Managing long term opioids and hypnotics

Dr Ravneet Batra
Consultant Liaison Psychiatrist
Western General Hospital, Edinburgh

Managing long term opioids and hypnotics

Illicit opioid use

Oral Substitution Therapy

Hypnotics - efficacy

Hypnotics - harm

Opiate quiz

Which of the following is an opiate?

A. Methadone

B. Codeine

C. Tramadol

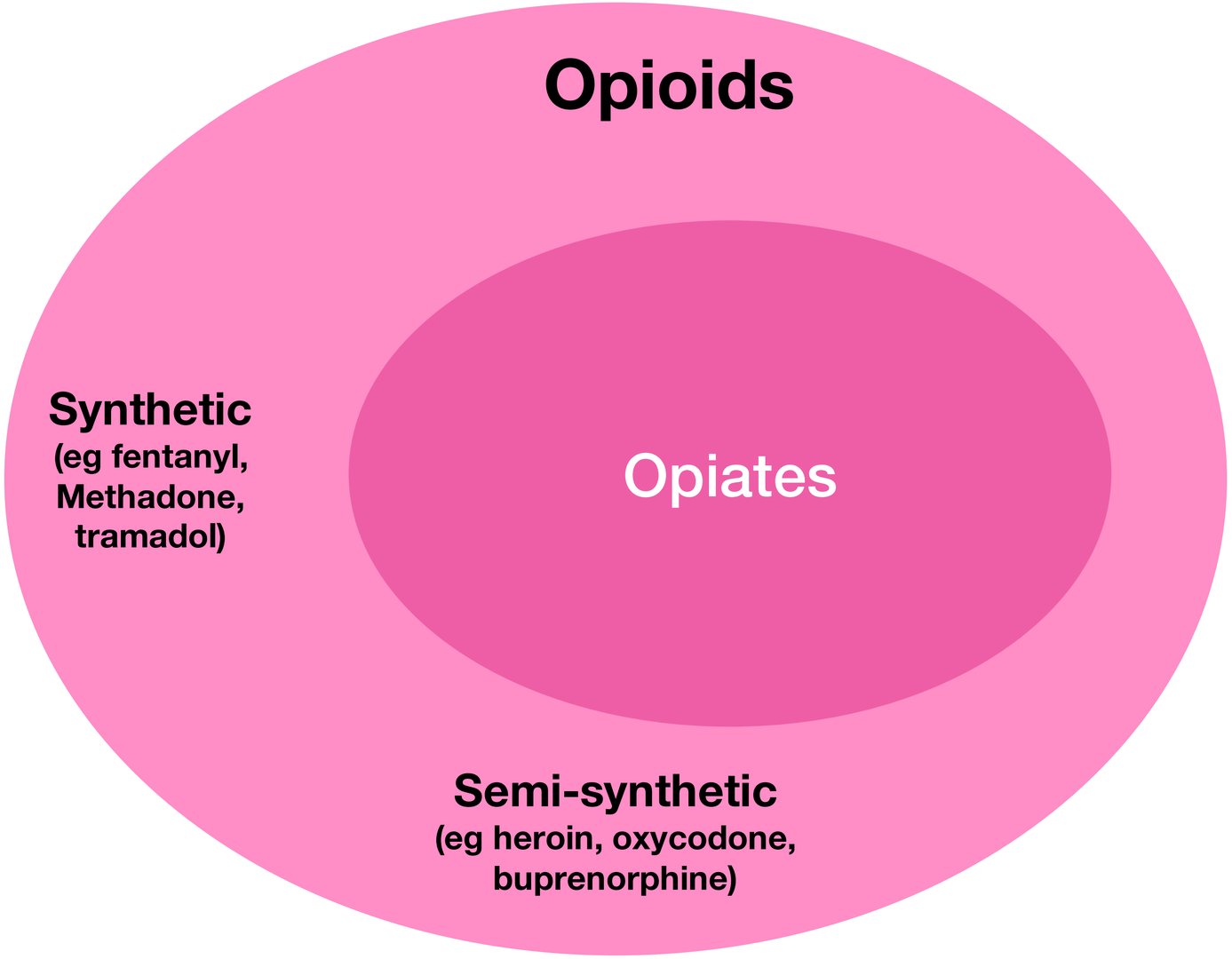
D. Fentanyl

Opiates

Opium -dry juice of the poppy Papaver somniferum

- Morphine
- Codeine
- Thebaine

Opiates & Opioids



Opioid receptors

1. Mu /π – 1,2

- analgesic activity, euphoria, sedation, respiratory depression, pupil constriction, constipation

