
**WHO Guidelines for psychosocially assisted pharmacological
treatment of persons dependent on opioids**

**A. Uchtenhagen, T. Ladjevic, J. Rehm
Research Institute for Public Health and Addiction
at Zurich University
Centre for Addiction and Mental Health
Toronto**

**BACKGROUND DOCUMENT PREPARED FOR THIRD MEETING OF
TECHNICAL DEVELOPMENT GROUP (TDG) FOR THE
WHO "GUIDELINES FOR PSYCHOSOCIALLY ASSISTED PHARMACOTHERAPY OF
OPIOID DEPENDENCE"**

**17-21 SEPTEMBER 2007
GENEVA, SWITZERLAND**

Contents

- 1 Aim and basis of this paper
 - The aim
 - Overview of materials
 - Review and analysis procedure
- 2 Definitions of terms used
- 3 Legal basis and regulations
- 4 Pharmacologically assisted detoxification
 - Agonist assisted detoxification
 - Antagonist assisted detoxification
- 5 Agonist maintenance treatment
 - Indication and contra-indications
 - Initial assessment and treatment planning
 - Medication and clinical management
 - Concomitant care
 - Special management issues
- 6 Antagonist maintenance treatment
 - Indication and contra-indications
 - Assessment and treatment planning
 - Medication and clinical management
 - Concomitant care
- 7 Service requirements
 - Staff
 - Facilities
 - Quality management by standardized procedures
- 8 The role of psychosocial care
 - Research evidence
 - Psychosocial care mentioned in the guidelines
- 9 An short analysis of findings
 - Areas of consensus
 - Areas of dissent and uncertainties
 - Missing information
- 10 Issues for discussion
 - Relevance of consensus
 - Minimal standards
 - Fixed rules versus flexibility
 - Role of socio-cultural background for good practice
- Annex List of guidelines
 - Other references

1 Aim and basis of this paper

The aim

This is a preparatory paper to the formulation of international guidelines for psychosocially assisted pharmacological treatments of persons dependent on opioids. WHO guidelines are defined as “systematically developed evidence-based statements which assist providers, recipients and other stakeholders to make informed decisions about appropriate health interventions” (Guidelines for WHO Guidelines 2003).

By ‘pharmacological treatments of patients dependent on opioids’ we understand treatments using opioid agonists or antagonists, for detoxification or for maintenance purposes. It is understood that in such treatments the use of medications is integrated into a comprehensive programme including psychosocial assistance.

This paper is based on reviewing a collection of existing guidelines, with an aim to identify the type and content of rules and recommendations expressed in those. It is not based on scientific evidence regarding the effects of rules and recommendations, nor does it contain systematic statements on the evidence base of the examined guidelines. Statements are made only to the extent such information is available from the guidelines. Also, in chapter 7 on psychosocial care, the evidence for a need to complement the pharmacological approach by psychosocial care elements is summarized.

Overview of materials

National and general guidelines have been collected systematically and through key persons in the respective countries. A total of 28 guidelines were found, whereof 6 cover more than one of the following topics :

- 7 guidelines on agonist assisted detoxification
- 1 guideline on antagonist assisted detoxification (rapid detoxification)
- 26 guidelines on agonist maintenance treatment
- 2 guidelines on antagonist maintenance treatment.

25 guidelines were provided by WHO headquarters, 3 were identified from an internet search in order to cover additional guidelines from USA, Germany and the European Union.

As to be expected, the guidelines differ in many ways; some are covering elementary issues only, others are more comprehensive and cover the whole range of issues that are relevant for the implementation and management of psychosocially assisted pharmacological treatments for opioid dependent persons.

All guidelines are listed alphabetically in the annex.

In addition, 2 Cochrane reviews and some additional studies on psychosocial care in pharmacological treatments have been consulted for chapter 7. The references are included in the annex.

Review and analysis procedure

In a first step, a structured template helped to break down information from the guidelines according to the range of issues to be covered in this paper.

In a second step, this information was reviewed and is described below in detail in a comparative manner. It is a systematic review of all items contained in the guidelines,

indicating the number of guidelines which mention the various items (numbers presented in brackets).

A special chapter is dedicated to the role of psychosocial care, including major evidence from research and comparing research results with recommendations made in the guidelines.

In a third step, an analysis is made indicating areas of consensus, of dissent and uncertainties, as well as missing information.

2 Definitions of terms used

Opioids

- substances interacting with opioid receptors in the brain (mainly mu receptors, mediating effects like analgesia, euphoria, respiratory depression, dependence)
- full agonists : binding to and activating opioid receptors (e.g. morphine, heroin, methadone, oxycodone, hydromorphone)
- partial agonists : binding and activating opioid receptors to a lesser degree than full agonists; ceiling effect at mu receptors; higher doses bind but do not activate receptors, and have effects comparable to antagonist effects (e.g. buprenorphine)
- antagonists : binding and blocking (not activating) opioid receptors (e.g. naltrexone, naloxone)

Opioid dependence

- criteria according to ICD-10 or DSM-IV

Neuroadaptation

- adaptive changes in the central nervous system as a result to exposure to opioids
- mainly functional and structural changes in the limbic system

Tolerance

- repeated administration of the drug produces a diminished effect
- to produce the same effect, a higher dose of the drug is needed

Withdrawal syndrome

- physiological and psychological symptoms which occur when stopping the administration of the drug after prolonged exposure to this drug
- symptoms of opioid withdrawal include anorexia, nausea, abdominal pain, vomiting, diarrhoea, hot and cold flushes, bone, joint and muscle pain, cramps, insomnia, intense craving for opioids, restlessness, dysphoria, agitation, ev. delirium
- spontaneous heroin withdrawal starts usually 8-24 hours after the last dose; symptoms peak at 24-28 hours and resolve after 5-7 days

Detoxification

- reversing or reducing neuroadaptation to opioids
- a process of providing symptomatic relief to assist patients to complete withdrawal and avoid adverse events associated with withdrawal (Bell et al 2001)

Maintenance

- maintenance to abstinence : mid-term pharmacologically assisted treatment by use of opioid agonists or antagonists
- maintenance : long-term pharmacologically assisted treatment by use of opioid agonists or antagonists, without limiting the duration of treatment.

