

Cognitive effects of opioids – safe to drive?

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Opioids and driving

- What do you do?
- Has this changed with the new law?
- What dose does 80 $\mu\text{g}/\text{L}$ correspond to?

Overview

- Legal aspects of driving whilst taking opioids
- Opioids
- Side effects
- Evidence on the cognitive effects of opioids
- Evidence of the effect of opioids on driving
- Clinical implications
- *In silico* study
- Questions

but first, some background....

'Illegal' drugs ('accidental exposure' – zero tolerance approach)	Threshold limit in microgrammes per litre of blood (µg/L)
benzoylecgonine	50µg/L
cocaine	10µg/L
delta-9-tetrahydrocannabinol (cannabis)	2µg/L
ketamine	20µg/L
lysergic acid diethylamide	1µg/L
methylamphetamine	10µg/L
Methylenedioxymethamphetamine (MDMA)	10µg/L
6-monoacetylmorphine (heroin)	5µg/L

'Medicinal' drugs (risk based approach)	Threshold limit in blood
clonazepam	50µg/L
diazepam	550µg/L
flunitrazepam	300µg/L
lorazepam	100µg/L
methadone	500µg/L
morphine	80µg/L
oxazepam	500µg/L
temazepam	1,000µg/L

<https://www.gov.uk/government/collections/drug-driving#table-of-drugs-and-limits>

Background

- Opioids *can* cause central nervous system side effects which can impair driving skills.
- The legal blood morphine concentration limit for driving is 80 $\mu\text{g}/\text{L}$ in England/Wales.
 - There is no dose-concentration guidance to aid prescribing in relation to this.



Legal aspects - Bottom line

- All about safety
- People who have impaired driving will be breaking the law, *irrespective* of blood morphine concentration
- People driving safely, taking morphine as prescribed have a medical defense, even if over the legal limit
- Need an understanding to advise patients
 - Should not change current good practice

Legal aspects of driving whilst taking prescribed opioid analgesics

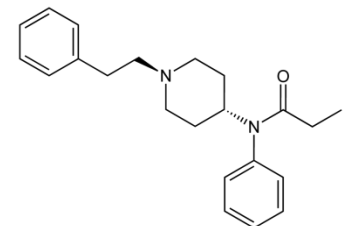
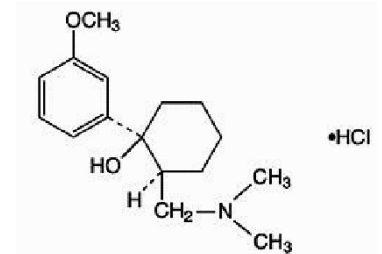
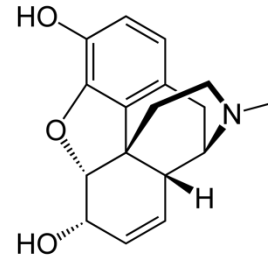
- Make it easier for police test people taking drugs
- For medicinal drugs, limit above normal doses
- The legal blood morphine concentration limit for driving is 80 $\mu\text{g/L}$ in England/Wales (2.3.2015)

Safety

- Breaking the law if impaired driving, *irrespective* of morphine concentration
- Medical defense if driving safely, taking morphine as prescribed, even if over the legal limit

What are opioids?

- Chemically diverse molecules
- Common property - activate opioid receptors
- Disparate physicochemical and pharmacological properties
 - Act in different ways on the opioid receptor
 - Act via non-opioid receptors



(Side) Effects of opioids on different organ systems

System	Effects
Gastrointestinal	Constipation, xerostomia, nausea and vomiting, delayed gastric emptying, gastro-oesophageal reflux, constriction of the sphincter of Oddi
Neurological	Analgesia, delirium, hallucinations, sedation, myoclonus, hyperalgesia, seizures, headaches, euphoria, dysphoria, dependence, withdrawal
Cardiovascular	Bradycardia, hypotension
Pulmonary	Respiratory depression, decreased cough reflex, non-cardiogenic pulmonary oedema
Urological	Urine retention, decreased urine production
Endocrinological	Hypogonadism/sexual dysfunction, osteoporosis
Immunological	Neutrophil, macrophage, natural killer cell, T cell and cytokine function effects