2. Delta / δ –1,2

- analgesia (spinal), constipation, respiratory depression

3. Kappa / χ –1,2, 3

- analgesia (spinal), dysphoria, sedation

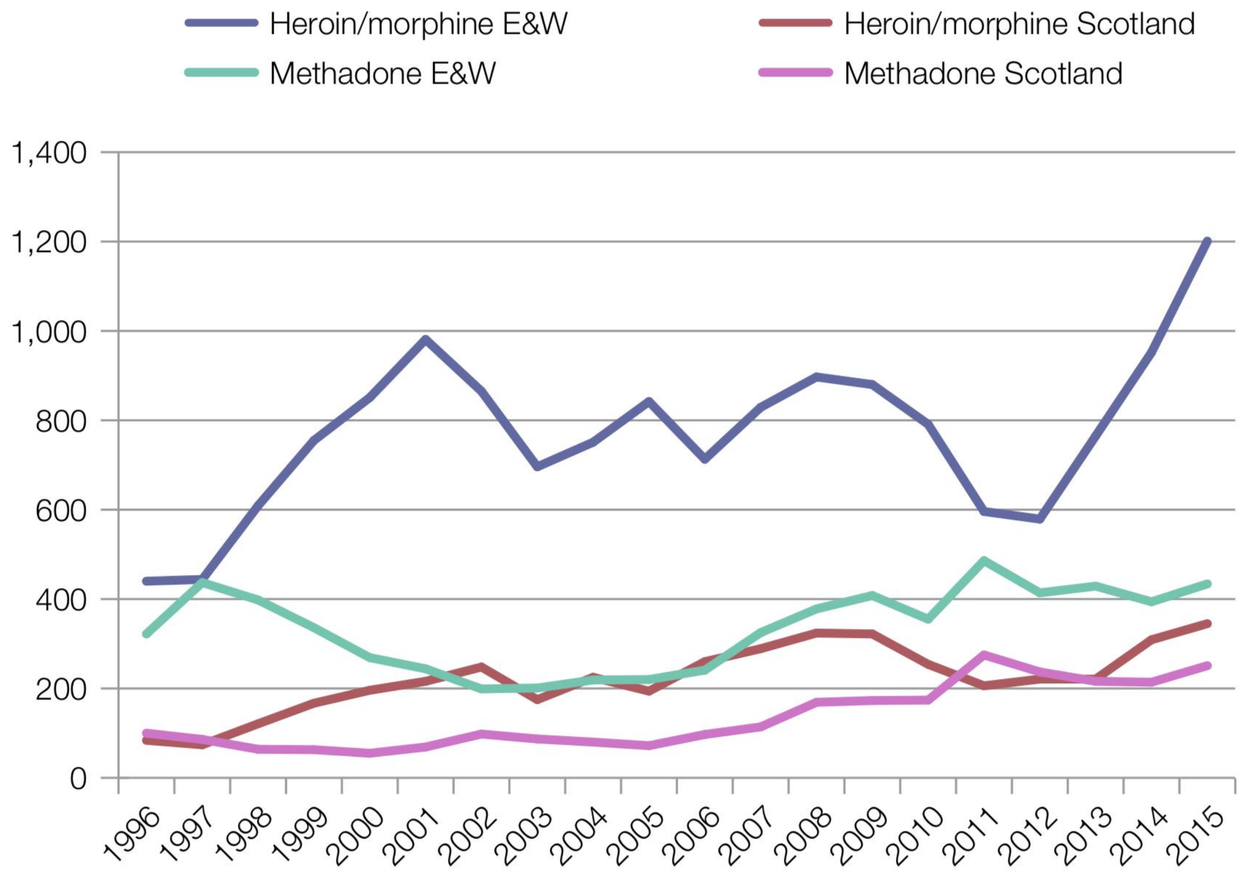
High risk drug users

The estimated number of high risk drug users in UK: number and rate per 1,000 population aged 15 to 64

