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International Guidelines and methods to develop evidence based recommendations

Guidelines for the psychosocially assisted pharmacological treatment of opioid dependence, by WHO

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Summary

- **Why an evidence based opioid guideline ?**
- **The process to develop evidence based guidelines _GRADE**
- **Principal results**
- **Advantages and limits**
- **DECIDE**
- AGREE

A prerequisite

Practitioners and policy makers must make much clearer that they need rigorous evaluative research to help ensure that they do more good than harm.

Iain Chalmers

GUIDELINES

Definition of clinical practice guidelines (CPG) by the Institute of Medicine:

"***systematically developed statements to assist practitioner and patient decisions about appropriate healthcare for specific clinical circumstance***"

Why evidence based GL: Problem

- In general, guidelines are insufficiently transparent and not evidence based
  - Lack of use of systematic reviews
  - Lack of transparency about judgements
  - Too much dependence on expert opinion
  - Lack of emphasis on adapting global guidelines to end users' needs
  - Tension between time taken and when advice needed
  - Lack of resources

Oxman, Lavis & Fretheim, Lancet. 2007;369(9576):1883-9.

Many grading systems

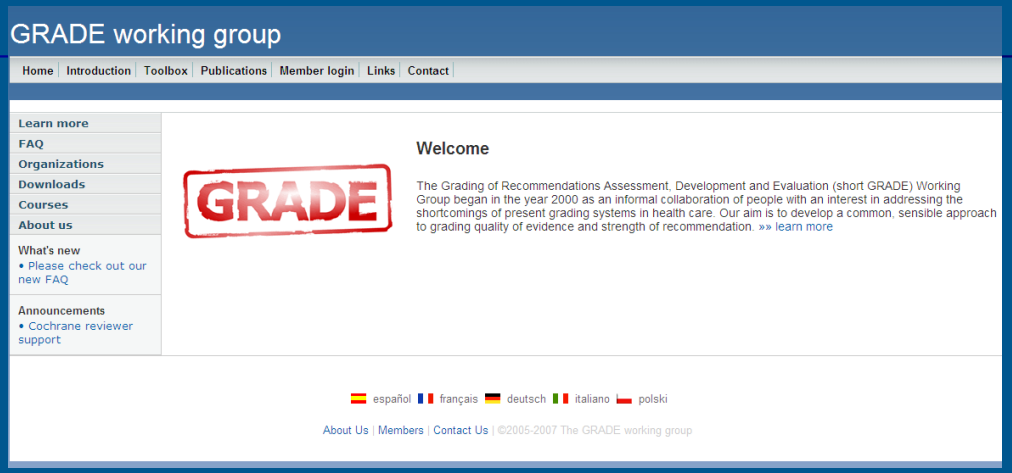
- Australian NMRC
- Oxford Center for Evidence-based Medicine
- Scottish Intercollegiate Guidelines (SIGN)
- US Preventative Services Task Force
- Professional organizations
  - AHA/ACC, ACCP, AAP, Endocrine society, etc....

Lots of confusion

Recommendation for use of oral anticoagulation in patients with atrial fibrillation and rheumatic mitral valve disease

Evidence	Recommendation	Organization
B	Class I	AHA
C+	1	ACCP
IV	C	SIGN

A common international grading system?



www.gradeworkinggroup.org

- International group
  - ACCP, AHRQ, Australian NMRC, BMJ Clinical Evidence, CC, CDC, NICE, Oxford CEBM, SIGN, UpToDate, USPSTF, WHO
- > 60 contributors
  - methodologists, guideline developers, systematic reviewers, researchers, clinicians, editors
- ~ 20 meetings over last seven years
  - ~10 – 40 participants

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Solution

- **WHO Guidelines Review Committee**
  - **Approval and review process**
  - **Tailored types of guidelines**
  - **Standards for use of evidence**
  - **Standards for reporting**
  - **Regular review and update**

2008;336;924-926 *BMJ*
2008;336;995-998 *BMJ*
2008;336;1049-1051 *BMJ*

RATING QUALITY OF EVIDENCE AND STRENGTH OF RECOMMENDATIONS

GRADE: an emerging consensus on rating quality of evidence and strength of recommendations

Guidelines are inconsistent in how they rate the quality of evidence and the strength of recommendations. This article explores the advantages of the GRADE system, which is increasingly being adopted by organisations worldwide

Guideline developers around the world are inconsistent in how they rate quality of evidence and grade strength of recommendations. As a result, guideline users face challenges in understanding the messages that grading systems try to communicate. Since 2006 the *BMJ* has requested in its "Instructions to Authors" on bmj.com that authors should preferably use the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system for grading evidence when submitting a clinical guidelines article.

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advantages and disadvantages but also by their confidence in these estimates. The cartoon depicting the weather forecaster's uncertainty captures the difference between an assessment of the likelihood of an outcome and the confidence in that assessment (figure). The usefulness of an estimate of the magnitude of intervention effects depends on our confidence in that estimate.

Expert clinicians and organisations offering recommendations to the clinical community have often erred as a result of not taking sufficient account of the quality

