Klinische Aspekte der Langzeitsubstitution mit Opioiden

Hans Haltmayer

19. Substitutions-Forum
9. April 2016, Mondsee
Natural history of Narcotic-Addiction

A 33-Year Follow-up of Narcotics Addicts

Yih-Ing Hser, PhD; Valerie Hoffman, PhD; Christine E. Grella, PhD; M. Douglas Anglin, PhD

Background: This study examined longitudinal patterns of heroin use, other substance use, health, mental health, employment, criminal involvement, and mortality among heroin addicts.

Methods: The sample was composed of 381 male heroin addicts admitted to the California Civil Addict Program (CAP) during the years 1962 through 1964; CAP was a compulsory drug treatment program for heroin-dependent criminal offenders. This 33-year follow-up study updates information previously obtained from admission records and 2 face-to-face interviews conducted in 1974-1975 and 1985-1986; in 1996-1997, at the latest follow-up, 284 were dead and 242 were interviewed.

Results: In 1996-1997, the mean age of the 242 interviewed subjects was 57.4 years. Age, disability, years since first heroin use, and heavy alcohol use were significant correlates of mortality. Of the 242 interviewed subjects, 20.7% tested positive for heroin (with additional 9.5% urine refusal and 14.0% incarceration, for whom urinalyses were unavailable), 66.9% reported tobacco use, 22.1% were daily alcohol drinkers, and many reported illicit drug use (eg, past-year heroin use was 40.5%; marijuana, 35.3%; cocaine, 19.4%; crack, 10.3%; amphetamine, 11.6%). The group also reported high rates of health problems, mental health problems, and criminal justice system involvement. Long-term heroin abstinence was associated with less criminality, morbidity, psychological distress, and higher employment.

Conclusions: While the number of deaths increased steadily over time, heroin use patterns were remarkably stable for the group as a whole. For some, heroin addiction has been a lifelong condition associated with severe health and social consequences.

Arch Gen Psychiatry. 2001;58:503-508
Natural history of Addiction
– 33 Y Follow-up of Narcotics Addicts

The natural history of narcotics addiction among a male sample (N=581).

Hser Y et al Arch Gen Psychiatry. 2001;58:503-508
Risk of death during and after opiate substitution treatment in primary care: prospective observational study in UK General Practice Research Database

Rosie Cornish, statistician; John Madeod, professor in clinical epidemiology and primary care; John Strang, professor in the psychiatry of the addictions; Peter Vickerman, senior lecturer in mathematical modelling; Matt Hickman, professor in public health and epidemiology

ABSTRACT

Objective To investigate the effect of opiate substitution treatment at the beginning and end of treatment and according to duration of treatment. Further research is needed to investigate the effect of average duration of opiate substitution treatment on drug related mortality.
Mortalität  ...*On Treatment / Off Treatment* 1
n=5.577, prospective observational study

<table>
<thead>
<tr>
<th>Variable</th>
<th>Deaths</th>
<th>Person years</th>
<th>Mortality/100 person years</th>
<th>Mortality rate ratio (95% CI)</th>
<th>P value</th>
<th>Mortality rate ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall on treatment</td>
<td>62</td>
<td>8939.7</td>
<td>0.69</td>
<td>1.00</td>
<td>&lt;0.001</td>
<td>1.00</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Overall off treatment</td>
<td>116</td>
<td>8791.8</td>
<td>1.32</td>
<td>1.90 (1.40 to 2.59)</td>
<td></td>
<td>2.29 (1.67 to 3.14)</td>
<td></td>
</tr>
<tr>
<td>Period:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weeks 1-2 of treatment</td>
<td>8</td>
<td>471.5</td>
<td>1.70</td>
<td>2.80 (1.33 to 5.91)</td>
<td>&lt;0.001</td>
<td>3.11 (1.47 to 6.59)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Weeks 3-4 of treatment</td>
<td>5</td>
<td>378.7</td>
<td>1.32</td>
<td>2.18 (0.87 to 5.47)</td>
<td></td>
<td>2.38 (0.95 to 5.99)</td>
<td></td>
</tr>
<tr>
<td>Remainder of time on treatment</td>
<td>49</td>
<td>8089.4</td>
<td>0.61</td>
<td>1.00</td>
<td></td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Weeks 1-2 off treatment</td>
<td>22</td>
<td>458.0</td>
<td>4.80</td>
<td>7.93 (4.80 to 13.12)</td>
<td>&lt;0.001</td>
<td>9.01 (5.43 to 14.90)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Weeks 3-4 off treatment</td>
<td>19</td>
<td>446.6</td>
<td>4.25</td>
<td>7.02 (4.11 to 11.93)</td>
<td></td>
<td>8.01 (4.70 to 13.66)</td>
<td></td>
</tr>
<tr>
<td>Remainder of time off treatment</td>
<td>75</td>
<td>7887.2</td>
<td>0.95</td>
<td>1.57 (1.10 to 2.25)</td>
<td></td>
<td>1.91 (1.32 to 2.76)</td>
<td></td>
</tr>
</tbody>
</table>

Cornish R et al. BMJ 2010;341:c5475
Mortalität  ..., On Treatment / Off Treatment 2
n=5.577, Prospective observational study

Während der ersten 4 Wochen in und nach einer Behandlung ist das Sterberisiko am höchsten.