Country	Year	Estimate	95% confidence interval	Rate	95% confidence interval
England	2011/12	256,163	253,751 - 263,501	7.32	7.25 - 7.53
Scotland	2012/13	61,500	59,900 – 63,300	17.4	16.9 – 17.9
Wales	2014/15	58,186	53,104 – 63,507	-	-

Source: (Hay et al 2014; Information Services Div, 2014a; Public Health Wales,2015)

Figure 6.5: Number of deaths mentioning heroin/morphine and methadone in England & Wales and Scotland, 1996 to 2015



Source: (National Records of Scotland, 2016; Office for National Statistics, 2016c)

BBVs among PWID

HIV

- 1% prevalence among current and former PWID across England, Wales & NI in 2015
- HIV prevalence among those who first injected during the preceding 3 years was 2.6 %
- Prevalence in Scotland during 2015/16 was found to be 1.9%

HCV

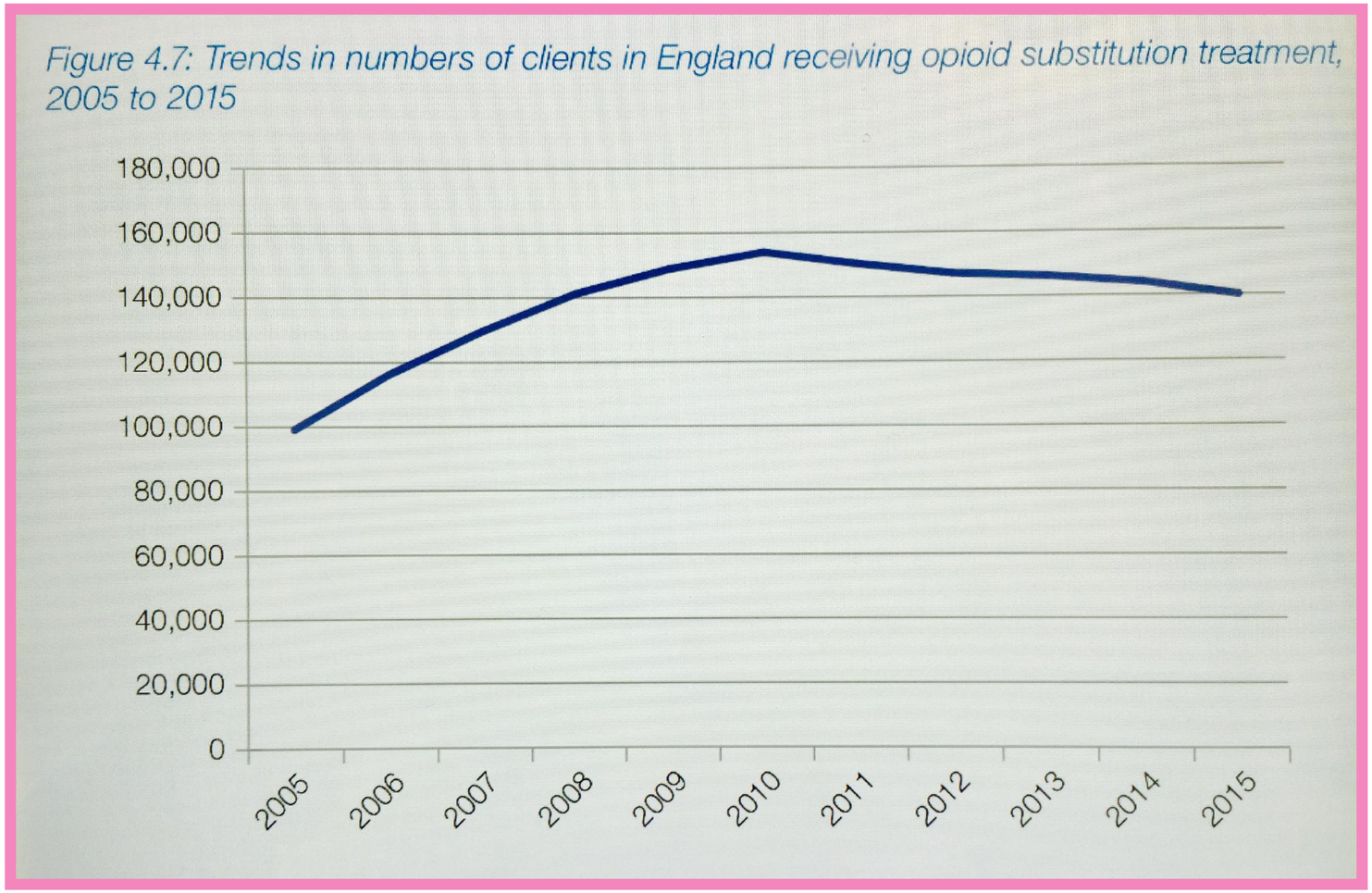
- Around 90% of Hepatitis C infections diagnosis in UK is acquired through injecting drug use

