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Substance Misuse Module

Developing people
for health and
healthcare

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Insert name of the LEP

Aims and Objectives (from handbook)

- Assessment, diagnosis and treatment of people with drug misuse
- To develop working knowledge of principles of opioid substitution treatment
- To increase awareness of other substances commonly misused
- To develop awareness of complications associated with drug misuse

Insert name of the LEP

To achieve this

- Case Presentation
- Journal Club
- 555 Presentation
- Expert-Led Session
- MCQs

- Please sign the register and complete the feedback

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Insert name of the LEP

Expert Led Session

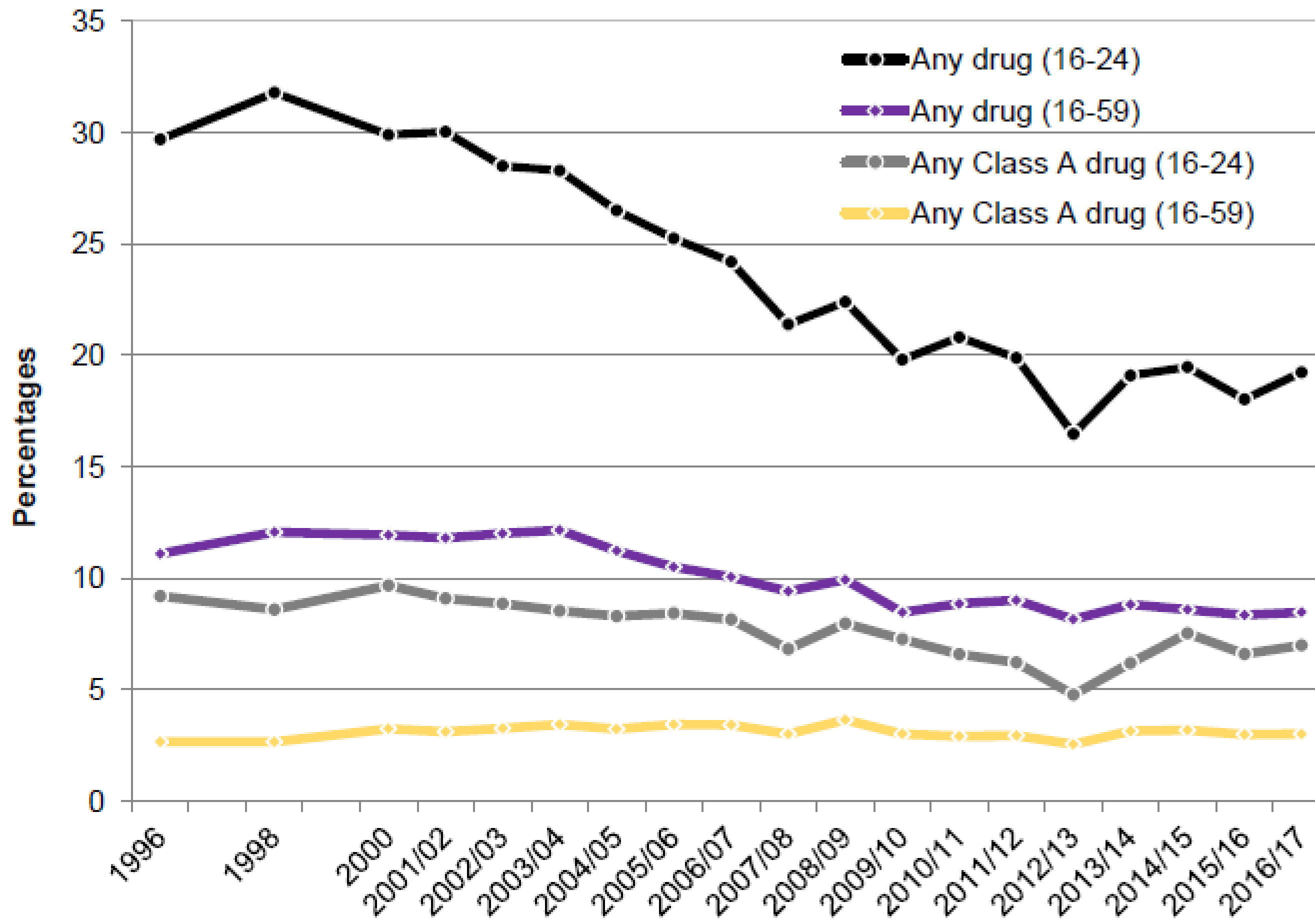
Diagnosis and treatment of people with problems with opioid dependence