GRADE Uptake

Agencia sanitaria regionale, Bologna, Italia
Agency for Health Care Research and Quality (AHRQ)
Allergic Rhinitis and Group - Independent Expert Panel
American College of Cardiology Foundation
American College of Chest Physicians
American College of Emergency Physicians
American College of Physicians
American Endocrine Society
American Society of Gastrointestinal Endoscopy
American society of Interventional Pain Physicians
American Thoracic Society (ATS)
BMJ Clinical Evidence
British Medical Journal
Canadian Agency for Drugs and Technology in Health
Centers for Disease Control
Cochrane Collaboration
EBM Guidelines Finland
Emergency Medical Services for Children National Resource Center
European Association for the Study of the Liver
European Respiratory Society
European Society of Thoracic Surgeons
Evidence-based Nursing Sudtirol, Alta Adiga, Italy
Finnish Office of Health Technology Assessment
German Agency for Quality in Medicine
Infectious Disease Society of America
Japanese Society of Oral and Maxillofacial Radiology
Joslin Diabetes Center
Journal of Infection in Developing Countries
Kidney Disease International Guidelines Organization
National and Gulf Centre for Evidence-based Medicine
National Institute for Clinical Excellence (NICE)
National Kidney Foundation
Norwegian Knowledge Centre for the Health Services
Ontario MOH Medical Advisory Secretariat
Panama and Costa Rica National Clinical Guidelines Program
Polish Institute for EBM
Scottish Intercollegiate Guideline Network (SIGN)
Society of Critical Care Medicine
Society of Pediatric Endocrinology
Society of Vascular Surgery
Spanish Society of Family Practice (SEMFYC)
Stop TB Diagnostic Working Group
Surviving sepsis campaign
Swedish Council on Technology Assessment in Health Care
Swedish National Board of Health and Welfare
University of Pennsylvania Health System for EB Practice
UpToDate
World Health Organization

GRADE process

PICO question and selection of outcomes

Evidence retrieval and Quality of evidence assessment

Risk/benefit, values and preferences, cost and feasibility

Recommendation:

Strong or Weak (conditional)

Formulate question

Select outcomes

Rate importance

Outcomes across studies

Create evidence profile with GRADEpro

Rate quality of evidence for each outcome

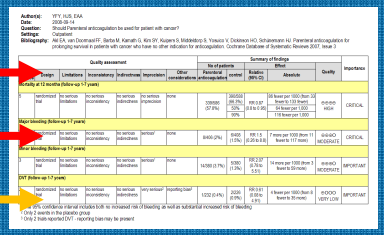
P
I
C
O

Outcome Critical

Outcome Critical

Outcome Important

Outcome Not important



Summary of findings & estimate of effect for each outcome

High ⊕⊕⊕⊕

Moderate ⊕⊕⊕◯

Low ⊕⊕◯◯

Very low ⊕◯◯◯

Grade down

1. Risk of bias
2. Inconsistency
3. Indirectness
4. Imprecision
5. Publication bias

Grade up

1. Large effect
2. Dose response
3. Confounders

Systematic review

Input?

Guideline development

Grade recommendations

•For or against (direction) ↓↑

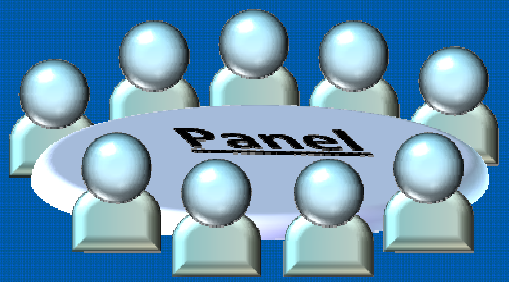
•Strong or conditional/weak (strength)

By considering balance of:

- ❑ Quality of evidence
- ❑ Balance benefits/harms
- ❑ Values and preferences

Revise if necessary by considering:

❑Resource use (cost)



Guideline

Grade overall quality of evidence across outcomes based on lowest quality of ***critical*** outcomes

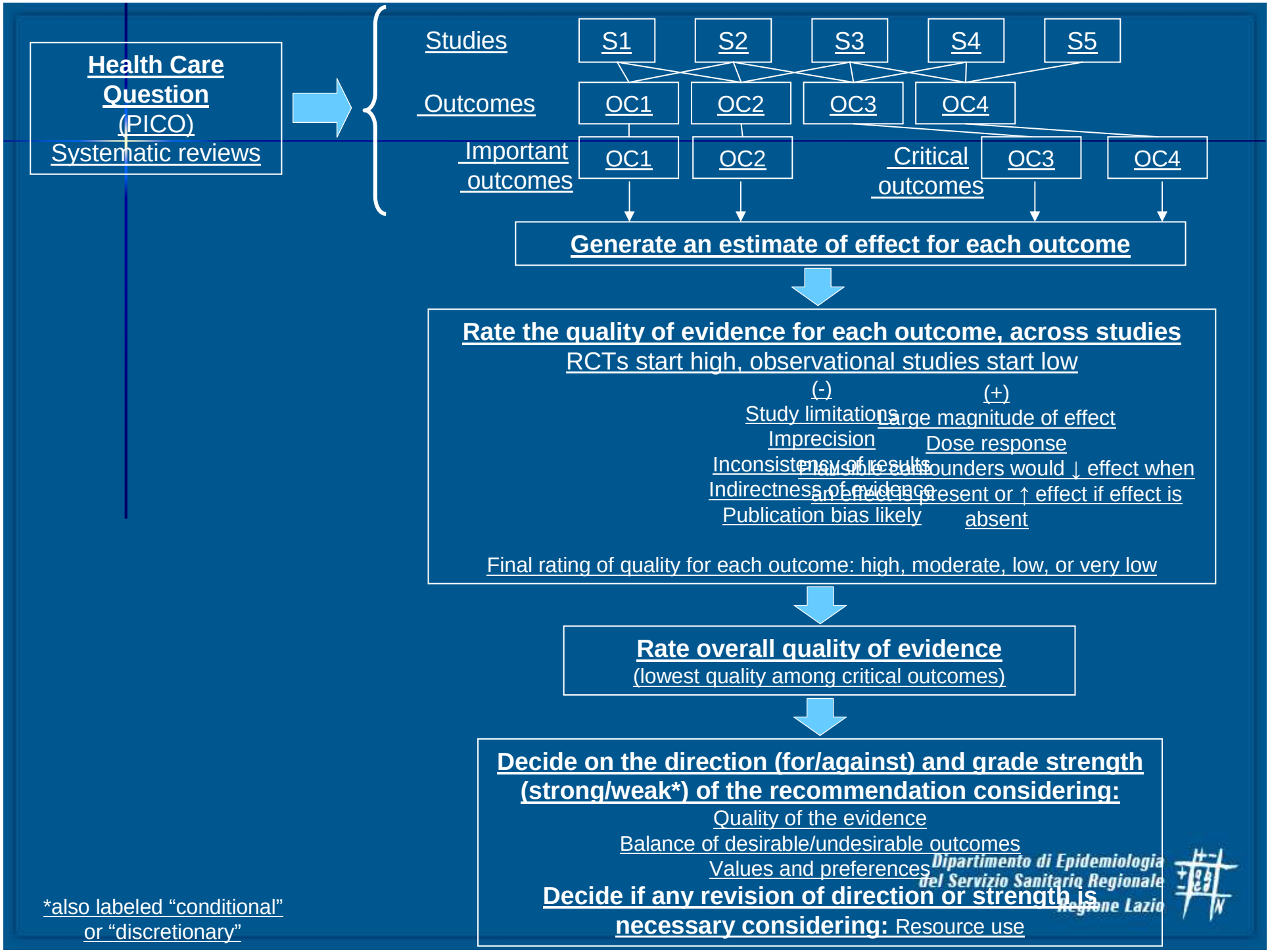
Formulate Recommendations (↓↑ | ⊕…)