3 Legal basis and regulations

Most of the guidelines have an official status (unknown in 3 cases). 17 guidelines were produced by Government bodies, 7 by expert committees or professional associations.

Special national and/or local commission to be implemented, with representatives of health care, pharmacies and addiction specialists (5)

Regarding the legal conditions for the use of agonists/antagonists in treatment, the following rules apply :

- clinics must be licensed (8)
- state owned clinics only (1)
- health care institutions only (1)
- prescribing doctors must be centrally registered (2)
- prescribing doctors must have a licence for psychiatry (1)
- doctors licence for prescribing is limited to 6 mths (1)
- doctors are allowed to prescribe for a maximum of 20 patients (1)
- patients must be centrally registered (9)
- central register accessible only to treating physician (1)
- patients need individual authorization by health authority or commission (3)
- parent consent obligatory if patient is less than 18 years old
- child psychiatrist consent obligatory if patient is less than 16 years old
- coercive treatment is allowed (2)
- *no legal rules are mentioned in 9 guidelines.*

4 Pharmacologically assisted detoxification

Agonist assisted detoxification

Objectives

- to relieve withdrawal symptoms by tapering off agonist medication, with the effect of replacing the abrupt cessation of opioid intake by a stepwise reduction of intake
- to improve retention during detoxification

Setting

- out-patient detoxification in cases with high motivation to stop drug use (1)
- in-patient detoxification preferred under the following conditions : previous failures or severe complications during detoxification, insufficient social support, unfavorable medical or psychiatric conditions (1)

Indication

- willingness of the patient to become abstinent (2)
- patient information on potential risks and advantages (1)
- patient information on alternative treatments (2)
- informed consent with treatment plan and procedures (2)
- unsuccessful other approaches (1)

Contra-indication

- sensitivity to agonist medication (1)

- first and third trimester of pregnancy (1)
- relative contraindication : involuntary detoxification is followed by high relapse rates and includes an increased mortality risk due to loss of tolerance (1)

Assessment

- medical risks of detoxification (1)
- determine appropriate setting (1)
- exploring patients expectations (1)
- explaining range of available options (1)
- history (somatic health, psychiatric conditions, drugs) (3)
- somatic and psychiatric status (3)
- need for concomitant somatic / psychiatric care (2)
- urine screening for drugs (3)

Agonists used in opioid detoxification

- full agonists (e.g. methadone, codeine) (2)
- partial agonists (e.g. buprenorphine) (1)
- preference for buprenorphine in cases of bradycardia and hypotension (1)
- preference for methadone in pregnancy and breastfeeding (1)

Medication and clinical management

- organization of daily dispensing (including weekends) in out-patient detoxification (1)
- preference for in-patient detoxification in cases of concomitant somatic or psychiatric illnesses in need of in-patient treatment (1)
- concomitant counseling, group and individual consultations (2)
- contact to self-help groups (1)
- work rehabilitation (1)

Duration of detoxification

- short : not longer than 4 weeks (1)
- slow : up to 6 months (1)

Follow-up treatment

- antagonist (naltrexone) maintenance (1)
- relapse prevention regime (1)

Antagonist assisted detoxification

Objectives

- rapid detoxification from opioids is “the process of accelerating withdrawal from heroin (or other opioids) by administration of an opioid antagonist, while providing symptomatic relief to enable patients to tolerate the procedure”
- rapid detoxification improves short-term induction onto naltrexone maintenance
- objective and protocol from guidelines by Bell et al 2001, Bell et al 2003
- recommendations are research-based

Conditions for antagonist-assisted (rapid) detoxification

- in specialist detoxification facilities only (not in primary care or other non-specialist settings)
- only in facilities where resuscitation equipment, trained staff and in-patient care is available in the event of severe reaction
- patient information on potential risks and benefits
- patient information on treatment alternatives

- patient is able to give informed consent

Indication

- patient committed to long-term abstinence
- sufficient external support to maintain abstinence
- to be confirmed in more than one interview only
- no firm evidence available on characteristics of patients who will profit best from rapid detoxification

Contraindications

- pregnancy
- exclude patients with risks from intercurrent medical problems
- history or evidence of heart disease
- chronic renal impairment
- decompensated liver disease
- current dependence on benzodiazepines, alcohol or stimulants
- history of psychosis
- relative contraindications : history of depression, unstable social circumstances

Assessment

- diagnosis of dependence
- history (medical, psychiatric, drug use)
- present status incl. mental state examination
- pregnancy test
- liver function tests
- urine tests on drugs of abuse
- naloxone challenge test
- motivation, reasons for seeking treatment
- discussion of treatment options
- treatment plan and informed consent

Medication

- antagonists : Naltrexone, Naloxone
- for symptomatic relief : clonidine (a centrally acting alpha-2-agonist) and octreotide (a synthetic somatostatin analog), buscopan, ondansetron, quinine sulphate
- sedation : from light sedation using diazepam to general anaesthesia with intubation

Clinical management

- decide on out-patient or in-patient setting for starting detoxification
- start not earlier than 48 hours after the last use of heroin or 7 days after the last use of methadone
- in the interval before starting rapid detoxification : opioids must be avoided; symptomatic medication is used
- in case of rapid detoxification under anaesthesia, one bolus dose of naloxone or naltrexone resolves physiological withdrawal symptoms after 4-6 hours
- monitor the severity of withdrawal
- naloxone challenge test : Narcan i.m. 0.4 mg (repeat after 10 min if no reaction) or i.v. 0.2 mg (repeat after 1 min with 0.6 mg if no reaction); if test is positive, delay induction of naltrexone and repeat challenge test after min 24 hours; if 0.4 mg are tolerated, 25 mg naltrexone can be administered orally
- induction regime : Clonidine (75-150 ug), diazepam (5 mg), octreotide 100 um s.c.), naltrexone (25 mg); observe patient for min 3 hours or longer if agitation or low blood pressure occur
- continue with 25-50 mg naltrexone each morning

- predictors of severity of withdrawal are : duration of interval since last use of opioids, level of dependence
- measures to increase the safety of rapid detoxification : prepare patients psychologically, provide supportive nursing care, respect indication and contraindication rules
- carefully balance the effects and interactions of medications applied (fatalities are mostly associated with multiple medications)
- in low level settings only minimal sedation is admissible
- aftercare : weekly visits, naltrexone maintenance contact to self-help groups, involve family or friends for supervising naltrexone intake
- detailed protocol in Bell et al 2001, 2003.

