Bijlage bewijstabellen bij de Multidisciplinaire richtlijn opiaatverslaving
Inhoud

Bewijstabellen ontgifting — 5

Bewijstabellen contingentiemanagement (CM) — 17
   CM als stand-alonebehandeling voor abstinentie — 17
   CM bij detoxificatie — 19
   CM bij naltrexononderhoudsbehandeling voor abstinentie — 20
   CM bij methadononderhoudsbehandeling — 21
   CM bij buprenorfineonderhoudsbehandeling — 24

Bewijstabellen psychosociale interventies — 29

Bewijstabellen heroïne op medisch voorschrift (HAT) — 37
   Cohortonderzoek HAT — 37
   Systematische reviews en trials HAT — 39
Bewijstabellen ontgifting

Deze bewijstabellen horen bij hoofdstuk 5, Behandeling voor abstinentie. Voor de volledige literatuurbeschrijvingen van de onderzoeken, zie hoofdstuk 5, Literatuur.


<p>| Study aim | To investigate the clinical effectiveness and cost-effectiveness of naltrexone for relapse prevention in detoxified formerly opioid-dependent individuals compared with any strategy that does not use naltrexone, including treatment with placebo, other pharmacological treatments, psychosocial interventions or no treatment |
| Study design | Systematic review. Blindness: researchers described for every study who was blinded for treatment. For most of the studies, there was no information on this subject. Location: University of Birmingham, UK |
| Number of studies | Effectiveness of naltrexone: 21 citations reporting 17 different studies: – 1 systematic review; – 13 RCTs; – 3 non-randomised comparative studies. Effectiveness of interventions to enhance naltrexone compliance: 10 citations, reporting 9 RCTs. N = 940 in the 13 included trials N = 841 in the other 9 RCTs |
| Inclusion | Inclusion criteria: – controlled trials of the use of oral naltrexone compared with any other relapse-prevention strategy (pharmacological, psychosocial, etc.) without naltrexone in detoxified formerly opioid-dependent individuals in both arms; – systematic reviews of analytical observational studies looking at adverse events or other outcomes, e.g. crime rates, for naltrexone use for the same indication; – RCTs of any intervention designed to enhance compliance with naltrexone treatment with the same naltrexone regimen in both arms. Exclusion: – studies of naltrexone treatment outside the licensed indications, such as subcutaneous implants or parenteral depot preparations; – studies of naltrexone use for alcohol dependence or other indication; – case reports and case series. |</p>
<table>
<thead>
<tr>
<th>Intervention(s)</th>
<th>Intervention:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>– naltrexone.</td>
</tr>
<tr>
<td></td>
<td>– Mean length of time for which patients stayed on naltrexone was 84-103 days with additional psychosocial therapy compared with 43-64 days for the control group.</td>
</tr>
<tr>
<td></td>
<td>– The initial doses of naltrexone in the studies were fairly standard: 25 mg (half a tablet) on day 1, followed by 50 mg (one tablet) daily from day 2 onwards. A three-times-a-week dosing schedule may be considered if it is likely to result in better compliance (e.g. 100 mg on Monday, 100 mg on Wednesday and 150 mg on Friday).</td>
</tr>
</tbody>
</table>

| Control:       | – any strategy that does not use naltrexone, including treatment with placebo, other pharmacological treatments, psychosocial interventions or no treatment. |

| Follow-up      | The mean length of follow-up in the RCTs was 29 weeks (range 3-52 weeks) |

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Primary:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>– changes in illicit drug use;</td>
</tr>
<tr>
<td></td>
<td>– drug-related morbidity;</td>
</tr>
<tr>
<td></td>
<td>– drug-related mortality;</td>
</tr>
<tr>
<td></td>
<td>– health-related quality of life.</td>
</tr>
</tbody>
</table>

| Secondary outcomes were: |
| – proportion of individuals being maintained opioid free; |
| – concordance with and retention to treatment; |
| – adherence to treatment, treatment dropout; |
| – societal function; |
| – criminal activity, (re)incarcerations. |

<table>
<thead>
<tr>
<th>Results</th>
<th>Naltrexon appears to have some effect in improving the risk of opioid use in naltrexone versus placebo.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>The pooled relative risk from six RCTs was 0.72 (95% CI 0.58 to 0.90), which is a statistically significant difference favouring naltrexone.</td>
</tr>
<tr>
<td></td>
<td>The pooled HR from three RCTs for being free of opioid relapse was significantly different from placebo in favour of naltrexone (HR 0.53, 95% CI 0.34 to 0.82). However, this effect can be seen to fall off over time and its clinical significance is unclear.</td>
</tr>
<tr>
<td></td>
<td>A meta-analysis of 7 included RCTs showed that the relative risk of loss of retention in treatment in the naltrexone arm was 0.94 (95% CI 0.84 to 1.06). The pooled hazard ratio (HR) from the 5 included RCTs for retention in treatment data followed up to 35 weeks was calculated as 0.90 (95% CI 0.69 to 1.17) in favour of naltrexone and did not reach statistical significance.</td>
</tr>
</tbody>
</table>
Quality assessment

Study question: +
Search: +
Selection: +
Quality assessment: +
Data extraction: +
Description of original studies: ?
Handling heterogeneity: +
Statistical pooling: +

Finance: This report was commissioned by NHS R&D HTA Programme

Quality of evidence

A1

Conclusion review:

- Following successful withdrawal from opioids, naltrexone may be administered on a chronic basis to block any future effects of opioids.
- Naltrexone appears to have some limited benefit in helping formerly opioid-dependent individuals to remain abstinent, although the quality of the evidence is relatively poor and heterogeneous.
- The limited quality and extent of the studies precluded an analysis of subgroups likely to benefit from naltrexone prescribing. Oral naltrexone is used infrequently in current UK practice, and this review suggests that this is appropriate as there is little evidence to support its wider implementation. There is an important deficit in information about the quality of life of people who use illicit opioids and this would perhaps be a worthwhile area of research in informing policy questions about the cost-effectiveness of different programs and interventions.

NHS R&D HTA Programme: National Institute for Health Research, Research & Development, Health Technology Assessment Programme; RCT: randomised controlled trial
De Jong e.a. (2004c) General anaesthesia does not improve outcome in opioid antagonist detoxification treatment: A randomized controlled trial

<table>
<thead>
<tr>
<th>Study aim</th>
<th>To determine whether rapid detoxification under general anaesthesia results in higher levels of opioid abstinence than rapid detoxification without anaesthesia</th>
</tr>
</thead>
</table>
| Study design | Randomized controlled open clinical trial  
Blinding: not possible  
Analysis: ITT  
Study duration: September 1999 to August 2001  
Setting: 4 addiction centres (Novadic, Jellinek, Parnassia and Kentron) in collaboration with three general hospitals in the Netherlands |
| Number of patients | N = 272 |
| Patient characteristics | Opioid-dependent patients whose previous attempts to abstain were unsuccessful  
Age: mean age 36 years  
Sex: 82% male |
| Inclusion | Inclusion:  
– diagnosed as opioid-dependent according to DSM-IV criteria;  
– underwent previously several unsuccessful attempts to become abstinent;  
– expressed the clear wish to be become abstinent;  
– were over 18 years of age;  
– were familiar with the Dutch language;  
– had at least one non-opioid user in their social network;  
– dependence on other drugs or drug abuse was not an exclusion factor.  
Exclusion:  
– severe somatic diseases or psychiatric disorders;  
– pregnancy;  
– AIDS;  
– doubts about the patient's willingness to co-operate and contraindications regarding general anaesthesia |
| Intervention(s) | Intervention: rapid detoxification with general anaesthesia (RD-GA).  
Control: rapid detoxification without general anaesthesia (RD). |
| Follow-up | 1 year  
All the patients were treated for 7 days at one of four addiction treatment centres. Opioid abstinence assessment took place 1 month after completion of detoxification treatment |
Outcome: Primary: the primary end-point was opioid abstinence assessed clinically by analysing urine samples. Secondary: the secondary end-point was the intensity of the signs and symptoms of the withdrawal syndrome experienced prior to, during and after treatment. Patients completed the Subjective Opioid Withdrawal Scale (SOWS) with 16 items to determine how they experienced the withdrawal symptoms.

Results: Urine analysis 1 month after treatment: 37.2% in the RD-GA group and 40.0% in the RD group were using opioids. 86.1% of the RD-GA group was still using the naltrexone compared to 84.4% in the RD group. Heroin-use: 38.7% in the RD-GA group and 43.7% in the RD group. A combination of these two data sources showed rates of 46.0% in the RD-GA group versus 46.0% in the RD group. The patients’ subjective reports and the trained nurse observers’ objective judgement about the intensity of withdrawal signs and symptoms were fairly similar. The average 1-month cost for RD was €2517 versus €4439 for RD-GA.

Quality assessment:
- Randomization: +
- Allocation concealed: -
- Therapist blinded: -
  - Not possible.
- Assessor blinded: -
- Patient blinded: +/-
- Intervention and control groups were similar: +
- Follow-up adequate: +
- Intention-to-treat analysis: +
- Funding: Ministry of Health, Welfare and Sports (VWS) and the Netherlands Organization for Health Research and Development (ZonMw)

Quality of evidence: A2
Conclusion: rapid detoxification under general anaesthesia did not result in higher levels of opioid abstinence than rapid detoxification without anaesthesia. The cost of the former intervention was much higher.