P Horgan

Consultant in Substance Misuse, Cumbria

Structure

- Epidemiology /Context
- Opioid related mortality morbidity
- Treatment with opioid replacement treatment
- Detoxification
- Risks with opioid replacement treatment



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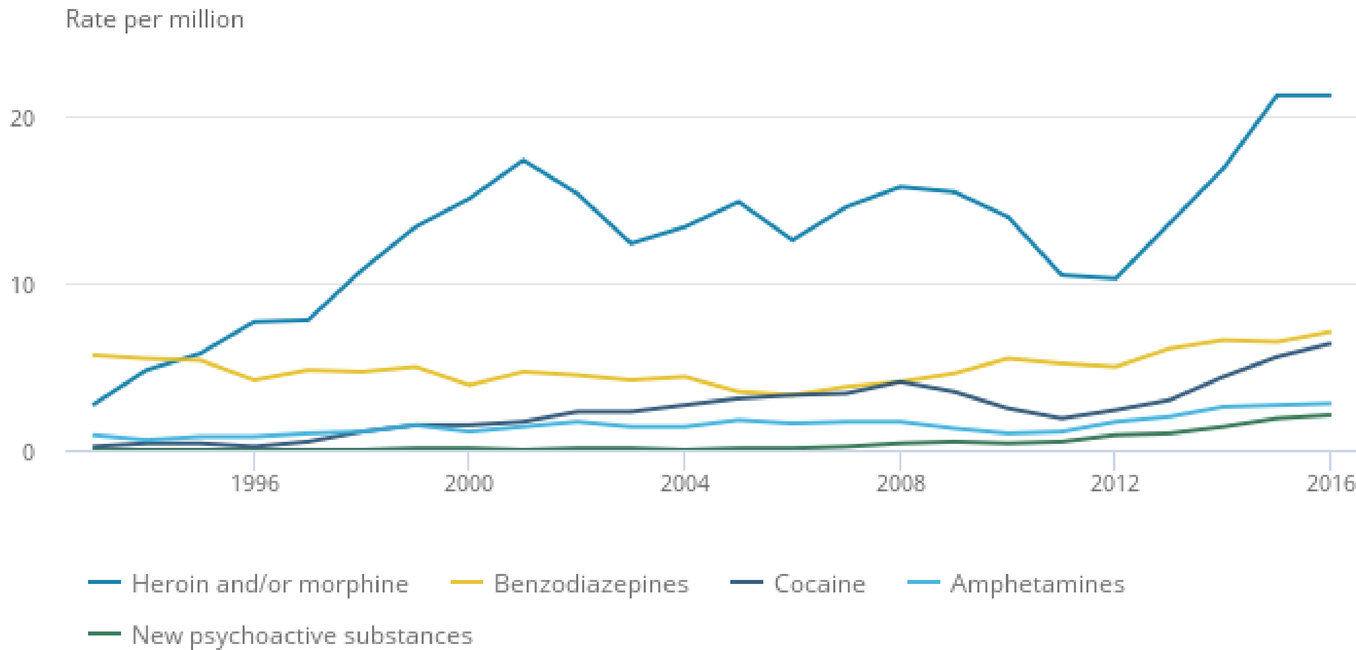
Trends in drug use in the last month among adults, 16 to 59 and 16 to 24 year old, 1996 to 2016/17 CSEW

SMR in people with opioid dependence

Causes of death	SMR	CI
All liver-related	11.4	(10.1–12.9)
Chronic liver disease	6.5	(5.3–8.0)
Viral hepatitis	46.3	(38.5–55.2)
Cardiovascular	2.1	(1.9–2.5)
Cancer	1.7	(1.4–1.9)
HIV AIDS	4.4	(3.5–5.3)
Alcohol-related	5.4	(4.4–6.6)
Chronic respiratory disease	3.9	(2.7–5.5)
Respiratory infections	7.9	(5.1–11.8)

Trends in deaths England and Wales



Heroin and morphine related deaths more than doubled since 2012

ONS 2017

Hepatitis C

- In England, 160,000 adults are estimated to be chronically infected with hepatitis C
- Injecting drug use continues to be the most important risk factor for HCV infection
- In 2015 for England, 52% of PWID tested positive for antibodies to HCV (anti-HCV)
- Target of 2030 to eliminate hepatitis C as a public health concern

