

The opioid agonist maintenance treatment: state of the art

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Opioid Dependence Treatment: Aims

- Abstinence/ Relapse prevention:
 - Abstinence of opioids
 - Reduction of severity, frequency and duration of relapses in illicit opioid use
- Harm reduction associated to opioid dependence
 - Mortality (i.e. overdoses, suicide)
 - Morbidity (i.e. HIV, HVC,...)
 - Social complications: illicit activities, violence, homelessness,..
 - Improvement of quality of life

Treatment strategies in opioid addiction

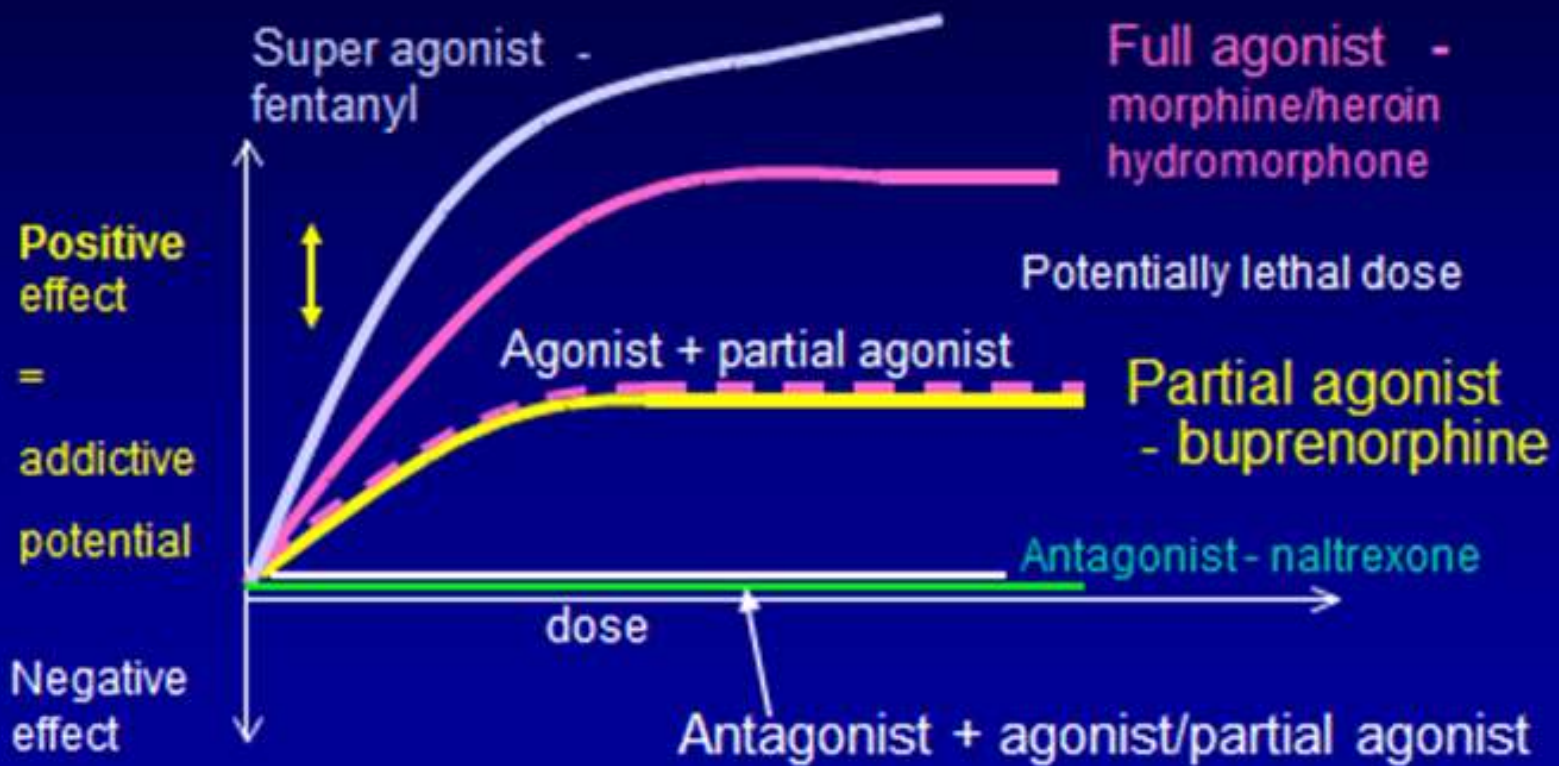
Type	Objective	Process	Treatment
Abstinence oriented	Remove the opioid	Detoxification + Relapse prevention	Met/Bupre/α2ag+/- Naltrexone
Opioid agonist maintenance	Stabilization Harm reduction	Stabilizes brain neurochemistry Functional improvement	MMT/BMT/HMT Needle exchange and other risk reduction strategies