ITT: intention to treat; RD: rapid detoxification without general anaesthesia; RD-GA: rapid detoxification with general anaesthesia.
**Krupitsky e.a. (2011) Injectable extended-release naltrexone for opioid dependence: a double-blind, placebo-controlled, multicentre randomised trial**

<table>
<thead>
<tr>
<th>Study aim</th>
<th>To assess the efficacy, safety, and patient-reported outcomes of an injectable, once monthly extended-release formulation of the opioid antagonist naltrexone (XR-NTX) for treatment of patients with opioid dependence after detoxification</th>
</tr>
</thead>
</table>
| Study design | RCT  
Blind: double blind  
Analysis: ITT  
Study duration: between July 3, 2008, and Oct 5, 2009  
Patients participated in the study for 24 weeks  
Setting: 13 clinical sites in Russia |
| Number of patients | N = 250 patients |
| Patient characteristics | Age: 18 < ; mean age 29 years  
Sex: intervention: 90% male, control: 86% male |
| Inclusion | Inclusion: - |
| Exclusion | - pregnancy or breastfeeding;  
- significant medical conditions (eg, acute renal failure, endocarditis, and tuberculosis);  
- positive naloxone challenge (increases in vital signs or opioid withdrawal symptoms);  
- hepatic failure; past or present history of an AIDS-indicator disease;  
- active hepatitis or aspartate amino transferase or alanine aminotransferase more than three times the upper limit of normal;  
- known intolerance or hypersensitivity to naltrexone, carmellose, or polylactideco-glycolide; psychosis, bipolar disorder, major depressive disorder with suicidal ideation, or present dependence on substances other than opioids or heroin, including alcohol;  
- positive urine test for cocaine or amphetamines; and  
- naltrexone use within the past 6 months |
| Intervention(s) | Intervention:  
- N = 126;  
- 380 mg injectable extended-release naltrexone (XR-NTX);  
- 67 completed trial, 126 included in primary analysis.  
Control:  
- N = 124;  
- placebo;  
- 47 completed trial, 124 included in primary analysis |
| Follow-up | 24 weeks |
Outcome

Primary: response profile for confirmed abstinence during weeks 5–24, assessed by urine drug tests and self-report of non-use
Secondary: self-reported opioid free days, opioid craving scores, number of days of retention, and relapse to physiological opioid dependence

Results

Proportion of weeks of confirmed abstinence:
- intervention: 90% (69.9 to 92.4);
- control: 35% (11.4 to 63.8);
- treatment effect: 55% (15.9 to 76.1).
Patients with total confirmed abstinence:
- intervention: 45 (35.7%) (27.4 to 44.1);
- control: 28% (22.6%, 15.2 to 29.9);
- treatment effect: 1.58 (1.06 to 2.36)

Secondary:
Proportion of self-reported opioid-free days over 24 weeks:
- intervention: 99.2% (89.1 to 99.4);
- control: 60.4% (46.2 to 94);
- treatment effect: 38.7 (3.3 to 52.5).
Number of days of retention:
- intervention: >168;
- control: 96 (63 to 165);
- treatment effect: 0.61 (0.44 to 0.86)

Quality assessment
Randomization: +
Allocation concealed: +
Therapist blinded: +
Assessor blinded: +
Patient blinded: +
Intervention and control groups were similar: +
Follow-up adequate: +
Intention-to-treat analysis: +
Funding: National Institute on Drug Abuse and National Institute on Alcohol Abuse and Alcoholism

Quality of evidence
A2

Conclusions
- The percentage of opioid-free weeks was significantly higher in the XR-NTX group than the placebo group.
- All four secondary endpoints also showed significant differences between the treatment groups.
- There was a substantial clinical response to placebo

RCT: randomised controlled trial
### Kunøe e.a. (2009). Naltrexone implants after in-patient treatment for opioid dependence: randomised controlled trial

| Study aim | Evaluate the safety and effectiveness of a 6-month naltrexone implant in reducing opioid use after in-patient treatment |
| Study design | RCT (open-label, trickle-inclusion study design) |
| Blinding: | - |
| Analysis: | ITT |
| Study duration: | 6 months |
| Setting: | receiving abstinence-oriented in-patient treatment |
| Location: | patients were recruited from in-patient drug clinics in southeastern Norway from 1 January 2006 to 1 July 2007, in a coordinated effort between two centres: the Norwegian Centre for Addiction Research at the University of Oslo and the Addiction Unit, Sørlandet Hospital, Kristiansand |
| Number of patients | N = 56 |
| Patient characteristics | Age: 34.2 (SD: 8.6). Sex: 36% female (20) |
| Inclusion | Inclusion: patients who passed the initial assessment were contacted at the end of their detoxification or residential treatment stay for informed consent, baseline assessments of outcome instruments, and randomisation. Patients were allowed to talk freely about implantation and participation both prior to and after entering into the trial. Exclusion criteria were: psychosis, pregnancy and serious hepatic disease. Baseline characteristics intervention group: all participants had to pass an oral naltrexone challenge (25 mg) before starting implant treatment |
| Intervention(s) | Intervention: naltrexone implants |
| Control: | usual care |
| Follow-up | 6 months |
| Outcome | Primary: heroin |
| – timeline: days used in past 180 days; | |
| – ASI: days used in past 30 days. | |
| Secondary: | – polydrug use |
Results: Short results: patients receiving naltrexone had on average 45 days less heroin use and 60 days less opioid use than controls in the 180-day period (both P < 0.05). Blood tests showed naltrexone levels above 1 ng/ml for the duration of 6 months.

On the 180-day timeline follow-back, the implant group reported heroin use on an average of 17.9 days (SD = 41.8) and opioid use on 37 days (SD = 63.8), compared with 63.6 days (SD = 70.6) and 97.1 days (SD = 80.9) respectively for controls.

These were reflected in significant differences in the ASI 30-day variable, with the implant group reporting a mean of 3.5 days (SD = 7.4) and 6.3 days (SD = 1.5) of heroin and opioid use respectively compared with the control group's 11.4 days (SD = 13.9) and 17.4 days (SD = 14.3).

Polydrug use: At the 6-month follow-up assessment, 18 of 27 controls v. 9 of 29 implant patients in the ITT group met criteria for DSM-IV opioid dependence using MINI (OR = 0.225, P = 0.015, 95% CI 0.07-0.69). In the naltrexone completers group, only 3 of 23 patients qualified for this diagnosis, compared with the 17 (of 26) who met sufficient criteria in the control completers group (OR = 0.08, P < 0.001). On this basis the NNT was 2.8 (95% CI 2-9) for the ITT analysis and 2.36 (95% CI 2-6) for the treatment completion sample.

Quality assessment

<table>
<thead>
<tr>
<th>Quality assessment</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient blinded:</td>
<td>-</td>
</tr>
<tr>
<td>Intervention and control groups were similar:</td>
<td>+</td>
</tr>
<tr>
<td>Follow-up adequate:</td>
<td>+</td>
</tr>
<tr>
<td>Intention-to-treat analysis:</td>
<td>+</td>
</tr>
<tr>
<td>Funding:</td>
<td>the study was approved by the regional ethics committee of southern Norway, and funded by a grant from the south-eastern Norway regional health authority</td>
</tr>
</tbody>
</table>

Quality of evidence

<table>
<thead>
<tr>
<th>Quality of evidence</th>
<th>B (A2)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>There is not much information about blindness.</td>
</tr>
</tbody>
</table>

Conclusions: naltrexone implant treatment safely and significantly reduces opioid use in a motivated population of patients.

ASI: Addiction Severity Index; ITT: intention to treat; MINI: Mini International Neuropsychiatric Interview; NNT: Numbers Needed to Treat; OR: odds ratio [relative risk]; RCT: randomised controlled trial; SD: standard deviation
### Lobmaier e.a. (2008) Sustained-release naltrexone for opioid dependence

#### Number of studies

Number of studies: N = 17 articles were included

#### Number of patients

Number of patients: Between 30 and 1791 for a treatment

#### Inclusion

Inclusion: adults or adolescents with opioid dependence:
- study of effectiveness of sustained-release naltrexone for opioid dependence;
- studies of adverse effects of sustained-release NTX.

Exclusion; reasons for exclusion of the remaining 50 reports were:
- publication was no clinical trial (25 reports);
- adverse effect data not provided (11 reports);
- intervention was oral naltrexone (9 reports);
- publication on pharmacokinetics of a non-recommendable formulation (3 reports);
- abstract available only (1 report);
- two references to same publication (1 report)

#### Intervention(s)

Types of interventions:
- sustained-release naltrexone versus oral naltrexone;
- sustained-release naltrexone versus placebo;
- sustained-release naltrexone versus agonist replacement therapy;
- sustained-release naltrexone versus psychosocial interventions;
- sustained-release naltrexone versus no treatment.

Retrieved from literature search, but not predefined in protocol:
- low-dose versus high-dose sustained-release naltrexone.

The investigated drugs included 3 depot formulations (Alkermes, Biotek, Drug Abuse Sciences) containing 150 to 400 mg of naltrexone and 2 implant formulations (GoMedical, Wedgewood) containing 1000 to approximately 2200 mg of naltrexone.

Control:
- opioid dependent samples;
- alcohol dependent samples;
- healthy volunteers
Bewijstabellen ontgifting

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Primary, effectiveness outcomes:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>– opioid use during and after treatment;</td>
</tr>
<tr>
<td></td>
<td>– treatment adherence.</td>
</tr>
<tr>
<td>Secondary, safety outcomes:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>– use of illicit drugs other than opioids during and after treatment;</td>
</tr>
<tr>
<td></td>
<td>– criminal activity and incarceration;</td>
</tr>
<tr>
<td></td>
<td>– quality of life;</td>
</tr>
<tr>
<td></td>
<td>– mental health;</td>
</tr>
<tr>
<td></td>
<td>– duration of achieved therapeutic naltrexone blood levels</td>
</tr>
</tbody>
</table>

| Results | Effectiveness, 1 report met inclusion criteria. Two dosages of naltrexone depot injections (192 and 384 mg) were compared to placebo. High-dose significantly increased days in treatment compared to placebo (WMD 21.00, 95% CI 10.68 to 31.32, p < 0.0001). High-dose compared to low-dose significantly increased days in treatment (WMD 12.00, 95% CI 1.69 to 22.31, p = 0.02). Number of patients retained in treatment did not show significant differences between groups. For adverse effects, seventeen reports met inclusion criteria analyses, six were RCTs. Side effects were significantly more frequent in naltrexone depot groups compared to placebo. In alcohol dependent samples only, adverse effects appeared to be significantly more frequent in the low-dose naltrexone depot groups compared to placebo (RR 1.18, 95% CI 1.02 to 1.36, p = 0.02). In the opioid dependent sample, group differences were not statistically significant. Reports on systematic assessment of side effects and adverse events were scarce |

| Quality assessment | Statistical pooling: + |
|                   | Finance: |
|                   | – Unit for Addiction Medicine, University of Oslo, Norway; |
|                   | – Norwegian Knowledge Centre for the Health Services, Norway |

| Quality of evidence | A1 |
|                    | Authors’ conclusion: there is insufficient evidence to evaluate the effectiveness of sustained-release naltrexone for treatment of opioid dependence. For naltrexone injections, administration site-related adverse effects appear to be frequent, but of moderate intensity and time limited. For a harm-benefit evaluation of naltrexone implants, more data on side effects and adverse events are needed |

CI: confidence interval [betrouwbaarheidsinterval]; RCT: randomised controlled trial; RR: risk ratio [relatieve risico]; WMD: weighted mean difference
Bewijstabellen
contingentiemanagement (CM)

Deze bewijstabellen horen bij hoofdstuk 6. Voor de volledige literatuurbeschrijvingen van de onderzoeken, zie hoofdstuk 6, Literatuur.