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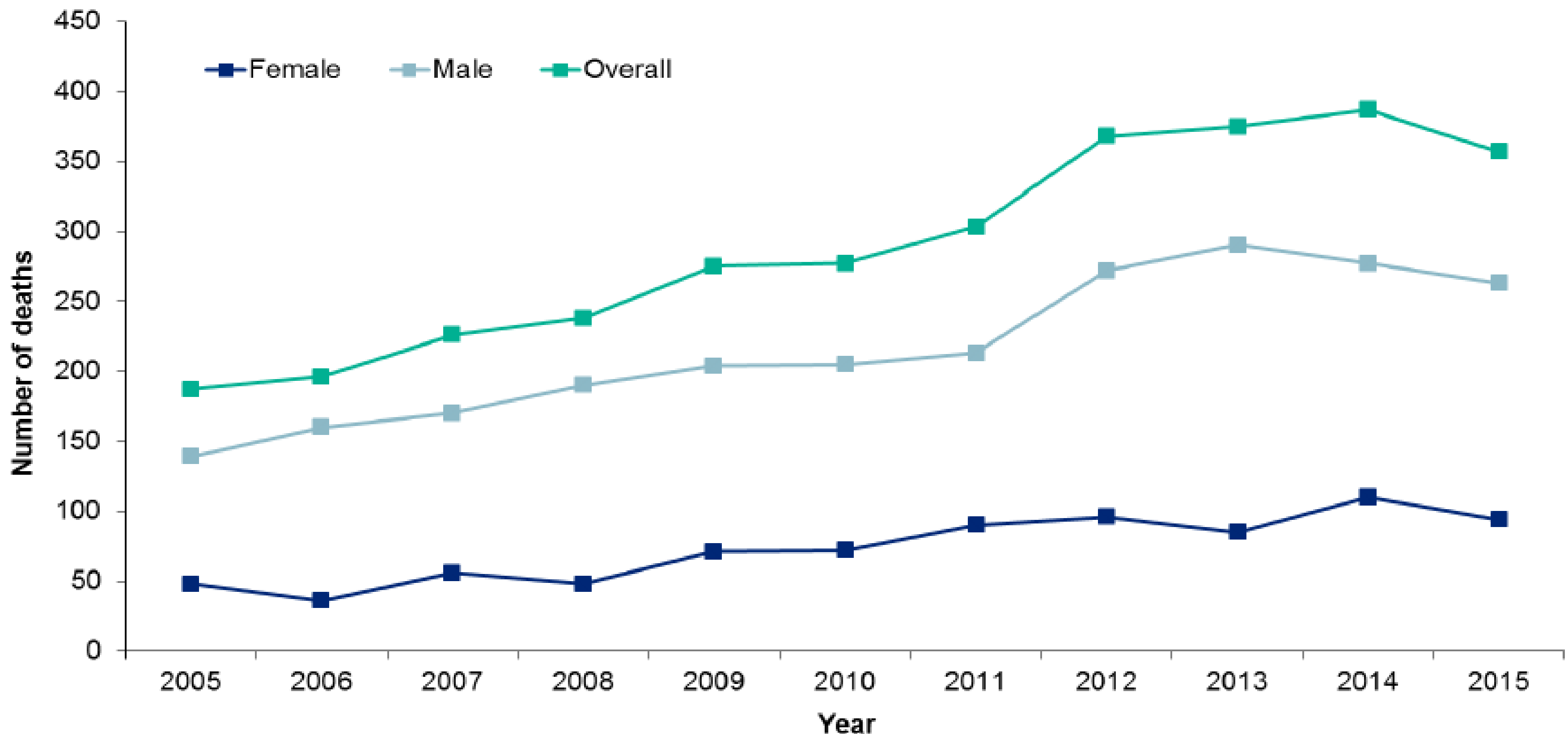
Deaths from ESLD or HCC in those with HCV mentioned on their death certificate in England: 2005-2015



Treatment opioid dependence

- The needs of all drug misusers should be assessed across the four domains of drug and alcohol misuse, health, social functioning and criminal involvement.
- Risks to dependent children should be assessed
- All drug misusers entering structured treatment should consent to their treatment plan which is regularly reviewed.
- A named individual should manage the care plan
- Drug testing can be a useful tool in assessment diagnosis and monitoring
- Drug misuse treatment involves a range of interventions, not just prescribing.