•"We recommend using…" | "Clinicians should…"

•"We suggest using…" | "Clinicians might…"

•"We suggest not using…" | "Clinicians …not…"

•"We recommend not using…"| "Clinicians should not…"


Health Care Question
(PICO)
Systematic reviews
Studies
S1
S2
S3
S4
S5
Outcomes
OC1
OC2
OC3
OC4
Important outcomes
OC1
OC2
Critical outcomes
OC3
OC4
Generate an estimate of effect for each outcome
Rate the quality of evidence for each outcome, across studies
RCTs start high, observational studies start low
(-)
Study limitations
Imprecision
Inconsistency of results
Indirectness of evidence
Publication bias likely
(+)
Large magnitude of effect
Dose response
Plausible confounders would ↓ effect when an effect is present or ↑ effect if effect is absent
Final rating of quality for each outcome: high, moderate, low, or very low
Rate overall quality of evidence
(lowest quality among critical outcomes)
Decide on the direction (for/against) and grade strength (strong/weak*) of the recommendation considering:
Quality of the evidence
Balance of desirable/undesirable outcomes
Values and preferences
Decide if any revision of direction or strength is necessary considering: Resource use
*also labeled "conditional" or "discretionary"
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World Health Organization
GUIDELINES FOR THE TREATMENT OF MALARIA
Policy Makers and Health Professionals
PREVENTION
THE INTERAGENCY LIST OF ESSENTIAL MEDICINES FOR REPRODUCTIVE HEALTH
2006
GUIDELINES
MANAGEMENT OF THE CHILD WITH A SERIOUS INFECTION OR SEVERE MALNUTRITION
Guidelines for care at the first-referral level in developing countries
World Health Organization
POCKET BOOK OF
Hospital care for children
GUIDELINES FOR THE MANAGEMENT OF COMMON ILLNESSES WITH LIMITED RESOURCES
World Health Organization
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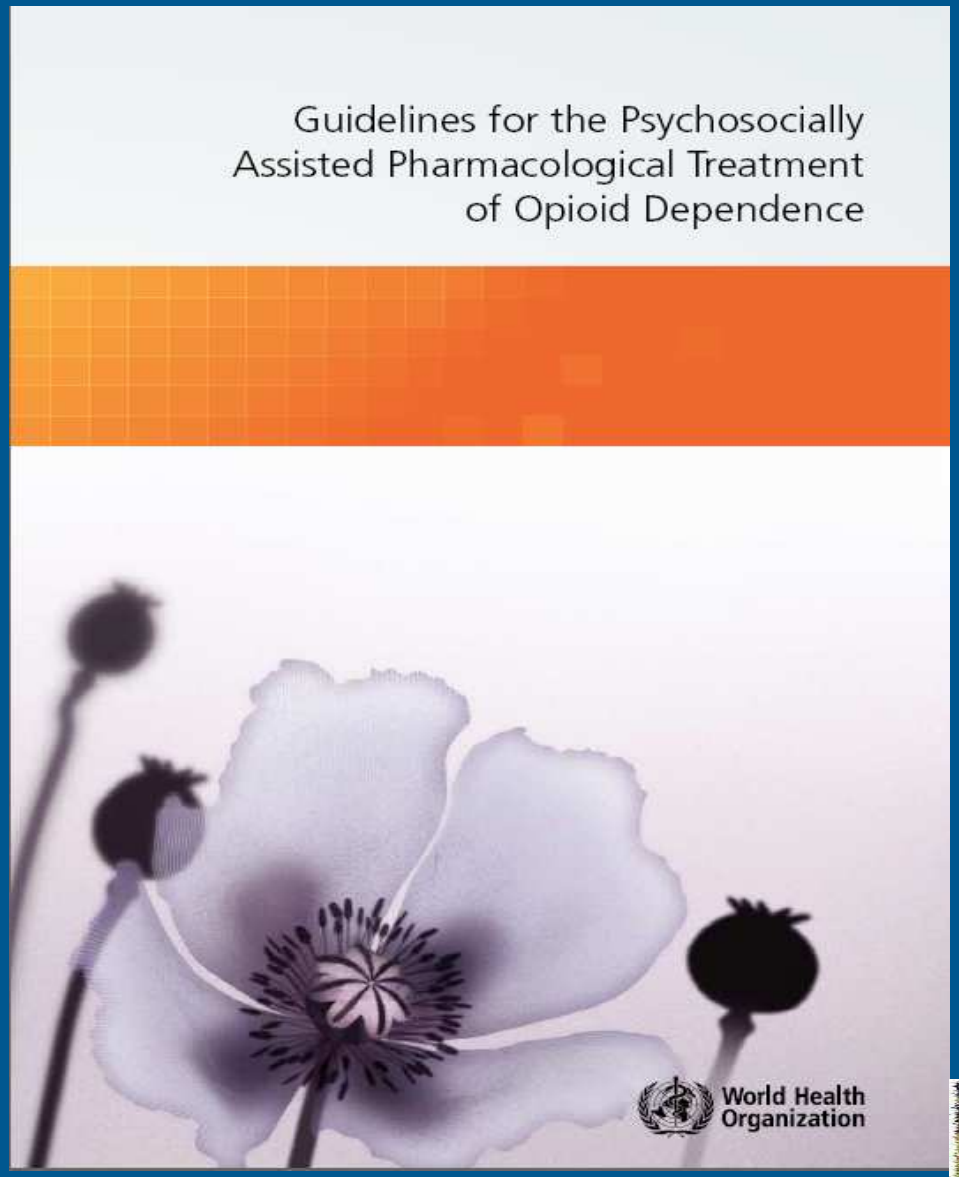
http://www.who.int/substance_abuse/publications/opioid_dependence_guidelines.pdf