CM als stand-alonebehandeling voor abstinentie

<table>
<thead>
<tr>
<th>Study aim</th>
<th>Effectiviteit van CM als stand-alonebehandeling bij cocain- en/of heroineverslaving</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study design</td>
<td>RCT</td>
</tr>
<tr>
<td>Number of studies</td>
<td>7</td>
</tr>
<tr>
<td>Number of patients</td>
<td>742</td>
</tr>
<tr>
<td>Patient characteristics</td>
<td>Leeftijd: gemiddelden van de studies tussen 29 en 35</td>
</tr>
<tr>
<td>Intervention(s)</td>
<td>CM</td>
</tr>
<tr>
<td>Follow-up</td>
<td>3-12 maanden follow-up</td>
</tr>
</tbody>
</table>
| Outcome | – Duration of treatment  
– Point abstinence  
– Illicit drug use |
| Results | Op alle uittkomstmaten komt CM als effectief naar voren. Omdat er slechts 1 onderzoek is naar heroine, is het lastig om de resultaten zonder meer over te nemen |
| Quality of evidence | A1 |

CM: contingentiemanagement; RCT: randomised controlled trial
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Study design</td>
<td>Meta-analyse</td>
</tr>
<tr>
<td>Number of studies</td>
<td>1</td>
</tr>
</tbody>
</table>
| Number of patients | Interventiegroep: n = 29  
Controlegroep: n = 23 |
| Patient characteristics | Leeftijd: 35,7  
Sekseratio: 59,6% mannen |
| Inclusion | Inclusie: patiënten die een klinische detoxificatie hadden afgerond.  
Leeftijd: tussen 18 en 50.  
Gerapporteerde regelmatig heroïnegebruik in de 30 dagen voorafgaand aan de behandeling |
| Intervention(s) | Interventie: CM + CBT.  
Controle: alleen CBT. |
| Outcome | Primaire uitkomstmaten:  
– gemiddeld aantal dagen behandeling;  
– gemiddeld aantal negatieve urine controles;  
– duur abstinentie;  
– percentage van deelnemers dat 4 weken abstinent is. |
| Results | Geen significante verschillen tussen de groepen |
| Quality of evidence | A2 |

CBT: cognitive behavioral therapy (cognitieve gedragstherapie); CM: contingentiemanagement; RCT: randomised controlled trial
## Bewijstabellen psychosociale interventies

### CM bij detoxificatie

<table>
<thead>
<tr>
<th><strong>Study aim</strong></th>
<th>Vergelijking van detoxificatie + CM versus detoxificatie plus standaardzorg</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study design</strong></td>
<td>5 RCT’s, 1 quasi-randomised</td>
</tr>
<tr>
<td><strong>Number of studies</strong></td>
<td>6</td>
</tr>
<tr>
<td><strong>Number of patients</strong></td>
<td>417</td>
</tr>
<tr>
<td><strong>Outcome</strong></td>
<td>Primaire uitkomstmaten:</td>
</tr>
<tr>
<td></td>
<td>· abstinencie;</td>
</tr>
<tr>
<td></td>
<td>· afmaken van de detoxificatie;</td>
</tr>
<tr>
<td></td>
<td>· ernst van onthoudingsverschijnselen;</td>
</tr>
<tr>
<td></td>
<td>· kosteneffectiviteit</td>
</tr>
<tr>
<td><strong>Results</strong></td>
<td>Abstinentie: RR 1,86</td>
</tr>
<tr>
<td></td>
<td>Afmaken ontgifting: RR 1,60 (RR &gt;1 in het voordeel van de interventie)</td>
</tr>
<tr>
<td></td>
<td>NICE voert voor CM een kosteneffectiviteitsanalyse uit, en geeft data over financiën en QUALY’s.</td>
</tr>
<tr>
<td></td>
<td>Voor beide geldt dat CM als interventie voor toepassing bij detoxificatie kosteneffectief is</td>
</tr>
</tbody>
</table>

**Quality of evidence** A1

CM: contingentiemanagement; QUALY: quality-adjusted life year; RCT: randomised controlled trial
# CM bij naltrexononderhoudsbehandeling voor abstinentie

**NICE (2007b) Drug misuse: Psychosocial Interventions**

<table>
<thead>
<tr>
<th>Study aim</th>
<th>Review; meta-analyse</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study design</td>
<td>De NICE-richtlijn bespreekt 3 onderzoeken (RCT’s):</td>
</tr>
</tbody>
</table>

Dutra et al bespreken alleen het onderzoek van Carroll. Carroll en Preston onderzoeken de effectiviteit van naltrexon + CM wordt vergeleken met naltrexon + standaardzorg.

| Number of studies | 3 |
| Number of patients | Carrol, 2001: 79  
Carrol, 2002: 54  
Preston, 1999: 39 |

| Intervention(s) | Interventie: naltrexon + verschillende vormen van CM  
Controle: standaard: naltrexon |

| Follow-up | Follow-upduur: 3-6 maanden |
| Outcome | NICE:  
− abstinentie: punt-abstinentie en duur abstinentie;  
− gebruik van illegale drugs: frequentie van gebruik over een gegeven periode;  
− invloed op naltrexon-compliance: aantal doses en dagen dat naltrexon is ingenomen.  
Dutra:  
− noemt effectsizes op basis van selfreport (0,04), urinesamples (dus over abstinentie) van 0,52 |
**Results**

Kwaliteit van het bewijs wordt door NICE als gemiddeld *(moderate)* beoordeeld. CM geeft een significante verbetering op alle uitkomstmaten. Er is echter geen informatie over effecten bij de follow-up.

**Quality of evidence**

A1

CM: contingentiemanagement

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### CM bij methadononderhoudsbehandeling

*NICE. (2007b). Drug misuse: Psychosocial interventions*

*(2) NICE Drug misuse: Psychosocial interventions over CM bij methadononderhoudsbehandeling*

**Study aim**

Meta-analyse

**Study design**

NICE includeert 12 studies

Studieduur: 8-52 weken

**Number of studies**

12

**Number of patients**

1.436

**Patient characteristics**

Leeftijd, gemiddelden over de studies: 35-44

**Intervention(s)**

Follow-upduur: 0-15 maanden

**Outcome**

Primaire uitkomstmaat:

– duur abstinentie;

– point-abstinentie;

– druggebruik: nooit abstinent van cocaïne of heroïne

**Results**

CM resulteert in langere periodes van abstinentie tijdens behandeling, en hogere point-abstinentie bij 6 en 12 maanden follow-up. Dit gold voor onderzoeken die vouchers, prijzen of privileges gebruikten als bekrachtigers

**Quality of evidence**

A1

CM: contingentiemanagement
Amato e.a. (2008) *Psychosocial combined with agonist maintenance treatments versus agonist maintenance treatments alone for treatment of opioid dependence*

1. Amato over CM bij methadononderhoudsbehandeling

**Study aim**
'To compare the effectiveness of the combination of psychosocial plus agonist maintenance interventions of any kind to any agonist maintenance treatments for opiate dependence, in retaining patients in treatment, reducing the use of substances'

**Study design**
Review, meta-analyse (de gereviewde onderzoeken zijn RCT’s)
Amato bespreekt 5 studies die ook in de NICE-richtlijn (NICE, 2007b: *Drug misuse: Psychosocial interventions*) worden besproken en 6 studies die daarin niet voorkomen.
NB Deze review brengt in meta-analyses de gegevens onder van onderzoeken naar CM bij zowel methadon- als bij buprenorfinebehandeling

<table>
<thead>
<tr>
<th>Number of studies</th>
<th>11</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>1245</td>
</tr>
<tr>
<td>Intervention(s)</td>
<td>Interventie: CM. Controle: methadononderhoudsbehandeling</td>
</tr>
<tr>
<td>Outcome</td>
<td>Primaire uitkomstmaten:</td>
</tr>
<tr>
<td></td>
<td>– aantal patiënten dat nog in behandeling was aan het einde van het onderzoek;</td>
</tr>
<tr>
<td></td>
<td>– primary substance: aantal patiënten met opeenvolgende positieve urine-uitslagen in minstens 3 weken;</td>
</tr>
<tr>
<td></td>
<td>– resultaten bij follow-up: aantal patiënten dat nog in behandeling is, en aantal patiënten dat abstinent is bij de follow-up.</td>
</tr>
<tr>
<td></td>
<td>Secundaire uitkomstmaten:</td>
</tr>
<tr>
<td></td>
<td>– compliance;</td>
</tr>
<tr>
<td></td>
<td>– craving;</td>
</tr>
<tr>
<td></td>
<td>– psychiatrische symptomen/ psychological distress;</td>
</tr>
<tr>
<td></td>
<td>– quality of life (QOL);</td>
</tr>
<tr>
<td></td>
<td>– ernst afhankelijkheid;</td>
</tr>
<tr>
<td></td>
<td>– dood</td>
</tr>
<tr>
<td>Results</td>
<td>Er zijn nauwelijks specifieke resultaten beschikbaar voor CM binnen deze review. De enige specifieke gegevens zijn dat CM in aanvulling op opiaatonderhoudsbehandeling een positief effect heeft (p.63, Comparison 2) op het in behandeling blijven.</td>
</tr>
<tr>
<td>Quality of evidence</td>
<td>A1</td>
</tr>
</tbody>
</table>

CM: contingentiemanagement; QOL: quality of life
**Study design**  
RCT

Dutra includeert 5 studies die we ook in de NICE-richtlijn zien; daarnaast nog 2 studies die daarin niet voorkomen:

Studieduur:
- Iguchi 12 weken
- Sigmon 24 weken

**Number of studies** 5

**Number of patients**  
Iguchi 62
Sigmon 30

**Patient characteristics**  
NB Er wordt in deze review gekeken naar *opiod maintenance treatment* (OMT). In de publicatie is bij het trekken van conclusies geen onderscheid gemaakt tussen methadon en buprenorfine. Gezien de uitkomsten van CM bij buprenorfine (zie bewijstabellen NICE, Amato en Dutra in de volgende paragraaf) beïnvloedt dit mogelijk de uitkomsten.