Oral substitution therapy (OST)

Aim of OST is attaining controlled, non-problematic drug use; avoiding all non-prescribed psychoactive drugs

- Reduces the risk of drug related morbidity and mortality
- Reduces the risk of criminal offending
- Reduces drug injection, needle sharing and risky sexual behaviour
- Reduces the risk of acquiring or transmitting blood-borne viruses
- Decreases likelihood of hospitalisation

Oral Substitution Therapy



Source: UK Focal Point on Drugs 2016 report

Methadone

- Synthetic, orally effective, opioid agonist
- Half life long and variable 13-50 hours (steady state blood levels 3-10 days)
- Higher doses (60-120 mg) have been shown to be more effective
- Levels altered by drugs that inhibit/ induce CYP3A4
- Causes QTc prolongation
- Other cautions: concomitant use with alcohol and other respiratory depressant drugs; severe hepatic / renal dysfunction

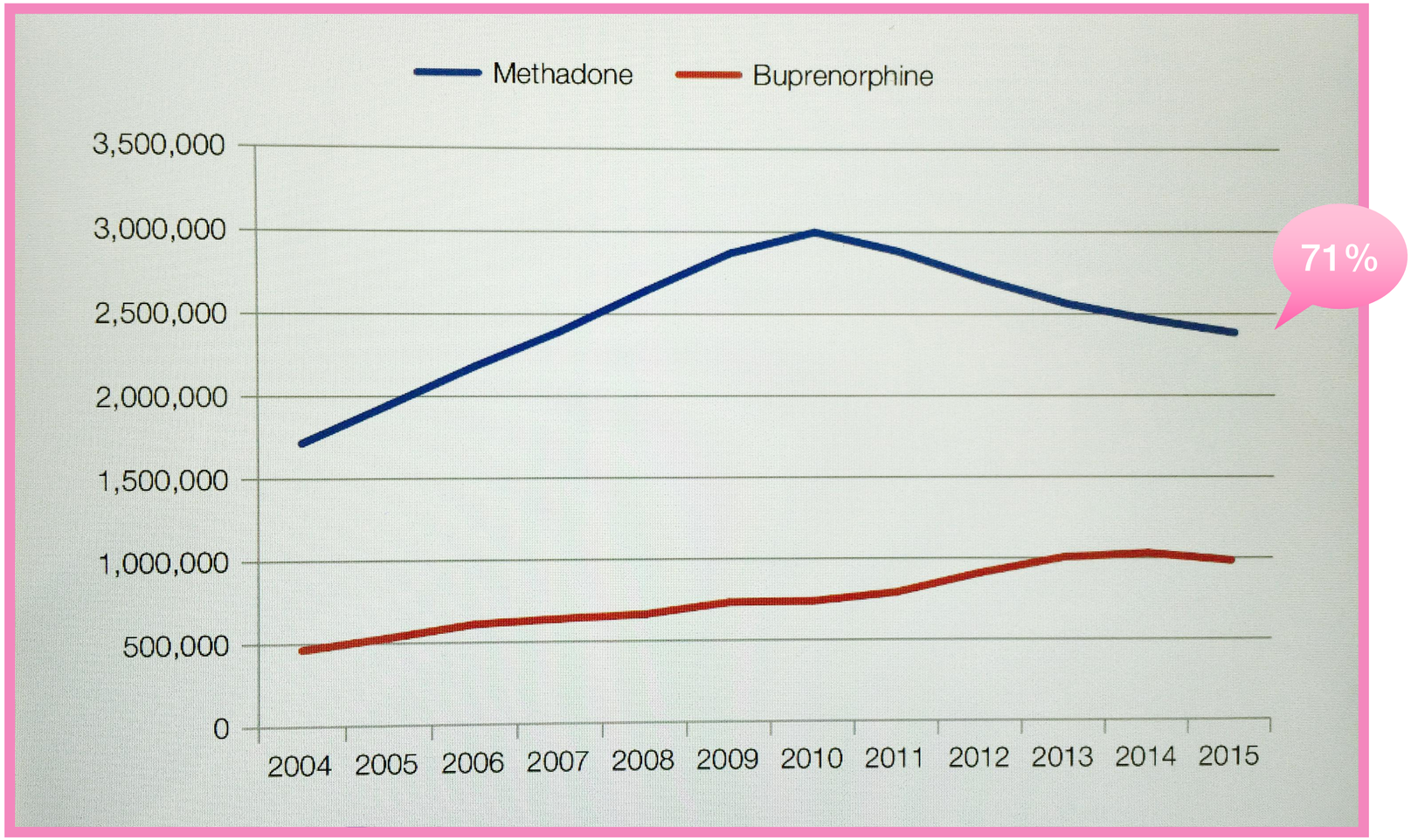
Buprenorphine

- Synthetic partial agonist, with high affinity for Mu opioid receptors, can cause precipitated withdrawals
- As a partial agonist has a dose ceiling effect for all opioid properties
- Administered sublingually, due to significant first pass hepatic metabolism; takes 5-10 minutes to administer
- Used alone or in co-formulation with naloxone in a 4:1ratio
- Effective maintenance doses are in the range of 12-24 mg daily
- Cautions: use with alcohol or other depressant drugs; high doses can derange LFTs

Methadone or Buprenorphine?

- Buprenorphine has a milder withdrawal syndrome than methadone, so preferred for detoxification programs
- Methadone is more sedating, is associated with more QTc prolongation, and has more drug interactions
- Higher dose methadone maintenance (>60 mg) appears to be more effective than buprenorphine
- Buprenorphine could interfere with pain management, on account of its opioid antagonist actions.
- Methadone preferred in women who are pregnant or planning a pregnancy.

OST prescriptions



Source: Health and Social Care Information Centre, 2016

