Oral Morphine Treatments
(in opioid dependence)

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Biarritz oct 10th, 2013
Conflict of Interest

- Reckitt Benckiser/Shering Plough
- Nepp/Mundipharma
- Lannacher

Travel support, payment for presentations, clinical research studies
Main considerations

• Pharmacological medication
  – Efficacy of medication
    • Retention
    • Reduced consumption of drug of dependence
  – Safety
  – Spectrum of side effects
  – Low diversion risk
  – Quality of life

• „Psychoeducative“ support
Diversification
possibilities for therapist and patient preferences

ABSTINENCE

• Naltrexone ER implant
• Naltrexone ER i.m.
• Naltrexone p.o.
• Methadone HD
• Buprenorphine HD s.l.
• Buprenorphine/Naloxon (Suboxone) s.l./film
• Methadone LD
• L-Methadone = Polamidon
• Slow release oral morphine p.o. (SROM)
• SROM with naloxone p.o.
• Burenpornphine i.m.
• Heroin p.o.
• Morphine i.v.
• Heroin inhalable and i.v.

Search for a safe high

Life without opioids

Life without illicit opioids
Opioid Medication Distribution across Europe

Percentage of patients

France | Finland | Greece | Sweden | Norway | Italy | Portugal | Austria | Denmark | UK | Germany | Belgium | Switz. | Luxembourg | Spain

- SROM
- Methadone
- Subutex/Generic Bupe
- Suboxone
POLAMIDON

(HOECHST 10820)

Stark wirkendes Analgeticum und Spasmolyticum

Ampullen / Tropfen / Tabletten
Patients in opioid maintenance in Austria depending on medication and age in 2011

Referring to 16,126 patients in 2011

Reduced life time expectancy
A 33 year FU of narcotic addicts (Hser et al., 2001)

<table>
<thead>
<tr>
<th>Year</th>
<th>Unknown</th>
<th>Dead</th>
<th>Incarcerated</th>
<th>Daily use</th>
<th>MMT</th>
<th>Occasional use</th>
<th>Abstinence</th>
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<th>Year</th>
<th>N</th>
<th>Age</th>
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<td>56</td>
<td>581</td>
<td>24.5 (3.9)</td>
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<td>60</td>
<td>439</td>
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<td>64</td>
<td>354</td>
<td>47.6 (5.1)</td>
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<tr>
<td>68</td>
<td>242</td>
<td>57.4 (4.0)</td>
</tr>
</tbody>
</table>
Mortality in Opioid-Maintained Patients after Release from an Addiction Clinic

Susanne M. Bauer\textsuperscript{a}  Rita Loipl\textsuperscript{a}  Reinhold Jagsch\textsuperscript{a}  Diego Gruber\textsuperscript{b}  
Daniele Risser\textsuperscript{c}  Kenneth Thau\textsuperscript{d}  Gabriele Fischer\textsuperscript{a}  

\textsuperscript{a}Department of Psychiatry and Psychotherapy, Division of Biological Psychiatry, Departments of \textsuperscript{b}Medical Statistics and \textsuperscript{c}Forensic Medicine, and \textsuperscript{d}Department of Psychiatry and Psychotherapy, Division of Social Psychiatry, Medical University of Vienna, Vienna, Austria
6-year follow up of opioid maintained patients after discharge from addiction clinic to GP´s office

**Mortality rate (SMR)**

<table>
<thead>
<tr>
<th>Condition</th>
<th>p-value</th>
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<tbody>
<tr>
<td>male</td>
<td>0.076</td>
</tr>
<tr>
<td>unemployed</td>
<td>0.012</td>
</tr>
<tr>
<td>frequent hospitalization</td>
<td>0.019</td>
</tr>
<tr>
<td>No opioid maintenance tx</td>
<td>0.024</td>
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<tr>
<td>Socially deprived</td>
<td>0.045</td>
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</tbody>
</table>

SMR: 29.3
Post-mortem-forensic Analyses

n=29

- HIV-related
- suicide
- other somatic reasons
- only morphine
- only methadone
- opioids plus benzodiazepines
Opioid maintenance treatment coverage in EU countries (EMCDDA, 2002)
Opioid maintenance Tx coverage in EU

