Diversion, misuse and trafficking of methadone and buprenorphine: Impact on recovery

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CRI: Driving Innovation and Delivering Excellence, 09.06.2014, London
Disclosure of interests, 2010-14

• Research Funding
  – Public funding, Finnish Academy, no funding from Pharmaceutical industry

• Other positions aiming to guide health care
  – International Society of Addiction Medicine, president
  – WHO, consultant for Guidelines for the Psychosocially Assisted Pharmacological Treatment of Opioid Dependence

• Advisory board member: H Lundbeck AB, Reckitt Benckiser, Mundipharma, Actavis

• Other commitments
  – Paid expert lectures by Lundbeck AS, MSD and Reckitt Benckiser Pharmaceutical
Definitions

MISUSE (at least 7 listed definitions\(^1\))

• **Use of a medication (for a medical purpose) other than as directed or as indicated, whether willful or unintentional, and whether harm results or not\(^2\)**
  
  – Misuse can be willful or unintentional use of substance in a manner not consistent with legal or medical guidelines
  
  • Such as altering dosing which potentially has harmful consequences

ABUSE (at least 10 listed definitions\(^1\))

• **Misuse with consequences**
  
  – **The use of substance to modify or alter mood in a manner that is illegal or harmful to oneself or others\(^2\)**
  
  • Potentially harmful consequences could include accidents, injuries, blackouts, legal problems, sexual behavior that increases the risk of HIV or HPC

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Diversion

At least 3 different definitions

1. The intentional transfer of a controlled substance from legitimate distribution and dispensing into illegal channels or obtaining a controlled substance by an illegal method
2. The unlawful channeling of regulated pharmaceuticals from legal sources to the illicit marketplace
3. The intentional removal of a medication from legitimate distribution and dispensing channels

What is an outcome?

- “…a predicted measure of change that demonstrates a valid and significant therapeutic impact following an intervention.”
Desired outcomes across the treatment continuum

Harm reduction
• Emphasis on reducing harms associated with drug use (crime, disease transmission, morbidity and mortality)

Medically-assisted supportive treatment
• Emphasis on reducing drug-related harms, stabilising patients’ physical and mental health, and retention in treatment

Recovery
• Emphasis on improving each individual’s well-being, building ‘recovery capital’, and reintegrating into society
• An individual journey, not a single endpoint for all

Effect of diversion to the outcomes
Misuse, abuse and diversion are forms of non-compliance

- Misuse, abuse and diversion can be considered forms of non-compliance (sign of suboptimal treatment)
  - Misuse, ie non-compliance, is not taking an opioid medication as directed by the patient it was prescribed to\(^1\)
  - Abuse, non-compliance too, is taking an opioid medication to alter the mood\(^1\)
  - Diversion refers to the supply of opioid medication from a legal source (eg, prescriber and patient) to the illicit drug market or to a user for whom the prescription was not intended\(^1\)

- As with the chronic relapsing condition of opioid dependence,\(^2\) medication non-compliance occurs with many chronic conditions such as diabetes\(^3\)
  - Non-compliance has been shown to affect treatment outcomes\(^3,4\) and increases mortality risk,\(^5\) therefore affecting the likelihood of recovery

2. WHO. 2009.
4. NICE. Clinical Guideline 76. 2009.
MISUSE AND ABUSE ARE COMMON BUT ARE WE ACHIEVING DESIRED REDUCTIONS IN ILLICIT DRUG USE?
On-top use of heroin among the countries surveyed


The European Quality Audit of Opioid Treatment (EQUATOR) project

The threat of relapse is a hallmark of opioid dependence as a chronic relapsing disorder, but country differences suggest that improvements are possible.
Can the formulation of maintenance medication effect on diversion?