Safe prescribing of OST

- Clear and effective communication
- Dose optimisation and evaluating benefit from treatment
- **Monitoring and minimising risks of toxicity**
- Reducing risk to others

Safe prescribing of OST

Monitoring and minimising risks of toxicity

A. Drug testing

B. Supervised consumption

C. Drug interactions and poly-pharmacy

D. QT interval monitoring

E. Overdose awareness and training

Safe prescribing of OST

Drug Testing

- To confirm treatment compliance
- To monitor illicit drug use
- Random intermittent
- Urine, or oral fluid (or hair)
- Screening test, and confirmation test if warranted

Safe prescribing of OST

Supervised Consumption

Potential **benefits** include:

- Ensures that medication is taken as prescribed
- Aids patient safety, and minimises the risk of toxicity
- Lessens the opportunity for diversion for illicit sale
- May help patients to establish a routine
- Pharmacists can assess patients' progress and compliance

Safe prescribing of OST

Supervised Consumption

Potential **disadvantages** include:

- May impede progress to normal routine, education & employment
- May increase contact with other drug users
- Daily travel and associated costs
- Lessens the development of personal responsibility
- May deter accessing appropriate treatment
- Increased workload and cost implications for the pharmacy and NHS

Safe prescribing of OST

Drug Interactions and Poly-pharmacy

- CYP3A4 plays a significant role in the metabolism of methadone and buprenorphine. However buprenorphine is less affected by drug interactions
- Methadone has significant interactions with a number of ARVs (PIs and NNRTIs), antibiotics (ciprofloxacin, clarithromycin, erythromycin), psychotropics, antifungals, anticonvulsants etc
- Caution is also required with using methadone with other medications with a potential to cause QT interval prolongation
- Problematic drug interactions with methadone may favour a switch to or selection of buprenorphine in certain circumstances to avoid opioid withdrawal symptoms or toxicities.