Table 1. Classification of pharmacological opioid ligands based on its affinity for the opioid receptors (μ , δ , κ)

	Mu	Delta	Kappa	Other
Morphine	Ag+++	Ag+	Ag+	
Diacetylmorphine	Ag+++	Ag+	Ag+	
Methadone	Ag+++	Ag+	Ag++	NMDA antagonist
Codeine	Ag++			
Buprenorphine	PAg	An+++	An++	
Oxycodone	Ag+++			
Hydromorphone	Ag+++		Ag+	
Hydrocodone	Ag+++			
Meperidine (pethidine)	Ag+++	Ag+	Ag+	Serotonergic activity
Tramadol	Ag+			Norepinephric & Serotoner activity
Pentazocine	An+	Ag+	Ag+	
Naloxone	An+++	An+	An++	
Naltrexone	An+++	An+	An+++	
Nalmefene	An+++	An+	An++	

Ag: Agonist, PAg: Partial agonist, An: Antagonist. The number of symbols "+" is an indication of potency.

Mu Affinity and Opioid Addiction



Opioid agonist for maintenance treatment

- Methadone
- Levo-methadone
- Buprenorphine
- Sustained release oral morphine
- Diacetylmorphine (Heroin)

Metabolism of opioids

CYP involved				
Methadone	3A4	2B6*	2D6	2C19
Buprenorphine	3A4	3A5	2C8	
Morphine	3A4	2C8		
Heroin	Largely	in	plasma	

In vivo methadone metabolism more responsive to inhibition of 3A4 than buprenorphine
*allele 2B*6 is a “slow metabolizer “ variant, compared to 2B6*1 or 4*: more risk of overdoses

Drug interactions

CYP 3A4 Inhibitors:  **opioid plasma levels:** **overdoses risk**

Antifungals (Ketokonazole)

HIV proteasa inhibitors (Ritonavir, Indinavir)

Antibiotics (Erythromycin)

Quick development after start drug

CYP 3A4 Inducers:  **opioid plasma levels:** **withdrawal risk**

Anticonvulsants (Phenobarbital, Carbamazepine, Phenytoin)

Antibiotics (Rifampicin)

Slow development after start drug

Opioid agonist for maintenance treatment

- Methadone
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Methadone

- Synthetic opioid μ , κ , δ agonist and NMDA antagonist
- Half life of 24-36 hours, daily dosage
- Oral dosage but also injectable form available
- Average dose between 60-120 mg

- High efficacy, effectiveness and efficiency
- Most prevalent opioid maintenance medication used
- Gold standard in OMT

Methadone

Potential serious side effects

- **Fatal respiratory depression during intoxication:**
 - Specially during initiation of treatment... careful induction (about 3-4 weeks to achieve stable treatment doses)
- **QTc interval prolongation with risk of ventricular arrhythmias (Torsades de point)**
 - Related to high doses (> 100 mg/d)
 - Polymedication (i.e. antipsychotics...)
 - Female
- **Relevant pharmacological interactions**
 - Opioid intoxication (Ritonavir, Indinavir, ketokonazole)
 - Opioid withdrawal (Riphampicin)