• Yes, but often at the expense of treatment costs
  Mono-buprenorphine
  Buprenorphine/naloxone
  Buprenorphine/naloxone film*

But not at the expenses of outcomes and overdoses

* Please note: Buprenorphine/naloxone film is NOT licensed in Europe
Street prices of buprenorphine and buprenorphine/naloxone 8 mg tablets and mean daily mg IV dosage

Inflation under the same time period $+€ \, 2,75$

Simojoki and Alho, J Alcoholism Drug Depend 2013, 1:2
A recognition on abuse of methadone: changing and evolving formulations

1968
• Introduction of prescribed injectable methadone

1970s
• Shift to prescription of oral methadone

1996
• Almost 10% of methadone prescriptions were for injectable formulations

1999
• New guidelines issued recommending non-injectable forms or oral medication, i.e. liquid, and to move away from tablet forms that are likely to be crushed and injected

2000
• Advisory Council on Misuse of Drugs advised ‘absolutely against the prescription of methadone tablets’

Present
• Methadone tablets are not currently licensed to treat opioid dependence

Future
• Crush resistant methadone/naloxone tablets

ARE WE GETTING THE RIGHT BALANCE BETWEEN TREATMENT ACCESS AND TREATMENT CONTROL MEASURES?
Many patients have diverted their OMT in the past

Patients reporting they have ever sold, given away or swapped their OMT

<table>
<thead>
<tr>
<th>Country</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Portugal</td>
<td>16%</td>
</tr>
<tr>
<td>Greece</td>
<td>16%</td>
</tr>
<tr>
<td>Germany</td>
<td>23%</td>
</tr>
<tr>
<td>Sweden</td>
<td>24%</td>
</tr>
<tr>
<td>Norway</td>
<td>26%</td>
</tr>
<tr>
<td>Italy</td>
<td>26%</td>
</tr>
<tr>
<td>Austria</td>
<td>28%</td>
</tr>
<tr>
<td>UK</td>
<td>30%</td>
</tr>
<tr>
<td>Denmark</td>
<td>38%</td>
</tr>
<tr>
<td>France</td>
<td>39%</td>
</tr>
</tbody>
</table>

Proportion of patients having every dose supervised

<table>
<thead>
<tr>
<th>Proportion</th>
</tr>
</thead>
<tbody>
<tr>
<td>21%</td>
</tr>
<tr>
<td>78%</td>
</tr>
<tr>
<td>40%</td>
</tr>
<tr>
<td>30%</td>
</tr>
<tr>
<td>46%</td>
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<tr>
<td>28%</td>
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<tr>
<td>20%</td>
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<tr>
<td>40%</td>
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<tr>
<td>15%</td>
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<tr>
<td>26%</td>
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</tbody>
</table>

Across countries, 16–39% of OMT patients have diverted their OMT medication. Between-country difference: \( p < 0.01 \)


The European Quality Audit of Opioid Treatment (EQUATOR) project
IS MEDICATION MISUSE AND DIVERSION A BARRIER TO RECOVERY?
Misuse and diversion of medication can result in mortality through unintended overdose.

Diversion is found in the majority of prisons, resulting in a variety of problems including drug debts and bullying.

Misuse and diversion of medication puts patients at risk of blood-borne viruses through the practice of injection drug use.

Diversion of medication has consequences for public health – not only the individual.

Consequences of diversion: a barrier to recovery?

Defining a new approach to measuring outcomes in opioid dependence management: an expert survey in EU, and expert panel in EU
Measuring outcomes: Executive summary

Background
Measuring outcomes of opioid dependence management can lead to better understanding of the important decisions over patient care in this area. There is no adequate tool to measure outcomes across different systems of opioid dependence management.

Aim
To define a universal system for measuring treatment outcomes in opioid dependence management at the system level, with expert consensus on the essential metrics.

Methods
Online consensus survey was used to test expert (n = 122) opinion. 65 experts replied and results were polled on their opinion of the specifics within 4 areas of measurement.

Results
The components of all 4 proposed measurement areas were validated.

Conclusion
There was strong consensus that the components suggested are valid. The proposed universal system should be developed further.
Of the 122 experts invited to take part in the Consensus process, 47 answered both phases of the opinion survey (unpublished).