→ 2-3x höher am Beginn (1-28 d) als im restlichen Verlauf
→ 8-9x höher im Monat nach Beendigung der Substitution

Kein Unterschied hinsichtlich der eingesetzten Substitutionsmittel (Meth/Bup)

Cornish R et al. BMJ 2010;341:c5475
Langzeitsubstitution in Österreich ...Haltequote

Haltedauer\(^1\) der Personen, die vom 1. 1. 2011 bis 31. 12. 2012 eine Substitutionsbehandlung begonnen haben, nach Wien und anderen Bundesländern (Überlebensfunktion nach Kaplan-Meier; n = 5.165)

Quelle: GÖG/ÖBIG; Epidemiologiebericht Drogen 2013
Langzeitsubstitution in Wien

Substitutionsstatistik Wien, Mai 2015
Substitutionsbehandlung in Wien

...Altersverteilung

Substitutionsstatistik Wien, Mai 2015

= 16%
Substitutionsbehandlung in Wien  ...Altersverteilung

Substitutionsstatistik Wien, Mai 2015

> 40a = 2.444 (39,3%)
Dear Minister,

RE: Time-limiting opioid substitution therapy

In June 2014, the then Minister of State for Crime Prevention, Norman Baker MP commissioned the Advisory Council on the Misuse of Drugs (ACMD) to provide advice to the Inter-Ministerial Group on Drugs, which was exploring the question of
Langzeitsubstitution mit Opioiden

Advisory Council on the Misuse of drugs (ACMD)
Minister for Crime Prevention and Inter-Ministerial Group on Drugs

Time-limiting opioid substitution therapy
Kein empfohlener Zeitrahmen für OST. Die Entscheidung für eine Long-term OST soll im Einvernehmen zwischen Patient und Arzt getroffen werden.


Starke Evidenz, dass eine zeitlich limitierte OST
- die Rückfallhäufigkeit erhöht
- die Beschaffungskriminalität fördert
- die Verbreitung von „blood-borne“ Virusinfektionen fördert
- die Rate an tödlichen Überdosierungen erhöht
- ein medizinrechtlicher Verstoß wäre (Gebot einer effektive Behandlung auf Basis der besten verfügbaren Evidenz)
Die Hypothalamus - Hypophysen - Gonaden - Achse
FIGURE 1: Interactions between opioids and the endocrine system

The Hypothalamic-Pituitary-Gonadal Axis

OPIOIDS

LHRH (GnRH) → Hypothalamus
Hypothalamus → LHRH (GnRH)
LHRH (GnRH) → Pituitary
Pituitary → LH, FSH
LH → Testosterone, Estrogen
LH, FSH → Ovaries

LHRH = luteinizing-hormone releasing hormone
GNRH = gonadotropin-releasing hormone
LH = luteinizing hormone
FSH = follicle-stimulating hormone
Methadone induces testosterone suppression in patients with opioid addiction

Monica Bawor 1,2, Brittany B. Dennis 2,3,4, M. Constantine Samaroo 5, Carolyn Plater 6, Andrew Worster 6,7, Michael Vorenbusch 8, Jeff Daiter 9, David C. Marsh 8,9, Dipika Desai 10, Meir Steinher 10,11, Rebecca Anglin 10,9, Margaret Coote 10, Guillaume Pare 10,4, Lehana Thabane 12 & Zainab Samaroo 3,4,9

Sex hormones may have a role in the pathophysiology of substance use disorders, as demonstrated by the association between testosterone and addictive behaviour in opioid dependence. Although opioid use has been found to suppress testosterone levels in men and women, the extent of this effect and how it relates to methadone treatment for opioid dependence is unclear. The present multi-centre cross-sectional study consecutively recruited 231 patients with opioid dependence from methadone clinics across Ontario, Canada between June and December of 2011. We obtained demographic details, substance use, psychiatric history, and blood and urine samples from enrolled subjects. The control group included 783 non-opioid using adults recruited from a primary care setting in Ontario, Canada. Average testosterone level in men receiving methadone treatment was significantly lower than controls. No effect of opioids including methadone on testosterone level in women was found and testosterone did not fluctuate significantly between menstrual cycle phases. In methadone patients, testosterone level was significantly associated with methadone dose in men only. We recommend that testosterone levels be checked in men prior and during methadone and other opioid therapy, in order to detect and treat testosterone deficiency associated with opioids and lead to successful methadone treatment outcomes.
Suppression von Testosteron

Table 2 | Summary of testosterone levels between men and women on methadone and controls

<table>
<thead>
<tr>
<th></th>
<th>MMT*</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>131</td>
<td>100.10 ng/dl [72.21]</td>
</tr>
<tr>
<td></td>
<td>3.47 nmol/L [2.51]</td>
<td>2.71 nmol/L</td>
</tr>
<tr>
<td>Women</td>
<td>100</td>
<td>36.61 ng/dl [23.19]</td>
</tr>
<tr>
<td></td>
<td>1.27 nmol/L [0.81]</td>
<td>0.98 nmol/L</td>
</tr>
<tr>
<td>Total</td>
<td>231</td>
<td></td>
</tr>
</tbody>
</table>

*Significant at the p < 0.001 level.