**Outcome**  
Primaire uitkomstmaten:
- drop-out uit behandeling;
- abstiniete

**Results**  
De resultaten worden gegeneraliseerd naar effectgroottes per:  
(1) soort middel, waarbij de resultaten voor opiaatverslaving klein tot gemiddeld zijn (voor de diverse behandelmomenten die in deze review worden besproken); en:
(2) soort behandelmoment, waarbij CM als beste scoort.
Er zijn geen specifieke gegevens beschikbaar over de effectiviteit van CM bij opiaatgebruikers anders dan al in de NICE-richtlijn zijn besproken.

**Quality of evidence** A2

**CM**: contingentiemanagement; **RCT**: randomised controlled trial
### Castells e.a. (2009) Efficacy of opiate maintenance therapy and adjunctive interventions for opioid dependence with comorbid cocaine use disorders: A systematic review and meta-analysis of controlled clinical trials

(1) Castells over CM bij methadononderhoudsbehandeling

<table>
<thead>
<tr>
<th>Study aim</th>
<th>Meta-analyse over opiaatverslaving met comorbid cocaïneverslaving</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study design</td>
<td>Meta-analyse</td>
</tr>
<tr>
<td>Outcome</td>
<td>Primaire uitkomstmaten:</td>
</tr>
<tr>
<td></td>
<td>– cocaïne- en heroïneabstinentie volgens urinecontroles van minimaal 3 weken;</td>
</tr>
<tr>
<td></td>
<td>– cocaïne- en heroïnegebruik, gemeten naar het aantal cocaïne- en/of heroïnevrije dagen</td>
</tr>
<tr>
<td>Results</td>
<td>Onderzoek naar alleen cocaïneabstinentie toont een positief effect van CM, ook op het aantal heroïnevrije dagen. Onderzoek naar abstinentie van zowel heroïne als cocaïne geven geen resultaten voor abstinentie voor beide drugs, en slechts een klein resultaat voor cocaïnegebruik</td>
</tr>
<tr>
<td>Quality of evidence</td>
<td>A1</td>
</tr>
</tbody>
</table>

CM: contingentiemanagement

### CM bij buprenorfineonderhoudsbehandeling

NICE (2007b) Drug misuse: Psychosocial interventions

(3) NICE Drug misuse: Psychosocial interventions over CM bij bij buprenorfineonderhoudsbehandeling

<table>
<thead>
<tr>
<th>Study aim</th>
<th>Effectiviteit van CM + buprenorfineonderhoudsbehandeling vergeleken met alleen buprenorfineonderhoudsbehandeling</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study design</td>
<td>RCT</td>
</tr>
<tr>
<td>Number of studies</td>
<td>4</td>
</tr>
<tr>
<td>Number of patients</td>
<td>23</td>
</tr>
<tr>
<td>Outcome</td>
<td>Primaire uitkomstmaten:</td>
</tr>
<tr>
<td></td>
<td>· abstinentie;</td>
</tr>
<tr>
<td></td>
<td>· gebruik van middelen</td>
</tr>
<tr>
<td>Results</td>
<td>Geen toegevoegde waarde van CM bij patiënten die buprenorfine als onderhoudsbehandeling ontvangen</td>
</tr>
<tr>
<td>Quality of evidence</td>
<td>A1</td>
</tr>
</tbody>
</table>

CM: contingentiemanagement; RCT: randomised controlled trial
Amato e.a. (2008) Psychosocial combined with agonist maintenance treatments versus agonist maintenance treatments alone for treatment of opioid dependence

(2) Amato over CM bij buprenorfineonderhoudsbehandeling

Study aim
‘To compare the effectiveness of the combination of psychosocial plus agonist maintenance interventions of any kind to any agonist maintenance treatments for opiate dependence, in retaining patients in treatment, reducing the use of substances’

Study design
RCT
Amato bespreekt 5 studies die ook in de NICE-richtlijn worden besproken en 6 studies die daarin niet voorkomen.
NB (1) de onderzoeken worden ondergebracht in een meta-analyse, samen met andere psychosociale interventies.
NB (2) Deze review brengt in meta-analyses onder: de gegevens van onderzoeken naar CM bij zowel methadon- als buprenorfinebehandeling

Number of studies 11
Number of patients 1245
Intervention(s) Interventie: CM
Controle: methadononderhoudsbehandeling

Outcome
Primaire uitkomstmaten:
- aantal patiënten dat nog in behandeling was aan het einde van het onderzoek;
- primary substance: aantal patiënten met opeenvolgende positieve urine-uitslagen in minstens 3 weken;
- resultaten bij follow-up: aantal patiënten dat nog in behandeling is, en aantal patiënten dat abstinent is bij de follow-up.

Secundaire uitkomstmaten:
- compliance;
- craving;
- psychiatrische symptomen/ psychological distress;
- quality of life (QOL);
- ernst afhankelijkheid;
- dood

Results
Er zijn nauwelijks specifieke resultaten beschikbaar voor CM binnen deze review. De enige specifieke gegevens zijn dat CM in aanvulling op opiaatonderhoudsbehandeling een positief effect heeft (p. 63, Comparison 2) op het in behandeling blijven

Quality of evidence A1

CM: contingentiemanagement; QOL: quality of life; RCT: randomised controlled trial
<table>
<thead>
<tr>
<th>Study aim</th>
<th>RCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dutra includeert 5 studies die we ook in de NICE-richtlijn zien; daarnaast nog 2 studies die daarin niet voorkomen:</td>
<td></td>
</tr>
<tr>
<td>Studieduur:</td>
<td></td>
</tr>
<tr>
<td>– Iguchi 12 weken</td>
<td></td>
</tr>
<tr>
<td>– Sigmon 24 weken</td>
<td></td>
</tr>
<tr>
<td>Study design</td>
<td>5</td>
</tr>
<tr>
<td>Number of studies</td>
<td>Iguchi 62</td>
</tr>
<tr>
<td></td>
<td>Sigmon 30</td>
</tr>
<tr>
<td>Number of patients</td>
<td>NB Er wordt in deze review gekeken naar opioid maintenance treatment (OMT). In de publicatie is bij het trekken van conclusies geen onderscheid gemaakt tussen methadon en buprenorfine. Gezien de uitkomsten van CM bij buprenorfine (zie bewijstabellen NICE, Amato en Dutra in de volgende paragraaf) beïnvloedt dit mogelijk de uitkomsten.</td>
</tr>
<tr>
<td>Patient characteristics</td>
<td>Primaire uitkomstmaten:</td>
</tr>
<tr>
<td></td>
<td>– drop-out uit behandeling;</td>
</tr>
<tr>
<td></td>
<td>– abstinente</td>
</tr>
<tr>
<td>Inclusion</td>
<td>De resultaten worden gegeneraliseerd naar effectgroottes per:</td>
</tr>
<tr>
<td></td>
<td>(1) soort middel, waarbij de resultaten voor opiaatverslaving klein tot gemiddeld zijn (voor de diverse behandelvormen die in deze review worden besproken); en:</td>
</tr>
<tr>
<td></td>
<td>(2) soort behandelvorm, waarbij CM als beste scoort.</td>
</tr>
<tr>
<td></td>
<td>Er zijn geen specifieke gegevens beschikbaar over de effectiviteit van CM bij opiatgebruikers anders dan al in de NICE-richtlijn zijn besproken.</td>
</tr>
</tbody>
</table>
Intervention(s) RCT

Dutra includeert 5 studies die we ook in de NICE-richtlijn zien; daarnaast nog 2 studies die daarin niet voorkomen:


Studieduur:
- Iguchi 12 weken
- Sigmon 24 weken

Outcome 5

Results Iguchi 62
Sigmon 30

Quality assessment NB Er wordt in deze review gekeken naar opioid maintenance treatment (OMT). In de publicatie is bij het trekken van conclusies geen onderscheid gemaakt tussen methadon en buprenorfine. Gezien de uitkomsten van CM bij buprenorfine (zie bewijstabellen NICE, Amato en Dutra in de volgende paragraaf) beïnvloedt dit mogelijk de uitkomsten.

Quality of evidence A2

CM: contingentiemanagement; RCT: randomised controlled trial
Bewijstabellen psychosociale interventies

Deze bewijstabellen horen bij hoofdstuk 6. Voor de volledige literatuurbeschrijvingen van de onderzoeken, zie hoofdstuk 6, Literatuur, Bronnen met bewijstabel Trimbos-instituut.