**Four proposed measurement domains**

<table>
<thead>
<tr>
<th>Domain</th>
<th>Proportion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>91.0</td>
</tr>
<tr>
<td>Individual patient response</td>
<td>86.0</td>
</tr>
<tr>
<td>Engagement with society</td>
<td>85.0</td>
</tr>
<tr>
<td>Harm reduction</td>
<td>93.0</td>
</tr>
</tbody>
</table>

**Figure 1.** Overall expert consensus for each outcome measure proposed in the Delphi survey: percentage of experts who "strongly agreed" or "agreed" that the suggested measurement domains are the right measurements for assessing treatment outcomes in opioid dependence management.
The consensus

47 experts completed the survey, ranking metrics across 4 different areas of measurement

Top 5 metrics experts agree on:

- Improvement in quality of life: 100%
- Reduction in deaths: 98%
- Reduction in criminal activity: 98%
- Abstinence of compulsive use of on top opioids: 94%
- Potential to work at appropriate skill level: 93%

There is strong overall consensus that developing a universal system for measuring treatment outcomes would be a useful advance in opioid dependence management and that the proposed universal system is an important framework for measuring above patient level outcomes.
• Can outcomes monitoring of opioid maintenance treatment be improved in Europe? A statement by some European experts with interests in opioid maintenance treatment and its safety
  
  • HEROIN ADDICTION AND RELATED CLINICAL PROBLEMS, Vol. 15 • N. 1 • March 2013 (pages: 63 - 64), Alho H., Auriacomb M., Fischer G., Maremmani I., Scherbaum N., Torrens M.

• How should we measure addiction recovery? Analysis of service provider perspectives using online Delphi groups.
  
  • Joanne Neale et al., 2014, Drugs: education, prevention and policy, Early Online: 1–14
Conclusions-I

• Diversion and abuse of opioid-dependence pharmacotherapy is a significant worldwide individual and public health issue

• Adverse consequences include overdose fatalities, increased incidence of dependence, and compromised public acceptance of long-term opioid prescribing

• Monitoring is essential to assessing prevalence and practices associated with diversion and abuse in order to direct national strategies aimed at neutralizing the problem
• Treatment outcomes and good quality of treatment are key factors preventing diversion
• Our findings demonstrate support to improve the current approaches used to measure treatment outcomes at the level above the individual patient in opioid dependence
• Treatment restrictions policies may restrict access to treatment, which in turn may fuel the demand for diverted opioid
• While additional large-scale epidemiological studies are required to confirm efficacy in reducing diversion and abuse, existing data is promising
ISAM, 16th Annual Meeting, 2nd - 6th October 2014, Yokohama

http://www.congre.co.jp/isam2014/
SUBOXONE SUBLINGUAL TABLETS 2 MG/0.5 MG, 8 MG/2 MG
ABBREVIATED PRESCRIBING INFORMATION

Please refer to the Summary of Product Characteristics before prescribing.

Indication: Substitution treatment for opioid drug dependence, within a framework of medical, social and psychological treatment. Naloxone is intended to deter intravenous abuse. For adults and adolescents aged over 15.

Presentation: Sublingual tablets containing buprenorphine hydrochloride, equivalent to 2 mg or 8 mg buprenorphine base, and naloxone hydrochloride dihydrate equivalent to 0.5 mg or 2 mg respectively of naloxone.

Dosage and administration: Treatment must be under the supervision of a physician experienced in the management of opioid dependence/addiction. Induction must only commence when there are clear objective signs of mild-to-moderate withdrawal (e.g. on the COWS scale).

Precautions before induction: Baseline liver function tests and viral hepatitis status. Monitor liver function regularly.

Patients dependent on heroin or short-acting opioids: give the first dose of Suboxone not less than 6 hours after opioids were last used.

Patients receiving methadone: Before beginning therapy, reduce methadone to a maximum of 30 mg/day. Give the first dose of Suboxone not less than 24 hours after methadone was last used. Buprenorphine may precipitate withdrawal in patients dependent upon methadone.

Induction: One to two tablets of Suboxone 2 mg/0.5 mg tablets. An additional one to two tablets 8 mg/0.5 mg tablets may be given on day 1 depending on the patient’s requirement.