5 Agonist maintenance treatment

Objectives

A range of reasons and objectives for agonist maintenance treatments are mentioned :

- to enable patients to obtain the needed amount of opioids in a legal way (1)
- to attract patients into medical and social care (1)
- to improve physical and mental health (6)
- to reduce mortality (2)
- to improve social integration and financial situation(5)
- to reduce drug-related crime (2)
- to reduce the spread of blood born infectious disease (5)
- to prevent complications from unsafe injecting (2)
- to assist pregnant women and provide them with medical care (2)
- to keep patients under control (1).

Indication and contra-indications

Criteria are listed in 22 out of 26 guidelines covering agonist maintenance treatment. The following list of criteria shows an important diversity :

- Diagnosis of opiate dependence (13), whereof according to DSM-IV or ICD-10 (10), confirmed by urine test (1)
- Personal identification of applicants (2)
- Indication to be made/reviewed by committee (5), by 2 psychiatrists (1)
- Minimal age of 18 (5), of 25 (2), of 15 for buprenorphine (1)
- Duration of dependence >3 years (4), >5 years (3), >10 years (1)
- Duration of injecting opiates >1 year (1), > 2 years (3), > 5 years (1)
- Shorter duration admissible in case of serious psychiatric illness (1)
- Unsuccessful drug-free treatments > 2 (3), > 3 (9), not specified (1)
- Informed consent (6)
- Polydrug use (1)
- HIV seropositivity (8)
- Pregnancy and breastfeeding : methadone only (8)
- Hepatitis B/C (4)
- Other somatic conditions (6)
- Good previous experience with agonist maintenance (1)
- Positive acceptance of agonist maintenance by patient (3)

Priority should be given to the following target groups :

- Spouse or partner of patient (2)
- Nationals (1)
- Pregnant women (8)
- Patients with children (2)
- Patients with HIV/Aids (9)
- Patients with hepatitis B / C (4)
- Patients with psychiatric illness (1).

Contra-indications are mentioned in 9 guidelines only; they cover an equally vast range :

- Legal contraindications : under age (3), not able to give informed consent (1)
- Short history of dependence (2)
- High risk for overdosing (2)(2)
- Upcoming imprisonment (1)
- Hypersensitivity to agonist (3)
- Pregnancy, breastfeeding : buprenorphine contraindicated (1)
- Epilepsy (1)
- HIV seropositivity (1)
- Hepatic failure (3)
- Respiratory deficiency, Asthma (3)
- Acute alcoholism (2)
- Anti-social personality disorder (1)
- Head injury, intracranial pressure (2)
- Ulcerative colitis (2)
- Biliary or renal spasms (2)
- Concurrent treatment with MAO inhibitors (2)

Precaution is recommended in the following situations :

- High risk polydrug use (6)
- Reduced opioid tolerance (1)
- Severe psychiatric / somatic comorbidity (4)
- Chronic pain (1).

Initial assessment and treatment planning

The following requirements are mentioned :

General and present state

- assure the applicant's identity (2)
- assure the diagnosis of opiate dependence (13)
- full clinical examination of the applicant (9)
- complete somatic / psychiatric status incl. comorbidities (7)
- assess risk taking behaviors (3)
- assess individual treatment needs (3)
- assess present social circumstances (4)
- assess applicant's motivation (4), preferences (2) and goals (1)
- assessment procedure should take 3-4 weeks (1)

Laboratory tests

- check for pregnancy and contraceptive practice (1)
- apply physiological tests (1) and screening instruments (2)
- urine testing (9)
- hair analysis (1)

- serological testing for viral infections (7)
- liver function tests (2)
- testing for venereal diseases (2), for Tuberculosis (2)
- degree of neuro-adaptation (1)

History

- drug history (10), age at onset (1)
- complete history incl. medical, social, legal aspects (10)
- past treatment history (3)

Treatment planning

- joint agreement on treatment plan incl. patient (5)
- treatment plan by physician only (1), by team only (1)
- individual treatment plan (1), to be revised every 3 months (1)
- choose appropriate setting (1)

Patient information

-
- explaining range of available treatments (4)
- explaining duration and risks of treatment (1)
- explaining effects and side-effects of agonist medication (2)
- explaining drug interactions (1)
- explaining treatment rules (3)
- explaining rules of confidentiality (1)
- explaining expected behavior (1)
- explaining and asking informed consent (5)
- explaining risks of polydrug use and overdose (1)
- explaining risks of motor vehicle driving while under the influence of agonists (1)
- explaining rules of discharge from treatment (1).

Medication and clinical management

Agonists used for maintenance treatment

- methadone oral (19), liquid only (1), injected (1)
- buprenorphine sublingual (4)
- buprenorphine plus Naloxone (1)
- LAAM (3)
- Retarded morphine (1)
- Diamorphine (1)

Criteria for differential indication of agonist medication

- sensitivity to specific agonist
- interactions of specific agonist with other medications needed (e.g. anti-retroviral medication, psychiatric medication)

Pharmacological information

- effects of medication (5)
- side-effects / adverse effects of medication (6)
- interactions with other drugs (4)
- pharmacokinetics / pharmacodynamics of medication (7)
- symptoms of intoxication and overdose (1)
- abuse potential of medication (1)
- identification of psychoactive substances in urine (1)

Methadone : induction and stabilization phase

- initial dose 10-20 mg (1), 10-30 mg (1), 10-40 mg (2), 20-30 mg (1), 5-40 mg (1)

- individual initial dose (9)
- split first daily dose (1), observe patient 4 hours after first dose (2)
- dose increase 5-10 mg/day during first week (1), 20 mg/week (1), 50% of initial dose/week (1), individually (1)