Levo-Methadone

- Contains the active part of methadone (only levo and not dextro)
 - Half the dosage
 - Expensive
 - Only prescribed in Germany: *Polamidon* [®]
-
- **Potential serious side effects**
 - Fatal respiratory depression during intoxication:
 - **No** QTc interval prolongation

Buprenorphine

- Partial agonist μ **opioid receptor**, full agonist δ opioid receptor and antagonist κ **opioid receptor**
- Sublingual administration
- Average dose between 16-32 mg
- Found relatively easy to withdraw from
- Ceiling effect

- High efficacy, effectiveness and efficiency
- Provision less stigmatizing than methadone

Buprenorphine

Potential serious side effects

- **Less** risk of fatal respiratory depression during intoxication:
 - Ceiling effect because partial agonist
 - **Quick induction to full doses**
- **No effect on QTc** interval prolongation neither risk on Torsades de point
- Less clinically relevant interactions than methadone
- **More risk of diversion**
 - Prescribed in combination with naloxone (Subuxone[®])

Slow release oral morphine

Opioid dependence treatment in:

- Austria 1998
- Slovakia 2005
- Slovenia 2005
- Bulgaria 2006
- Luxembourg 2006
- France: exceptionally prescribed

Slow release oral morphine

- opioid μ , κ , and δ agonist
 - Formulations suitable for once-daily dosing
 - Peak plasma concentrations 2-6 after administration, and release of the drug over a 24-hour period.
-
- Few studies
 - Retention in treatment appeared superior to 80%
 - Opioids use varied from lower to NS or clinically different from comparison interventions.
 - No differences in the use of other substances.

Slow release oral morphine

Articles included: summary of study design

Study design	Number of study	Article	Notes
Randomized controlled trial	1	2. Winklbauer <i>et al.</i> (2008) [15] 6. Eder (2005) [19]	Crossover Same data set for articles 2 and 6
Controlled trial	1	3. Mitchell <i>et al.</i> (2006) [16] 8. Mitchell <i>et al.</i> (2004) [21] 9. Mitchell <i>et al.</i> (2003) [22]	Crossover Same data set for articles 3, 8 and 9
Prospective uncontrolled study	5	1. Kastelic <i>et al.</i> (2008) [14] 12. Vasilev <i>et al.</i> (2006) [25] 11. Kraigher <i>et al.</i> (2005) [24] 10. Kraigher <i>et al.</i> (2002) [23] 13. Rao <i>et al.</i> (2005) [26]	–
Cross-sectional study	2	4. Giacomuzzi <i>et al.</i> (2006) [17] 5. Giacomuzzi <i>et al.</i> (2005a) [18] 7. Giacomuzzi <i>et al.</i> (2005b) [20]	Same data set for articles 5 and 7

Slow release oral morphine

- Good retention rates: 81-95%
 - Similar to methadone
 - Quality of life, withdrawal symptoms, craving and additional drug use improved with SROM
 - There were no comparison with other treatments
 - Most of the studies were uncontrolled
-
- Patients with long QTc values in MMT, and high doses of methadone are switched to SROM

Slow-release oral morphine as maintenance therapy opioid dependence (Review)

Ferri M, Minozzi S, Bo A, Amato L



2013

Slow release oral morphine

- Respect to other interventions:
 - reduce cravings, depressive symptoms, physical complaints and anxiety symptoms
 - No differences in quality of life
 - Worse in other social functioning measures (finances, family and overall satisfaction) than people maintained with methadone or buprenorphine.
 - **More adverse effects**

Diacetilmorphine (Heroin)

- Opioid analgesic, semi synthetic derived from morphine
- Illegal in most countries
- 4 hours half-life and 3 to 4 dosages per day
- Expensive form of treatment
- Found hard to withdraw from
- High risk of overdose

Table 2: International supervised injectable heroin (SIH) (plus flexible supplementary doses of oral methadone) trials' key features and outcomes