MMT: Methadone Maintenance Treatment.

SD: standard deviation.

SI conversion factor: To convert testosterone to nmol/L, multiply values by 0.0347.

Figure 2 | Methadone dose and serum total testosterone level in men. Description: Inverse linear relationship between serum total testosterone level and methadone dose in men on methadone treatment (n = 131).

Bawor M et al.: srep 2014;4:6189
Suppression von Testosteron

Review

Testosterone suppression in opioid users: A systematic review and meta-analysis

Monica Bawor*a, Herman Bam†, Brittany B. Dennisb,†,‡, Carolyn Platerb,b,†, Andrew Worsterb,b,‡, Michael Varenbub,‡, Jeff Daiterb,‡, David C. Marshc,d,‡, Moir Steinerb,b,‡, Rebecca Anglinb,b,‡, Margaret Cooteb,‡, Guillaume Pareb,b,‡, Lehana Thabanea,b,‡, Zainab Samaana,b,‡

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‡Graduate Studies Program, Faculty of Health Sciences, McMaster University, 1280 Main St. W., Hamilton, ON L8S 4L8, Canada
§Health Research Methodology/Graduate Program, McMaster University, 1280 Main St. W., Hamilton, ON L8S 4L8, Canada
¶Department of Clinical Epidemiology and Biostatistics, McMaster University, 1280 Main St. W., Hamilton, ON L8S 4L8, Canada
*Ontario Addiction Treatment Centre, 1209 Yonge St., Suite 402, Toronto M4S 1M6, ON L8S 4L8, Canada
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| Northern Ontario School of Medicine, 935 Ramsey Lake Rd., Sudbury, ON P3E 2J6, Canada
| Department of Psychiatry and Behavioural Neurosciences, McMaster University, 1280 Main St. W., Hamilton, ON L8S 4L8, Canada
| Women’s Health Centre, St. Joseph’s Healthcare Hamilton, 50 Charter Avenue E., Hamilton, ON L8N 4G6, Canada
| Department of Obstetrics and Gynecology, McMaster University, 1280 Main St. W., Hamilton, ON L8S 4L8, Canada
| Biostatistics Unit, Centre for Evaluation of Medicine, St. Joseph’s Healthcare Hamilton, 50 Charter Avenue E., Hamilton, ON L8N 4G6, Canada

ARTICLE INFO

Article history:
Received 30 November 2014
Received in revised form 13 January 2015
Accepted 29 January 2015
Available online 8 February 2015

Keywords:
Testosterone
Sex hormones
Opiates
Prescription opioids
Methadone

ABSTRACT

Background: Whether used for pain management or recreation, opioids have a number of adverse effects including hormonal imbalance. These imbalances have been reported to primarily involve testosterone and affect both males and females to the point of interfering with successful treatment and recovery. We conducted a systematic review and meta-analysis to determine the extent that opioids affect testosterone levels in both men and women, which may be relevant to improved treatment outcomes for opioid dependence and for pain management.

Methods: We searched PubMed, EMBASE, PsycINFO, and CINAHL for relevant articles and included studies that examined testosterone levels in men and women while on opioids. Data collection was completed in duplicate.

Results: Seventeen studies with 2769 participants (800 opioid users and 1969 controls) fulfilled the review inclusion criteria; 13 studies were cross-sectional and seven were cohort studies. Results showed a significant difference in mean testosterone level in men with opioid use compared to controls (MD = −164.78, 95% CI: −245.47, −84.08; p < 0.0001). Methadone did not affect testosterone differently than other opioids. Testosterone levels in women were not affected by opioids. Generalizability of results was limited due to high heterogeneity among studies and overall low quality of evidence.

Conclusion: Our findings demonstrated that testosterone level is suppressed in men with regular opioid use regardless of opioid type. We found that opioids affect testosterone levels differently in men than women. This suggests that opioids, including methadone, may have different endocrine disruption mechanisms in men and women, which should be considered when treating opioid dependence.

