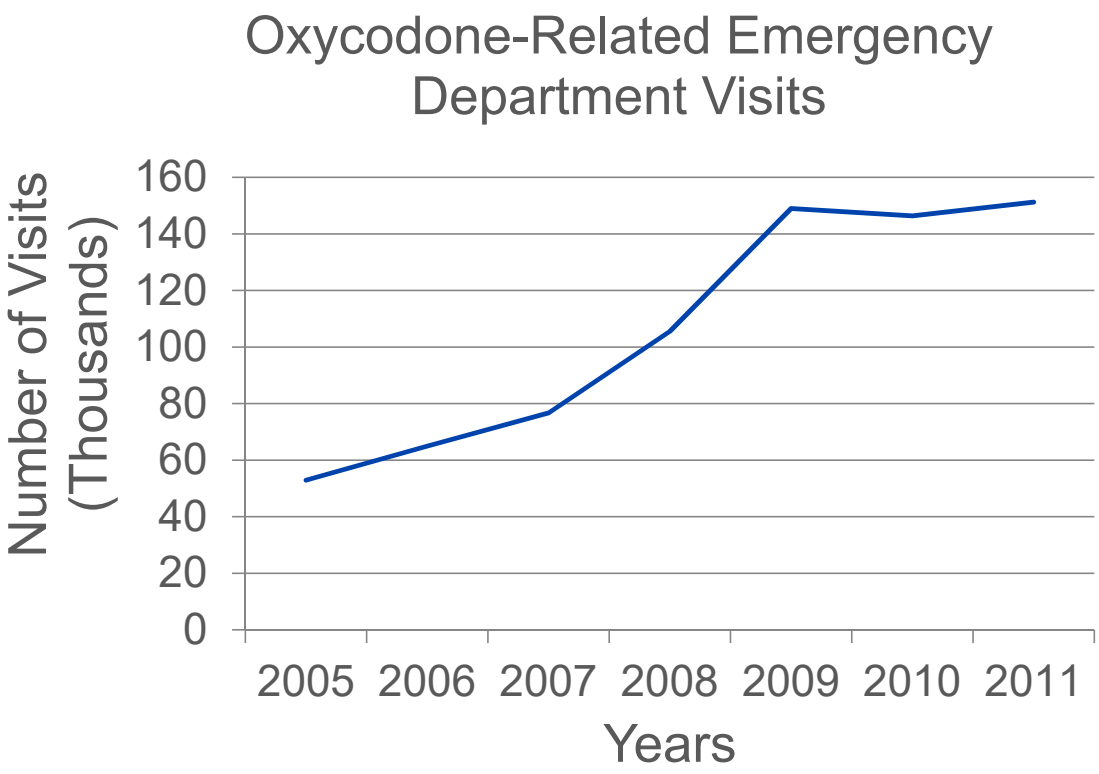
CNS = central nervous system
MAOIs= monoamine oxidase inhibitors
TCAs = tricyclic antidepressants

CYP = cytochrome P450
SSRIs=selective serotonin reuptake inhibitor

Tramadol [package insert]. Johnson & Johnson, 2014.

Tramadol Safety Issues





SAMHSA. DAWN Report. 2015.

Safety in Pediatric Populations

- In 2017 FDA recommended avoiding usage in children younger than 12 years of age
- Recommend against use in obese adolescents
- Recommend against use in children with obstructive sleep apnea or severe lung disease
- New recommendations based on WHO pharmacovigilance database demonstrating cases of respiratory depression in children
- Three deaths and 18 case reports of severe respiratory depression

FDA= Food & Drug Administration
WHO= World Health Organization

Front Pharmacol. 2018;9:148.