Main paper	Country	Sample size; groups studied	Time to Follow-up	Outcomes
Perneger et al., 1998	Switzerland	N=51 SIH (+OM): n=27 OM, detox, rehab: n=24	6 months	<ul style="list-style-type: none"> Retention: SIH 93 %, OM 92 %. Self-reported illicit heroin use: SIH 22 %, OM 67 % (p=0.002). Serious adverse events data not reported
Van den Brink et al., 2003	Netherlands	Injectable trial: N=174 SIH (+OM): n=76 OM: n=98 (also SinH trial, N=73)	12 months	<ul style="list-style-type: none"> Retention: SIH 72 %, OM 85 %. Self-reported 40 % improvement in at least one domain (physical, mental, social): SIH 56 % vs. OM 31 % (p=0.002). Serious adverse events: reported data limited to 11 SAEs (two definitely or probably, and nine possibly related to injectable heroin)
March et al., 2006	Spain	N=62 SIH (+OM): n=31 OM: n=31	9 months	<ul style="list-style-type: none"> Retention: SIH 74 %, OM 68 %. Self-reported illicit heroin use in past 30 days (mean days): SIH=8.3 vs. OM=16.9 (p=0.02). Serious adverse events: SIH=seven (two unrelated and five probably, or definitely related to study drug) vs. OM=seven
Haasen et al., 2007	Germany	N=1015 SIH (+OM): n=515 OM: n=500	12 months	<ul style="list-style-type: none"> Retention: SIH 67 %, OM 40 %. Improvement in drug use (measured by either UDS and self-report): SIH 69 %, OM 55 % (p<0.001). Improvement in physical/mental health: SIH 80 %, OM 74 % (p=0.023). Combined reduced drug use and improved physical/mental health (responder): SIH 57 %, OM 45 % (p<0.001). Serious adverse events: SIH=177 (58 possibly, probably, or definitely related to study drug) vs. OM=15
Oviedo-Josles et al., 2009	Canada	N=251 SIH (+OM): n=115 OM: n=111 (also SIHM +OM, n=25)	12 months	<ul style="list-style-type: none"> Retention: SIH 88 %, OM 54 % (p<0.001). Self-reported reduction in illicit drug use or other illegal activities (improvement of 20 % for either domain): SIH=67 %, OM=48 % (p=0.004). Serious adverse events: SIH=51 vs. OM=18
Strong et al., 2010	England	N=127 SIH (+OM): n=43 OOM: n=42 (also SIM +OM, n=42)	6 months	<ul style="list-style-type: none"> Retention: SIH 88 % vs. OOM 69 %. Reduction in 'street' heroin — 50 % or more negative UDS during weeks 14-26 (responder): SIH 66 % vs. OOM 19 % (p<0.0001). Serious adverse events: SIH=7 (2 likely related to study drug) vs. OOM=9

Note: SAE, serious adverse event; OM, oral methadone; OOM, optimised oral methadone; SIM, supervised injectable methadone; SinH, supervised inhalable heroin; SIHM, supervised injectable hydromorphone.

Table 6: Key features of SIH clinical practice and service provision in Europe and Canada

Country	Number of clinics	Total capacity (range)	Numbers in treatment (as of July 2011)	Catchment area	Number of block opening hours	SIH is part of routine clinical practice
Switzerland	23	1 454 (15–210)	1 356	German-speaking part (22 clinics) and Geneva (1 clinic)	2–3	Yes
Netherlands	17	745 (20–75)	650 (1)	Country-wide	3	Yes
Spain	1	56	17	Granada city	2 (weekdays only)	No (2)
Germany	7	300 (12–70)	300	Seven towns across Germany	2–3	Yes
Canada	2	140–180	0	Vancouver and Montreal	N/A	No (2)
England	3	100 (24–40)	100	South-east London, Brighton and Darlington	2	Yes
Denmark	5	300 (40–120)	120	Municipalities of Copenhagen, Odense, Glostrup, Århus and Esbjerg	2	Yes