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Suppression von Testosteron

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Opioid Users</th>
<th>Control</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Total</td>
</tr>
<tr>
<td>1.5.1 MMT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Azizi 1973</td>
<td>340</td>
<td>110</td>
<td>6</td>
</tr>
<tr>
<td>Bavor 2014</td>
<td>100.1</td>
<td>72.2</td>
<td>131</td>
</tr>
<tr>
<td>Blesener 2005</td>
<td>280</td>
<td>120</td>
<td>37</td>
</tr>
<tr>
<td>Cushman 1973</td>
<td>577</td>
<td>284</td>
<td>54</td>
</tr>
<tr>
<td>Mendelson 1975</td>
<td>406.1</td>
<td>181.9</td>
<td>14</td>
</tr>
<tr>
<td>Ragni 1988</td>
<td>520</td>
<td>190</td>
<td>42</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>284</td>
<td></td>
<td>35.5%</td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 19473.62; Chi² = 91.22, df = 5 (P < 0.00001); I² = 95%
Test for overall effect: Z = 2.98 (P = 0.003)

1.5.2 Non-MMT

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Opioid Users</th>
<th>Control</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Total</td>
</tr>
<tr>
<td>Abs 2000</td>
<td>198.9</td>
<td>149.9</td>
<td>29</td>
</tr>
<tr>
<td>Azizi 1973</td>
<td>440</td>
<td>320</td>
<td>16</td>
</tr>
<tr>
<td>Blick 2012</td>
<td>280</td>
<td>170</td>
<td>90</td>
</tr>
<tr>
<td>Blesener 2005</td>
<td>510</td>
<td>120</td>
<td>17</td>
</tr>
<tr>
<td>Cushman 1973</td>
<td>523</td>
<td>279</td>
<td>23</td>
</tr>
<tr>
<td>Daniell 2002</td>
<td>188.5</td>
<td>193.4</td>
<td>23</td>
</tr>
<tr>
<td>Finch 2000</td>
<td>141.2</td>
<td>105.1</td>
<td>11</td>
</tr>
<tr>
<td>Malik 1992</td>
<td>376.3</td>
<td>215.4</td>
<td>33</td>
</tr>
<tr>
<td>Mendelson 1975</td>
<td>227.5</td>
<td>116.6</td>
<td>12</td>
</tr>
<tr>
<td>Ragni 1988</td>
<td>550</td>
<td>120</td>
<td>15</td>
</tr>
<tr>
<td>Wang 1978</td>
<td>521.6</td>
<td>211.6</td>
<td>54</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>323</td>
<td></td>
<td>64.5%</td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 19507.34; Chi² = 118.62, df = 10 (P < 0.00001); I² = 92%
Test for overall effect: Z = 3.43 (P = 0.0006)

Total (95% CI)      | 607   | 1417 | 100.0% | -164.78 | -245.47, -84.08 |

Heterogeneity: Tau² = 25635.21; Chi² = 369.90, df = 16 (P < 0.00001); I² = 96%
Test for overall effect: Z = 4.00 (P < 0.00001)
Test for subgroup differences: Chi² = 0.12, df = 1 (P = 0.73), I² = 0%

Fig. 2. Effect of opioid use on testosterone level in men. Caption: forest plot representing the relationship between opioid use and testosterone in men using methadone for treatment compared to other opioids.

Bawor M et al.: Drug and Alcohol Dependence 149 (2015);1-9
Suppression von Testosteron

- Testosteronspiegel ist bei Männern in MMT signifikant reduziert
- Testosteronspiegel korreliert bei Männern reziprok mit der Methadon-Dosishöhe
- Effekt tritt bei allen Opioiden auf.
- Testosteronspiegel korrelierte positiv mit der Anzahl geraucher Zigaretten
- Empfehlung: Testosteronspiegel bei Männern vor und während OST bestimmen

Bawor M et al.: srep 2014;4:6189
Bawor M et al.: Drug and Alcohol Dependence 149 (2015);1-9
Plasma Testosterone and Sexual Function in Men Receiving Buprenorphine Maintenance for Opioid Dependence

Niclaas Bliesener, Susanne Albrecht, Andra Schwager, Klaus Weckbecker, Dirk Lichtermann, and Dietrich Klingmüller

Department of Clinical Biochemistry (N.B., A.S., D.K.), Division of Endocrinology; Department of Psychiatry (S.A., D.L.), and Café Ersatz Methadone Maintenance Clinic (S.A., D.L.), University of Bonn, 53105 Bonn, Germany; and General Practitioner (K.W.), Bad Honnef, Germany