Pharmacological components

- Methadone or buprenorphine are are effective medicines for heroin dependence especially at optimal dose
- Dose induction with buprenorphine may be carried out more rapidly with less risk of overdose
- Care with children
- Supervised consumption should be available
- Methadone, buprenorphine, lofexidine are effective in detoxification regimens

Opioid substitution treatment (OST) effectiveness

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- The evidence is good that OST
  - OST reduces the risk of death among heroin users participating in treatment
  - Suppresses illicit use of heroin
  - Prevents people dropping out of treatment reduces crime – OST reduces involvement in crime among heroin users participating in treatment
  - OST reduces the risk of BBV transmission, including in prisons

Opioid substitution treatment (OST) effectiveness

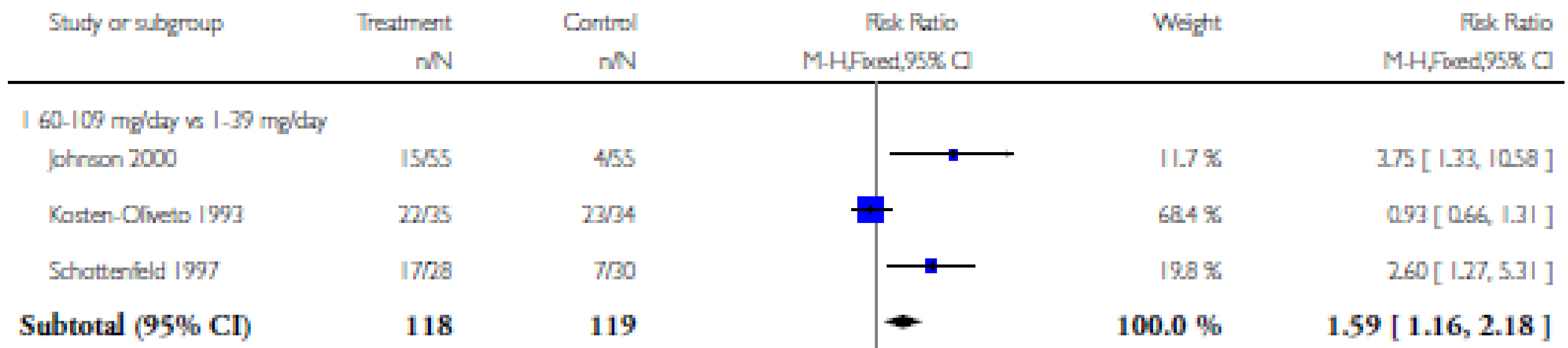
- Evidence is less good that OST
  - Suppresses other drug use
  - Promotes abstinence from all drugs
  - Improves physical and mental health –the evidence suggests rapid and substantial improvements on treatment entry, which may or may not be maintained or further improved
  - Improves social reintegration of marginalised heroin users

How long to continue treatment

- Increased length of time in OST associated with improved outcomes
- Short-term treatment associated with poorer outcomes
- Study on people on methadone treatment over 30 year period demonstrated that 40% with stable remission spent between five to eight years in OST
- English government has used findings that heroin users need at least 12 weeks in OST for benefit to underpin policy on treatment
- Some USA authors suggest a 1 year minimum time on OST

ACMD 2014
Time limiting opioid substitution therapy

Comparison 1 RCT, Outcome 6 Opioid abstinence at >3-4 weeks (urine based).



Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 60-109 mg/day vs 1-39 mg/day					
Johnson 2000	15/55	4/55		11.7 %	3.75 [1.33, 10.58]
Kosten-Oliveto 1993	22/35	23/34		68.4 %	0.93 [0.66, 1.31]
Schottenfeld 1997	17/28	7/30		19.8 %	2.60 [1.27, 5.31]
Subtotal (95% CI)	**118**	**119**		**100.0 %**	**1.59 [1.16, 2.18]**

Faggiano 2003

MMT vs No MMT Morphine positive urine or hair analysis.