Methadone : maintenance phase

- daily dose 30-40 mg (1), 40-100 mg (1), 60-100 mg (1), >60 mg (1), 80-120 mg (1)
- individual dosing (1)

Methadone : maximum daily dose

- 60 mg (1), 80 mg (1), 60-120 mg (4), 150 mg (2)
- „as low as possible“ (1)

Methadone : special safety measures

- after missed doses, re-introduction is needed with reduced dosages (4)
- no refills /replacements in case of loss (1)

Buprenorphine : induction and stabilization phase

- 2-8 mg (at least 6 hours since last heroin use) (1)
- criteria for determining the initial dose : degree of neuro-adaptation, degree of withdrawal symptoms, concurrent drug use, concurrent medical conditions (1)
- individual dose increase schemes (1)

Buprenorphine : maintenance phase

- daily dose 12-24 mg (1)
- maximum daily dose 32 mg (1)
- dose adjustment if on a stable dose for at least 2 weeks (1)

Switching agonist medication

- from methadone to buprenorphine :
rules : slowly reducing methadone, stabilize on low dose, switch to buprenorphine (1)
- from buprenorphine to methadone :
reasons : dose increase has little or no effect, dose increase considered to be unsafe (1)

Intake of agonist medication

Methadone :

Daily supervised intake (12), for min.1 mth (1), min. 3 mths (1), min. 6 mths (1)

Supervised intake at pharmacy (2)

Patient signs up for every dose received (1)

Providing professional signs up for every dose going out (1)

Take-out is allowed on the following conditions :

- after stabilization of dose and patient situation (10)
- no positive urines during 3 mths (1)
- for weekends and holidays only (3)
- after 2 mths only (1)
- after 6 mths only (1)
- for a maximum of 1 week (3)
- in case of illness or injury (1)
- for vacations of 2 weeks maximum (1)
- handing out to relatives (4)

Take-out is also allowed from pharmacies (2)

Buprenorphine :

Options

- alternate day intake (1)
- 4 times weekly (1)
- 3 times weekly (1)

Observe patient until sublingual tablet is melted (in order to prevent injection) (1)

Take-out after stabilization, if compatible with legislation (1)

Review of regime and treatment plan

Induction and stabilization phase

- min once per week (2)
- min. once per 3 months (2)

Full review

- every 3 mths (3)
- at individual intervals (1)

Medical examination

- every 6 mths (1)

Concomitant care

The following interventions are mentioned :

- regular counseling with patient (6)
- counseling with family/relatives (2)
- links to social services (2)
- case management (2)
- somatic medical care (1)
- psychiatric care (1)
- drug education (1)
- psychotherapy (1)
- vocational training (1)
- aftercare (1).

Special management issues

In-patient regime during induction phase

- for one week obligatory (2)

Monitoring non-prescribed drug use

- clinical observation (1)
- self-report (1)
- urine tests (10)

Urine controls on non-prescribed substances

- at random (5)
- weekly (2)
- monthly (2)

- “regular” (2)
- no specification (5)

Precautions against overdosing in general

- daily observation before intake (2)
- check for injection marks (3)
- dose increase exclusively to be made by the prescribing physician (1)

Precautions against overdosing during initial phase

- 1-2 consultations in first week (1)
- review the patient status before the 3. and 4. dose (1)

Driving a motor vehicle

- not allowed in the induction phase (1)
- not allowed while on agonist maintenance (1)

Pregnancy

- avoid detoxification in first and third trimester (1)
- breastfeeding allowed (2)
- neonatal care (2)

Agonist maintenance in prison

- not allowed, detoxification inevitable (1)
- to be continued in case of imprisonment (2)
- starting maintenance treatment in prison (1)

Treatment costs

- to be covered by government (2)
- free of charge (2)
- to be covered by patient / family (3)

Special regimes required

- psychiatric comorbidity (1)
- HIV/Aids (1)
- chronic pain (1)

Transfer from specialist to general practitioner / primary health care (1)

Termination of treatment

Duration of treatment to be determined individually (1)

Voluntary termination

- condition : stable lifestyle changes during min 1 year (1)
- determine post-treatment regime (1)
- make relapse prevention plan (1)
- dose reduction 5-10 mg methadone/day (1)

Reasons for involuntary termination

- violence or threats (1)
- diversion of agonist medication (1)
- illegal activities (2)
- non-attendance (3)
- non-compliance (3)
- drug use (2)
- 3 positive urine tests (2)

- fresh injection marks (1)
- no progress (1)

Obligations in case of involuntary termination

- offer detoxification (3)

6 Antagonist maintenance treatment

Objectives

- Relapse prevention by blocking the effects of opioid intake, thereby assisting motivated patients to remain abstinent (1)
- The objective is not to reduce craving or to increase motivation for abstinence (1)

Indication and contra-indications

Indication

- willingness to achieve abstinence (1)
- minimal age 18 (1)
- capable of giving informed consent (1)

Contra-indications

- current physiological dependence on opioids (1)
- acute withdrawal syndrome (1)
- patient needs opioids for chronic pain control (1)
- liver failure (2)
- sensitivity to antagonist medication (2)
- respiratory deficiency (1)

Precautions are recommended

- in cases with asthma and epilepsy (1)
- in pregnancy and during breastfeeding (1)
- in cases dependent on multiple drugs (1)
- in cases with impaired renal function (1)
- in cases with major psychiatric illness incl. depression (1)
- primary drug problem with stimulants or cannabis (1).

Assessment and treatment planning

Preparatory examination

- history : drugs, medical / psychiatric, psychosocial (1)
- present state : physical and mental (1)
- signs of withdrawal or intoxication (1)
- explore reasons for presenting and goals for treatment (1)
- readiness for supervised intake (1)
- where indicated : pregnancy test, urine toxicology, liver function test, virus serology, naloxone challenge test (1)

Patient information

- potential risks of treatment incl. risk of overdose after cessation (1)
- arrangements for induction (1)
- maintenance regime (1)
- warnings against irregular and intermittent intake (1)
- costs of treatment (1)
- procedure if analgesia is required (1)

- availability of supportive services (1)
- availability of harm reduction measures (1)

Documented informed consent on treatment plan (1).