Steps of the Process

Prioritise problem, establish panel
Identify the questions to be answered
Define the relative importance of the outcomes
Find the evidence (RS, RCTs…..CPS)
Rate quality of evidence for each outcome
Rate overall quality of evidence
Balance of benefits and harms (does the intervention do more good than harm?)
Balance of benefits and costs
Define the strength of the recommendation
Implementation and evaluation

Prioritise the problem

These guidelines have been developed in response to the resolution of the United Nations Economic and Social Council (ECOSOC).

The resolution invited the World Health Organization (WHO), in collaboration with United Nations Office on Drugs and Crime (UNODC), "to develop and publish minimum requirements and international guidelines on psychosocially assisted pharmacological treatment of persons dependent on opioids, taking into account regional developments in the field, in order to assist the member states concerned"

Establish PANEL

- A group of technical experts – international scientists with expertise in opioid dependence
- Clinicians involved in the treatment of opiid addiction
- Methodologists / epidemiologists
- Consumers
- Economists and stakeholders

GUIDELINES DEVELOPMENT GROUP

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  - Drug and Alcohol Services Council, Adelaide, Australia
  - Institute of Health Science Research, Bangkok, Thailand
  - Mental Health Institute, Hunan, China
  - National Drug Research Institute, Perth, Australia
- Other organizations
  - American Association for the Treatment of Opioid Dependence
  - American College of Neuropsychopharmacology
  - American Society of Addiction Medicine
  - International Harm Reduction Association
  - International Center for Advancement of Addiction Treatment (ICAAT)
  - National Alliance of Methadone Advocates, New York, United States
  - National Institute on Drug Abuse, United States
  - National Institute for Health and Clinical Excellence (NICE), United Kingdom
  - Quest for Quality, the Netherlands
  - Service d'Abus de Substances, Département de Psychiatrie, Genève
  - South African National Council on Alcohol and Drug Dependence
  - Turning Point Alcohol & Drug Centre, Melbourne, Australia
  - World Psychiatric Association
  - South African National Council on Alcohol and Drug Dependence
  - Turning Point Alcohol & Drug Centre, Melbourne, Australia
  - World Psychiatric Association

The recommendations in the guidelines operate at three levels:

- treatment systems at national and subnational levels (policy, legislation, funding, regional and country planning) (see Chapter 4)
- treatment programmes (methods of organization and provision of care) (see Chapter 5)
- treatment of the individual patient (see Chapter 6).

Define the clinical questions

- In their first meeting, the group defined the key questions to be addressed by the guidelines, using PICO.

Choice of treatment approach

1. Should agonist maintenance therapy (i.e. methadone or buprenorphine maintenance) be used in preference to withdrawal and oral antagonist therapy (naltrexone) or withdrawal alone?

Opioid agonist maintenance treatment

2. What are the indications for opioid agonist maintenance treatment?
3. In patients to be treated with agonist maintenance treatment, should preference be given to methadone or buprenorphine?
4. What initial doses of methadone or buprenorphine should be used?
5. Should methadone and buprenorphine doses by fixed or individually tailored?
6. What maintenance doses of methadone and buprenorphine should be used?
7. Should opioid agonist maintenance treatment doses be
8. supervised?
9. What is the optimal duration of opioid agonist treatment?
10. Should psychosocial treatments be used in addition to pharmacological maintenance treatments?

Management of opioid withdrawal

11. What treatments should be used to assist withdrawal from opioids?
12. Should antagonists with minimal sedation be used for opioid withdrawal?
13. Should antagonists with heavy sedation or anaesthesia be used for opioid withdrawal?
14. Should withdrawal from opioids be conducted in inpatient or outpatient settings?
15. Is psychosocial assistance plus pharmacological assistance for opioid withdrawal more useful than pharmacological assistance alone?

Opioid antagonist (naltrexone) treatment

16. Should opioid antagonist therapy be used for opioid dependence and, if so, what are the indications for use?

Define the relative importance of the outcomes

- For each question, the panel identified the outcomes to be considered and rated their relative importance

Choice of outcomes

all important outcomes should be considered in making a recommendation, but only critical ones should be considered when making judgements about the overall quality of the evidence underlying a recommendation

studies using surrogate outcomes generally provide weaker evidence than those using outcomes that are important, and these only should be included when evidence for important outcomes is lacking.