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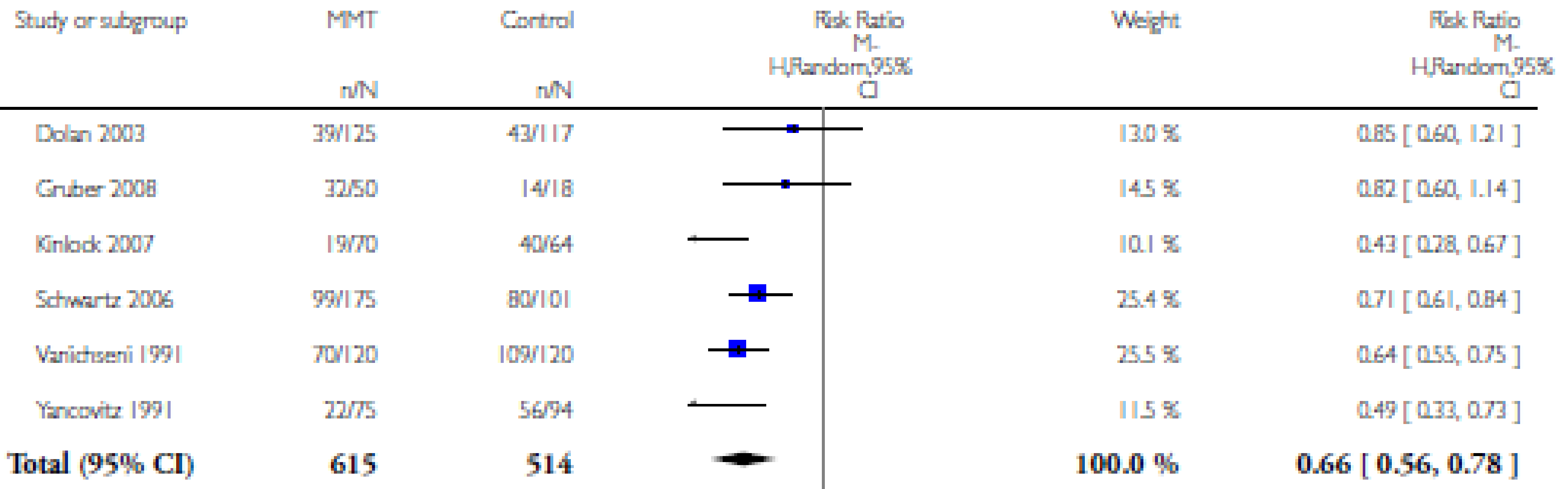
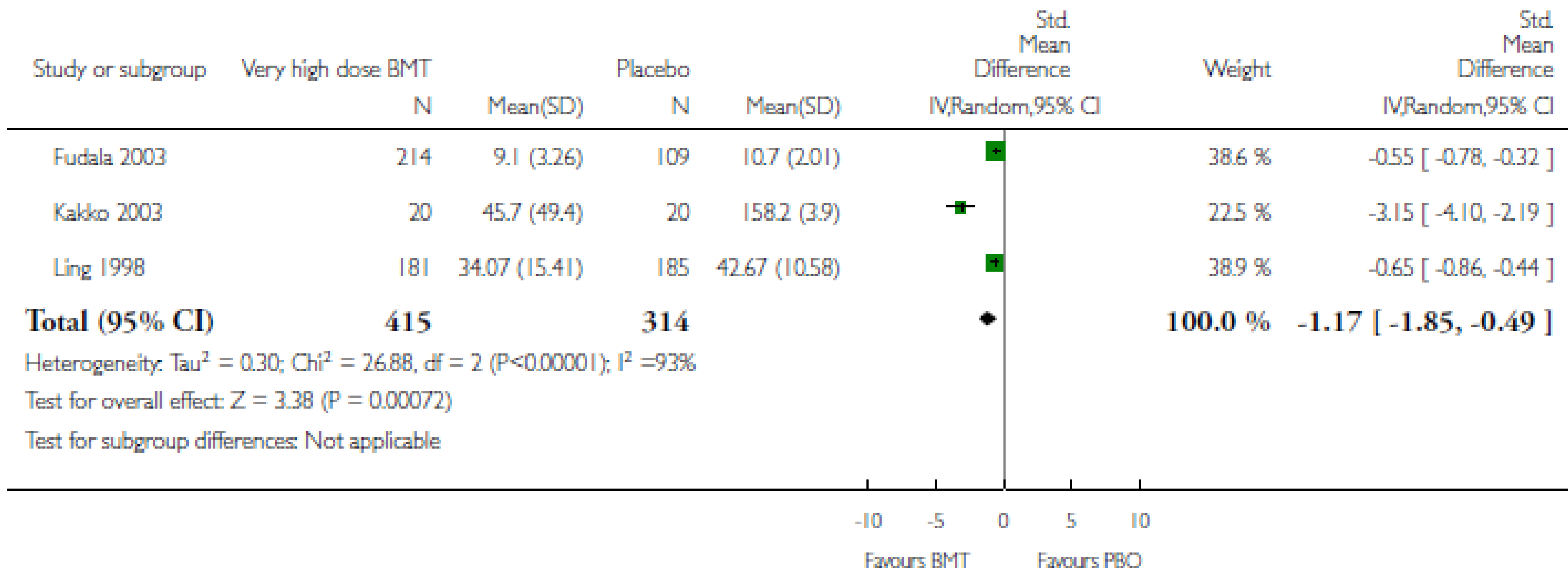


