Electronic Compliance Monitoring in Opioid Substitution Treatment with Buprenorphine/Naloxone: Can abuse be reduced?

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Conflict of interest: none

Europe

Serbia and Montenegro have asserted the formation of a joint independent state, but this entity has not been formally recognized as a state by the United States.
Macedonia has proclaimed independent statehood but has not been formally recognized as a state by the United States.
Greenland (DENMARK)
Jan Mayen (NORWAY)
Greenland Sea
Norwegian Sea
Barents Sea
Hammerfest
Murmansk
White Sea
Arkhangel'sk
Arctic Circle
Reykjavík
ICELAND
NORWAY
Kiruna
Oulu
Umeå
Gulf of Bothnia
FINLAND
Lake Onega
Lake Ladoga
Trondheim
SWEDEN
Tampere
Tórshavn
Faroe Islands (DENMARK)
Helsinki
Gulf of Finland
St. Petersburg
Shetland Islands
Gävle
Bergen
Oslo
Stockholm
Aland Islands
Tallinn
ESTONIA
Rockall (U.K.)
Orkney Islands
RUSSIA
Hebrides
Skagerrak
Göteborg
Gotland
Rīga
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Aberdeen
North Atlantic Ocean
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Baltic Sea
Edinburgh
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Öland
LITHUANIA
Smolensk
Belfast
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Copenhagen
Bornholm
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Minsk
Newcastle
Isle of Man (U.K.)
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Irish Sea
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Hamburg
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Corfu
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Balearic Islands
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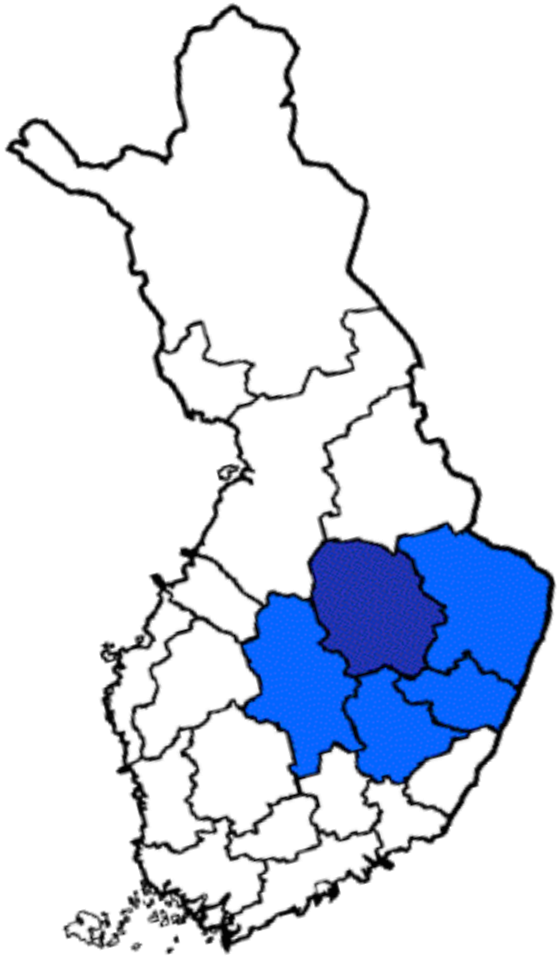
802176 (R01083) 9-93

The Kuopio University Hospital District



Some facts about the Finnish situation concerning abuse of buprenorphine (National Report 45/2009, EMCDDA)

- **Buprenorphine is the most frequently drug abused i.v.**
- **At entering treatment 34% of patients mentioned buprenorphine as their ”primary problem substance”**
- **Until 2004 many opioid addicted individuals went to Estonia for Subutex® but are now seeking treatment in Finland**
- **Generally buprenorphine/naloxone (Suboxone®) is used in substitution treatment for opioid-addiction**
- **In 2005-2007 buprenorphine was ”most significant finding” in 1/3 of autopsies after death from poisoning**
- **<u>New law (2008)</u>: more patients treated in primary care; possibility of Rx of Suboxone®**

Problems of opioid substitution treatment with buprenorphine/naloxone

- **In Finland buprenorphine is abused iv, in spite of the formulation with naloxone, causing**
  - **some euphoria when injected (in less experienced users)**
  - **diversion from substitution treatment with effect on**
    - **patient's own rehabilitation (↓)**
    - **availability of street-buprenorphine (↑)**
    - **reputation of treatment-services (↓)**
  - **complications from injection of crushed tablets**
  - **buprenorphine-intoxications**

Types of administration and monitoring in opioid substitution treatment

- **<u>Supervised administration</u>**
  - near optimal compliance and safety, **BUT**
  - high workload for staff, high costs
  - possible interference with patient´s daily life
- **<u>Unsupervised administration</u>**
  - patient-friendlier
  - cheaper, allowing more patients to be treated, **BUT**
  - **higher risk of diversion, abuse, overdose**
  - **need for clinical monitoring (reviews, random urine drug screens etc.)**
- **<u>Unsupervised with compliance-monitoring</u>**
  - clinical feasibility ?
  - cost-savings?