Schünemann HG et al. Health Res Policy Syst 2006;4:18

Rating the outcomes

The GRADE convention on the rating of outcomes is as follows:

- **ratings of 7–9 are for critical health outcomes**
- **ratings of 4–6 are for outcomes that are considered important but not critical to the decision; they should be used in judgements about tradeoffs and recommendations, but not in judgements about the overall quality of evidence across critical outcomes**
- **ratings of 1–3 are generally removed from the evidence profile and are not considered in judgements about the overall quality of evidence, tradeoffs or recommendations.**

Outcome	
Retention in treatment	Critical
Side effects	Critical
Mortality	Critical
Level of social functioning	Critical
Quality of life	Critical
HIV seroconversion	Critical
Hepatitis seroconversion	Critical
patient satisfaction	Critical
use of primary substance	Important but not critical
patients who have relapsed at follow-up at 12 months	Important but not critical
patients who have relapsed at follow-up > 12 months	Important but not critical
frequency of high risk behaviours	Important but not critical
criminal and delinquent behaviour	Important but not critical
use of other drugs	Important but not critical
relapse rate in abstinence oriented treatment program	Not important
disability	Not important
psychiatric comorbidity	Not important
compliance with treatment	Not important
diversion of medication (not naltrexone)	Not important
cost of treatment	Not important

Searching the literature

- For each key clinical question, the literature was searched for recent systematic reviews on the topic.
- Where a Cochrane review existed, that review was used in preference to other reviews.
- Where no suitable systematic review existed, a review was conducted.

Rate quality of evidence

The quality of the evidence was assessed according to the methodology described by the GRADE working group.
This approach involves assessing the quality of evidence on a particular question, taking into consideration the magnitude of the effect, the relevance of the data to the clinical question being asked, the sample size in the relevant trials, the methodology of the trials and the consistency of the findings

Determinants of quality

Study design: RCTs start high, observational studies start low.

What can lower quality?

- **Limitations:** concealment, intention to treat, blinding, loss to follow-up
- **Inconsistency:** variability in results, variation in size of effect, overlap in confidence intervals, statistical significance of heterogeneity
- **Indirectness: differences in patients:** interventions, comparators. **differences in outcomes:** surrogates
- **Other consideration:** imprecise or sparse data; publication bias

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Interpretation of quality

- High quality— Further research is very unlikely to change our confidence in the estimate of effect
- Moderate quality— Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
- Low quality— Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
- Very low quality— Any estimate of effect is very uncertain

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Some examples

The question:
Should methadone maintenance treatment versus opioid withdrawal or no treatment be used for opioid dependence?

Outcome	Importance
Mortality	9
Retention in Treatment	7
Use of opiate	7
Criminal behaviour	6

A1.1 Is methadone effective for the treatment of opioid dependence?

GRADE evidence profile

Author(s): Amato L
Date: 23 August 2006
Question: Should methadone maintenance treatment versus opioid withdrawal or no treatment be used for opioid dependence?
Patient or population: opioid addicts
Settings: outpatient
Systematic review: Mattick RP et al. (in press) *Methadone maintenance therapy versus no opioid replacement therapy for opioid dependence* (CLIB 3, 2003)[105]; Bargagli AM et al. (2007) *A systematic review of observational studies on treatment of opioid dependence.*[197]

(Throughout this annex, –1 is used to indicate that the score has been reduced by one because of a weakness in this area).

Quality assessment						Summary of findings					
						No of patients		Effect		Quality	Importance
No. studies	Design	Limitations	Consistency	Directness	Other considerations	Methadone maintenance treatment	No treatment	Relative risk (RR) (95% CI)	Absolute risk (AR) (95% CI)		
Use of opiates[66,188,189] (subjective follow-up: 1 month–2 years)											
3[a]	Randomized trials[b]	Some limitations[b] (–1)	No important inconsistency	No uncertainty	None	28/104 (26.9%)	110/126 (87.3%)	RR 0.323 (0.23 to 0.44)	AR 630/1000 less (830 less to 430 less)	⊕⊕⊕○ Moderate	7
Criminal behaviour[66,188,189] (objective follow-up: 1 month–2 years)											
3[a]	Randomized trials[b]	Some limitations[b] (–1)	No important inconsistency	No uncertainty	Imprecise or sparse data (–1)	5/178 (2.8%)	18/185 (9.7%)	RR 0.393 (0.12 to 1.25)	AR 250/1000 less (700 less to 19 more)	⊕⊕○○ Low	6
Mortality from randomized controlled trials[188,196,198] (RCTs) (objective follow-up: 2–3 years)											
3[d]	Randomized trials[e]	No limitations	No important inconsistency	No uncertainty	Imprecise or sparse data (–2)	3/216 (1.4%)	7/219 (3.2%)	RR 0.493 (0.06 to 4.23)	AR 16/1000 less (100 less to 30 more)	⊕⊕○○ Low	9
Mortality (any cause) from observational studies[190,191,192,193,194] (objective follow-up: 2.5 years–21 years)											
5[f]	Observational studies[g]	No limitations	No important inconsistency	No uncertainty	None	257/19421 (1.3%)	1063/23614 (4.5%)	RR 0.37 (0.29 to 0.48)	AR 20/1000 less (30 less to 10 less)	⊕⊕○○ Low	9
Mortality (overdose) from observational studies [190,191,195,193,196] (objective follow-up: 2.5 years–12 years)											
5[h]	Observational studies[i]	No limitations	Inconsistent results between studies (–1)10	No uncertainty	Extremely strong effect (+2)	70/37516 (0.2%)	416/32454 (1.3%)	RR 0.17 (0.05 to 0.63)	AR 10/1000 less (20 less to 0.00)	⊕⊕⊕○ Moderate	9
Retention in treatment[106,108,197] (objective follow-up: 1 month–2 years)											
3[k]	Randomized trials[l]	No limitations	No important inconsistency	No uncertainty	None	173/254 (68.1%)	63/251 (25.1%)	RR 3.053 (1.75 to 5.35)	AR 460/1000 more (270 more to 650 more)	⊕⊕⊕⊕ High	7

[a] Three studies in an outpatient setting; two were conducted in the United States and one in Sweden.
[b] Three randomized controlled trails (RCTs): one with adequate allocation concealment, one unclear and one inadequate.
[c] Random effect model.
[d] Three RCTs, one conducted in the United States, one in Sweden and one in China.
[e] One adequate and two unclear allocation concealment.
[f] Five studies in an outpatient setting; conducted in Italy, Australia, Sweden, the United States and Spain (one in each).
[g] Quality of studies using Newcastle–Ottawa Scale: selection, two studies rated 3 and three studies rated 2; comparability, one study rated 3, three studies rated 1 and one study rated 0; outcome, two studies rated 2 and three studies rated 1.
[h] Five studies in an outpatient setting: two conducted in the Netherlands and one each in Italy, the United States and Spain.
[i] Quality of studies using Newcastle–Ottawa Scale: selection, four studies rated 3 and one study rated 2; comparability, two studies rated 2 and three studies rated 1; outcome, one study rated 2 and four studies rated 1.
[j] High statistical heterogeneity $P < 0.00001$, but all consistent results.
[k] Three studies in an outpatient setting, conducted in Hong Kong, Thailand and the United States (one each).
[l] Three RCTs, all with unclear allocation concealment.