Safety in Elderly Populations

- Retrospective cohort study
- Patients 50 years or older taking pain medication for osteoarthritis
- Examined all-cause mortality following first year of analgesic initiation
- Compared tramadol to other common analgesic regimens
- Overall 88,902 patients were included from 2000-2015
- Propensity score matching to control for underlying comorbidities

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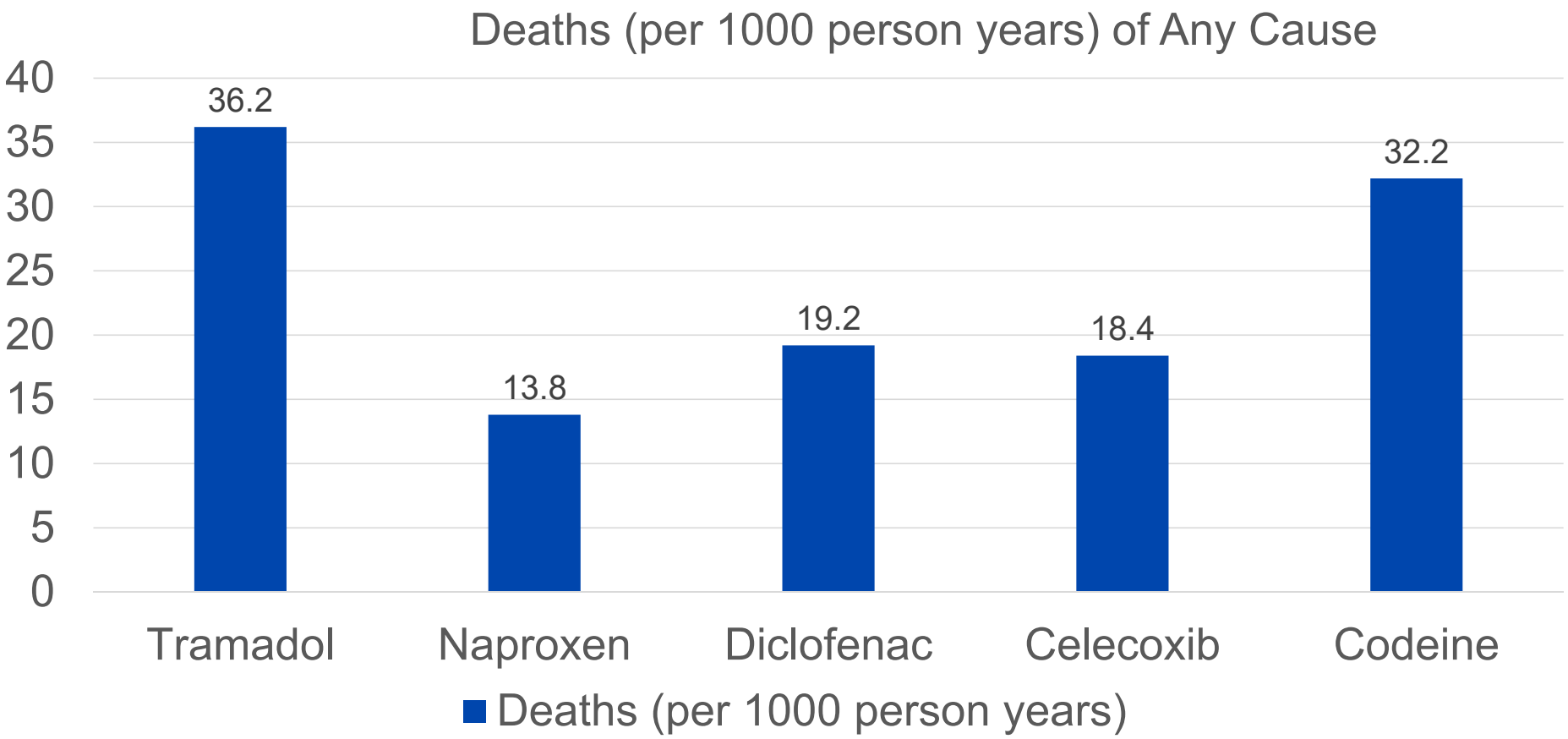
UK= United Kingdom
NSAIDS= non-steroidal anti-inflammatory drugs
CNS = central nervous system

JAMA. 2019;321(10):969-982.

Safety in Elderly Populations



JAMA. 2019;321(10):969-982.

Patient Case

DK is an 87 yo male presenting with complaints of knee pain related to his osteoarthritis.