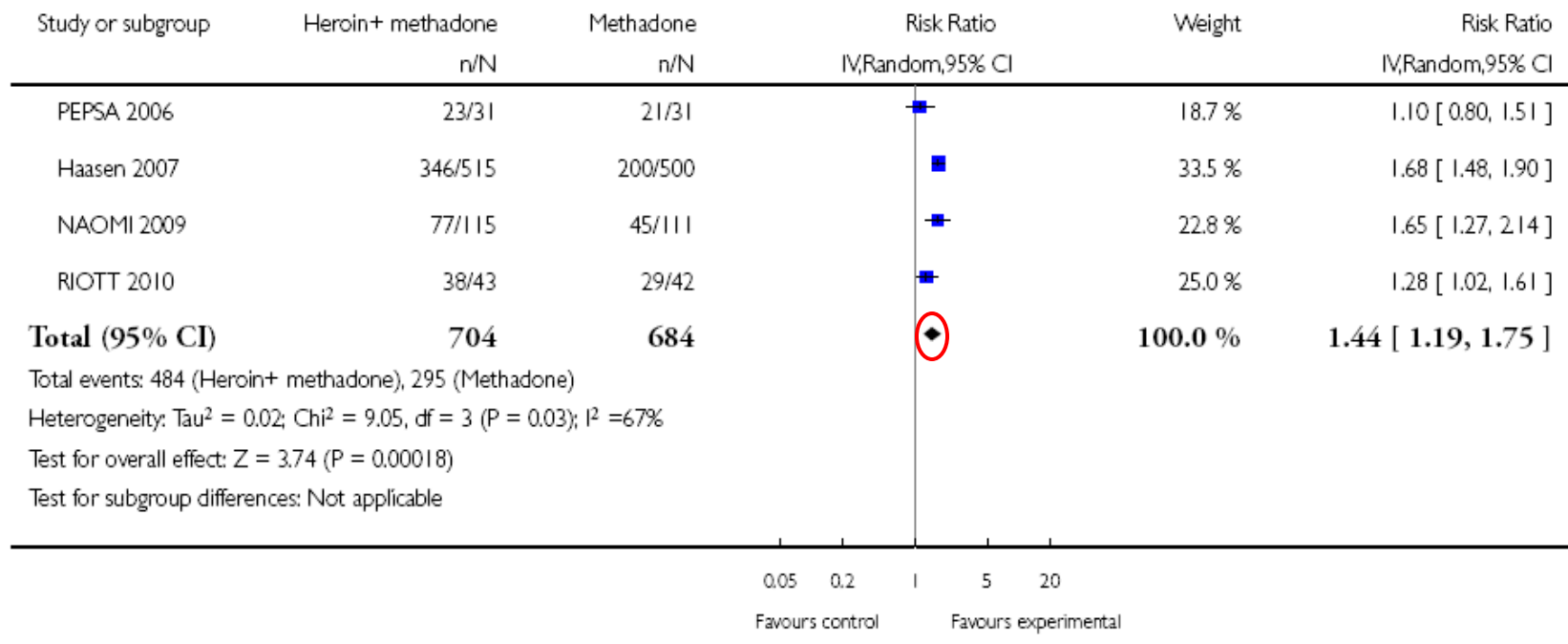
Diacetylmorphine

Analysis 1.1. Comparison 1 Supervised Injected Heroin + methadone vs oral methadone, Outcome 1 Retention in treatment.