Author(s): Amato L, Minozzi S
Date: 22 May 2006
Question: Should agonist maintenance treatment be used for the prevention of HIV infection or reduction of high-risk behaviours?
Patient or population: injecting opioid dependent
Settings: Outpatient
Systematic review: Gowing L et al. (2004) *Substitution treatment of injecting opioid users for prevention of HIV infection* (CLIB 4, 2004)[213].

Quality assessment						Summary of findings					
						No of patients		Effect		Quality	Importance
No. studies	Design	Limitations	Consistency	Directness	Other considerations	Agonist maintenance treatment	No treatment	Relative risk (RR) (95% CI)	Absolute risk (AR) (95% CI)		
Injecting behaviour: prevalence of injecting, cohort study[198] (subjective follow-up: 18 months)											
1[a]	Observational studies[b]	No limitations	No important inconsistency	No uncertainty	None	125/152 (82.2%)	97/103 (94.2%)	RR 0.87[c] (0.80 to 0.95)	AR 120/1000 less (200 less to 40 less)	⊕⊕○○ Low	6
Injecting behaviour: prevalence of injecting[199] (subjective follow-up: 4 months)											
1[e]	Randomized trials[e]	No limitations	No important inconsistency	Some uncertainty (–1)[f]	None	44/129 (34.1%)	93/124 (75.0%)	RR 0.45[d] (0.35 to 0.59)	AR 410/1000 less (520 less to 300 less)	⊕⊕⊕○ Moderate	6
Injecting behaviour: proportion of patients sharing injecting equipment, observational studies[198, 200, 201] (subjective follow-up: 0–18 months)											
3[g]	Observational studies[h]	No limitations	No important inconsistency	No uncertainty	None	83/301 (27.6%)	424/1020 (41.6%)	RR 0.54[c] (0.37 to 0.79)	AR 230/1000 less (400 less to 60 less)	⊕⊕○○ Low	7
Sexual behaviour: commercial sex [198] (follow-up: 18 months)											
1[e]	Observational studies[i]	No limitations	No important inconsistency	No uncertainty	None	43/152 (28.3%)	47/103 (45.6%)	RR 0.62[c] (0.45 to 0.86)	AR 170/1000 less (290 less to 50 less)	⊕⊕○○ Low	7
Sexual behaviour: unprotected sex[198, 200] (follow-up: 3–6 months)											
2[j]	Observational studies[k]	No limitations	No important inconsistency	No uncertainty	None	174/213 (81.7%)	554/654 (84.7%)	RR 0.94[d] (0.87 to 1.02)	AR 60/1000 less (130 less to 10 more)	⊕⊕○○ Low	6
Seroconversion to HIV [198, 200] (variable follow-up: up to 5 years)											
2[l]	Observational studies	No limitations	No important inconsistency	No uncertainty	None	16/579 (2.8%)	24/297 (8.1%)	RR 0.36[c] (0.19 to 0.66)	AR 50/1000 less	⊕⊕○○ Low	8

[a] One study in an outpatient setting, conducted in the United States (Metzger, 1993)[198].
[b] One descriptive study in which the author rated the quality of the study on the basis of six items (description of the population, description of eligibility criteria, adjustment for confounding, less than 20% loss to follow-up, presence of co-intervention, inconsistency in data collection between groups) rated from 0 to 1 where 0 = no bias. On the basis of this rating system the study was rated 1.
[c] Random effect model.
[d] One study conducted in Australia, in an inpatient setting (in prison).
[e] The study was rated 1 (see footnote 2).
[f] Opioid-dependent prisoners.
[g] All three studies were conducted in an outpatient setting, two in the United States and one in Germany.
[h] Three cohort studies, two rated 1 and one 2 (see footnote 2).
[i] One cohort study rated 1 (see footnote 2).
[j] Both outpatient, one conducted in the United States and one in Germany.
[k] Both rated 1 (see footnote 2).
[l] Two cohort studies: Metzger (1993)[198] a non-treatment control group selected by methadone group, and Moss (1994)[202] a control group selected from contemporaneous entry to opioid withdrawal programme.

A1.3 Is buprenorphine effective for the treatment of opioid dependence?

GRADE evidence profile

Author(s): Amato L, Minozzi S
Date: 23 May 2006
Question: Should buprenorphine maintenance versus placebo be used for opioid addiction?
Patient or population: Opioid dependent
Settings: Outpatient and inpatient
Systematic review: Mattick RP et al. *Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence* (2008, in press)[110].