PMH: anxiety, hypertension, Type 2 diabetes mellitus, history of alcohol abuse, osteoarthritis

Medications:

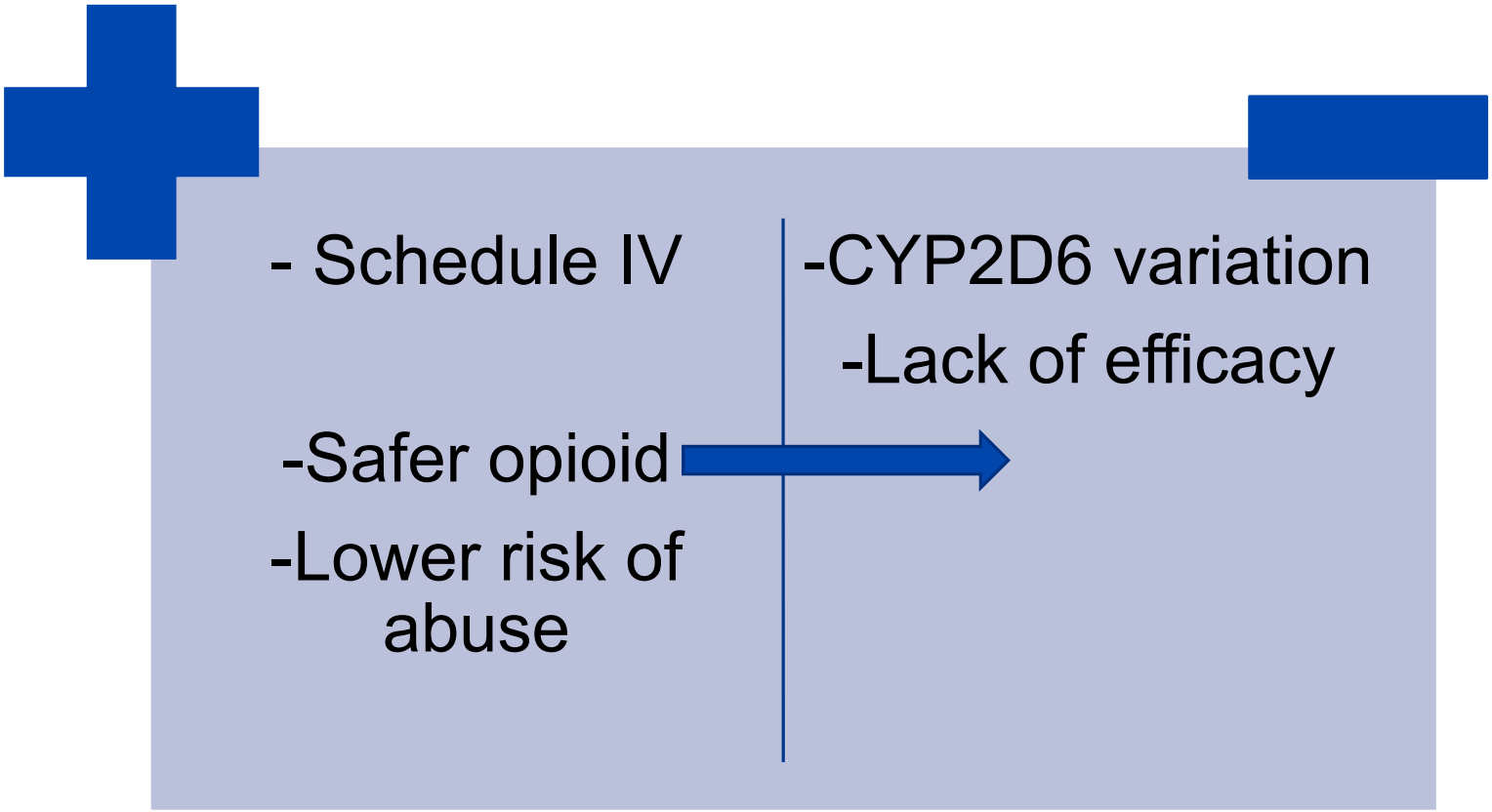
- Metformin
- Alprazolam PRN anxiety
- Amlodipine
- Acetaminophen PRN pain
- Ibuprofen PRN pain

Assessment Question #2

Which of the following would be a safety concern when considering tramadol initiation for DK?

- History of alcohol abuse
- Respiratory depression
- Age
- All of the above

Tramadol Pros & Cons



Tra
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This is 10% of total documented drug abuse!