- Treatment coverage expanded 2002–2005
  - Norway: 15% ➔ 40%
  - Italy: 25% ➔ 40%

- EU Coverage (2005)
  - Opioid-dependent: 1.6m
  - In treatment: 462,412
  - Methadone: 422,655
  - Buprenorphine: 36,807
  - Mean Coverage: 29%

- EMCDDA 2007: 99% of maintenance either methadone or buprenorphine

EMCDDA Annual Report, 2007
Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence

Richard P Mattick¹, Jo Kimber¹, Courtney Breen¹, Marina Davoli²

¹National Drug and Alcohol Research Centre, University of New South Wales, Sydney, Australia. ²Cochrane Drugs and Alcohol Group, Dept. of Epidemiology ASL RME, Italy, Rome, Italy

Contact address: Richard P Mattick, National Drug and Alcohol Research Centre, University of New South Wales, National Drug and Alcohol Research Centre, University of New South Wales, Sydney, New South Wales, 2052, Australia. r.mattick@unsw.edu.au.

Editorial group: Cochrane Drugs and Alcohol Group.
Publication status and date: Edited (no change to conclusions), published in Issue 3, 2008.
Review content assessed as up-to-date: 5 December 2007.


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Maintenance Treatment

Standard

• methadone reduces heroin use, injection and needle sharing (A)

• methadone is more effective at doses ranging from 60-120 mg/day (A) and in combination with psychosocial interventions (B)

• buprenorphine is effective alternative for methadone, but maybe less effective than high dose methadone (A)

• Higher doses of bruprenorphine (> 8 mg) are more effective (A)

• naltrexone may be useful adjunct to treatment in highly motivated individuals (C)
Opioids – Maintenance Treatment

Standard

New

• slow release morphine may be effective (C)

• heroin assisted treatment is effective in treatment resistant methadone patients (B)
SROM
slow release oral morphine

- Morphinsulphate-
  - capsules

- Morphinhydrochloride-
  - tablets
Slow-release oral morphine

- Formulated for a longer half-life than standard morphine, enabling use for once-daily maintenance
- Suitable for patients responding poorly to methadone

Mitchell et al, DAD, 2003; ....... Oral slow-release for maintenance ....
Mitchell T, White J, Somodyi A, Bochner F; Addiction 99: 940-946; 2004

- 18 methadone maintained patients
- Transfer & at least over 4 weeks stable dosing on SROM
- Dose Ratio: METHADONE: SROM 1:4.6 with mean SROM dose: 350 mg.

**Results:**

- SROM was associated with improved social functioning, weight loss, fewer and less troublesome side-effects. Greater drug liking, reduced heroin craving, an enhanced sense of feeling „normal“ - the majority (78%) preferred SROM (78%) over methadone (22%)
RESEARCH REPORT

Comparison of methadone and slow-release morphine maintenance in pregnant addicts

GABRIELE FISCHER,¹ REINHOLD JAGSCH,¹ HARALD EDER,¹ WOLFGANG GOMBAS,¹ PETRA ETZERSDORFER¹, KATRIN SCHMIDL-MOHL,² CHRISTIAN SCHATTEN,³ MANFRED WENINGER⁴ & HARALD N. ASCHAUER¹

¹Department of General Psychiatry, ²Department of Social Psychiatry and Evaluation Research, ³Department of Gynaecology & ⁴Department of Neonatology, University Hospital of Vienna, Vienna, Austria
SR-morphine vs methadone in pregnancy

Fischer et al., 1999; Addiction 94 (2), 231-239

- Both are safe and well tolerated
- Prevention of preterm delivery - healthy neonates
- Both induce a NAS - no difference in intensity and duration of NAS

- **But:** Significant lower concomitant consumption of heroin and benzodiazepines in SR-morphine-group

- **Limitations:** SR-morphine was given twice a day in contrast to methadone once a day
  Use of phenobarbiturates in the treatment of NAS - mean duration of NAS treatment 16 days
Comparative study of the effectiveness of slow-release morphine and methadone for opioid maintenance therapy