Quality assessment						Summary of findings					
						No of patients		Effect		Quality	Importance
No. studies	Design	Limitations	Consistency	Directness	Other considerations	Buprenorphine	Placebo[a]	Relative risk (RR) (95% CI)	Absolute risk (AR) (95% CI)		
Retention in treatment: 2–4 mg buprenorphine versus placebo or 1 mg buprenorphine[104, 204, 109, 110] (objective follow-up: 2–16 weeks[d])											
2	Randomized trials[b]	No limitations	No important inconsistency	One inpatient study (–1)	None	141/242 (58%)	114/245 (47%)	RR 1.24[c] (1.06 to 1.45)	AR 100/1000 more (30 more to 210 more)	⊕⊕⊕○ Moderate	7
Morphine positive urines: 2–4 mg buprenorphine versus placebo or 1 mg buprenorphine											
2	Randomized trials[b]	No limitations	Inconsistent results between studies (–1)	One inpatient study (–1)	None	242	245	–	SMD 0.10[c] (–0.8 to 1.01)	⊕⊕○○ Low	7
Retention in treatment: 8 mg buprenorphine versus placebo or 1 mg buprenorphine[104, 204, 109, 110] (objective follow-up: 2–16 weeks[d])											
2	Randomized trials[b]	No limitations	No important inconsistency	One inpatient study (–1)	None	119/218 (54%)	114/245 (47%)	RR 1.21[c] (1.02 to 1.44)	80/1000 more (9 more to 191 more)	⊕⊕⊕○ Moderate	7
Morphine positive urines: 8 mg buprenorphine versus placebo or 1 mg buprenorphine											
2	Randomized trials[b]	No limitations	Inconsistent results between studies (–1)	One inpatient study (–1)	None	218	245	–	SMD –0.28[c] (–0.47 to -0.10)	⊕⊕○○ Low	7
Retention in treatment: 16 mg buprenorphine versus 1 mg buprenorphine[104, 204, 109, 110] (objective follow-up: 2–16 weeks[d])											
1	Randomized trials[b]	No limitations	No important inconsistency	No uncertainty	None	110/181 (61%)	74/185 (40%)	RR 1.52[c] (1.23 to 1.88)	210/1000 more (90 more to 350 more)	⊕⊕⊕⊕ High	7
Morphine positive urines: 16 mg buprenorphine versus placebo or 1 mg buprenorphine											
1	Randomized trials[b]	No limitations	No important inconsistency	No uncertainty	None	181	185	—	SMD –0.65[c] (–0.44 to –0.86)	⊕⊕⊕⊕ High	7

[a] Two RCTs: one inpatient, one outpatient, both conducted in the United States.
[b] Both with unclear allocation concealment.
[c] Random effect model.
[d] Length of treatment.
[e] Placebo or 1 mg buprenorphine daily.

Recommendation

For the pharmacological treatment of opioid dependence, clinicians should offer opioid withdrawal, opioid agonist maintenance and opioid antagonist (naltrexone) treatment, but most patients should be advised to use opioid agonist maintenance treatment.

- Strength of recommendation — strong
- Quality of evidence — low to moderate
- Remarks — There is moderate evidence that agonist maintenance treatment results in less illicit opioid use in the medium term than opioid withdrawal or antagonist therapy. Opioid-dependent patients should be encouraged to use opioid agonist maintenance treatment in preference to these other approaches. There is a spectrum of severity of opioid dependence. In less severe cases of opioid dependence (e.g. non-injectors and those who have recently commenced opioid use), treatment with agonist maintenance is still recommended for most patients, but a significant number are also likely to do well with opioid withdrawal-based treatments, and it would be reasonable to recommend these to some patients.

A1.11 Should antagonist pharmacotherapy, naltrexone, be used for the treatment of opioid dependence?

GRADE evidence profile

Author(s): Minozzi, Amato
Date: 23/03/2006
Question: Should oral naltrexone be used for opioid dependence?
Patient or population: Opioid-dependent patients
Settings: Outpatient
Systematic review: Minozzi et al.; *Oral naltrexone treatment for opioid dependence* (CLIB 1, 2006)[170].

Quality assessment						Summary of findings					
						No of patients		Effect		Quality	Importance
No. studies	Design	Limitations	Consistency	Directness	Other considerations	Oral naltrexone	Placebo	Relative risk (RR) (95% CI)	Absolute risk (AR) (95% CI)		
Retention in treatment[220, 240, 241, 242, 243] (Objective follow-up: 2-9 months[d])											
5[a]	Randomized trials	No limitations[b]	No important inconsistency	No uncertainty	Imprecise or sparse data (-1)	35/105 (33,3%)	31/98 (31,6%)	RR 1.08[c] (0.74 to 1.57)	20/1 000 more (90 less to 140 more)	⊕⊕⊕○ Moderate	6
Use of opioids [220, 240, 240, 241, 242, 243] (Objective[e] follow-up: 2-9 months[d])											
6[a]	Randomized trials	Serious limitations (-1)[g]	No important inconsistency	No uncertainty	Imprecise or sparse data (-1)	68/139 (48,9%)	69/110 (62,7%)	RR 0.72[c] (0.58 to 0.90)	180 less / 1 000 (290 less to 60 less)	⊕⊕○○ Low	7
Relapsed at follow-up[241, 242] (follow-up: 6 months-1 year)											
2[h]	Randomized trials	No limitations[i]	No important inconsistency	No uncertainty	Imprecise or sparse data (-2)[j]	26/43 (60,5%)	24/38 (63,2%)	RR 0.94[c] (0.67 to 1.34)	40 less / 1 000 (250 less to 180 more)	⊕⊕○○ Low	7
Criminal behaviour[240, 240] (objective[e] follow-up: 6-10 months[d])											
2[m]	Randomized trials	No limitations[n]	No important inconsistency	Specific population (prison release) (-1)	Imprecise or sparse data (-2)	13/54 (24,1%)	15/32 (46,9%)	RR 0.50[c] (0.27 to 0.91)	240 less / 1 000 (440 less to 30 less)	⊕○○○ Very low	6

[a] Outpatient. Country of origin: Israel 2,USA 1, Russia 1, Spain 1
[b] 2 adequate allocation concealment, the other unclear; all double blind
[c] Fixed effect model
[d] Length of treatment
[e] All outpatient. Country of origin: Israel 2, USA 1, China 1, Russia 1, Spain 1
[f] Based on urinalysis
[g] 2 adequate allocation concealment, the other unclear; all double blind. ITT analyses not used.
[h] Both outpatient, one conducted in Israel, the other in Spain
[i] 1 with adequate allocation concealment, 1 unclear, both double blind
[j] Few patients, result not statistically significant
[k] All outpatient, conducted in USA, China and Russia 1 each
[l] 1 adequate allocation concealment, 2 unclear, all double blind
[m] Number of subjects with at least one side effect
[n] Both outpatient and both conducted in USA
[o] Number re-incarcerated
[p] Both unclear allocation concealment and open design
[q] 2 studies, few patients

Recommendation

For opioid-dependent patients not commencing opioid agonist maintenance treatment, consider antagonist pharmacotherapy using naltrexone following the completion of opioid withdrawal.