Safe prescribing of OST

QT Interval Monitoring

Patients with the following risk factors should have a baseline and subsequent ECG monitoring:

- Methadone dose of 100 mg or more
- Concomitant use of other QT interval prolonging agents and CYP3A4 inhibitors
- History of heart disease (IHD, long QT syndrome, myocarditis, LVF) or bradycardia
- Patients with liver disease, hypothyroidism, malnourishment, HIV infection, anorexia nervosa and alcohol dependence

Safe prescribing of OST

Overdose Awareness and Training

- People who misuse and are dependent on opioids have a mortality rate of 1-2 % per year.
- Naloxone is potentially life saving and its pre-provision to opioid users and their families can help in reversing overdoses
- Training in delivering ‘take-home’ naloxone covers identification of overdose, and its management including how to administer naloxone.
- Naloxone kits supplied in Scotland contains one pre filled syringe containing 2 ml of naloxone (5 doses), 2 needles and information leaflet

Drug and Alcohol Dependence 167 (2016) 214–223

Contents lists available at ScienceDirect

Drug and Alcohol Dependence

journal homepage: www.elsevier.com/locate/drugalcdep

Full length article

Risk-factors for methadone-specific deaths in Scotland's methadone-prescription clients between 2009 and 2013*

Lu Gao[a], Polyxeni Dimitropoulou[a], J. Roy Robertson[b], Stuart McTaggart[c], Marion Bennie[c,d], Sheila M. Bird[a,e,*]

[a] MRC Biostatistics Unit, Cambridge CB2 0SR, United Kingdom
[b] Usher Institute of Population Health Sciences and Informatics, Edinburgh University, EDINBURGH EH16 4UX, United Kingdom
[c] Information Services Division, NHS National Services Scotland, Edinburgh EH12 9EB, United Kingdom
[d] Strathclyde Institute of Pharmacy and Biomedical Sciences, University of Strathclyde, Glasgow G4 0RE, United Kingdom
[e] Department of Mathematics and Statistics, Strathclyde University, Glasgow G1 1XH, United Kingdom

Hazard ratio significantly higher in patients aged 45 years and over

Also increased hazard for the top quintile of prescribed methadone; over 90 mg daily

ARTICLE INFO

Article history:
Received 10 June 2016

ABSTRACT

Aim: To quantify gender, age-group and quantity of methadone prescribed as risk factors for drugs-related deaths (DRDs), and for methadone-specific DRDs, in Scotland's methadone-prescription clients.

Open Access Research

BMJ Open

The relative risk of fatal poisoning by methadone or buprenorphine within the wider population of England and Wales

Dave Marteau,[1] Rebecca McDonald,[2] Kamlesh Patel[1]

To cite: Marteau D, McDonald R, Patel K. The relative risk of fatal poisoning by methadone or buprenorphine within the wider population of England and Wales. *BMJ Open* 2015;**5**:e007629. doi:10.1136/bmjopen-2015-007629

▶ Prepublication history for this paper is available online. To view these files please

ABSTRACT

Objective: To examine the population-wide overdose risk emerging from the prescription of methadone and buprenorphine for opioid substitution treatment in England and Wales.

Design: Retrospectiv

Setting: National data

Participants/cases:

drawn from the Office

prescription data for m

were obtained from the National Health Service for the years 2007–2012. During this 6-year period, a total of 2366 methadone-related deaths and 52 buprenorphine-

Buprenorphine is 6 times safer than methadone with regard to overdose risk

Strengths and limitations of this study

- Study is the first relative risk study of methadone versus buprenorphine in England and Wales, and the second only national study globally.
- Study draws on a very large source of data, comprising more than 19 million prescriptions across 6 years.
- Study presents an evaluation of risk across a full drug-using culture.
- Data do not allow the identification of differences in severity of drug dependence between patients prescribed methadone and those prescribed

Table 1: Number of drug-related deaths where selected substances were mentioned on the death certificate, deaths registered in England and Wales 2012-20161,2,3,4

England and Wales					
Number of deaths					
	2012	**2013**	**2014**	**2015**	**2016**
All drug poisoning deaths	2,597	2,955	3,346	3,674	3,744
Any opioid	1,290	1,592	1,786	1,989	2,038
- Heroin and/or morphine	579	765	952	1,201	1,209
- Methadone	414	429	394	434	413
- Tramadol	175	220	240	208	184
- Oxycodone	37	51	51	51	75
- Fentanyl	22	22	40	34	58
Cocaine	139	169	247	320	371
Any amphetamine	97	120	151	157	160
Any new psychoactive substance	55	63	82	114	123
Any benzodiazepine	284	342	372	366	406
Pregabalin	4	33	38	90	111
Gabapentin	8	9	26	49	59
All antidepressants	468	466	517	447	460
Paracetamol	182	226	200	197	219
Propranolol	39	46	54	55	45
Source: Office for National Statistics					