Cognitive effects of opioids

- High incidence of opioid-related side effects such as dizziness, sedation, cognition and psychomotor impairment
- Others report no significant problems
- Systematic review: most studies are heterogeneous and fail to report confounders, limiting the generalizability of the results

Driving

- Requires numerous skills
 - prolonged concentration
 - receive multiple sensory stimuli
 - process them
 - make decisions
 - respond appropriately
- Requires preserved cognitive abilities
 - concentration
 - attention
 - perceptual skills
 - insight
 - memory

Measures of Driving Performance

- Best way to evaluate driving skills is the on-the-road driving test
 - 100-km drive on a public highway, under regular traffic conditions
 - time consuming, difficult to apply
- Cognitive and psychomotor tests used but poor predictor of driving performance
- Driving simulators sensitive for alcohol, drug, sleep deprivation impairments
 - Can predict on the road driving outcomes

Helland A et al. Traffic injury prevention. 2016;17(3):245-50.

Jongen S et al. PLoS one. 2015;10(2):e0117045.

Vakulin A et al. Annals of internal medicine. 2009;151(7):447-55.

Effect of opioids on driving

- Systematic Review: impact of opioid on driving-related psychomotor skills
 - Three studies (n=99)
 - All chronic non-malignant pain
 - All Driving-Simulator
 - None randomised
- No significant impact of opioids on driving-related psychomotor skills ported
 - Pain worsened driving performance (Nilsen et al, 2011)

Stopping driving has risk

Being unable to drive 2x the rate of depression

Social isolation linked to

- higher risk of admission into long-term care
- higher mortality

Stop driving?

- If people take drugs as prescribed
 - Are not impaired and drive safely
 - Have evidence of prescription when drive
- They should continue to drive
 - Protect QoL/independence/socialisation
- We need to assess and inform patients

King MD et al. Journal of Gerontological Social Work. 2011;54(1):29-52.

Mezuk B et al. Psychological Sciences and Social Sciences. 2008;63(5):S298-S303.

So,

Don't want to stop patients driving but want them to be safe

Opioids might have a risk

New law has blood morphine concentration limit

To help inform clinical practice and patients, in context of new law

Relationship between morphine dose and morphine plasma concentration above 80 $\mu\text{g/L}$ in different patient groups