Medication and clinical management

Induction phase

- conventional opioid detoxification : induction not earlier than 5 days since last intake of short-acting opioid or 10 days since last intake of long-acting opioid (1)
- naltrexone precipitated detoxification (rapid detoxification) (1)
- buprenorphine-assisted detoxification : 2 days after last dose of buprenorphine of 4 mg, or starting on low dose of naltrexone with 12.5 mg while dosing down buprenorphine (1).
- symptomatic medication with clonidine and diazepam if needed (1)
- in case of out-patient induction, supervision by a suitable person and access to prescribing doctor must be assured (1).

Maintenance phase

- usual daily maintenance dose is 50 mg; in case of side effects 25 mg may be sufficient (1)
- optimal duration of treatment to be determined individually, taking into account life-style, craving, environmental risk factors (1)
- minimal recommended duration is 6 months (1)
- consultations / clinical reviews with prescribing doctor 2 times weekly during first week, then every week during first month, then every 2 weeks or monthly (1)
- recommended daily intake of medication supervised by family member or friend (1)
- recommended support by self-help group or other supportive care (1)
- in case of sleep disturbances, benzodiazepines can help but restrict period to less than 2 weeks (1)
- pain management : use non-opioid medications, discontinue naltrexone at least 72 hours before surgery (1)
- pregnancy : if a patient becomes pregnant during naltrexone maintenance, inform on the risks, ask for informed consent to continue, consider methadone maintenance in case of relapse (1)
- re-induction after relapse (1)

Side-effects reported by >10% of patients (1)

- sleep disturbance
- anxiety
- loss of energy
- nausea and vomiting
- headache
- abdominal pain
- joint and muscle pain

Greatest problems :

- increased risk for heroin overdose death if patients return to opioid use after naltrexone maintenance, due to a loss of tolerance (1)
- low attractiveness and high drop-out rates (1).

Transfer to agonist maintenance treatment (if indicated after relapses) :

- transfer to methadone : delay first dose of methadone until 72 hours after last intake of naltrexone or use starting dose of max. 20 mg daily for 3 days (1)
- transfer to buprenorphine : initial dose of max. 4 mg, then increase (1).

7 Service requirements

Staff

Interdisciplinary staff includes

- doctors (8)
- nurses (6)
- GP (1)
- psychiatrist (2)
- psychologist (3)
- social worker (2)
- pharmacists (3)
- laboratory technician(1)
- an addiction team (4)

Special training is required for

- doctors and pharmacists (6)

Supervision of team is required (2)

Communication protocol for physicians and pharmacists is required (1)

Standardized information material for staff

- guidelines for shared care and responsibility (2)
- list of patient informations and warnings (1)
- criteria to identify patients at high risk (1)
- Methods to reduce high-risk drug use (1)
- rules for external review (1)
- definition of optimal dose (1)
- reasons for urine testing (1)
- concerns and benefits of a take-out policy (1)
- reasons for refusing take-out (2)
- rules for number of take-out doses (1)
- dose replacement rules (1)
- rules in case of relapse (1)
- rules for injectable methadone (1)
- rules for traveling with methadone (1)
- information on withdrawal syndrome (2)
- information on overdose management (1)
- list of drug interactions (1)
- information on pregnancy and antenatal care (1)
- policy for involuntary termination of treatment (1)
- arguments pro – contra maintenance treatment (1)
- criteria and evidence for positive outcomes (1)
- how to develop a maintenance program in the community (2).

Facilities

The following requirements are mentioned

- central location, easy access by public transport (2)
- neutral exterior (1)
- separate unit or room (1)
- flexible opening hours (1)
- safe storage of medications (2), no access for patients (1)

- stored amount to cover need for max. 1 week (1)
- access to laboratory services (1)
- access to specialists (1)

Quality management by standardized procedures

Standardized prescription forms

- name of patient (1)
- name of dispensing pharmacy (1)
- precise dosage in words and figures (1)
- total and single dose (1)
- application of medication (1)
- date for first dispensing of prescribed dose (1)
- date of expiry of authorization to dispense (1)
- date and signature of prescribing physician (1)

Standardized presentation of prescribed medication

- single dose containers with safety caps (2)
- warning text on container (2)
- standard procedure for administering (1)

Standardized patient records

- goal of treatment (1)
- dosages and application (1)
- assessment form (1)
- treatment agreement / contract with patient (2)
- consent form to participate in surveys and follow-up research (1)
- coordination with psycho-social care (1)
- all activities undertaken for the patient (1)
- list of processes to be documented (2)
- record keeping for min. 3 years (1)

Standardized patient certificate / passport

- contains name, address, treatment, treatment institution incl. Tel number (1)
- includes patient photo (1)
- last entry not older than 3 mths (1)

Standardized rules for confidentiality and respect of privacy (2)

Standardized policy and rules for

- injectable methadone regime (1)
- traveling with methadone (1)
- how to safely store take-out doses at home (1).

8 The role of psychosocial care

Research evidence

Two Cochrane reviews are to be considered here :

The review on "psychosocial and pharmacological treatments versus pharmacological treatments for opioid detoxification" (Amato et al 2004a) included studies dealing with the following psychosocial treatments in combination with Methadone Detoxification Treatment (MDT:

- Contingency Management, which is a behavioral treatment based on positive and negative reinforcers. In order to achieve abstinence, patients receive vouchers or payment for drug-free urine samples. This was combined with the Community Reinforcement Approach, which often involves significant others.
- Psychotherapeutic counseling, which assesses the patient's needs and provides services to fulfill these.
- Family therapy, which includes significant relationships being discussed and involvement of family members in sessions.

This review gives 4 types of comparisons. One comparison relates any psychosocial intervention plus MDT to MDT alone. Another comparison is due to the inclusion of one study using buprenorphine detoxification treatment (BDT) named "any psychosocial intervention plus any pharmacological intervention compared to any pharmacological intervention alone". The other comparisons consist of Contingency Management plus MDT/BDT, Psychotherapeutic Counseling plus MDT and Family Therapy plus MDT, respectively compared to MDT/BDT (in case of Contingency Management) alone.