- Post-marketing surveillance showed rate of
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patients
nitial
tive data
from Germany, however this abuse & dependence data was from IV utilization
- In 2014 DEA reports 3.2 million people utilized tramadol for non-medical reasons

FDA = Food & Drug Administration
DEA = Drug Enforcement Agency

Drug Alcohol Depend. 1999;57(1):7-22.
Psychiatry. 2019;10(704):1-11.
National Survey on Drug Use and Health, 2015.

2016 CDC Opioid Prescribing Report

- Insurance claims data from 1.3 million opioid-naïve non-cancer patients between 2000-2015
- Found that 30% of patients receiving opioids for one month or more initially ended up using chronically

Drug	% on Opioids at One Year
Tramadol	13.7%
Hydrocodone	5.1%
Oxycodone	4.7%

Tramadol & Prolonged Opioid Use

Thiels et al 2019	
Design	Observational cohort study
Methods	Utilized US & Medicare Advantage insurance claims to obtain prescription opioid information
Population	Included 357,884 opioid-naïve patients undergoing elective surgery from 2009-2018
Primary Outcome	Risk of persistent opioid use after discharge for patients treated with tramadol alone compared to other short acting opioids
Measurement	Assessed using commonly defined definitions of additional & persistent opioid use, in addition to a CONSORT definition for chronic use

BMJ. 2019;365:1849.

Tramadol & Prolonged Opioid Use

Prolonged Use Type	Definitions	RRR & 95% Confidence Interval	P-Value
Additional	At least one fill 90-180 days post-op	1.06 (1.00-1.13)	P=0.049
Persistent	Any span of opioid use starting 180 days post-op and lasting at least 90 days	1.47 (1.25-1.69)	P<0.001
CONSORT definition	Opioid use starting 180 days post-op lasting >90 days and including either >10 opioid fills or >120 day supply of opioids	1.41 (1.08-1.75)	P=0.013

RRR= relative risk ratio

BMJ. 2019;365:1849.

Tramadol Related Deaths

Little data on the true incidence of tramadol-related death due to reporting details

Northern Ireland study from 1996-2012

- A 10% increase in tramadol-related deaths noted
- Increased from 9% of all drug deaths to 40% of all drug deaths
- 49% of all tramadol- related deaths were in combination with other drugs

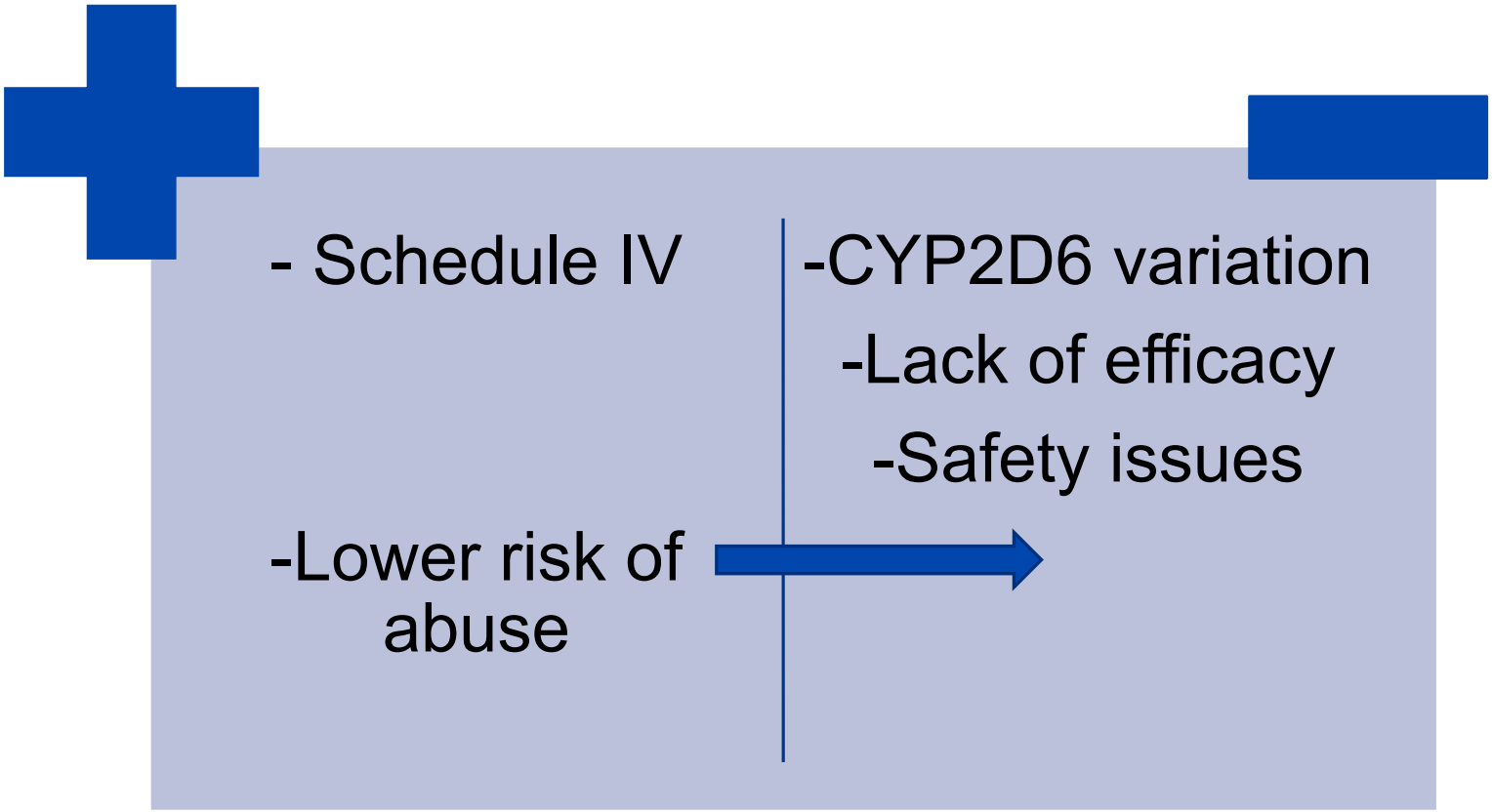
One of the top three causes of drug overdose in Finland between 2000-2012