Harald Eder¹, Reinhold Jagsch², Dominik Kraigher¹, Andjela Primorac¹, Nina Ebner¹ & Gabriele Fischer¹

Addiction Clinic, Department of Psychiatry, Medical University, Vienna¹ and Institute for Psychology, University of Vienna, Austria²

Ratio: Methadone - SROM: 1: 7.75
Comparative Study of the Effectiveness of Slow-Release Morphine Capsules and Methadone Oral Solution for Opioid Maintenance Therapy

-3 screening days
0 methadone
1 SR-morphine
7 cross-over
15 weeks
12* driving simulating performance

Double-blind, double-dummy
### Demographical data

Sample: 64 patients with opioid dependence (DSM IV 304.0)

do double-blind, double-dummy

<table>
<thead>
<tr>
<th></th>
<th>A (SR Morphine/ Methadone)</th>
<th>B (Methadone/ SR Morphine)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=32</td>
<td>n=32</td>
</tr>
<tr>
<td>Sex</td>
<td>5f (15.6%)</td>
<td>3f (9.4%)</td>
</tr>
<tr>
<td>age (years)</td>
<td>29.5 (7.5) [19; 57]</td>
<td>27.9 (5.6) [19; 38]</td>
</tr>
<tr>
<td>Age of first injecting heroin</td>
<td>21.8 (5.0) [15; 35]</td>
<td>21.4 (4.7) [15; 30]</td>
</tr>
<tr>
<td>Duration of opioid dependence (months)</td>
<td>64.2 (52.7) [6; 180]</td>
<td>60.2 (49.2) [6; 192]</td>
</tr>
<tr>
<td>Heroin use in the last 30 days</td>
<td>25.7 (8.4) [15; 30]</td>
<td>22.5 (12.2) [11; 30]</td>
</tr>
</tbody>
</table>

n.sign.
Retention rate

Retention percentage

- A (Mo/Me) 81.3%
- B (Me/Mo) 90.6%
Injection sites

Number

Test1  Test3  Test5  Test7  Test9  Test11  Test13  Test15  Test17  Test19  Test21  Test23  Test25  Test27  Test29  Test31

(A (Mo/Me

(B (Me/Mo

Number

Test1  Test3  Test5  Test7  Test9  Test11  Test13  Test15  Test17  Test19  Test21  Test23  Test25  Test27  Test29  Test31
List of complaints

Time $p=.001$, group n.sign., interaction time*group $p<.001$
Beck Depression Inventory

Time $p=.001$, group n.sign., interaction time*group $p<.001$
Stait/Trait Anxiety Inventory

Time $p = .008$, group n.sign., interaction time*group $p < .003$
Results

- Methadone - SROM: 1: 7.75
  - methadone (mean): 85 mg
  - SR- morphine (mean): 680 mg

- High retention rate in both treatment groups - no significant difference (84% SR morphine vs 88% methadone) in a 15 weeks study duration with daily attendance

- Significant reduction in injection sites (p<0.001)

- No significant differences in concomitant consumption of benzodiazepines and cocaine between the groups, however a time effect is significant for cocaine (p<0.001)

- Significant better clinical well-being on SR morphine maintenance (p<0.001)

- Discussion: future – SR morphine/naloxone (?)
New horizon: sustained release morphine as agonist treatment

George Woody
Addiction, 2005; 100: 1758-1759
Maintenance treatment with SROM appears to be a clinically useful alternative treatment in subjects not tolerating methadone or with inadequate withdrawal suppression.