Primary outcome measures are "completion of treatment" (number of participants completing treatment), "use of opioid drugs" (number of participants having positive urinalysis during treatment) and "results at follow-up" (number of participants abstinent at follow-up). As secondary outcomes are "compliance", "use of other drugs" and "mortality" looked into.

The review on "psychosocial combined with agonist maintenance treatments versus agonist maintenance treatments alone for treatment of opioid dependence" (Amato et al 2004b) includes studies with these psychosocial treatments in combination with Methadone Maintenance Treatment (MMT):

- Biofeedback, a behavioral treatment which aims at teaching people to control their EMG activity and therefore their reaction to certain cues that would usually lead to the tendency to take drugs.
- Cognitive-Behavioral Therapy, which aims at unveiling, understanding and changing automatic thoughts and encourages pleasant activities.
- Contingency Reinforcement as stated above.
- Enhanced Methadone services, which include counseling and medical, psychiatric, employment and family therapy services.
- Subliminal stimulation, which tries to mobilize positive affect by the precipitation of innate positive thoughts and metaphors.
- Supportive-expressive therapy, which aims at helping the patient to work through problematic relationships.
- Short-term interpersonal Psychotherapy, which deals with disturbances in interpersonal functioning, believing that these are associated with opiate addiction.

This review compares all of the seven treatments named above respectively in combination with MMT to MMT alone. It also compares the above as a whole in combination with MMT to MMT alone. Furthermore the review constitutes groups of treatments and compares them in combination with MMT to MMT alone. Groups are: Any behavioral intervention (Biofeedback, Cognitive-Behavioral, Contingency Reinforcement) and any psychoanalytic oriented interventions (Supportive-Expressive Therapy, Subliminal Stimulation).

Primary outcome measures are "retention in treatment" (number of participants retained at end of study), "use of primary substance" (number of participants with consecutive positive urines for at least three weeks) and "results at follow-up" (number of participants still in treatment at end of follow-up, and number of participants abstinent at that time). Secondary outcome measures are "compliance", "craving", "psychiatric symptoms/psychological distress", "quality of life" and "severity of dependence".

Significant outcomes

The two reviews find significant outcomes for different treatments concerning a number of outcome measures.

In the review on “psychosocial and pharmacological treatments versus pharmacological treatments for opioid detoxification” (Amato et al 2004a) there can be observed five significant outcomes. *Any Psychosocial* plus any pharmacological treatment was found to be better than the latter alone in terms of “completion of treatment”. *Contingency Management* plus MDT is found to be significantly better than MDT alone concerning “completion of treatment”. But this result was only achieved after excluding one category C study, leaving a total of two studies for the calculation.

Family therapy plus MDT is found to be significantly better than MDT alone concerning “results at follow-up”.

Concerning “compliance”, there are two treatments to be mentioned that created significant outcomes in combination with MDT compared to MDT alone. These are *Contingency Management* and *Psychotherapeutic counseling*. It has to be mentioned that for contingency management only two studies could be included in the calculations. Furthermore there is also a significant outcome concerning “compliance” when relating *any psychosocial intervention* plus MDT to MDT alone.

The results show a benefit from adding *Any Psychosocial Treatment* to any pharmacological detoxification treatment regarding the measures “completion of treatment”, “results at follow-up” and “compliance”. At least when regarding significant outcomes and tendencies. It has to be considered, according to the authors, that limitations to the interpretation are due to the heterogeneity of the assessment of outcomes. Detailed information lacked.

In the review on “psychosocial combined with agonist maintenance treatments versus agonist maintenance treatments alone for treatment of opioid dependence” (Amato et al 2004b) there are to be mentioned four significant outcomes. On behalf of “use of primary substance” *any psychosocial treatment* plus MMT, as well as *contingency management* plus MMT are found to be significantly better than MMT alone.

In one of three studies *Psychoanalytic oriented interventions* plus MMT are found to be significantly better than MMT alone concerning “psychiatric symptoms”.

Also in one study *enhanced methadone services* plus MMT are found to be significantly better than MMT alone concerning “severity of dependence”.

The result of this review seems to show benefit from adding any psychosocial treatment to MMT. The use of opioid drugs seems to be less likely in this case. The other outcomes are not based on sufficient evidence and therefore should not be overrated. These outcomes do not offer sufficient evidence for the one or the other treatment method, but they provide an insight into which treatments might be promising.

Some of the earlier studies on the role of psychosocial care may be mentioned also:

- patients in programs with rehabilitation and long-term maintenance orientation, which also delivered more counseling services and had more effective directors, tended to have better outcomes than patients in programs characterized by favorable staff/patient ratios in better facilities, where there was emphasis on administrative functioning rather than provision of services; such services include regular adequate counseling as the most important component (based on a comparative analysis of six methadone maintenance programs by Ball & Ross 1991)

- enhanced methadone maintenance, adding regular medical/psychiatric care, social work assistance, family therapy and employment counseling to the basic program, has the best outcome in terms of reduction in opiate-positive urines (based on a randomized controlled trial of three types of programs, minimal-basic-enhanced, McLellan et al 1993)
- patients randomized to enhanced maintenance programs often have difficulties to be involved and to take advantage of the services offered, but still show better retention in comparison to standard programs (Grella et al 1994)
- randomly assigned treatment without psychosocial services, providing only the medication, had less reduction of opiate use in comparison to standard and enhances methadone programs (Saxon et al 1996)
- a confrontative style of counseling is less effective than an emphatic alliance building with the patient (review in Mattick et al 1998)
- the provision of basic counseling services is a cost-effective method of enhancing the effects of methadone maintenance, and the addition of professional services is associated with even better outcomes than with counseling alone (review by McLellan 2003).

Psychosocial care mentioned in the guidelines

Almost all of the included guidelines contain some passage about the importance of counseling. 12 out of 28 give more or less detailed information about possibilities of psychosocial treatment. The other guidelines give general information on the necessity of psychosocial treatment. Most guidelines just offer lists of possible services without giving advice concerning their integration into pharmacological treatments.

In most guidelines, timing of counseling is not specified. Two guidelines opt for weekly consultations, one for 1-4 consultations per month, one for individual timing.