Synthetic opioid deaths in US increasing

- Driven by fentanyl overdose

J Forensic Medicine. 2014;23:32-36.
University of Helsinki Department of Forensic Medicine. 2014.
WONDER. CDC, National Center for Health Statistics; 2017.

Tramadol Pros & Cons



Tramadol Pros & Cons

- Schedule IV

-CYP2D6 variation

-Lack of efficacy

-Safety issues

-No lower risk of abuse & dependence

Assessment Question #3

Based on your clinical experiences, do you think that tramadol is over utilized in clinical practice?

- Yes
- No

When is it appropriate to use tramadol?

Already in Use

- Continue in patients using as part of pain regimen
- Assess safety & ensure they have had no adverse events

Patients who are:

- Young
- Have good renal function
- Have no history of seizure
- Take no interacting medications

Alternatives to Tramadol

- Start with our mainstays for pain control
  - Ibuprofen, acetaminophen, etc.
- If inadequate, consider adding on opioid therapy
  - Oxycodone
  - Hydromorphone
- If needing opioid for pain relief, why use tramadol over other opioids with more reliable efficacy?

Tramadol Clinical Pearls

Remember that pharmacogenomic variation makes it difficult to predict efficacy & safety

If used ensure doses remain under 400 mg daily

Evaluate age and renal function to assess risk of adverse effects

Always watch for potential drug interactions that may increase risk for severe side effects

Ask “why tramadol?”

Summary

- Utilization of tramadol has increased with awareness surrounding opioid epidemic
- Pharmacology of tramadol gives it properties of an opioid and SNRI and widen its side effect profile
- Overall there is minimal efficacy data to support its use over other pain medications
- Tramadol is likely not “safer” than other opioids and still carries risk for abuse and dependence
- As clinicians we can educate each other on efficacy and safety concerns of tramadol

SNRI=serotonin norepinephrine reuptake inhibitor

Questions?

Tramadol Overdose

- Opioid overdose considerations with high doses
  - Respiratory depression --> naloxone only partially effective
  - Cardiovascular collapse
- Seizure concerns
- Serotonin syndrome (less likely)
  - Hyperactivity
  - Tachycardia
  - Agitation or confusion
  - Hypertension

Clin Toxicol (Phila). 2015;53(6):545-550.