Dosage adjustment and maintenance: Titrate the dose in steps of 2-8 mg according to the clinical and psychological status of the patient, up to a maximum single daily dose of 24 mg.

Less-than-daily dosing: After stabilisation, the frequency of dosing may be decreased to every other day at twice the individually titrated daily dose, up to 24 mg daily.

Medical withdrawal: After stabilisation, the dosage may be reduced gradually to a lower maintenance dose; in some cases, treatment may be discontinued.

Older people: Safety and efficacy has not been established in patients over 65 years of age.


Renal impairment: Caution in severe renal impairment (creatinine clearance <30 ml/min).

Paediatrics: Not recommended for use below age 15 years.

Method of administration: Warn patients that Suboxone is only for sublingual administration, and that they should place the tablet under the tongue until completely dissolved.

Contra-indications: Hypersensitivity to buprenorphine, naloxone or any other component of the tablet; severe respiratory or hepatic insufficiency; acute alcoholism or delirium tremens.

Warnings and precautions:

Misuse, abuse and diversion: Can occur similar to other opioids. Monitor patients to minimise the risk. Suboptimal treatment may prompt medication misuse, which can lead to overdose or treatment dropout. Naloxone is included to deter misuse and abuse.

Respiratory depression: Reports of death, particularly in combination with benzodiazepines or when not used according to prescribing information. Deaths have also been reported through concomitant ingestion with other depressants such as alcohol or other opioids. Use with care in asthma or respiratory insufficiency. Potentially fatal respiratory depression can occur in children and people not tolerant to opioids. Warn patients to store medication out of reach and never take in front of children. Contact emergency unit in case of accidental ingestion or suspicion of ingestion.

Central nervous system (CNS) depression: Drowsiness, particularly with alcohol or CNS depressants.

Dependence: Chronic administration produces opioid-type dependence. Do not stop abruptly, because this may result in a delayed withdrawal syndrome.

Hepatitis and hepatic events: Cases of acute hepatic injury have been reported. In many cases, there was a pre-existing mitochondrial impairment (genetic disease, liver enzyme abnormalities, infections with hepatitis B or C virus, alcohol abuse, anorexia, concomitant use of other potentially hepatotoxic medicines), and ongoing injecting drug use. Consider these underlying factors before prescribing Suboxone and monitor during treatment.

Precipitation of opioid withdrawal syndrome: Suboxone can precipitate withdrawal in opioid-dependent patients particularly if given <6 hours after the last use of heroin or other short-acting opioid, or <24 hours after the last dose of methadone. Monitor patients during the switch from buprenorphine or methadone, because withdrawal symptoms have been reported. Undertake induction when objective signs of withdrawal are evident. Withdrawal may also be associated with sublingual doses.

Hepatic impairment: A reduced dose may be needed.

Renal impairment: Renal elimination may be prolonged. Metabolites accumulate. Caution in creatinine clearance <30 ml/min.

General: May produce orthostatic hypotension. Caution in patients with head injury, intracranial lesions, conditions that raise cerebrospinal fluid pressure, history of seizures, hypotension, prostatic hypertrophy or urethral stenosis, myoxoedema, hypothyroidism, adrenal cortical insufficiency, dysfunction of the biliary tract, or in elderly or debilitated patients. Miosis, changes in level of consciousness and attenuation of pain may make clinical assessment and management difficult.

Use in adolescents (13–18 years): Monitor patients more closely.

CYP3A inhibitors: May give rise to increased concentrations of buprenorphine, so a reduced dose may be needed. Do not give to patients with rare hereditary problems of galactose intolerance, because Suboxone contains lactose.