Review: Heroin maintenance for chronic heroin-dependent individuals

Comparison: 1 Supervised Injected Heroin + methadone vs oral methadone

Outcome: 1 Retention in treatment



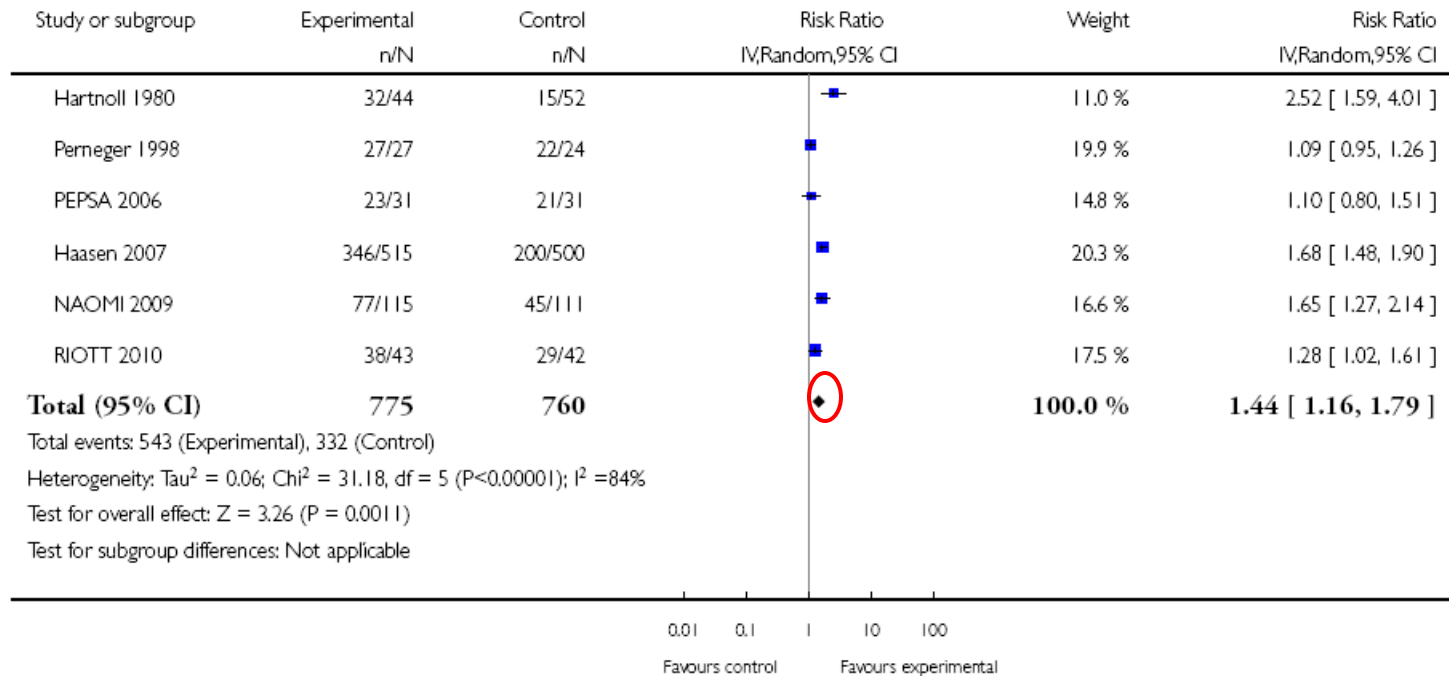
Diacetylmorphine

Analysis 2.1. Comparison 2 Heroin Provision (various modality and route of administration) vs any other treatment, Outcome 1 Retention in treatment.

Review: Heroin maintenance for chronic heroin-dependent individuals

Comparison: 2 Heroin Provision (various modality and route of administration) vs any other treatment