Benzodiazepine high –dose/ illicit drug use

- Misuse of benzodiazepines is often associated with other substance abuse, frequent among heroin users and those on OST.
- Use pattern in high dose abusers include – once daily dosing to maximise effect, seeking euphoric or sedative effects, escalating dosages, ‘binge’ use and very high self reported doses (Wilson et al 2010)
- Maintenance prescribing in high- dose and or illicit drug users is not recommended, but is reasonably common (Reed et al 2011)
- Doses greater than 30 mg are rarely necessary. Reduction from a high dose to a therapeutic dose level may be a useful objective in some dependent users

Sedative -hypnotics

- An effective sedative (anxiolytic) agent should reduce anxiety and exert a calming effect with little or no effect on motor or mental functions

- A hypnotic drug should produce drowsiness and encourage the initiation and maintenance of sleep that as far as possible resembles the natural sleep sate

- Chemically heterogeneous classes of drugs including barbiturates, benzodiazepines, Z drugs, antihistamines, melatonin etc

Chronic insomnia

- Chronic insomnia – 3 times/ week and for longer than 1 month, difficulty falling asleep, maintaining sleep or having non-refreshing sleep
- Chronic insomnia is said to affect around 9-12% of UK adults every year. And 75% of these patients reported symptoms lasting a year (Morphy et al, 2007)
- In those over 60 years of age 12-25% are said to be affected by insomnia. (Montgomery et al 2010)
- The course of insomnia is more likely to be persistent in those with more severe insomnia at baseline, in women and older adults (Morin et al, 2009)

Consequences of chronic insomnia

- Impaired quality of life, increased functional impairment
- Poor performance on psychomotor tasks, and complex cognitive tasks
- Increased risk of developing depression and anxiety disorder
- Increased risk of hypertension, and cardiovascular disease
- Increases absenteeism, accidents at work and road accidents

What would you choose?

If you were to suffer from chronic insomnia, what would be your treatment preference?

A. No treatment

B. Cognitive Behavioural Therapy

C. Over the counter hypnotics

D. Hypnotic medication prescription, for up to 4 weeks only

E. Hypnotic medication prescription, long term

Psychological treatment of insomnia

- Cognitive behavioural therapy for insomnia (CBTi) is considered the first line treatment, carrying a significantly favourable benefit:risk ratio, and is backed by a number a systemic reviews (Montgomery et al 2002, Trauer et 2015, Wu et al 2015)

- The beneficial effects of CBT, in contrast to medication, may last well beyond the termination of active treatment

- Various delivery methods are found be efficacious including internet-based, self administered through a book or manual, small group or individual

- Benefits limited on account of its patchy accessibility and acceptability, being time and effort consuming, with the effects not being immediately apparent

Neurotransmitters and sleep

Endogenous transmitter	Maintains wakefulness	Promotes sleep
GABA		✓
melatonin		✓
adenosine		✓
noradrenaline	✓	
dopamine	✓	
serotonin	✓	
histamine	✓	
acetylcholine	✓	
orexin	✓	

Use of hypnotic drugs

- Benzodiazepines and Z drugs are widely prescribed. Actions mediated by enhancing the activity of GABA
- Often a wide divergence between published guidelines, clinical practice and patient preference.
- Approximately 16 million prescriptions issued in England in 2015. More than a quarter of million people in the UK on long term prescription (Davies et al, 2017)
- Prescriptions are mainly for treatment of anxiety, insomnia, or dependence

Efficacy of long term hypnotics

- The available evidence does not suggest there is unfavourable risk/benefit transition at 3-4 weeks for any agent
- There are some studies supporting nightly use up to 1 year with eszopiclone, zolpidem and ramelteon (Ancoli-Israel et al 2005; Richardson et al,2009)
- Some evidence about sustained efficacy and safety for 6 months of ‘as needed’ treatment with zolpidem (controlled release)
- A 2014 meta analysis by Winkler et al showed benzodiazepines and Z drugs to be significantly more effective hypnotics than antidepressants
- However, strikingly there is absence of good quality, longer term studies about efficacy and safety, more so for benzodiazepines

Hypnotics and harm

Main long term concerns include:

- Cognitive effects
- Psychomotor effects
- Tolerance, dependence and withdrawal symptoms
- Effects on physical health and increased mortality