Interactions: Should not be taken with alcohol or medications containing alcohol due to increased sedative effect. Use cautiously with benzodiazepines, other CNS depressants, other opioid derivatives (e.g. methadone, analgesics, antidepressants), certain antiepileptics, sedative H₁-receptor antagonists, barbiturates, anxiolytics, neuroleptics, clonidine and related substances. The reduced level of alertness can make driving and using machines hazardous. Adequate analgesia may be difficult to achieve using a full opioid agonist and there is potential for overdose. Do not give naloxone, because this may precipitate sudden severe withdrawal. Use with CYP3A4 inhibitors (e.g. azole antifungals, protease inhibitors, macrolide antibiotics) or inducers (e.g. phenobarbital, carbamazepine, phenytoin, rifampicin) may require dose adjustment. Concomitant use of monoamine oxidase inhibitors may exaggerate the opioid effect.

Pregnancy and breastfeeding: Use only if the benefit outweighs the risk. Administration of buprenorphine in the last 3 months of pregnancy may cause a delayed withdrawal syndrome in the neonate, and use late in pregnancy may induce respiratory depression in the newborn. Monitor the neonate for several days. Discontinue breastfeeding during treatment.

Effects on ability to drive and use machines: May cause drowsiness, dizziness or impaired thinking. Caution patients about driving or operating hazardous machinery.

Undesirable effects: The most commonly reported reactions in clinical trials were constellation and drug withdrawal symptoms. Some reports of seizure, vomiting, diarrhoea and elevated liver function tests were considered serious.

Very common (≥1/10): Insomnia, headache, constipation, nausea, hyperhidrosis, drug withdrawal syndrome.

Common (≥1/100 to <1/10): Influenza, infection, pharyngitis, rhinitis, anxiety, depression, decreased libido, nervousness, abnormal thinking, migraine, dizziness, hypertonia, paraesthesia, oedema, asthenia, lacrimal disorder, vasodilation, hypertension, cough, abdominal pain, diarrhoea, vomiting, dyspepsia, flatulence, rash, pruritus, urticaria, back pain, arthralgia, muscle spasm, myalgia, urinary abnormality, erectile dysfunction, asthenia, pain, chest pain, chills, pyrexia, malaise, peripheral oedema, abnormal liver function test, decreased weight, injury. Please refer to SPC in relation to other undesirable effects.

Oversed: General supportive measures including close monitoring of respiratory and cardiac status. Institute symptomatic treatment of respiratory depression and transfer the patient to an environment with full resuscitation facilities. Use an opioid antagonist (i.e. naloxone).

Presentation and basic UK NHS price: 2 mg/0.5 mg, 28 tablets = £55.40; 8 mg/2 mg, 28 tablets = £76.19

Legal category: CD (Srch 3), POM

Marketing authorisation numbers: EU/1/06/359/001-4

Further information is available on request from RB Pharmaceuticals Ltd, 103–105 Bath Road, Slough, Berkshire, SL1 3HU, UK.

Date of preparation: June 2013

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard (UK) and www.imb.ie (Ireland). Adverse events with this product can also be reported to RB Pharmaceuticals Ltd. Drug Safety Department at +800 270 81 901.
SUBUTEX 0.4MG, 2MG AND 8MG SUBLINGUAL TABLETS
ABBREVIATED PRESCRIBING INFORMATION

Consult Summary of Product Characteristics before prescribing.

Uses: Substitution treatment for opioid drug dependence, within a framework of medical, social and psychological treatment.

Presentation: sublingual tablets containing buprenorphine hydrochloride, equivalent to 0.4 mg, 2 mg or 8 mg buprenorphine base.

Dosage:
Adults and adolescents aged 16 years and over: Perform baseline liver function tests and viral hepatitis status before starting treatment. Monitor liver function regularly.

Induction dose: 0.8 to 4 mg, administered as a single daily dose. Opioid-dependent drug addicts who have not undergone withdrawal: The first dose of Subutex should be taken when signs of withdrawal appear, but not less than 6 hours after the last use of opioids.

Patients receiving methadone: Before beginning therapy, methadone must be reduced to a maximum of 30 mg/day. Buprenorphine may precipitate symptoms of withdrawal.

Dosage adjustment and maintenance: Increase the dose progressively according to the individual's clinical and psychological status up to a maximum daily dose of 32 mg.