Commercially available compliance-monitoring devices, used in our studies

- **PharmaDDSi®:** Stora Enso Ltd (Finland/Sweden)
  - microchips and printed electronics by Cypak AB (Sweden)
  - **registration (time and location)** when tablet pushed from original blister
  - **patient feed-back** (e.g. intensity of abstinence sympt.)
  - child-proof locking device
  - possibility for monitoring in real-time (Medixine Ltd)
- **Med-O-Wheel Smart®**: Addoz Oy (Finland)
  - electronic dispensing system with **reminder** and **time-lock (3h)**
  - possibility for **monitoring in real-time** (not used in our study)

Study A (= PharmaDDSi®-pilot): Patients and their substitution treatment

- **Patients in subst. treatment with bupr./naloxone**
  - **N=12 (9 women, 3 men)**
- **Allowances/week (pre-trial)**
  - **0-6 (4,17±2,08)**
- **Number of additional psychiatric diagn. (ICD-10)**
  - **0-3 (1,5±0,91)**
- **Suboxone®-dose (mg)**
  - **5-30 (19.58±7.35)**
- **Number of tablets/day**
  - **1-6**

Protocol of study A after modification of the commercial PharmaDDSi® for substitution treatment

Week 1:

- Informed consent, instructions, demonstration (e.g. feedback –button, reading-device on nurse's desk)
- supervised medication
- receipt of PharmaDDSI® package with 6 daily doses

Weeks 2,3,4 (as week 1), additionally:

- **patient returns package to clinic; compliance-data displayed on computer-screen**
- **integration of information into therapeutic interview**

Week 5 (after which normal routine treatment):