High-dose methadone is well known to cause testosterone deficiency and sexual dysfunction in opioid-dependent men. Buprenorphine is a new drug for the pharmacotherapy of opioid dependence. Its influence on the gonadal axis has not been investigated to date. We therefore assayed testosterone, free testosterone, estradiol, SHBG, LH, FSH, and prolactin in 17 men treated with buprenorphine. Thirty-seven men treated with high-dose methadone and 51 healthy blood donors served as controls. Sexual function and depression were assessed using a self-rating sexual function questionnaire and the Beck Depression Inventory. Patients treated with buprenorphine had a significantly higher testosterone level [5.1 ± 1.2 ng/ml (17.7 ± 4.2 nmol/liter)] vs. 2.8 ± 1.2 ng/ml (9.7 ± 4.2 nmol/liter); P < 0.0001] and a significantly lower frequency of sexual dysfunction (P < 0.0001) compared with patients treated with methadone. The testosterone level of buprenorphine-treated patients did not differ from that of healthy controls. In conclusion, we demonstrated for the first time that buprenorphine, in contrast with high-dose methadone, seems not to suppress plasma testosterone in heroin-addicted men. To this effect, buprenorphine was less frequently related to sexual side effects. Buprenorphine might therefore be favored in the treatment of opioid dependence to prevent patients from the clinical consequences of methadone-induced hypogonadism. (J Clin Endocrinol Metab 90: 203–206, 2005)
Suppression von Testosteron

Buprenorphin: n = 17
d/l-Methadon: n = 37
Controll: n = 51

\[ \text{d/l-Methadon: } 88,4\text{mg } \pm 16\text{mg} \]
\[ \text{Buprenorphin: } 11,2\text{mg } \pm 4,3\text{mg} \]

Bliesener et al. *Gonadal Function in Men Receiving Buprenorphine*
Suppression von Testosteron

Clinical factors associated with sexual dysfunction among men in methadone maintenance treatment and buprenorphine maintenance treatment: a meta-analysis study

A Yee¹, HS Loh², HMB Hisham Hashim¹ and CG Ng¹

Eingeschlossen: 2.619 P. aus 16 Studien (ab Dez. 2012)

• Prävalenz von sexueller Dysfunktion unter Methadon höher als unter Buprenorphin.
  → Aber: keine randomisierten Studien!

• Post hoc Analyse einer randomisierten Studie (Lofwall et al 2005) fand keine Unterschiede zwischen METH und BUP.

Datenlage zu „schwach“ für eine generelle Empfehlung von METH auf BUP umzustellen.
Klinik von Testosteronmangel bei Männern

- Müdigkeit
- Kraftlosigkeit
- Stimmungsschwankungen
- Libidoverlust
- Sexuelle Dysfunktion, insbes. Erektile Dysfunktion
- Hypogonadismus

Borjesson G et al. (2011) Eur J Pain (Suppl) 5;178
The Prevalence of Sexual Dysfunction among Male Patients on Methadone and Buprenorphine Treatments: A Meta-Analysis Study

Anne Yee, MPM,* Huai Seng Loh, FRACGP,† Helenna Maria bt Hisham Hashim, BSc Psychology (Hons),* and Chong Guan Ng, PhD*

*Department of Psychological Medicine, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia; †Clinical Academic Unit (Family Medicine), Newcastle University of Medicine, Johor, Malaysia

DOI: 10.1111/jsm.12352
Sexuelle Dysfunktion - Prävalenz

• Ergebnisse sind kaum zu vergleichen: wenig valide Prävalenz-Daten, methodische Unterschiede in der Datenerfassung, Unterschiede in der Definition von SD.
• Prävalenz und Häufigkeit sexueller Dysfunktion unter Methadon höher als unter Buprenorphin.
• Die Umstellung von METH auf BUP bei SD unter METH ist eine therapeutische Option.

MMT und sexuelle Dysfunktion

40 Männer in MMT (min. 12 Monate, davor min. 3J. Heroin
40 Männer in Kontrollgruppe

MMT und sexuelle Dysfunktion

• Signifikant höhere Rate an sexueller Dysfunktion (SD), reduziertem Testosteron- und erhöhtem Prolaktin – Plasmaspiegel.

• Die sexuelle Dysfunktion - mit Ausnahme der erektilen Dysfunktion - und die Hormonwerte korrelieren nicht mit der individuellen Methadon-Dosis aber mit dem Auftreten von
  – traumatischen/vernachlässigenden Kindheitserfahrungen
  – psychiatrischen Begleiterkrankungen

• Kausalzusammenhänge sind nicht ableitbar

Sexuelle Dysfunktion bei OST  ...weitere Ursachen

• Frühe stressvermittelnde Umstände (Gerra et al.)
  – Traumatische/vernachlässigte Kindheit
  – Psychiatrische Begleiterkrankungen
  ➔ psychotherapeutisch-/psychosozialer statt primär pharmakologischer Ansatz

• Begleitmedikation mit Psychopharmaka und/oder Antihypertensiva, etc

• Nikotinabusus

Feldman HA (1994) J Urol;
Verminderung von GnRH

→ bei Männern: Hypogonadismus, Testosteronmangel, sexuelle Dysfunktionen, Infertilität, Müdigkeit,

→ Testosteronmangel möglicherweise mit erhöhtem Risiko von Insulinresistenz und metabolischem Syndrom assoziiert.
Hauptprädiktoren neben vermindertem Testosteron:
  - Übergewicht
  - zunehmendes Alter