In more detail, the following approaches are mentioned :

Psychological interventions

- counseling (12), not mandatory (2)
- psychosocial care, supportive care (2)
- group counseling (3)
- motivational interviewing (1)
- social skills training (1)
- coping skills training (1)
- cognitive-behavioral therapy (2)
- group therapy (2)
- family therapy (2)
- individual psychotherapy (4)
- self-help group (5)
- crisis support (1)
- drug education (1)
- parenting education (1)
- relapse prevention (3)

Social interventions

- resocialisation (3)
- help with employment (2)
- vocational training (1)
- financial support (1)
- support for housing (1)
- support for transportation (1)

- child care (1)
- home management (1)
- legal support (1)

Other

- close cooperation with family (2)
- supervised intake by family / friend (2)
- psychiatric care (2)
- medical care (3)
- all services which are needed (2).

Relationship between research and practice in guidelines

The studies mentioned above and the two Cochrane reviews come to the conclusion that there is additional benefit in adding any psychosocial treatment to either pharmacological maintenance or detoxification treatments. Most of the included guidelines share this opinion, but provide little information on how to integrate these promising treatments.

The Cochrane reviews find contingency management plus pharmacological treatment effective in terms of “completion of treatment” (Amato et al 2004a), “compliance” (Amato et al 2004a) and “use of primary substance” (Amato et al 2004b). This kind of treatment, which might be viewed promising, is not explicitly named in any of the included guidelines. Two guidelines mention cognitive-behavioral treatments, which would seem reasonable to be included. Family Therapy plus agonist detoxification treatment is considered a promising approach in terms of “results at follow-up” (Amato et al 2004a). This treatment is mentioned in two guidelines.

In conclusion, most of the recommendations in the reviewed guidelines are not linked to the research evidence presented in the Cochrane reviews, as the reviews are of more recent date. But also other research findings are only rarely named as a basis for recommendations. However, most guidelines are in line with the general finding that psychosocially assisted pharmacological treatments have a superior outcome in comparison to pharmacological treatment alone.

9 An short analysis of findings

Areas of consensus

There is no complete consensus on any issue to be found across guidelines. Relative consensus across a minority of guidelines however can be found regarding the following :

- central registration of patients on agonist-assisted treatment (9)
- authorizing pharmacies to dispense medication (9)
- reserving agonist treatment to patients who unsuccessfully tried other approaches (9)
- relative contraindication for agonist / antagonist treatment in case of high-risk polydrug use (6)
- comprehensive assessment : standardized diagnoses (13), clinical examination (9), history (10), urine toxicology (8), informed consent (6)
- joint agreement on treatment plan (6)
- availability of oral methadone as an agonist medication (19)
- individual initial dosing of agonist medication (9)
- supervised daily intake of medication (12), but take-out if patient is stabilized (10)
- staff must include physician (8) and nurse (6), special training needed (6)

- guidance by a national and / or local special commission (5)
- psychosocial care must include counseling (12) or other supportive care (5), links to self-help groups (5).

Areas of dissent and uncertainties

In all other issues mentioned, there is no consensus regarding the content, the details and the flexibility of rules and recommendations.

Examples of major dissens and/or insufficient information are :

- treatment permitted in private office, private clinics or state clinics
- type and content of information for prescribers and staff
- type and content of information for patients
- indication criteria (minimal age, minimal duration of dependence, priority groups)
- contraindications
- details of dosage schemes
- rules for take-out
- details of control policy
- financing of treatment
- facilities needed
- rules for terminating treatment
- standardized procedures and other quality management issues.

Missing information

Some issues that may be relevant for international guidelines have not be dealt with here. Examples are :

- Place of pharmacological treatments in a treatment system
- Cost-effectiveness of pharmacological treatments
- Pharmacological treatment recommendations for adolescents
- Pharmacological treatments for opium dependence.

10 Issues for discussion

Based on the findings of this review, some questions must be raised that seem relevant to the construction of international guidelines on psychosocially assisted pharmacological treatments for persons dependent on opioids.

Relevance of research evidence ?

It must be discussed to what extent and for which parts of guidelines the recommendations should be evidence-based, what type of evidence applies, and where there is a need for more research evidence.

Relevance of consensus ?

It has to be determined where a consensus statement on recommendations is needed, and what are the reasons for such a need.

There may be a necessity to formulate consensus statements for countries where pharmacological treatment for opioid dependence is a new or recent approach, in contrast to

countries where a long-standing experience has accumulated and is integrated into the treatment system.

There may also be a necessity to differentiate consensus statements with regard to the available resources in a given country.

Minimal standards ?

It has to be determined which rules are conditional for good practice in the pharmacological treatment of opioid dependence, based on clinical and research evidence. This is especially important for countries with limited resources.

Fixed rules versus flexibility ?

Fixed rules may impede the possibilities to take the individual situation of patients fully into consideration. Flexible rules may lead to insecurity and partiality. It is necessary, therefore, to determine for which issues fixed rules are needed and justified, and on what conditions flexible rules are to be preferred.

Role of socio-cultural background for good practice ?

It must be discussed how, for which issues and to what extent the different social and cultural background in a given country is to be taken into consideration for good practice and for a good acceptance of the treatment by patients and the population in general.

Annex

List of guidelines

APA-Guidelines (American Psychiatric Association, no further indications possible)

Azerbajdzan. *Statement of prescribing of narcotic drugs to patients with mental or behavioral disorders caused by opiate drug use.* (no further indications possible)

Bell, J., Kimber, J., Lintzeris, N., White, J., Monheit, B., Henry-Edwards, S., Mattick, R., Ali, R., Ritter, A., Quigley, A. (2002). *(Confidential draft) Clinical guidelines and procedures for the use of naltrexone in the management of opioid dependence.*

Bosnia and Herzegovina. *Guidelines for methadone maintenance therapy in B&H.* (no further indications possible)

Bundesaerztekammer (ed.) (2002). *Richtlinien der Bundesaerztekammer zur Durchfuehrung der substituionsgestuetzten Behandlung Opiatabhaengiger.* (no further indications possible)

College of Physicians of Ontario (2001). *Methadone maintenance guidelines.* Toronto.