Study aim
To review all published research to date that examined the use of the community reinforcement approach (CRA) in the treatment of opioid dependence

Study design
Systematic review

Number of studies
4

Number of patients
– Abbott e.a., 1998: N = 181;

Patient characteristics
Overall criteria:
– opioid dependence;
– age 18 or older;
– eligible for methadone maintenance according to the Food and Drug Administration (FDA) requirements;
– (free of psychosis, dementia or major medical disorders and were not pregnant)
<table>
<thead>
<tr>
<th>Intervention(s)</th>
<th>Intervention:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>– CRA group;</td>
</tr>
<tr>
<td></td>
<td>– CRA with naltrexone;</td>
</tr>
<tr>
<td></td>
<td>– CRA with vouchers for opioid- and cocaine-free urines delivered by a therapist;</td>
</tr>
<tr>
<td></td>
<td>– CRA with vouchers delivered by the computer.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Control:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>– standard;</td>
</tr>
<tr>
<td></td>
<td>– CRA plus relapse prevention;</td>
</tr>
<tr>
<td></td>
<td>– voucher incentive program;</td>
</tr>
<tr>
<td></td>
<td>– methadone maintenance program</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Follow-up</th>
<th>12 weeks till 6 months</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Outcome</th>
<th>– Reduction of opioid use and other drugs of abuse</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>– Improved legal status</td>
</tr>
<tr>
<td></td>
<td>– Less psychiatric symptoms</td>
</tr>
<tr>
<td></td>
<td>– Improved vocational</td>
</tr>
<tr>
<td></td>
<td>– Social functioning</td>
</tr>
</tbody>
</table>

| Results | CRA and methadone maintenance have shown improvement in a number of critical areas. These include the reduction of opioid use as well as other drugs of abuse, and in one study, improved legal status, less psychiatric symptoms, and improved vocational and social functioning. CRA coupled with vouchers can assist in the difficult task of retaining patients in treatment long enough to improve opioid detoxification rates from buprenorphine |

[Remarks] CRA may have utility for opioid-dependent individuals not yet in treatment. More recent data has demonstrated that CRA strategies are not only effective for patients in treatment, but also useful in encouraging individuals to access treatment. Much of this work has been done with families concerned about their loved ones who are in need of treatment, but need motivation and encouragement to access treatment services

<table>
<thead>
<tr>
<th>Quality assessment</th>
<th>Question: +</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Search: -</td>
</tr>
<tr>
<td></td>
<td>Quality assessment: -</td>
</tr>
<tr>
<td></td>
<td>Data extraction: -</td>
</tr>
<tr>
<td></td>
<td>Description of original studies: +</td>
</tr>
<tr>
<td></td>
<td>Handling heterogeneity: -</td>
</tr>
<tr>
<td></td>
<td>Statistical pooling: -</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Quality of evidence</th>
<th>B</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No description of search strategy, data extraction, no pool, no outcome measures, et cetera</td>
</tr>
</tbody>
</table>

CRA: community reinforcement approach
Castells e.a. (2009) Efficacy of opiate maintenance therapy and adjunctive interventions for opioid dependence with comorbid cocaine use disorders: A systematic review and meta-analysis of controlled clinical trials

(2) Castells over psychosociale interventies

<table>
<thead>
<tr>
<th>Study aim</th>
<th>To determine the efficacy of opiate maintenance therapy (OMT) and adjunctive interventions for dual heroin and cocaine dependence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study design</td>
<td>Meta-analysis</td>
</tr>
<tr>
<td></td>
<td>Blinding: none of the studies had a double-blind design.</td>
</tr>
<tr>
<td></td>
<td>Analysis: ITT or per protocol.</td>
</tr>
<tr>
<td></td>
<td>Location: all studies were conducted in the United States and were funded by national institutions, commonly National Institute on Drug and Alcohol Abuse (NIDA)</td>
</tr>
<tr>
<td>Number of studies</td>
<td>N = 37 articles</td>
</tr>
<tr>
<td>Number of patients</td>
<td>N = 3,029 patients</td>
</tr>
<tr>
<td>Patient characteristics</td>
<td>Age: range of mean age 32.0-42.6</td>
</tr>
<tr>
<td></td>
<td>Sex: 63% men</td>
</tr>
<tr>
<td>Inclusion</td>
<td>Inclusion:</td>
</tr>
<tr>
<td></td>
<td>· studies had to be randomized controlled clinical trials with parallel groups, which assessed the efficacy of an OMT strategy or adjunctive interventions for opiate dependent patients with a comorbid cocaine use disorder.</td>
</tr>
<tr>
<td></td>
<td>· studies available before September 2007.</td>
</tr>
<tr>
<td>Exclusion</td>
<td>Inclusion:</td>
</tr>
<tr>
<td></td>
<td>· laboratory studies as well as those published as abstracts were excluded.</td>
</tr>
<tr>
<td>Baseline characteristics</td>
<td>Baseline characteristics:</td>
</tr>
<tr>
<td></td>
<td>· all patients were heroin dependent and most (93%) had a comorbid cocaine dependence, and 7% were cocaine abusers;</td>
</tr>
<tr>
<td></td>
<td>· psychiatric diagnoses were performed using the DSM-III and DSM-IV</td>
</tr>
<tr>
<td>Intervention(s)</td>
<td>Intervention:</td>
</tr>
<tr>
<td></td>
<td>· opioid maintenance treatment (OMT).</td>
</tr>
<tr>
<td>Control</td>
<td>Control:</td>
</tr>
<tr>
<td></td>
<td>· placebo;</td>
</tr>
<tr>
<td></td>
<td>· other OMT intervention.</td>
</tr>
<tr>
<td>Follow-up time</td>
<td>Follow-up time: - (there’s a table online with information)</td>
</tr>
</tbody>
</table>
Outcome Primary: proportion of patients achieving sustained heroin abstinence and the proportion achieving sustained cocaine abstinence.
Secondary: secondary outcomes were heroin and cocaine use, defined as the number of drug free urinanalysis (UA) over the course of the intervention period, and study retention, defined as the proportion of randomized patients that completed the intervention protocol.

Results
High doses of OMT were more efficacious than lower ones in the achievement of sustained heroin abstinence (RR = 2.24) but had no effect on cocaine abstinence.
Higher doses were associated with increased heroin-free UA (SMD = .40) but no effect was found for cocaine-free UA.
In addition, higher OMT doses were associated with higher retention (RR = 1.23).
At equivalent doses, methadone was more efficacious than buprenorphine on cocaine abstinence (RR = 1.63) and also appeared to be superior on heroin abstinence (RR = 1.39).

Quality assessment
Question: +
Search: +
Quality assessment: ?
Data extraction: +
Description of original studies:?
Handling heterogeneity: +
Statistical pooling: +
Funding/conflicts of interest: authors have contact/relations with Cephalon, Forrest, Reckitt Benkizer, Novartis, Celtic, Alkermes, Synosia, Catalyst, Lannacher, Gerson Lerman, stock in Pfizer and Johnson and Johnson, Janssen-Cilag and Laboratorios Rubi'o

Quality of evidence A2
In conclusion, the meta-analysis shows that OMT is efficacious for dual heroin–cocaine dependence, although higher OMT doses are preferable to lower ones and methadone to buprenorphine. Indirect dopamine (DA) agonists and contingency management (CM), particularly when reinforcing only cocaine abstinence, can improve cocaine outcomes in cocaine abusers on OMT.

ITT: intention to treat; OMT: opioid maintenance treatment; RR: risk ratio [relatieve risico]; SMD: standard mean difference
Dutra e.a. (2008) *A meta-analytic review of psychosocial interventions for substance use disorders*

(5) Dutra over psychosociale interventies

**Study aim**
To provide effect sizes for various types of psychosocial treatments, as well as abstinence and treatment-retention rates for cannabis, cocaine, opiate, and polysubstance abuse and dependence treatment trials.

**Study design**
34 well-controlled treatment conditions: 5 for cannabis, 9 for cocaine, 7 for opiate, and 13 for poly substance users representing the treatment of 2,340 patients.

Psychosocial treatments evaluated included:
- contingency management;
- relapse prevention;
- general cognitive behavioral therapy;
- treatments combining cognitive behavioral therapy and contingency management.

Blinding:-
Location: from the Department of Psychology, Boston University, Boston

<table>
<thead>
<tr>
<th>Number of studies</th>
<th>N = 34 studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>2340 patients</td>
</tr>
</tbody>
</table>

**Patient characteristics**
- Age: mean age 34.9
- Sex: 62% male
- Ethnicity: 61% caucasian
- 10.1 years substance use
Inclusion:
- investigations of the efficacy of any individual psychosocial treatments for substance abuse/dependence, with the exception of alcohol abuse/dependence and nicotine abuse/dependence;
- randomized, controlled trials including a comparison group that could consist of inactive (e.g., waitlisted) or active (e.g., treatment as usual) treatments;
- studies including adult (18 years and older) participants only;
- studies including one or more of our posttreatment outcome measures (described below) to allow for comparable outcome data across studies;
- investigations of the efficacy of nonintensive outpatient treatments, which we defined as consisting of no more than three 2-hour treatment sessions per week.

Exclusion:
- Controlled trials comparing the efficacy of various treatment intensities (e.g., once per week versus twice per week individual therapy of the same therapy type) were excluded if a clear control group (e.g., one receiving inactive treatment or treatment as usual) was unavailable (seven studies).

Baseline characteristics:
- randomized, controlled clinical trials:
  - PsycINFO: articles published between 1840 and march 2005;
  - Cochrane register;
  - search terms are described.

Intervention(s) Intervention (psychosocial treatment):
- CM = contingency management;
- CBT = other cognitive behavior therapy;
- RP = relapse prevention;
- DBT = dialectical behavior therapy;
- GDC = group drug counseling.

Control:
- TAU = treatment as usual;
- ME = motivational enhancement interviewing;
- TSF = 12-step facilitation;
- NCM = non contingency management;
- STN = standard care;
- GDC = group drug counseling;
- WL = wait listing.

Follow-up Average 21 weeks (range 4-52, SD = 14).
Outcome Primary: effect sizes (for various types of psychosocial treatments, as well as abstinence and treatment-retention rates for cannabis, cocaine, opiate, and poly substance abuse and dependence treatment trials)

Results

- The aggregate effect size across all conditions and all substances was in the moderate range (d = 0.45), with a 95% confidence interval (CI) of 0.27 to 0.63.
- Independent-sample t tests revealed that psychosocial treatments had their lowest efficacy for polysubstance use, with a significant difference between outcomes for polysubstance use (d = 0.24, 95% CI 0.03-0.44) and cannabis use (d = 0.81, 95% CI 0.25-1.36) disorders (t = 2.42, df = 17, p < 0.03).
- Treatments targeting cocaine use yielded medium-large effect sizes (d = 0.62, 95% CI 0.16-1.08), and treatments targeting opiate use yielded small-medium effect sizes (d = 0.39, 95% CI 0.18-0.60).
- There were no other significant differences between the substance use disorders treated. The results indicate that treatments incorporating both cognitive behavior therapy and contingency management had the highest effect sizes (d = 1.02); however, this result must be interpreted cautiously as there were few studies in this category (N = 2; 95% CI −0.05-2.09).