Study or subgroup	MMT n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Dolan 2003	39/125	43/117		13.0 %	0.85 [0.60, 1.21]
Gruber 2008	32/50	14/18		14.5 %	0.82 [0.60, 1.14]
Kinlock 2007	19/70	40/64		10.1 %	0.43 [0.28, 0.67]
Schwartz 2006	99/175	80/101		25.4 %	0.71 [0.61, 0.84]
Vanichseni 1991	70/120	109/120		25.5 %	0.64 [0.55, 0.75]
Yancovitz 1991	22/75	56/94		11.5 %	0.49 [0.33, 0.73]
Total (95% CI)	**615**	**514**		**100.0 %**	**0.66 [0.56, 0.78]**

Mattick 2009

High-dose buprenorphine versus placebo, Morphine-positive urines



Study or subgroup	Very high dose BMT N	Mean(SD)	Placebo N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
Fudala 2003	214	9.1 (3.26)	109	10.7 (2.01)		38.6 %	-0.55 [-0.78, -0.32]
Kakko 2003	20	45.7 (49.4)	20	158.2 (3.9)		22.5 %	-3.15 [-4.10, -2.19]
Ling 1998	181	34.07 (15.41)	185	42.67 (10.58)		38.9 %	-0.65 [-0.86, -0.44]
Total (95% CI)	**415**		**314**			**100.0 %**	**-1.17 [-1.85, -0.49]**

Heterogeneity: $Tau^2 = 0.30$; $Chi^2 = 26.88$, df = 2 (P<0.00001); $I^2 = 93\%$

Test for overall effect: Z = 3.38 (P = 0.00072)

Test for subgroup differences: Not applicable

Opioid pharmacology

Mu	Delta	Kappa
Mu 1 – Analgesia Mu 2 – Sedation, vomiting, respiratory depression, pruritus, euphoria, anorexia, urinary retention, physical dependence	Analgesia, spinal analgesia	Analgesia, sedation, dyspnea, psychomimetic effects, miosis, respiratory depression, euphoria,dysphoria, dyspnea

Actions of opioids

Drug	Mu	Delta	Kappa
Morphine	Agonist		Weak agonist
Codeine	Weak agonist	Weak agonist	
Fentanyl	Agonist		
Methadone	Agonist		
Buprenorphine	Partial agonist		Partial agonist

Pharmacokinetics Methadone

- Well absorbed from the gastrointestinal tract with peak plasma levels occurring 1-5 hours after a single dose.
- Wide variations in plasma levels occur during maintenance therapy.
- Plasma levels may decrease due to auto-induction of hepatic microsomal enzymes.
- Gradual accumulation in tissues and on discontinuation low concentrations in the plasma are maintained by slow release from extravascular binding sites accounting for the relatively mild but protracted withdrawal syndrome.
- N-demethylation occurs in the liver and metabolites are excreted in the faeces and urine together with unchanged methadone
- The elimination half-life is long and varies considerably with a range of 15-60 hours having been reported

https://www.medicines.org.uk/emc/medicine/25342

Pharmacokinetics Buprenorphine

- Used sublingually as undergoes extensive first-pass metabolism in the small intestine and the liver.
- Peak plasma concentrations are achieved 90 minutes after sublingual administration
- The absorption of buprenorphine is followed by a rapid distribution phase (distribution half-life of 2 to 5 hours).
- CYP3A4 is responsible for the N-dealkylation of buprenorphine.
- Elimination of buprenorphine is bi- or tri- exponential, and has a mean half-life from plasma of 32 hours
- Buprenorphine excreted in the faeces by biliary excretion of the glucuroconjugated metabolites (70%), the rest excreted in the urine.

https://www.medicines.org.uk/emc/medicine/26614

Opioid detoxification General 1

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- Clearly defined process supporting safe and effective discontinuation of opiates while minimising withdrawals.
- Varies from 28 days as inpatient to 12 weeks as outpatient
- A detoxification alone is rarely successful especially at the first attempt- need to have clear access back into treatment
- Important factors
  - The patient is fully committed to and informed about the process (including risk of relapse)
  - the patient is fully aware of the high risk of relapse
  - The patient is in stable situation or in stable situation following detoxification.
  - Plans for continuing support and treatment are in place.