Outcome: 1 Retention in treatment



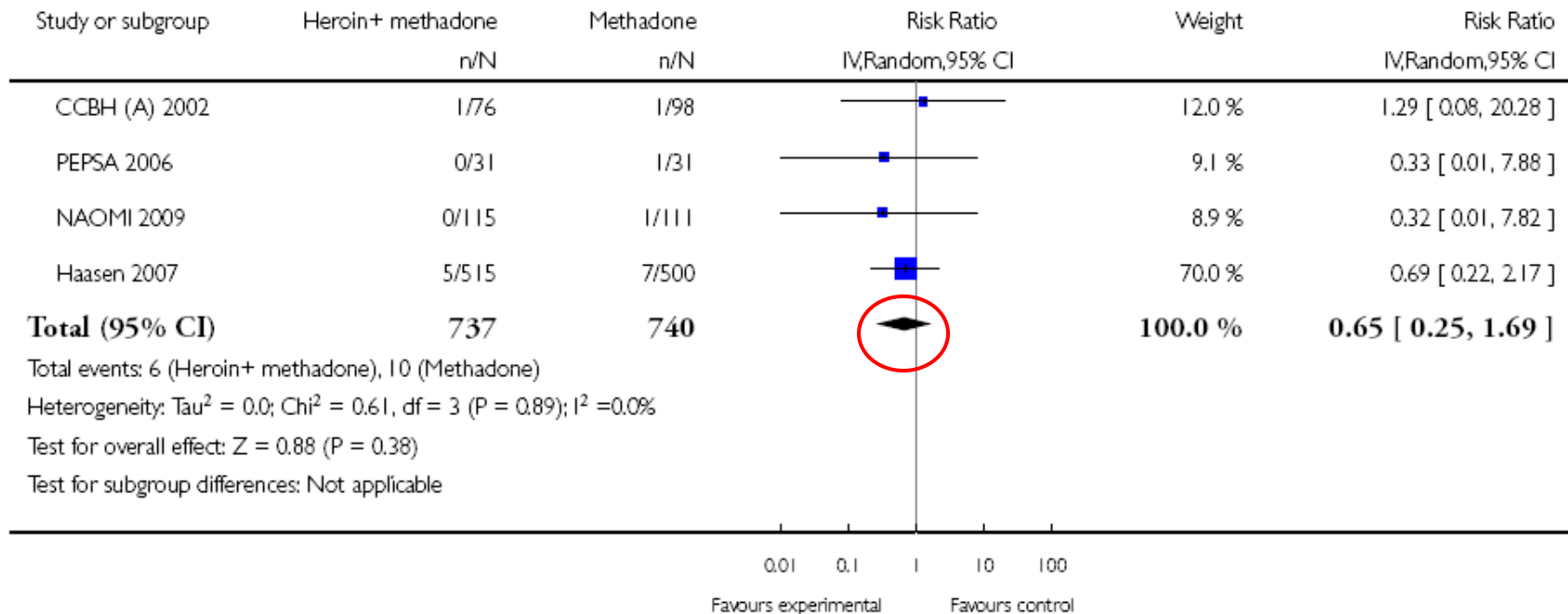
Diacetylmorphine

Analysis 1.2. Comparison 1 Supervised Injected Heroin + methadone vs oral methadone, Outcome 2 Mortality.