→ Osteoporose, Amenorrhoe, Oligomenorrhoe, Galaktorrhoe

• Veränderungen sind reversibel (z.B. Dosisreduktion, Antagonisten)
• Keine generelle Indikation für Testosteron-Substitution

Rajagopal A et al. Cancer 2004;100(4):851-858
Methadone Maintenance Treatment and Cognitive Function: A Systematic Review

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Abstract: Methadone has been used as a pharmacotherapy for the treatment of opiate dependence since the mid-1960s. Many studies examining the benefits of methadone maintenance treatment (MMT) for opiate dependence have documented a significant reduction in both criminal behavior and the use of other opiates. Nevertheless, emerging evidence suggests that MMT may impair cognitive function. However, it is unclear as to the part methadone dose, duration of MMT or plasma level may play in any observed deficits. Given the large number of people enrolled in MMT world-wide and the potential for deficits in cognitive function, a systematic review of the research investigating the association between MMT and cognitive function seemed warranted. The following databases were searched with a combination of free-text and thesaurus terms (methadone AND cognition): MEDLINE In-Process, EMBASE, PsycINFO and EBM Reviews-Cochrane Central Register of Controlled Trials. Seventy-eight articles were retrieved of which 35 met the inclusion criteria. The majority of research suggests that MMT is associated with impaired cognitive function and that deficits extended across a range of domains. However, caution is required when interpreting these results due to the methodological limitations associated with many studies. Further research that includes a combination of psychological and physiological measures within well-controlled group comparison studies is required to more accurately assess which cognitive domains are affected.

Keywords: Methadone maintenance, opiate dependence, cognition, neuropsychological test, systematic review.
MMT und kognitive Funktionen

• Die Mehrzahl der Studien legt nahe, dass MMT mit einer Verschlechterung kognitiver Funktionen assoziiert ist insb. Aufmerksamkeit, Gedächtnis, Wortfindung, Entscheidungsfindung, emotionale Interpretation
• Verschlechterungen waren assoziiert mit höherer Dosis (> 60mg/Tag) und längerer Drogenkonsum - Anamnese
• Einige Studien zeigten auch verbesserte kognitive Funktionen unter MMT

Fazit:
• Methodologische Unterschiede und kleine Sample-Größen lassen keinen eindeutigen Schluss zu, ob MMT zu einer Verschlechterung kognitiver Funktionen führt oder nicht

Wang G et al. Current Drug Abuse Reviews 2013, 6(2)
Decreased bone density in men on methadone maintenance therapy

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ABSTRACT

Aims Opioid use may impact adversely upon skeletal health. Participants in methadone maintenance programmes commonly have prolonged exposure to opioids. We sought to determine whether participants in a methadone maintenance programme have evidence of altered bone mineral density (BMD) and bone turnover. Design Cross-sectional study of people taking methadone maintenance therapy (MMT). Setting Clinical research centre. Participants Eighty-three people (48 men, 35 women) who had taken MMT for a median (interquartile range) of 11 (6–16) years. Comparison data were from both a normative database and control subjects recruited and assessed at the same location as the participants taking MMT. Measurements BMD at lumbar spine, total hip and total body; biochemical markers of bone turnover. Findings In men taking MMT, BMD was lower than normal at each skeletal site [mean, 95% confidence interval Z-score −1.1 (−1.6 to −0.7) at the lumbar spine, −1.0 (−1.3 to −0.7) at the total hip, and −1.1 (−1.4 to −0.8) at the total body; P < 0.001 at each site]. BMD in the women taking MMT was not different from control values. Bone turnover was within the normal range in both genders. Serum testosterone was lower in the men taking MMT than in controls. Conclusions BMD is lower than normal throughout the skeleton in men, but not women, taking MMT. Assessment of skeletal health, including estimation of absolute fracture risk, should be undertaken in men participating in methadone maintenance programmes.

MMT und Knochendichte

Männliche Kontrollgruppe: n=40

Table 1 Demographic data in study subjects.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>48</td>
<td>35</td>
</tr>
<tr>
<td>Age (years)</td>
<td>47 ± 6</td>
<td>45 ± 7</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>80 ± 19</td>
<td>71 ± 15</td>
</tr>
<tr>
<td>Methadone dose (mg/day)</td>
<td>90 (70–120)</td>
<td>80 (60–105)</td>
</tr>
<tr>
<td>Duration of methadone therapy (years)</td>
<td>12 (6–16)</td>
<td>11 (7–17)</td>
</tr>
<tr>
<td>Duration of opioid exposure in years</td>
<td>23 (16–33)</td>
<td>28 (24–34)</td>
</tr>
<tr>
<td>Current smoking n (%)</td>
<td>39 (81)</td>
<td>31 (89)</td>
</tr>
<tr>
<td>Current alcohol n (%)</td>
<td>20 (42)</td>
<td>17 (49)</td>
</tr>
<tr>
<td>&gt;2 drinks/day n (%)</td>
<td>6 (13)</td>
<td>3 (35)</td>
</tr>
<tr>
<td>Fractures n (%)</td>
<td>5 (10)</td>
<td>3 (9)</td>
</tr>
<tr>
<td>Calcium intake (mg/day)</td>
<td>1018 ± 681</td>
<td>938 ± 430</td>
</tr>
<tr>
<td>Exercise (METS/day)</td>
<td>31 ± 6.7</td>
<td>31 ± 8.7</td>
</tr>
<tr>
<td>Comorbidities n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>5 (10)</td>
<td>5 (14)</td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>33 (67)</td>
<td>17 (49)</td>
</tr>
<tr>
<td>HIV</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Data are mean ± standard deviation, median (interquartile range) or n (%)..