Treatments using contingency management alone produced moderate-high effect sizes (d = 0.58, 95% CI 0.25-0.90). Cognitive behavior therapy alone and relapse prevention evidenced low moderate effect sizes: d = 0.28 (95% CI 0.06-0.51) and d = 0.32 (95% CI 0.06-0.56), respectively.

Quality assessment

Question: +
Search: +
Quality assessment: +
Data extraction: ?
Description of original studies: +
Handling heterogeneity: +
Statistical pooling: +

Quality of evidence A1

Controlled trial data suggest that psychosocial treatments provide benefits reflecting a moderate effect size according to Cohen's standards. These interventions were most efficacious for cannabis use and least efficacious for polysubstance use. The strongest effect was found for contingency management interventions. Approximately one-third of participants across all psychosocial treatments dropped out before treatment completion compared to 44.6% for the control conditions.

CI: confidence interval [betrouwbaarheidsinterval]; SD: standard deviation
Bewijstabellen heroïne op medisch voorschrift (HAT)

Hier vindt u de bewijstabellen over heroïne op medisch voorschrift (heroin assisted treatment, HAT). Deze bewijstabellen horen bij hoofdstuk 6. Voor de volledige literatuurbeschrijvingen van de onderzoeken, zie hoofdstuk 6, Literatuur, ‘Bronnen HAT met bewijstabelf door Trimbos-instituut’.

Cohortonderzoek HAT

<table>
<thead>
<tr>
<th>Study design</th>
<th>Observational cohort study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Setting:</td>
<td>out-patients treatment in specialized treatment centres</td>
</tr>
<tr>
<td>Location:</td>
<td>The Netherlands</td>
</tr>
<tr>
<td>Number of patients</td>
<td>149</td>
</tr>
<tr>
<td>Patient characteristics</td>
<td>Age: average 39.2 years old</td>
</tr>
<tr>
<td></td>
<td>Sex: 83% males</td>
</tr>
<tr>
<td></td>
<td>Ethnicity: 89,9% were Dutch or Western European</td>
</tr>
<tr>
<td>Inclusion</td>
<td>Heroin dependent patients who had responded positively to the HAT in two randomized controlled trials were eligible for long-term heroin-assisted treatment</td>
</tr>
<tr>
<td>Intervention(s)</td>
<td>Methadone plus injectable or inhalable heroin offered 7 days per week, three times a day.</td>
</tr>
<tr>
<td></td>
<td>The average doses of heroin prescribed was 268 mg per visit an 502 mg per day.</td>
</tr>
<tr>
<td></td>
<td>Patients were supplemented with individual psychosocial and medical support</td>
</tr>
<tr>
<td>Follow-up</td>
<td>After 4 years</td>
</tr>
</tbody>
</table>

Outcome Prognostic factor: injectable methadone treatment or inhaling heroin, three times a day, 7 days a week. Long-term response (4 years) to heroin-assisted treatment (HAT) in chronic therapy resistant heroin-dependent patients. Response was defined as:
- improvement (compared to baseline) of at least 40% at the 4-year follow-up in at least one of the domains of inclusion at baseline assessment, i.e. physical, mental or social health;
- no serious deterioration (≥40%) in any of the other outcome domains, compared to baseline;
- no substantial increase (>6 days/month) of cocaine or amphetamine use compared to baseline.
Outcome measure: improvement of the physical, mental and social health and reduction of illicit drug use and alcohol consumption.

Results
- 56% of clients (83), completed the 4 years HAT treatment.
- Response was significantly better for patients continuing 4 years of HAT compared to patients who discontinued treatment: 90.4% versus 21.2% (difference 69.2%; odds ratio (OR) = 48.4; 95% CI: 17.6-159.1).
- Following the HAT treatment was associated with an increasing % healthy patient who stopped illegal drugs and excessive alcohol consumption, 12% after the first year to 25% after 4 years HAT.

Quality assessment
There is no feedback from all clients who are not working, this may have influenced the results.

Quality of evidence
[Additional comments]
Follow-up:
- nearly half the patients who discontinued long-term HAT were not reached or refused to cooperate in the 4-year follow-up assessment. The outcome status of these patients could not be determined. But even in the unlikely ‘worst-case’ scenario, where all non-reached patients who discontinued HAT were considered to be responders, 4-year outcome status of patients who continued long-term HAT was still significantly better;
- HAT 4 years is associated with a stable, physical, mental and social health;
- prevent illicit heroin use and provides a significant reduction in cocaine use;
- HAT should be continued as long as there is no compelling reason to stop treatment.

HAT: heroin assisted treatment
**Systematische reviews en trials HAT**

*Ferri e.a. (2010) Heroin maintenance for chronic heroin-dependent individuals*

**Study aim**
To assess what treatment (heroin maintenance versus. Methadone or other replacement therapy) is effective for heroin users, so the health and social functioning improve.

**Study design**
Systematic review of RCTs

Analysis: the studies could not be analysed cumulatively because of heterogeneity of interventions and outcomes

**Number of studies**
4 RCTs

**Number of patients**
$N = 577$

**Patient characteristics**
- **Study 1:**
  - $N = 174$
  - gender = male 82.2%
  - age = 38.5 years (5.7 SD).
- **Study 2:**
  - $N = 256$
  - gender: 79.7% male.
  - age: 39.6 (5.7 DS).
- **Study 3:**
  - $N = 96$
  - age = 18-35 years; mean 23.9;
  - sex = 75% male; 25% female.
- **Study 4:**
  - $N = 51$
  - age > 20.

**Inclusion**
- chronic heroin users;
- 18 years and older.

**Exclusion**
- design of study not in the inclusion criteria of this review;
- study outcomes or participants differing from inclusion criteria;
- seven studies are ongoing
### Intervention(s)

**Intervention:**
- heroin (single or combined with heroin, methadone) maintenance treatment regardless of dosage, preparation, route of administration, establishment and duration of treatment.

**Control:**
- no intervention;
- methadone treatment;
- waiting list for conventional treatment;
- other pharmacological treatment for heroin dependence

### Outcome

**Outcome measures:**
- retention in treatment;
- relapse to street heroin use;
- use of other substances;
- death;
- medical adverse events

### Results

- One study showed a statistically significant higher retention in treatment for heroin treatment in clients due methadone, while one of the most recent large studies was statistically significantly higher retention in methadone patients.
- Relapse to heroin was analyzed in two studies.
- One of the two studies analyze results showing heroin treatment helps to keep people away from illegal activities

### Quality assessment

**Study question:** +
**Search:** +
**Selection:** +
**Quality assessment:** +
**Data extraction:** +
**Description of original studies:** +
**Handling heterogeneity:** +
**Statistical pooling:** +
**Funding/conflicts of interest:** no conflicts

### Quality of evidence

A2

---

SD: Standard Deviation; RCT: randomised controlled trial
<table>
<thead>
<tr>
<th>Study aim</th>
<th>To study heroin-assisted treatment in people on methadone who continue intravenous heroin and in those who are heroin dependent but currently not in treatment.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study design</td>
<td>Open-label RCT injectable heroin or oral methadone Analysis: intention to treat Location: Germany</td>
</tr>
<tr>
<td>Number of patients</td>
<td>Injectable heroin: N = 515 Oral methadone N = 500</td>
</tr>
<tr>
<td>Patient characteristics</td>
<td>Age: mean age 36 years Sex: 80% male</td>
</tr>
</tbody>
</table>
| Inclusion | Inclusion:  
- minimum 23 years;  
- ICD-10 diagnosis of opioid dependence for at least 5 years;  
- poor physical and/or mental health, with a minimum of 13 symptoms of the Opiate Treatment Index;  
- for methadone treatment:  
  - they did not succeed in treating intravenous use of street heroin.  
Exclusion:  
- people a prison sentence hangs over;  
- those who were abstinent for more than 2 months;  
- serious physical illness (no/failure);  
- pregnant women and lactating women.  
Baseline characteristics:  
- participants came from two groups:  
  - people with heroin dependence with an inadequate response to treatment with continuous intravenous heroin use (n = 492);  
  - people with a heroin addiction that were not handled during the previous 6 months (n = 540)  
| Intervention(s) | Intervention:  
- injectable heroin, max. 3 times a day, 7 days a week;  
- max. single dose: 400 mg;  
- max. daily dose of 1000 mg. Could be given up to 60 mg of methadone for the night.  
Control:  
- oral methadone, minimum dose of 60 mg. per day.  
Participants from both groups were randomized to receive one of two treatments:  
- psycho-education and individual guidance;  
- case management and motivational interviews |
Follow-up | 12 months
---|---
Outcome | Primary: improve the physical and/or mental health secondary: a decline in illicit drug use. 
Secondary: a decline in illicit drug use

Results | – Treatment retention was higher in the heroin (67.2%) than in the methadone group (40.0%).
– The heroin group showed a significantly greater response to both outcomes.
– Effects during ITT: Improving health:
  – heroin: 80%;
  – methadone: 74%.
– Reducing illicit drug use:
  – heroin: 69.1%;
  – methadone: 55.2%.
– More serious side effects were found in the heroin group and were mainly associated with intravenous use.
– Limitations displayed properly.
– Other findings indicated

Quality assessment | Randomization: +
Allocation concealed: +
Clinician blinded:?
– Double blinding was not possible because of medication method.
Patient blinded:? 
– Patient knows what treatment he gets: you can’t ignore it.
Impact assessor blinded: ?
Intervention and control groups were similar: +
Adequate follow-up: +
Intention-to-treat analysis: +
Funding: Working Group of the German Ministry of Health and the seven participating cities.