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Opioid detoxification General 2

- Avoid coerced detoxification
- During detoxification offer
  - Full psychosocial support
  - Access to drug-free support
  - Overdose training
- Do not encourage patients on stable doses to start a very gradual reduction
- However patients may want to gradually reduce – evidence about this to be discussed with them

Methadone Buprenorphine Detox

- Methadone
  - Following stabilisation reduce at around 5 mg every one or two weeks.
  - Usual higher decrements at the start
- Buprenorphine
  - Reduce by 2 mg every two weeks with final reductions being around 400 micrograms.
  - Patients report being able to reduce buprenorphine doses more quickly than methadone.
- Detoxification from either medication similar in terms of outcomes from detoxification

Symptomatic treatment of withdrawal Lofexidine

- Adrenergic alpha-2-receptor agonist with high affinity for 2A receptor subtypes
- Less anti-hypertensive activity than clonidine- a non-selective alpha-2-receptor agonist.
- Hypotension and bradycardia may occur
- Stopping suddenly may result in transient increased BP
- Dry mouth and mild drowsiness can occur
- Course between 7–10 days
  - start at 800 micrograms
  - rise to maximum of 2.4 mg in divided doses
  - reducing subsequently
- Consider in those not using methadone or buprenorphine for detoxification, those wanting to detoxify within a short time period and those with mild / uncertain dependence (including young people)

SPC lofexidine
Clinical Guidelines 2017

Adjunctive medication

- Diarrhoea – loperamide
- Nausea, vomiting metoclopramide /prochlorperazine
- Stomach cramps – mebeverine / hyoscine butylbromide
- Agitation and anxiety, sleeplessness – zopiclone 7.5 mg at bedtime
- Muscular pains and headaches –paracetamol, aspirin and other non-steroidal anti-inflammatory drugs

Setting

- Community detoxification generally to be used
- Consider inpatient detoxifications in those
  - not benefited from previous community-based detoxification
  - With significant co-morbid physical or mental health problems
  - require complex polydrug detoxification, (alcohol or benzodiazepines)
  - Have significant social problems that will limit the benefit of community-based detoxification.

Clinical guidelines 2017

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Relapse prevention with Naltrexone

- Naltrexone is an opioid antagonist used orally in UK
- Liver function tests should be conducted before and during naltrexone treatment (due to risks of hepatoxicity).
- Prior to first dose need negative drug screen
- First dose of naltrexone is (25 mg) orally
- Continues at 50 mg
- Patient information card should be given
- Programme of supervision for compliance helpful

Complications with OST

- Older populations with OST
- Frequent comorbid physical health problems
- Two main concerns
  - QTc
  - Respiratory depression

QTc Prolongation

- Methadone prolongs QTc in a dose dependent manner
- Upper limits
  - 450 ms in adult males
  - 460 ms in adult females
- 10 ms increase in QTc - 5-7% increase in TdP Risk
- QTc >500 ms, - risk of TdP markedly increased
- Other factors for QTc prolongation include: Drugs/ Metabolic Factors / Cardiac disease

Mujtaba 2013; BMJ 2016

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Review

- Epidemiology /Context
- Opioid related mortality morbidity
- Treatment with opioid replacement treatment
- Detoxification
- Risks with opioid replacement treatment

Substance Misuse

MCQs

1. Common term for illicit diazepam:
   A. Plant food
   B. Blues
   C. Spice
   D. Horse
   E. Whizz

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MCQs

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Substance Misuse

Health Education England

MCQs

2. The following are true of Novel psychoactive substances except for:

A. GHB (gammahydroxybutrate) and GBL (gammabutyrolactone) act similarly to hallucinogens such as LSD

B. Mephedrone is part of the cathinone family of drugs

C. Piperazines substances have stimulant effects

D. Paramethoxyamphetamine (PMA) is an methylenedioxymetamphetamine (MDMA) like substance

E. Ketamine use can results in haemorrhagic cystitis

Substance Misuse

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Substance Misuse

Health Education England

MCQs

3. The following are true of methadone except for:

A. Cases of QT interval prolongation and torsade de pointes have been reported during treatmentwith methadone, particularly at high doses (>100mg).