• Knochendichte bei Männern vermindert, bei Frauen nicht. (Ursache unklar!)
• 2-fach erhöhtes Frakturrisiko (RR)
• Männer hatten niedrigere Testosteronspiegel
• Unklar, ob Knochendichteverlust während des i.v.-Opioidkonsums vor der MMT oder während der MMT erfolgte

Fazit:
Männer in MMT scheinen ein höheres Risiko für Osteoporose zu haben

Entwicklung von Opioid-Toleranz

Opioid tolerance in methadone maintenance treatment: comparison of methadone and levomethadone in long-term treatment

Stefan Gutwinski*, Nikola Schoofs, Heiner Stuke, Thomas G. Riemer, Corinde E. Wiers and Felix Bermpohl

Abstract

Background: This study aimed to investigate the development of opioid tolerance in patients receiving long-term methadone maintenance treatment (MMT).

Methods: A region-wide cross-sectional study was performed focusing on dosage and duration of treatment. Differences between racemic methadone and levomethadone were examined. All 20 psychiatric hospitals and all 110 outpatient clinics in Berlin licensed to offer MMT were approached in order to reach patients under MMT fulfilling the DSM IV criteria of opiate dependence. In the study, 720 patients treated with racemic methadone or levomethadone gave information on the dosage of treatment. Out of these, 679 patients indicated the duration of MMT.

Results: Treatment with racemic methadone was reported for 370 patients (54.5 %), with levomethadone for 309 patients (45.5 %). Mean duration of MMT was 7.5 years. We found a significant correlation between dosage and duration of treatment, both in a conjoint analysis for the two substances racemic methadone and levomethadone and for each substance separately. These effects remained significant when only patients receiving MMT for 1 year or longer were considered, indicating proceeding tolerance development in long-term treatment. When correlations were compared between racemic methadone and levomethadone, no significant difference was found.

Conclusions: Our data show a tolerance development under long-term treatment with both racemic methadone and levomethadone. Tolerance development did not differ significantly between the two substances.

Keywords: Opioid, Tolerance, Long-term, Maintenance treatment
### Entwicklung von Opioid-Toleranz