- return of last package
- 12-item questionnaire

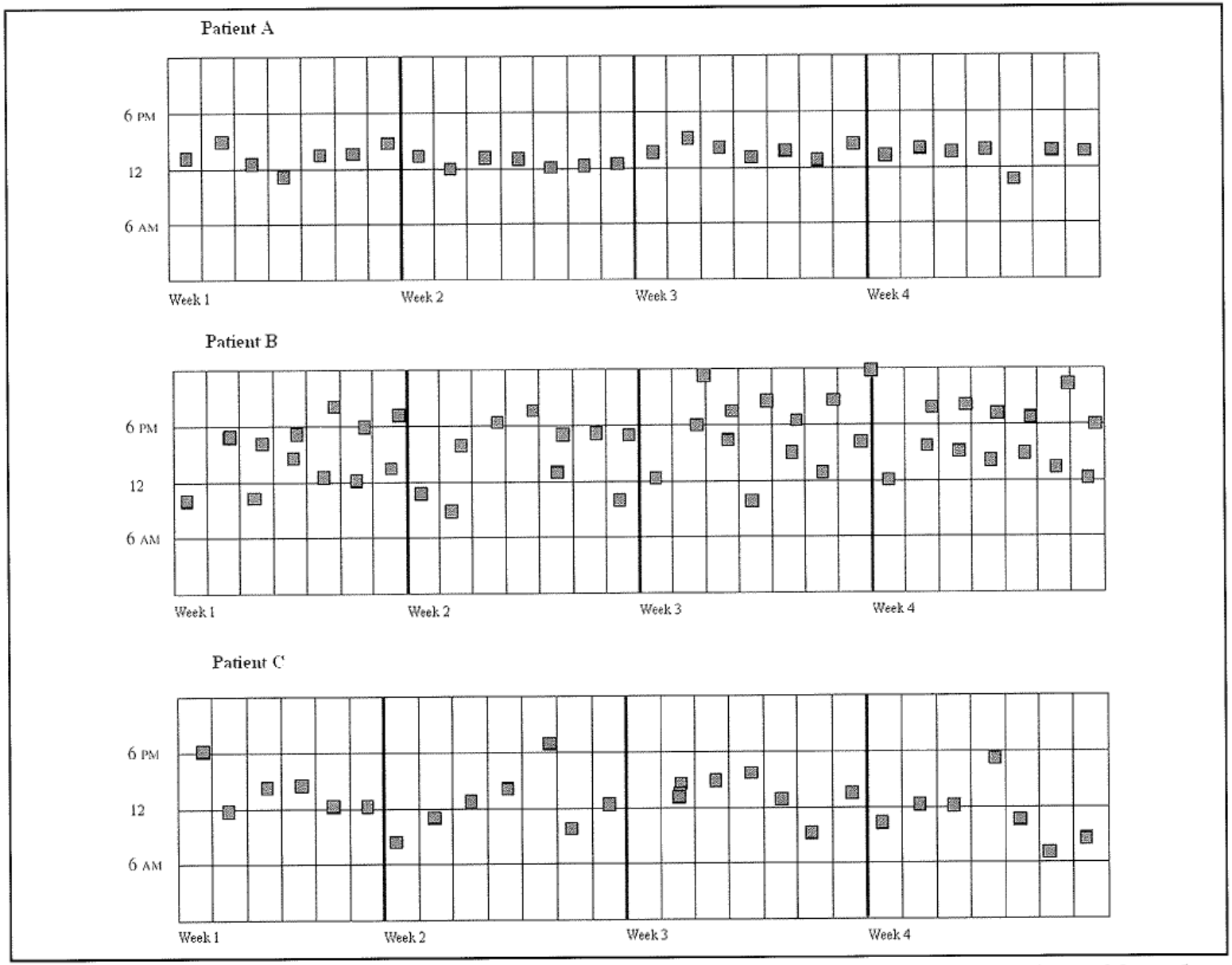


Figure 2. Computer-generated diagrams (slightly modified) of time cues for tablet removal during the trial from three different patients. Patient A showed optimal compliance with little variations in time, patient B was found to take split doses at irregular times. During week 3, patient C skipped his medication once, but doubled his dose the following day. Also, dose-splitting occurred, but some of these irregularities cannot be seen, due to the scale of the diagram.

Responses to questionnaire (4 questions shown, total of 11 questionnaires returned)

- **How has compliance -monitoring influenced your substitution treatment?**

  neg: 1 no effect: 5 pos: 5

- **Has the package stopped you from diverting your medication? (frequent answer: ”I never do that”)**

  no: 8 yes: 3

- **Is the package too big?**

  no: 4 yes: 7

- **Is the package difficult to use ? (one answer missing)**

  no: 9 yes: 1

General results

- **Small between-day variability: mean interval 23.6 ± 1.2 h**

- **All patients with max. number (6) of allowances before entering the study showed optimal compliance**
  - **Optimal compliance: 8 patients**
  - **Minor irregularities: 2 patients**
  - **Major compliance-violations: 2 patients**

- **All patients with less than optimal compliance had psychiatric comorbidity**

- **Possibly substantial cost-savings (39%), if all patients seen only x1/week (e.g. 1 PharmaDDSi®=49,4£/week)**

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CONTENTS

Daily compliance monitoring in real-time
(StoraEnso Ltd and Medixine Ltd)

Patient

Tablets from PharmaDDSi package

Reading package with NFC-phone or SMS-lreader

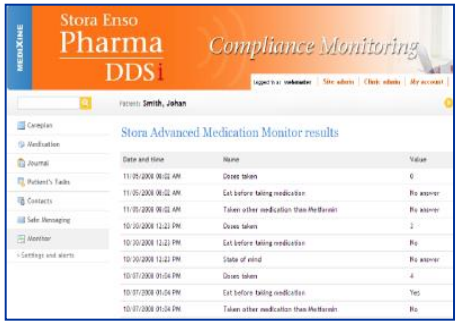
SMS-reminder

Server

Nurse

SMS- message in case info of drug-taking not received

Nurse can check compliance on computer



Used in 2 patients, so far (Study B)

Study C (in progress): Med-O-Wheel Smart® (Addoz Ltd.)

- **Hypothesis: Abuse and diversion of bupenorphine can be reduced in Kuopio (93.000 inh.) by dispensing Suboxone® and Subutex® in a compliance-monitoring device**
- **Possible change will be documented by:**
  - **TOP interview at treatment centres; other questionnaire at needle-exchange services**
  - **Results from police-interviews of drug offenders**
  - **Urine drug-screens at treatment services, hospital emergency departments and critical care units**
  - **Local incidence of fatal and non-fatal poisinings with buprenorphine**
- **All 42 buprenorphine-patients in Kuopio are using Med-O-Wheel Smart®, 36 of them are followed according to protocol (informed consent)**

Speculative mechanisms by which electronic compliance-monitoring could influence behaviour

- Patient's awareness, that violations (e.g. odd time-points, higher than normal doses) will be detected
- Reduction of impulsive medication-related behaviour
- → high-risk situation for non-compliance may pass,
- → diversion and/or abuse of medication may be prevented

Differences between the 2 devices and remaining questions

- **PharmaDDSi® registers the exact time, but drug is always accessible**
- **Med-O-Wheel Smart operates with a time-lock (21 h), outside the 3 h/day window tablets are not available (advantage of a smaller window?)**
- **Both devices can document, that the drug was taken out**
- **Monitoring in real-time may help to detect compliance-violation ”in the making” (?). Remaining questions: e.g.:**
  - **HOW WAS THE MEDICATION USED (p.o. or i.v.) ?**
  - **BY WHOM ?**
  - **CAN METHADONE BE MONITORED IN A SIMILAR WAY?**
    - **Liquid preparations represent a special challenge**