Quality of evidence | B

ITT: intention to treat; RCT: randomised controlled trial
<table>
<thead>
<tr>
<th>Study aim</th>
<th>In-depth analysis of the German HAT trail to determine if alcohol effect in patients who undergo the HAT and MMT</th>
</tr>
</thead>
</table>
| Study design | RCT  
Blinding: not possible  
Analysis:  
– self-reported data with alcohol consumption units (CU = consumption or alcohol units used);  
– Addiction Severity Index composite scores (ASI CSS);  
– carbohydrate-deficient transferrin (CDT) measures.  
Duration: 12 months  
Setting: clinics (7)  
Location: Germany |
| Number of patients | 1015 |
| Patient characteristics | Age: average age about 36 years  
Sex: about 80% male  
participants came from two groups:  
– people with heroin dependence with an inadequate response to treatment with continuous intravenous heroin use (n = 492);  
– people with a heroin addiction that were not handled during the previous 6 months (n = 540).  
Data collected from 902 patients about alcohol use in 12 months and 955 months in August. Information from two months in 850 patients known |
| Intervention(s) | Intervention, HAT group (N = 515):  
– maximum 3 times a day, 7 days a week;  
– max. Single dose: 400 mg;  
– max. daily dose of 1000mg. Could be given up to 60mg of methadone for the night.  
Control, MMT group (N = 500):  
– minimal-dose of 60 mg. per day;  
– average dose was 99mg/dag.  
Alcohol Test 0 was required for people receiving methadone or diamordine.  
Participants from both groups were randomized to receive one of two treatments:  
– psycho-education and individual guidance;  
– case management and motivational interviews |
| Outcome | Primary: effect of HAT compared with MMT in the possible reduction of alcohol consumption.  
Calculated: with CU, CDT and ASI-CS |
Results

- Significant reduction of CU and CDT in both groups, but larger effects in the HAT group.
- ASI CS shows a significant reduction in the HAT group, but not in the MMT group. Overall reduction in ASI alcohol CS is related to the reduction of CS for ASI drug use and legal problems.
- Biggest advantage to back rings of alcohol in the HAT treatment may be due to the increased frequency of daily heroin.

Quality assessment

<table>
<thead>
<tr>
<th>Randomization: +</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allocation concealed: +</td>
</tr>
<tr>
<td>Clinician blinded:</td>
</tr>
<tr>
<td>Double blinding was not possible because of medication method.</td>
</tr>
<tr>
<td>Patient blinded:</td>
</tr>
<tr>
<td>Assessor blinded:</td>
</tr>
<tr>
<td>Intervention and control groups were similar: +</td>
</tr>
<tr>
<td>Adequate follow-up: +</td>
</tr>
<tr>
<td>Intention-to-treat analysis: +</td>
</tr>
<tr>
<td>Funding: Working Group of the German Ministry of Health and the seven participating cities</td>
</tr>
</tbody>
</table>

Quality of evidence B

ASI-CS: Addiction Severity Index, composite scores; CDT: carbohydrate-deficient transferrin; CU: consumption or alcohol units used; HAT: heroin assisted treatment; MMT: methadone maintenance treatment; RCT: randomised controlled trial

<table>
<thead>
<tr>
<th>Study aim</th>
<th>Compared injectable diacetylmorphine with oral methadone maintenance therapy in patients with opioid dependence that was refractory to treatment</th>
</tr>
</thead>
</table>
| Study design | RCT  
Analysis: Intention to treat  
Location: Canada: Montreal, Quebec, and Vancouver, British Columbia |
| Number of patients | N = 251 clients |
| Patient characteristics | Age: average 39.7 years  
Sex: 61% are men |
| Inclusion | Inclusion:  
– opioid dependence (3 or more criteria from the criteria list, *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition;  
– 25 years or older;  
– minimum 5 years opioid users;  
– use daily injections;  
– no change of city or residence last year;  
– at least 2 prior opioid dependence regimens including at least have a methadone maintenance program where they received 60mg daily minutes, for at least 30 days. |
| Exclusion |  
– methadone maintenance treatment undergone past six years;  
– serious medical or psychiatric disorders that a contradiction for diacetylmorphine;  
– pregnancy;  
– involvement in a criminal case that could result in imprisonment during the study period |
| Intervention(s) Intervention (not blind): |  
– 115 received injectable diacetylmorphine (45.8%);  
– average 2x per day;  
– the average daily dose was 365.5 mg. |
| Control (double blind): |  
– 111 clients received oral methadone (44.2%), average daily dose 96 mg;  
– 25 clients received injectable hydromorphone (10.0%). |
| Follow-up: |  
– evaluations were performed at baseline and 3, 6, 9, and 12 months |
| Outcome | Primary: retention in addiction treatment at 12 months  
Secondary: reduction in illegal drug use or other illegal activities (improvement at least 20% of the European Addiction Severity Index) |
|-----------------|--------------------------------------------------------------------------------------------------------------------------------|
| Results | Results (primary outcomes were determined in 95.2% of the participants):  
– retention in addiction treatment after 12 months:  
  diacetylmorphine 87.8%; methadone: 54.1%;  
– reduction of illegal drugs or other illegal activities:  
  diacetylmorphine 67% methadone: 47.7%;  
– the use of street heroin in the diacetylmorphine clients decreased more than the methadone group;  
– cocaine use was virtually unchanged |
| Quality assessment | Randomization: +  
Allocation concealed: +  
Therapist blinded: +  
Patient blinded: +  
Intervention and control groups were similar: +  
Follow-up adequate: +  
Intention-to-treat analysis: +  
Funding: Supported by grants from the Canadian Institute for Health Research.  
Good quality article, almost all patients were included for follow-up |
| Quality of evidence | B |

**RCT**  randomised controlled trial
### Perneger et al. (1998) Randomised Trial of Heroin Maintenance Programme for Addicts Who Fail in Conventional Drug Treatments

<table>
<thead>
<tr>
<th>Study aim</th>
<th>Experimental evaluation of heroin-maintenance program</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study design</td>
<td>Randomized trail</td>
</tr>
<tr>
<td></td>
<td>Blinding: allocation blinded.</td>
</tr>
<tr>
<td></td>
<td>Analysis: ITT</td>
</tr>
<tr>
<td></td>
<td>Follow-up: 6 months</td>
</tr>
<tr>
<td></td>
<td>Setting: outpatient</td>
</tr>
<tr>
<td></td>
<td>Location: Geneva, Switzerland</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>N = 51:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>- intervention N = 27;</td>
</tr>
<tr>
<td></td>
<td>- control subjects N = 24</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>Age:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>- intervention group: 31.1 years;</td>
</tr>
<tr>
<td></td>
<td>- control group: 32.8 years.</td>
</tr>
<tr>
<td></td>
<td>Sex:</td>
</tr>
<tr>
<td></td>
<td>- intervention group: 67% male;</td>
</tr>
<tr>
<td></td>
<td>- control group: 83% male</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Inclusion</th>
<th>Stayed in the canton of Geneva since 1994</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>At least 20 years old</td>
</tr>
<tr>
<td></td>
<td>Minimum 2 years addicted to intravenous heroin</td>
</tr>
<tr>
<td></td>
<td>Daily use of opiates</td>
</tr>
<tr>
<td></td>
<td>Social anxiety and/or poor health</td>
</tr>
<tr>
<td></td>
<td>Failed in at least two previous treatments with medication.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Intervention(s)</th>
<th>Intervention: patients (N = 27) received intravenous heroin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>and other health and psychosocial support.</td>
</tr>
<tr>
<td></td>
<td>Daily average 480 mg.</td>
</tr>
<tr>
<td></td>
<td>Control: clients (N = 24) received another conventional drug</td>
</tr>
<tr>
<td></td>
<td>treatment (usually methadone)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Outcome measures:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>- all outcomes were self reported by the patients with the</td>
</tr>
<tr>
<td></td>
<td>SF-36 health survey.</td>
</tr>
<tr>
<td></td>
<td>Outcome variables</td>
</tr>
<tr>
<td></td>
<td>- drug use;</td>
</tr>
<tr>
<td></td>
<td>- use of street heroin in past month;</td>
</tr>
<tr>
<td></td>
<td>- daily use past month;</td>
</tr>
<tr>
<td></td>
<td>- health status (for example: numbers of days ill in past</td>
</tr>
<tr>
<td></td>
<td>month, use of health services, workstatus, quality of social</td>
</tr>
<tr>
<td></td>
<td>relationships, criminal behaviour)</td>
</tr>
</tbody>
</table>
Results

Street-heroin use:
- 1 person in intervention group and 10 (48%) in control group.
- everyone stopped benzodiazepines street and took enormous overdose rate down.

Health, experimental group:
- treatments for psychological problems has increased (from 15% to 65%);
- the number of days with health declined (11.8% to 9.9%);
- severe anxiety decreased (82% to 44%), difficulties in controlling violent behavior decreased (30% to 18%);
- number of suicide attempts (22% to 4%).