Review: Heroin maintenance for chronic heroin-dependent individuals

Comparison: 1 Supervised Injected Heroin + methadone vs oral methadone

Outcome: 2 Mortality



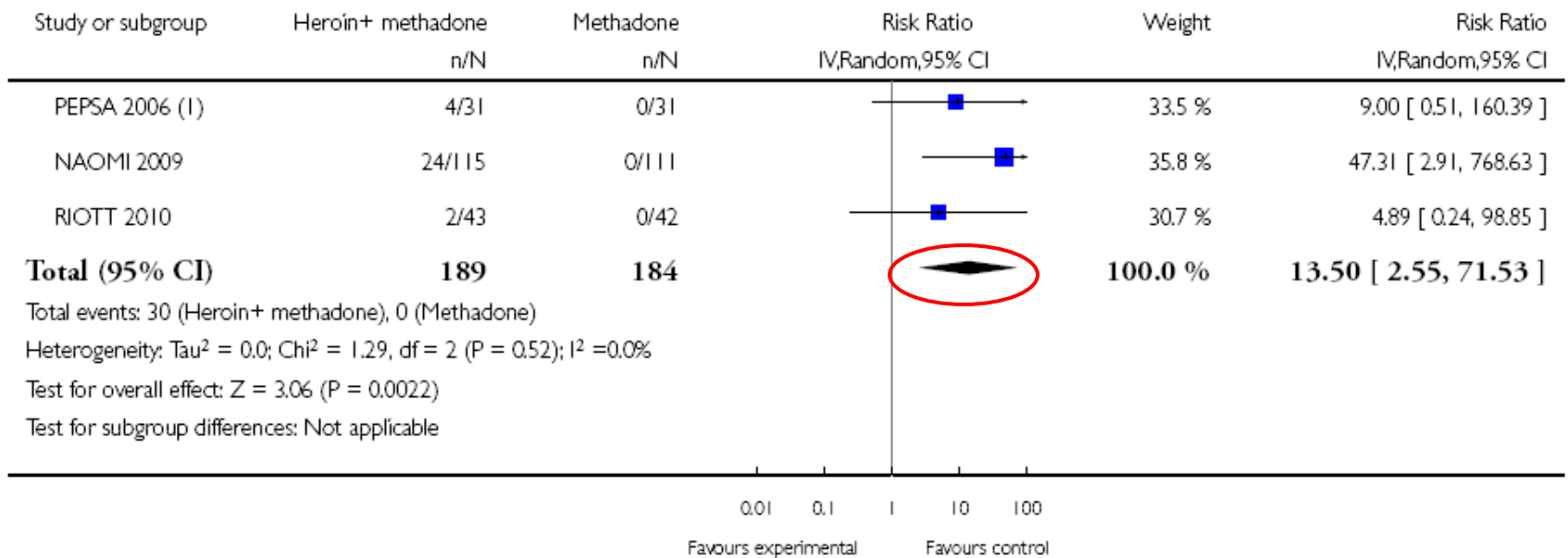
Diacetylmorphine

Analysis 1.3. Comparison 1 Supervised Injected Heroin + methadone vs oral methadone, Outcome 3 Adverse events related to intervention medications.

Review: Heroin maintenance for chronic heroin-dependent individuals

Comparison: 1 Supervised Injected Heroin + methadone vs oral methadone

Outcome: 3 Adverse events related to intervention medications



Diacetylmorphine

- Patient satisfaction
 - Patients were satisfied
 - Complaints about organizational details
- Impact on public health
 - Decreases the risk of infectious diseases
 - Reduction in drug trafficking
 - Reduction in crime involvement
- Cost-benefit
 - Favorable cost-benefit ratios in the Swiss, Dutch and German studies

Diacetylmorphine

- A treatment for refractory opioid users that can help to:
 - Decrease illicit substances
 - Decrease the involvement in criminal activity
 - Probably decrease mortality
 - Increase in retention in treatment
- Should be provided in clinical settings that can control for overdoses and/or severe adverse events



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EMCDDA

INSIGHTS

New heroin-assisted treatment

Recent evidence and current
practices of supervised
injectable heroin treatment
in Europe and beyond

11

Other alternatives

- Other injectable opiate maintenance medication:
 - supervised injectable **hydromorphone** seen with the small subset of the Canadian NAOMI trial
 - Injectable methadone (*Strang et al 2010*)
- Administration of diacetylmorphine by different possible routes,
 - heroin by smoking/chasing the dragon (*van den Brink et al., 2003*)
 - oral heroin (*Frick et al., 2006, 2010*)
 - intranasal diacetylmorphine (*Mitchell et al., 2006*)

Table 5: Summary of currently available commercial pharmaceutical diacetylmorphine products used in addiction treatment

Company and country of origin	Product	Amount per ampoule/vial	Re-usable membrane	Licensed or safety-tested for multi-dose use
Auralis, UK	Diamorphine hydrochloride powder for solution for injection	100 mg and 500 mg	N/A	Yes
TEVA, UK	Diamorphine hydrochloride (for injection)	2 ml clear glass vial (5 mg, 10 mg and 30 mg strengths) 5 ml clear glass vial (100 mg and 500 mg strengths)	Yes	Yes
Wockhardt UK Ltd, UK	Diamorphine hydrochloride powder for solution for injection	30 mg, 100 mg, 500 mg ampoules BP	N/A (single-use)	No
DiaMo, Switzerland	Diamorphine hydrochloride monohydrate (Diaphin®)	10 g vial	Yes	Yes
Diacetyl-M BV, Netherlands	Diamorphine hydrochloride solution for injection	3 g multi-dose vial	Yes	Yes
	Diamorphine base (for inhalation)	75 mg, 100 mg, 150 mg, 200 mg sachets	N/A	N/A

Opioid agonist for maintenance treatment

- Methadone
- Levo-methadone
- Buprenorphine
- Sustained release oral morphine
- Diacetylmorphine (Heroin)

Thanks for your attention !

Questions?

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