B. Typical starting doses are in the range of 10 to 30 mgs

C. Methadone tablets are the preferred formulation for commencing treatment in opioid dependence

D. Use of Cimetidine may lead to potentiation of opioid activity due to displacement of methadone from protein binding sites

E. Peak plasma levels occur 1-5 hours after a single dose of Methadone Mixture 1mg/1ml

Substance Misuse

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MCQs

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Substance Misuse

MCQs

4. The following are true about opioid substitution treatment except for:

   A. Reduces the risk of death among heroin users

   B. Suppresses illicit use of heroin

   C. Reduces involvement in crime among heroin users participating in treatment

   D. Reduces the risk of Blood Bourne Virus transmission, including in prisons

   E. Promotes abstinence from all drugs

Substance Misuse

MCQs

4. The following are true about opioid substitution treatment except for:

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E. Promotes abstinence from all drugs

Substance Misuse

MCQs

5. For long term treatment of pain using opioids – the following dose of oral morphine or equivalent should not be exceeded

A. 10 mg

B. 40 mg

C. 80 mg

D. 120 mg

E. 240 mg

Substance Misuse

MCQs

5. For long term treatment of pain using opioids – the following dose of oral morphine or equivalent should not be exceeded

A. 10 mg

B. 40 mg

C. 80 mg

D. 120 mg

E. 240 mg

Substance Misuse

EMIs

Medication used in treatment of opioid dependence:

A. Hyoscine butylbromide
B. Naloxone
C. Codeine phosphate
D. Clonidine
E. Lofexidine
F. Suboxone
G. Loperamide
H. Oxycodeine
I. Fentanyl
J. MXL morphine capsules

1a. This medication is a selective adrenergic alpha-2-receptor agonist

1b. This medication can be used to reduce risk of injecting behaviour

1c. This medication is frequently used for symptomatic relief of abdominal cramps during opioid detoxification

Substance Misuse EMIs

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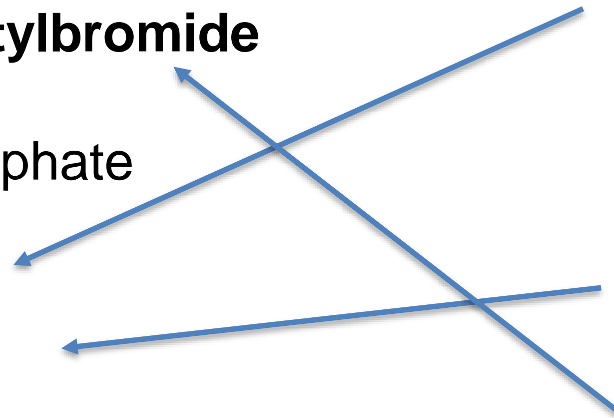

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1b. This medication can be used to reduce risk of injecting behaviour

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Substance Misuse EMIs

Analgesics of misuse:

A. Fentanyl
B. Diacetlymorphine
C. Dihydrocodeine
D. MXL
E. Diconal
F. Buprenorphine
G. MST Continus
H. Tramadol
I. Methadone
J. MXL morphine capsules

2a. This compound is a combination of an antiemetic and a opioid

2b. This compound has effects on serotonin reuptake as well as effects on opioid receptors

2c. This compound is approximately 80 times more potent than morphine and is available as lozenges and transdermal formulation

Substance Misuse EMIs

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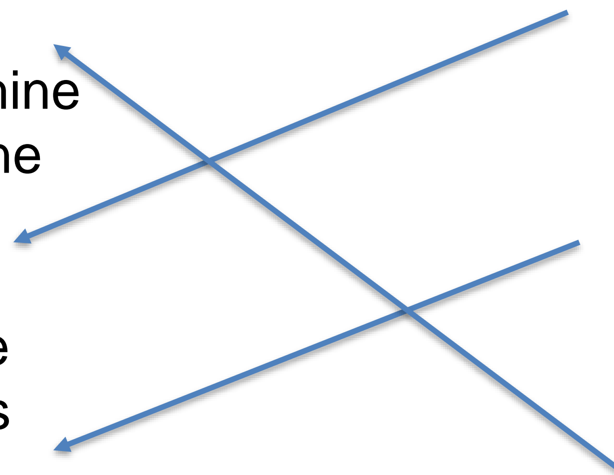

2a. This compound is a combination of an antiemetic and a opioid

2b. This compound has effects on serotonin reuptake as well as effects on opioid receptors

2c. This compound is approximately 80 times more potent than morphine and is available as lozenges and transdermal formulation