Czech substitution treatment guidelines (no further indications possible)

Department of Health, Scottish Office Department of Health, Welsh Office, Department of Health and Social Services (Northern Ireland) (1999). *Drug misuse and dependence – guidelines on clinical management.* Her Majesty's Stationery Office: Norwich.

Erdelyan, M. (Year not provided). *Methadone maintenance treatment: A community planning guide*.

Health Ministry of Latvia (1996). *Introduction of methadone programme for treatment*. Riga.

Henry-Edwards, S., Gowing, L., White, J., Ali, R., Bell, J., Brough, R., Lintzeris, N., Ritter, A., Quigley, A. (2002). *Clinical guidelines and procedures for the use of methadone in the maintenance treatment of heroin dependence*. Australia.

Lingford-Hughes, A. R., Welch, S., Nutt, D. J. (2004). Evidence-based guidelines for the pharmacological management of substance misuse, addiction and comorbidity: Recommendations from the British Association for Psychopharmacology. In: *Journal of Psychopharmacology*, 18 (3) (2004), p. 293-335. British Association for Psychopharmacology: London.

Minister of Social Affairs Estonia (1998). *On providing the drug users (DUs) with maintenance and detoxification treatment in various phases*.

Ministry of Health Bulgaria (2000). *Regulation No.24 - For the conditions and the order of accomplishing substitution and maintenance programs for reduction of the health damages of the drug addicted individuals*.

Ministry of Health, Myanmar (ed.) (2004). *Myanmar methadone guidelines – Prescribers and dispensers – draft*.

Minister of Health and Social Care Poland (1999). *873 Decree on substitution treatment*. (no further indications possible)

Minister of Health and Welfare Canada (ed.) (1994). *Drugs Directorate Guidelines – Dispensing Methadone for the Treatment of Opioid Dependence – Guidelines for Pharmacists*. Ottawa, Ontario.

Ministry of Healthcare of Kyrgyz Republic. *Guidelines Concerning terms and conditions of methadone substitution treatment in Kyrgyz Republic*. (no further indications possible)

Ministry of Health New Zealand (2003). *Opioid substitution treatment New Zealand practice guidelines*. Wellington. <http://www.moh.govt.nz>

Ministry of Health of the Republic of Lithuania (1997). *Confirmation of the application procedure of substitution therapy to opioid addicts*. Vilnius.

Ministry of Health of the Republic of Moldova (2003). *Order concerning substitution therapy for drug addicts*. (no further indications possible)

Psychiatric Special College of Hungary. *Professional guidelines of methadone treatment*. (no further indications possible)

Serbia and Montenegro. *Methadone maintenance program*. (no further indications possible)

U.S. Department of Health and Human Services – Substance Abuse and Mental Health Services Administration – Center for Substance Abuse Treatment (2004) *Clinical guidelines for the use of buprenorphine in the treatment of opioid addiction – a treatment improvement protocol TIP 40*. (DHHS Publication nr. 04-3939). Rockville MD

Vester, A., Buning, E. (2000). *Methadone Guidelines*. Euro Methwork.

Vievskiy, A. N., Vlasenko, L. V., Dvoriak, S. V. (2003). *Application of substitutive therapy in the course of treatment and rehabilitation of those having opioid addiction syndrome*. Ministry of Health of Ukraine: Kiev.

Vorrath, E. (Ed.), Lintzeris, N., Clark, N., Muhleisen, P., Ritter, A., Ali, R., Bell, J., Gowing, L., Hawkin, L., Henry Edwards, S., Mattick, R. P., Monheit, B., Newton, I., Quigley, A., Whicker, S., White, J. (2001). *National Clinical Guidelines and Procedures for the use of Buprenorphine in the Treatment of Heroin Dependence – National Drug Strategy*. Commonwealth of Australia. Department of Health and Aged Care.

Other references

Amato L, Minozzi S, Davoli M, Vecchi S, Ferri M, Mayet S. (2004a). Psychosocial and pharmacological treatments versus pharmacological treatments for opioid detoxification. *The Cochrane Database of Systematic Reviews* 2004, Issue 4, Art. No.: CD005031. DOI: 10.1002/14651858.CD005031.

Amato L, Minozzi S, Davoli M, Vecchi S, Ferri M, Mayet S (2004b). Psychosocial combined with agonist maintenance treatments versus agonist maintenance treatments alone for treatment of opioid dependence. *The Cochrane Database of Systematic Reviews* 2004, Issue 4, Art. No.: CD004147.pub2. DOI: 10.1002/14651858.CD004147 .pub2.

Ball, J.C., Ross, A. (1991). *The Effectiveness of Methadone Maintenance Treatment*. Springer, New York

Grella, C.E, Anglin, M.D, Wugalter, S.E, Rawson, R.A, Hasson, A. (1994). Reasons for discharge from methadone maintenance for addicts at high risk of HIV infection or transmission. *J Psychoactive Drugs* 26:223-232

Mattick, R.P., Ward, J., Hall, W. (1998). The role of counseling and psychological therapy. In Ward, J., Mattick, R.P., Hall, W. (Eds.) *Methadone maintenance treatment and other opioid replacement therapies*, pp. 265-304. Harwood, Amsterdam

McLellan, A.T, Arndt, I.O, Metzger, D.S, Woody, G.E, O'Brien, C.P. (1993). The effects of psychosocial services in substance abuse treatment. *JAMA* 269:1953-1959

McLellan, A.T. (2003). The role of Psychosocial Services in Drug Abuse Treatment. In Waal, H., Haga, E. (Eds.) *Maintenance Treatment of Heroin Addiction. Evidence at the crossroads*, pp. 265-295. Cappelen, Oslo

Saxon, A.J, Wells, E.A, Fleming, C, Jackson, T.R, Calsyn, D.A. (1996). Pre-treatment characteristics, program philosophy and level of ancillary services as predictors of methadone maintenance treatment outcome. *Addiction* 91:1197-1209

World Health Organisation (2003). *Guidelines for WHO guidelines. Global Programme on Evidence for Health Policy*, WHO, Geneva (EIP/GPE/EQC/2003.1)