Control group:
- minimal changes to the above are not present or even worse

Quality assessment

Randomization: +
- sealed envelopes placed patients in one of the two groups

Allocation concealed: +

Clinician blinded: -
- self reported questionnaires

Patient blinded: -

Assessor blinded: -

Intervention and control groups were similar: +

Adequate follow-up: +

Intention-to-treat analysis: +

Funding: Swiss Federal Office of Public Health

Quality of evidence B

Study limitations:
- small study;
- self-reported outcomes may be biased;
- this study assessed global programme effects it cannot differentiate between specific effects of heroin administration and those of other medical and social services, such as mental health care and benzodiazepine substitution

ITT: intention to treat; SF-36: Short Form (36) Health Survey
**Rehm e.a. (2001) Feasibility, safety, and efficacy of injectable heroin prescription for refractory opioid addicts: a follow-up study**

<table>
<thead>
<tr>
<th>Study aim</th>
<th>To assess the feasibility, safety and efficacy of the treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study design</td>
<td>Follow-up study/cohort</td>
</tr>
<tr>
<td>Number of patients</td>
<td>1969</td>
</tr>
</tbody>
</table>
| Patient characteristics | Age: mean age: 32  
Sex: 77% male |
| Intervention(s) | HAT treatment, psychosocial support, access to medical care. When patients needed it, they got methadone instead of heroin. Average daily intravenous heroin was 474 mg (SD 206.1) and an average of 2.6 intakes per day  
No control group |
| Follow-up | Follow-up: after 7 years  
N = 237  
Survival curves on Kaplan-Meier estimates, and residual analysis done on categorical variables |
| Outcome | Primary: assessment of the somatic, mental health, social inclusion, and treatment outcomes (through questionnaires, interviews and medical examinations) |
| Results | The treatment is relatively high in participation in HAT: 1693 (86%) of patients followed the program at least three months, 1,378 (70%) at least one year, 985 (50%) at least 2.5 years, and 669 (34%) 5 years and longer.  
Reasons for failure are described.  
Socio-economic status is evaluated:  
(N=37). Below you will find the measurements between brackets.  
The first percentage reflects the measurement at baseline, the second percentage reflects the measurement at 18 months follow-up.  
- unstable housing situation (43%, 21%);  
- nomadic life (18%, 1%);  
- unemployment (73%, 45%);  
- receiving a benefit (63%, 54%);  
- being in debt (74%, 67%);  
- income from illegal activities (69%, 11%);  
- visiting illegal drug events (84%, 41%).  
Disability allowance and increased (22%, 27%) |
| Quality of evidence | C |
| Conclusion: | The treatment showed positive effects concerning the health and social impacts. A long stay in treatment was associated with a higher risk of initiating abstinence-oriented therapy than a short stay.  
HAT would be an effective treatment option for chronically addicted clients where other treatments have failed |

HAT: heroin assisted treatment
### Strang e.a. (2010) Supervised injectable heroin or injectable methadone versus optimised oral methadone as treatment for chronic heroin addicts in England after persistent failure in orthodox treatment (RIOTT): A randomised trial

<table>
<thead>
<tr>
<th>Study aim</th>
<th>To compare the effectiveness of supervised injectable treatment with medicinal heroin (diamorphine or diacetylmorphine) or supervised injectable methadone versus optimised oral methadone for chronic heroin addiction</th>
</tr>
</thead>
</table>
| Study design | RCT  
Blindness: blind (open label study)  
Analysis: intention to treat  
Setting: 3 supervised injecting clinics  
Location: England. Patients were enrolled from the local catchment areas of supervised injecting clinics in south London, Darlington, and Brighton |
| Number of patients | N = 127 |
| Patient characteristics | Age: 37.2  
Sex: 73% men  
Ethnicity: 96% white |
| Inclusion | Inclusion:  
– chronic heroin addicts;  
– receiving conventional oral maintenance treatment (≥ 6 months).  
Baseline characteristics:  
– 95% unemployed;  
– 73% had spent time in prison;  
– patients had used opiates for a mean of 16.6 years and received treatment for mean of 9.8 years;  
– all were daily using street heroin;  
– 43% also reported regular use of cocaine or crack cocaine;  
– all patients were receiving methadone treatment at enrolment (continuously for ≥ 6 months), and 39% were receiving optimized methadone treatment |
| Intervention(s) | Intervention:  
– supervised injectable heroin, N = 43;  
– or injectable methadone, N = 42.  
Control:  
– optimized oral methadone, N = 42 |
| Follow-up | 26 weeks |
Outcome: Primary: 50% or more of negative specimens for street heroin on weekly urinalysis during weeks 14-26.
Secondary: examined more stringent tests of reduction of regular use of street heroin.
Outcome measures: percentages were calculated with Rubin’s rules and were then used to estimate numbers of patients in the multiple imputed samples.

Results:
- self-reported: abstinence from street heroin at weeks 23-26 was recorded in a significantly higher proportion of patients on injectable heroin (51% [n = 22]) than in those on injectable methadone (29% [n = 12] or oral methadone (17% [n = 7]);
- urine sample: injectable heroin was associated with the greatest proportion of participants with urine samples negative for street heroin within the first 6 weeks of treatment and thereafter. The injectable heroin group was associated with the largest increase in abstinence by the end of 6 weeks.

Other results:
- for injectable heroin versus injectable methadone, a significant difference was recorded (4.26, 1.63, 11.14, p = 0.003), but the study was not powered for this comparison.

Quality assessment:
Randomization: +
Allocation concealed: +
Clinician blinded: -
Patient blinded: -
Assessor blinded: -/+ -/+;
- urinalysis was done by laboratory personnel who were masked to treatment allocation;
- statistician analysing primary outcome data was masked to injectable group but not to oral versus injectable treatment for the entirety of the primary analysis.

Intervention and control groups were similar: + Adequate follow-up: +
Intention-to-treat analysis: +
Funding:
- Community Fund (Big Lottery) Research section, through Action on Addiction.

Quality of evidence:
A2
Conclusion:
Good quality article. The study was open-label, which meant that patients’ awareness of their treatment allocation could have affected expectancy and behavior.

RCT: randomised controlled trial
### Van den Brink e.a. (2003) Medical prescription of heroin to treatment resistant heroin addicts: two randomised controlled trials

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>N = 549</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient characteristics</strong></td>
<td>Age: mean age 39</td>
</tr>
<tr>
<td><strong>Inclusion</strong></td>
<td><strong>Exclusion:</strong></td>
</tr>
<tr>
<td>– last 6 months attending a methadone treatment program;</td>
<td>– pregnant or breastfeeding women</td>
</tr>
<tr>
<td>– at least 25 years old;</td>
<td></td>
</tr>
<tr>
<td>– minimum 5 years diagnostic criteria for heroin dependence;</td>
<td></td>
</tr>
<tr>
<td>– use at least 50 mg (inhaling trial) or 60 mg (injecting trial) methadone per day for a uninterrupted period of at least four weeks in the last 5 years;</td>
<td></td>
</tr>
<tr>
<td>– use (almost) daily illicit heroin;</td>
<td></td>
</tr>
<tr>
<td>– poor physical or mental health or poor social functioning;</td>
<td></td>
</tr>
<tr>
<td>– last year voluntarily waived heroin for more than two months.</td>
<td></td>
</tr>
<tr>
<td><strong>Intervention(s)</strong></td>
<td><strong>Intervention:</strong></td>
</tr>
<tr>
<td>Two separate open label randomized controlled groups:</td>
<td>Two separate open label randomized controlled groups:</td>
</tr>
<tr>
<td>– Inhaling heroin (n = 375) with methadone. Within the group; there were 3 treatment groups:</td>
<td>– Inhaling heroin (n = 375) with methadone. Within the group; there were 3 treatment groups:</td>
</tr>
<tr>
<td>– group A: control group (N = 139); only methadone (up to 150mg per day);</td>
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</tr>
<tr>
<td>– group B: experimental group (N = 117) methadone and heroin;</td>
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</tr>
<tr>
<td>– group C Comparison group (N = 119). Six months of methadone alone followed by 6 months of methadone and heroin.</td>
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</tr>
<tr>
<td>– Injectable heroin (n = 174) with methadone. Within the group; there were 2 treatment groups:</td>
<td>– Injectable heroin (n = 174) with methadone. Within the group; there were 2 treatment groups:</td>
</tr>
<tr>
<td>– group A: Control group (N = 98); only methadone (up to 150mg per day);</td>
<td>– group A: Control group (N = 98); only methadone (up to 150mg per day);</td>
</tr>
<tr>
<td>– group B: experimental group (N = 76) methadone and heroin.</td>
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</tr>
<tr>
<td><strong>Doses:</strong></td>
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</tr>
<tr>
<td>– heroin: max 1000mg per day;</td>
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</tr>
<tr>
<td>– methadone up to 150mg per day.</td>
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</tr>
<tr>
<td>Clients were 2.1× average daily heroin use and get an average of 260 mg per visit.</td>
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</tr>
<tr>
<td>Period of 12 months.</td>
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<tr>
<td>All patients also received psychotherapy.</td>
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</tr>
<tr>
<td><strong>Outcome</strong></td>
<td>Primary: dichotomous, multidomain response index, including validated indicators of physical health, mental status, and social functioning</td>
</tr>
</tbody>
</table>
Results:

- Treatment with heroin plus methadone was significantly more effective than treatment with methadone alone in the trial of inhalable heroin and in the trial of injectable heroin treatment. Inhalable heroin: (response rate 49.7% vs. 26.9%; 95% confidence interval 11% to 34.6%, NNT: 4.4, 2.9 to 9.1);
- Injectable heroin (response rate 55.5% vs. 31.2%; 9.6% to 39.0%, NNT: 4.1 2.6 to 10.4).

Further decline after 12 months of illegal activities and daily cocaine use. Patients also made more personal contact;

- Cessation of heroin prescription led to a rapid deterioration of 82% (94/115);
- Heroin should be prescribed long before the positive results remain stable.

Conclusion article:

- Monitoring prescribing heroin is feasible, effective, and probably as safe as methadone alone in reducing the many physical, mental and social problems of treatment resistant heroin addicts

<table>
<thead>
<tr>
<th>Quality assessment</th>
<th>Randomization: +</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allocation concealed: ?</td>
<td></td>
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<tr>
<td>Clinician blinded: ?</td>
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<tr>
<td>Patient blinded -</td>
<td></td>
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<tr>
<td>Assessor blinded:+</td>
<td></td>
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<tr>
<td>Intervention and control groups were similar: +</td>
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</tr>
<tr>
<td>Adequate follow-up: +</td>
<td></td>
</tr>
<tr>
<td>Intention-to-treat analysis: +</td>
<td></td>
</tr>
<tr>
<td>Funding: the study was commissioned by the Ministry of Health, Welfare and Sport and also financed by them</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Quality of evidence</th>
<th>B (?)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conclusion:</td>
<td></td>
</tr>
<tr>
<td>- the study is clear and the quality seems good;</td>
<td></td>
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<tr>
<td>- it wasn’t a double-blind study;</td>
<td></td>
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<tr>
<td>- and only self reported data were used (collected by researchers)</td>
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</tbody>
</table>

NNT: number needed to treat