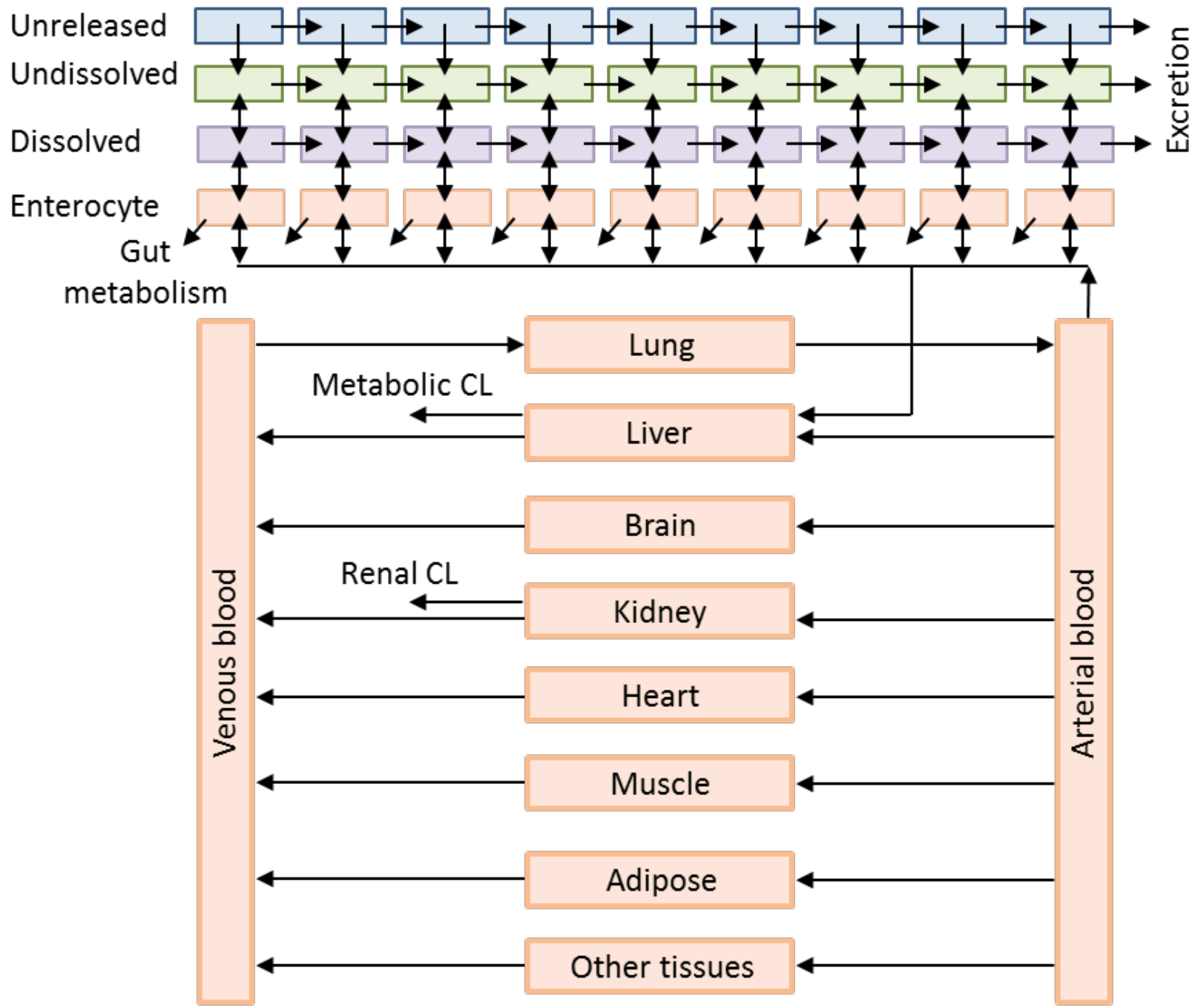
Methods

In silico dose-concentration model

- using Simcyp[®], a population-based pharmacokinetic simulator
- validated against clinical pharmacokinetic data

36,000 simulated human subjects (100 *per* modelled group of different ages and gender) received repeated morphine dosing with modified-release or immediate-release morphine formulations

ACAT model for absorption



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Summary of Results

- Older age, women, modified-release formulation and worse renal function were associated with higher plasma concentrations for a given dose
- Across all groups, morphine doses below 80 mg/day were estimated to be unlikely to result in a morphine plasma concentration above 80 $\mu\text{g/L}$

Original Article

Assessing the practice of Palliative Care Doctors – What driving advice do they give patients with advanced disease?

Dr Nashringi Weir, [Amanda Fischer](#) , [A/Prof Phillip Good](#)Accepted manuscript online: 1 August 2017 [Full publication history](#)

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- Wide variability in practice
- Substantial discordance with driving guidelines
- 94% had asked a patient to stop driving
- 27% had reported a patient to the DLA
- 64% advise patients to temporarily refrain from driving post short acting oral morphine
 - 4 hours (36%) the most common time

Conclusions

- People who have impaired driving will be breaking the law, *irrespective* of blood morphine concentration
- Knowledge of the dose-concentration relationship could inform individualised prescribing decisions
- The decision and patient-communication must be informed by clinical judgment taking into account the individual patient's level of impairment and insight for *any* plasma concentration