Methadone / SR morphine ratio 1:8
BAP updated guidelines: evidence-based guidelines for the pharmacological management of substance abuse, harmful use, addiction and comorbidity: recommendations from BAP

AR Lingford-Hughes¹, S Welch², L Peters³ and DJ Nutt¹

Slow-release oral morphine. A small number of short-term cross-over studies (in special populations, e.g. patients intolerant to methadone) of slow-release oral morphine (SROM) have been published. These show similar efficacy to methadone, but no long-term data are available (Bond et al., 2011; Eder et al., 2005; Mitchell et al., 2004; Winklbaur et al., 2008) (Ib). However, experiences in Austria show that SROM is frequently abused and dominates the black market (Beer et al., 2010).
Buprenorphine diversion and injection in Melbourne, Australia: An emerging issue?
Jenkinson RA et al.; Addiction (2005) 100; 197-205

Setting: Syringe & needle exchange programme in Melbourne
Patients: 156 current IDU

Results: 37% reporting injection of bup during lifetime, 33% within the last 6 months. 47% reported to have bup obtained illicitly

_Buprenorphine injection was associated with:_
- Injection of other drugs
- Buprenorphine maintenance
- Injection-related health problems
- Involvement in crime

Conclusion: Monitoring & Education in addiction medicine
Respondents were willing to pay significantly (p<0.0001) higher street price for buprenorphine than for the combining product.

- 89% were willing to pay €25 for 8mg buprenorphine – only 3% would pay that for 8mg buprenorphine-naloxone.

% of respondents willing to purchase the substance at a particular price:

![Graph showing the percentage of patients willing to purchase buprenorphine and buprenorphine-naloxone at different street prices.](Image)
Diversion and abuse of buprenorphine: Findings from national surveys of treatment patients and physicians

Chris-Ellyn Johanson\textsuperscript{a,b,*}, Cynthia L. Arfken\textsuperscript{a}, Salvatore di Menza\textsuperscript{b}, Charles Roberts Schuster\textsuperscript{a,b,1}

\textsuperscript{a} Department of Psychiatry and Behavioral Neurosciences, Wayne State University, 2761 E. Jefferson Ave., Detroit, MI 48207, USA
\textsuperscript{b} CRS Associates, LLC, 1530 S State Street, Ste 900, Chicago, IL 60605, USA
Key EQUATOR publications

Methods

• Fischer G, Stöver H. *HARCP* 2012;14(3):5–70.

Results

• Stöver H. *HARCP* 2012;14(4):51–64.

Full questionnaires are published as appendices to the methods paper
What is EQUATOR?

Project Improve survey

Project Access

EQUATOR analysis

Extension to new countries

Original study in Germany

Adaptation of Project Improve survey in 10+ EU countries

Combined analysis of first 10 country surveys in EU

Belgium, Netherlands, and Switzerland

Treatment experts from across the world participated as advisors or collaborators in the implementation of the survey

EQUATOR: European Quality Audit of Opioid Treatment

# EQUATOR: General recruitment procedures

<table>
<thead>
<tr>
<th>Category</th>
<th>Recruitment Methods</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Physicians (treating)</strong></td>
<td>• Identified by research collaborators, official lists or internet research</td>
</tr>
<tr>
<td></td>
<td>• Telephone or face-to-face interviews, ~60 questions</td>
</tr>
<tr>
<td><strong>Patients (currently in OMT)</strong></td>
<td>• Recruited via physicians, treatment/user groups or drug support centres</td>
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<tr>
<td></td>
<td>• Self-completion questionnaire or face-to-face interviews, ~50 questions</td>
</tr>
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<td><strong>Opioid users (currently out of OMT)</strong></td>
<td>• Recruited via treatment/user groups or drug support centres</td>
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*Many users had past treatment experience*
Austria: SROM is associated with a high risk of injectable misuse

- More than half of patients on SROM reported injecting their OMT compared with only 17% of patients on buprenorphine and 7% on buprenorphine–naloxone (p<0.01 SROM vs other options)

SROM: slow-release oral morphine
Antagonist–agonist combinations as therapies for heroin addiction: back to the future?

David J Nutt
FUTURE

EudraCT Number: 2011-005903-34
Sponsor's Protocol Code Number: KKSMUW2011-09
National Competent Authority: Austria - BASG
Clinical Trial Type: EEA CTA
Trial Status: Ongoing
Date on which this record was first entered in the EudraCT database: 2012-03-29
Thank you for your attention…

Edvard Munch (1918-1919) “Women With Poppies”