#### Table 1: Clinical data

<table>
<thead>
<tr>
<th>Clinical data</th>
<th>Substance</th>
<th>Methadone (N = 370)</th>
<th>Levomethadone (N = 309)</th>
<th>Statistic</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>18-20</td>
<td></td>
<td>6 (1.6)</td>
<td>1 (0.3)</td>
<td>0.474; X = 0.54</td>
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<tr>
<td>21-30</td>
<td></td>
<td>84 (22.7)</td>
<td>65 (21.0)</td>
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<tr>
<td>31-40</td>
<td></td>
<td>102 (27.6)</td>
<td>87 (28.2)</td>
<td></td>
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<tr>
<td>41-50</td>
<td></td>
<td>135 (36.5)</td>
<td>117 (37.9)</td>
<td></td>
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</tr>
<tr>
<td>51-60</td>
<td></td>
<td>35 (9.5)</td>
<td>37 (12.0)</td>
<td></td>
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</tr>
<tr>
<td>61-70</td>
<td></td>
<td>8 (2.2)</td>
<td>2 (0.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td>275 (75.3)</td>
<td>203 (65.7)</td>
<td>0.006; X = 7.5</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td>90 (24.7)</td>
<td>106 (34.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Years of education mean ± SD</strong></td>
<td></td>
<td>10.3 ± 1.7</td>
<td>10.4 ± 1.4</td>
<td>0.751; T = −0.32</td>
<td></td>
</tr>
<tr>
<td><strong>Years of methadone maintenance treatment mean ± SD</strong></td>
<td></td>
<td>6.8 ± 5.6</td>
<td>8.3 ± 6.2</td>
<td>0.002; T = −3.2</td>
<td></td>
</tr>
<tr>
<td><strong>Years of dependency</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>≤1</td>
<td></td>
<td>1 (0.3)</td>
<td>3 (1.1)</td>
<td>1.0; X = 0.007</td>
<td></td>
</tr>
<tr>
<td>2–3</td>
<td></td>
<td>9 (2.7)</td>
<td>9 (3.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3–5</td>
<td></td>
<td>25 (7.6)</td>
<td>15 (5.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5–10</td>
<td></td>
<td>68 (18.6)</td>
<td>39 (13.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥10</td>
<td></td>
<td>227 (62.8)</td>
<td>216 (76.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Continued use of illegal drugs despite MMT</strong></td>
<td></td>
<td>225 (63.8)</td>
<td>205 (67.9)</td>
<td>0.286; X = 1.2</td>
<td></td>
</tr>
<tr>
<td><strong>Continued use of multiple illegal drug despite MMT</strong></td>
<td></td>
<td>82 (23.6)</td>
<td>81 (26.7)</td>
<td>0.275; X = 1.3</td>
<td></td>
</tr>
<tr>
<td><strong>Methadone dose/methadone equivalent (mg/d) mean ± SD</strong></td>
<td></td>
<td>90.0 ± 41.3</td>
<td>99.1 ± 46.9</td>
<td>0.007; T = −2.7</td>
<td></td>
</tr>
<tr>
<td><strong>Inpatientment in the past</strong></td>
<td></td>
<td>212 (60.7)</td>
<td>170 (58.1)</td>
<td>0.660; X = 1.9</td>
<td></td>
</tr>
<tr>
<td><strong>Withdrawal treatment in the past</strong></td>
<td></td>
<td>172 (50.0)</td>
<td>159 (51.5)</td>
<td>0.372; X = 0.8</td>
<td></td>
</tr>
<tr>
<td><strong>Comorbid psychiatric disorder</strong></td>
<td></td>
<td>90 (26.4)</td>
<td>99 (33.3)</td>
<td>0.06; X = 3.7</td>
<td></td>
</tr>
<tr>
<td><strong>Chronic infection</strong></td>
<td></td>
<td>180 (52.2)</td>
<td>144 (48.2)</td>
<td>0.31; X = 1.0</td>
<td></td>
</tr>
<tr>
<td><strong>HV</strong></td>
<td></td>
<td>18 (5.2)</td>
<td>25 (8.3)</td>
<td>0.117; X = 2.5</td>
<td></td>
</tr>
<tr>
<td><strong>Hepatitis C</strong></td>
<td></td>
<td>163 (47.2)</td>
<td>124 (41.5)</td>
<td>0.141; X = 2.1</td>
<td></td>
</tr>
<tr>
<td><strong>Hepatitis B</strong></td>
<td></td>
<td>25 (7.2)</td>
<td>27 (9.0)</td>
<td>0.407; X = 0.66</td>
<td></td>
</tr>
<tr>
<td><strong>Lues</strong></td>
<td></td>
<td>1 (0.3)</td>
<td>2 (0.7)</td>
<td>0.483; X = 0.05</td>
<td></td>
</tr>
</tbody>
</table>

*Data shown as N (%) if not otherwise specified. Out of the 679 patients who specified type of substance, dosage, and duration of MMT, some patients did not give information concerning further data. 5 concerning gender, 67 concerning duration of dependence, 31 concerning detoxification therapies, 23 concerning continued use of illegal drugs, 42 concerning continued use of multiple illegal drugs, and 32 concerning imprisonment.

*aDosage of levomethadone was calculated into equivalent methadone dosage.

*bChi-square for group ≤5 versus >5 years of dependency.

*cMultiple answers were possible. Comorbid psychiatric disorders reported N > 5: depression N = 108; psychotic disorder and schizophrenia N = 13; anxiety disorders N = 30; personality disorder N = 36; and ADHD N = 10.*
Entwicklung von Opioid-Toleranz

> 1a OST (n=51): 81,6 mg
< 20a OST (n=26) 125,4mg

• Signifikante Korrelation mit
  – Dauer der Behandlung
  – Höhe der Tagesdosis

• Tagesdosis über 20 Jahre um das 1,5fache erhöht
Take Home Messages

Klinisch positive Effekte:
- deutliche und anhaltende Reduktion der Mortalität, Rückfallhäufigkeit und Prävalenz von „blood borne“-Infektionen

Klinisch negative Effekte:
- verminderte Testosteron-Plasmaspiegel (vor und während OST bestimmen)
- höhere Prävalenz Sexueller Dysfunktionen (außer ED keine Korr. mit Dosishöhe)
- erhöhtes Risiko für Diabetes Mellitus Typ II und metabolischem Syndrom
- verminderte Knochendichte, höheres Osteoporose-Risiko (Testosteron, Ernährung, Vitamin D)
- kein eindeutiger Hinweis darauf, dass OST kognitive Funktionen beeinträchtigt
- evtl. Entwicklung einer Opioid-Toleranz (abhängig von Dauer und Dosishöhe)

Fazit:
Langzeit-Opiodsubstitution hat neg. klinische Effekte, die zu beachten sind. Die positiven Effekte überwiegen aber bei weitem.