Hypnotics and harm

Cognitive effects

- Dose dependent mental slowing and anterograde amnesia
- Likely to result in reduced social functioning over a period of time
- In older people can cause confusion, night wandering, and ‘pseudo-dementia’
- Effects may be reversible, but can take 6-12 months after stopping
- Less prevalent with drugs with short half-lives

Hypnotics and harm

Psychomotor effects

- Impairment of driving performance, increased risk of road traffic accidents
- Increased risk of ataxia, falls and fractures in older people
- Effects compounded by alcohol, and other CNS depressant drugs

Hypnotics and harm

Tolerance, dependence and withdrawal symptoms

- Tolerance to hypnotic drug effect is not a frequent problem in clinical experience
- Psychological dependence is seen in many patients
- Temporary worsening of sleep, with increased sleep onset latency is reported during the withdrawal period
- A longer withdrawal syndrome is rare and includes symptoms such as agitation, headache, dizziness, dysphoria, irritability, fatigue, depersonalisation, hypersensitivity to stimuli. Physical symptoms described include nausea, vomiting, muscle cramps, sweating, weakness, muscle pain or twitching, tinnitus, abnormal sensations.
- Mostly resolves in a few weeks, while persisting in a minority for 6-12 months

Hypnotics and harm

Effects on physical health and increased mortality

- Epidemiological studies have suggested a possible link between hypnotic use and infection (Joya et al 2009; Obiora et al 2013)
- Several observational studies have found an association between use or prescription of hypnotic drugs and all cause mortality and/ or cancer.
- A large UK retrospective case control study (Weich et al 2014) found evidence of an association between prescription of hypnotic drugs with an estimated overall statistically significant doubling of hazard of death, over an average 7.6years of follow up.
- On a whole these epidemiological studies have many limitations

Long term hypnotic prescribing

Following are some clinical situations where long term prescribing may be considered, on the understanding that dependency may likely develop . This is backed by Department of Health, 2017 drug misuse and dependence guidelines.

- Clear evidence of relevant pre-existing and concurrent comorbid mental health problems (persistent severe anxiety or insomnia, panic disorder, generalised anxiety disorder, social phobia etc)

- Clear sustained deterioration following previous adequate benzodiazepine detoxification

- Long duration of previous benzodiazepine prescribing where the harm from alcohol or illicit benzodiazepines reduces significantly when on a benzodiazepine script, specially if the patient has chronic active hepatitis C. Script to be stopped if the patient relapses to alcohol or illicit use (Ford and law 2014)

Managing long term ‘therapeutic dose’ use

- Periodic re-assessment of ongoing need and efficacy of a hypnotic; trials of tapering and discontinuing medication (Krystal 2009)
- Inform patients about personalised risk assessment, and consider drug - drug interactions
- In early/ mild dependence, use of minimal interventions such as advisory letters about dose reduction with booklets on self-help strategies may suffice
- In established dependence, offer gradual dose reduction (from several weeks to over a year or more)
- Additional psychological therapies - CBT during taper improves outcome
- Additional pharmacotherapy such as antidepressants, melatonin could be considered on an individual basis

Benzodiazepine and z-drug withdrawal

Last revised in April 2015

Scenario: Benzodiazepine and z-drug withdrawal

Back to top

Age from 16 years onwards

Assessment

Back to top

How do I assess someone who wants to stop benzodiazepines or z-drugs?

- **Assess whether this is a suitable time for the person to stop taking the drugs.**
  - The chances of success are improved when a person's physical and psychological health and personal circumstances are stable. In some circumstances it may be more appropriate to wait until other problems are resolved or improved before starting drug withdrawal.
  - **Enquire about:**

Take home messages

Long term opioids

- Consider drug-drug interactions & switch to burpenorphine
- Regular QT monitoring, at least annually in those over 35
- Take home naloxone

Long term hypnotics

- Limited evidence
- Periodic individualised risk and benefit assessment
- Referral for CBTi

Managing long term opioids and hypnotics

Other useful resources

- Department of Health - Drug misuse and dependence guidelines 2017
- British Association of psychopharmacology guidelines on
  - management of substance abuse
  - consensus statement on evidence based treatment of insomnia
- Guidance for the use and reduction of misuse of benzodiazepines and other hypnotics and anxiolytics in general practice (Ford and Law)