Dosage reduction and termination of treatment: After stabilisation the dosage may be reduced gradually to a lower maintenance dose; treatment may be discontinued if appropriate.

Elderly: No data are available.

Paediatrics: Not recommended in children below age 16 years.

Patients with impaired hepatic function: hepatic metabolism of buprenorphine may be altered.

Patients with impaired renal function: renal elimination may be prolonged.

Contra-indications: Hypersensitivity to buprenorphine or any other component of the tablet; children under 16; severe respiratory or hepatic insufficiency; acute alcoholism or delirium tremens; breastfeeding.

Precautions and Warnings: Treatment should be prescribed by a physician who ensures comprehensive management of the patient. Consider the risk of abuse and misuse especially at the beginning of treatment, including diversion. Withdrawal can be precipitated particularly if administered <6 hours after the last use of heroin or other short acting opioid or <24 hours after the last dose of methadone. Withdrawal symptoms may also be associated with suboptimal dosing and the risk of serious adverse events is increased if the patient continues to self medicate withdrawal symptoms. Chronic administration produces opioid type dependence. Subutex may cause drowsiness, particularly when taken with alcohol or central nervous system depressants. Cases of death due to respiratory depression have been reported, particularly in combination with benzodiazepines or not used according to prescribing information. Cases of acute hepatic injury have been reported. The presence of pre-existing liver abnormalities, infection with hepatitis B or hepatitis C virus, concomitant use of other potentially hepatotoxic medicines, and ongoing injecting drug use may have a causative or contributory role. Subutex can cause orthostatic hypotension. Subutex may produce a positive reaction to 'anti-doping tests' in athletes. Use with care in patients with asthma or respiratory insufficiency, renal or hepatic insufficiency. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take Subutex.

Interactions: Subutex should not be taken with alcoholic or medications containing alcohol, due to increased sedative effect. Use cautiously with benzodiazepines (combination may result in death due to respiratory depression), other central nervous system depressants, other opioid derivatives (analgesics and anititusives), certain antidepressants, sedative H1-receptor antagonists, barbiturates, anxiolytics other than benzodiazepines, neuroleptics, clonidine and related substances: these combinations increase central nervous system depression. Warn patients not to drive or operate machinery. MAOIs may exaggerate the effect of buprenorphine. A suspected interaction between buprenorphine injection and phenprocoumon, resulting in purpura, has been reported. Medicines that inhibit the enzyme CYP3A4 may give rise to increased concentrations of buprenorphine. If CYP3A4 enzyme inducers (eg phenobarbital, carbamazepine, phenytoin, rifampicin) are prescribed, the dose of buprenorphine may need to be increased.

Pregnancy and Breastfeeding: Do not use during pregnancy or breastfeeding.

Side Effects: The most frequently observed symptoms are constipation, headaches, insomnia, asthenia, drowsiness, nausea and vomiting, fainting and dizziness, orthostatic hypotension and sweating. Other side effects that have been reported are: respiratory depression, hepatic necrosis and hepatitis, hallucinations, urinary retention, bronchospasm, angioneurotic oedema, anaphylactic shock, withdrawal. In cases of IV misuse, local reactions, sometimes septic, and acute hepatitis have been reported.

Overdose: General supportive measures including dose monitoring of respiratory and cardiac status. Institute symptomatic treatment for respiratory depression, including resuscitation. Use an opioid antagonist (e.g. naloxone). See Summary of Product Characteristics for more detailed information.

Package Quantities: Cartons of 7 tablets, contained in blister packs

NHS Price: 7 tablets 0.4mg: £1.60; 2mg: £6.35; 8mg: £19.05

Legal Category: CD (Sch 3), POM

Marketing Authorisation Numbers: PL 36699/001, 002, 003

Further information is available on request from RB Pharmaceuticals Ltd, 103-105 Bath Road, Slough, Berkshire, SL1 3JH, UK.

Date of preparation: March 2012

Please refer to the full SPC text before prescribing this product. Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard. Adverse events can also be reported to RB Pharmaceuticals Ltd. Drug Safety Department at +800 270 81 901.