- Strength of recommendation – standard
- Quality of evidence – low
- Remarks – This recommendation acknowledges that not all patients are able to access opioid agonist maintenance treatment, and that not all patients who can access it want it. In these circumstances, the use of naltrexone after withdrawal appears to have advantages over opioid withdrawal without naltrexone, in those patients who are prepared to take naltrexone.

A1.4 Methadone versus buprenorphine

GRADE evidence profile

Author(s): Amato L, Minozzi S
Date: 22 March 2006
Question: Should buprenorphine maintenance flexible doses versus methadone maintenance flexible doses be used for opioid maintenance treatment?
Patient or population: Opiate dependents
Settings: Outpatient
Systematic review: Mattick RP et al. *Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence* (2008, in press).[105]

Quality assessment						Summary of findings					
						No of patients		Effect		Quality	Importance
No. studies	Design	Limitations	Consistency	Directness	Other considerations	Buprenorphine maintenance flexible doses	Methadone maintenance flexible doses	Relative risk (RR) (95% CI)	Absolute risk (AR) (95% CI)		
Retention in treatment flexible doses buprenorphine versus flexible doses methadone[105, 106, 68, 107, 125, 208, 209] (objective follow-up: 6–48 weeks[d])											
7[a]	Randomized trials	No limitations[b]	No important inconsistency	No uncertainty	None	255/484 (52.7%)	310/492 (63.0%)	RR 0.82[c] (0.72 to 0.94)	130/1 000 (220 less to 40 less)	⊕⊕⊕⊕ High	7
Use of opiate during the treatment[e][210, 105, 107, 125, 208, 209] (better indicated by: lower scores)											
6[e]	Randomized trials	No limitations[f]	No important inconsistency	No uncertainty	None	411	426	—	SMD –0.12 (–0.26 to +0.02)	⊕⊕⊕⊕ High	7
Use of cocaine during the treatment[g][210, 105, 107, 208, 209] (better indicated by: lower scores)											
5[h]	Randomized trials	No limitations[i]	No important inconsistency	No uncertainty	None	384	395	—	SMD 0.11 (–0.03 to +0.25)	⊕⊕⊕⊕ High	5
Use of benzodiazepine during the treatment[g][210, 107, 208, 209] (better indicated by: lower scores)											
4[j]	Randomized trials	No limitations[k]	No important inconsistency	No uncertainty	None	329	340	—	SMD 0.11 (–0.04 to +0.26)	⊕⊕⊕⊕ High	4
Criminal behaviour [207] (better indicated by: lower scores)											
1[l]	Randomized trials	No limitations[m]	No important inconsistency	No uncertainty	Imprecise or sparse data (–1)[n]	95	117	—	SMD –0.14 (–0.41 to +0.14)	⊕⊕⊕◯ Moderate	6

[a] All outpatient, country of origin: three United States, one Austria, one Switzerland, one Australia, one United Kingdom.
[b] Two studies with adequate allocation concealment, for the others five not described; 5/7 double blind.
[c] Random effect model.
[d] Length of treatment.
[e] All outpatient, country of origin: three United States, one Austria, one Australia, one Switzerland.
[f] 5/6 double blind; one adequate allocation concealment, five not stated.
[g] Data based on urinalysis.
[h] All outpatient, country of origin: three United States, one Austria, one Australia.
[i] 4/5 double blind; one adequate allocation concealment, five not stated.
[j] All outpatient, country of origin: two United States, one Austria, one Australia.
[k] 3/4 double blind; one adequate allocation concealment, five not stated.
[l] Outpatient, conducted in Australia.
[m] Double blind, adequate allocation concealment.

GRADE evidence profile

Author(s): Amato L, Minozzi S
Date: 23 March 2006
Question: Should buprenorphine maintenance moderate doses (6–12 mg/day) versus methadone maintenance moderate doses (50–80 mg/day) be used for opioid dependence?
Patient or population: Opiate dependents
Settings: Outpatient
Systematic review: Mattick RP et al. *Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence* (2008, in press)[105].

Quality assessment						Summary of findings					
						No of patients		Effect		Quality	Importance
No. studies	Design	Limitations	Consistency	Directness	Other considerations	Buprenorphine maintenance high doses (6–12 mg/day)	Methadone maintenance high doses (50–80 mg/day)	Relative risk (RR) (95% CI)	Absolute risk (AR) (95% CI)		
Retention in treatment [205, 206, 68, 207, 125, 208, 209] **(follow-up: 17–52 weeks[a])**											
7[a]	Randomized trials	No limitations[b]	Important inconsistency (–1)[c]	No uncertainty	None	158/356 (44.4%)	199/352 (56.5%)	RR 0.79[d] (0.64 to 0.99)	120/1000 (230 less to 10 less)	⊕⊕⊕○ Moderate	7
Use of opiates[e] [210, 205, 207, 125, 208, 209] **(better indicated by: lower scores)**											
3[f]	Randomized trials	No limitations[g]	No important inconsistency	No uncertainty	Imprecise or sparse data (–1)	157	157	—	SMD 0.27 (0.05 to 0.50)	⊕⊕⊕○ Moderate	7
Use of cocaine[e] [210, 205, 207, 208, 209] **(better indicated by: lower scores)**											
1[h]	Randomized trials	No limitations[g]	No important inconsistency	No uncertainty	Very imprecise or sparse data (–2)[i]	29	28	—	SMD 0.22 (–0.30 to 0.74)	⊕⊕○○ Low	5

[a] All outpatient, six conducted in the United States, one in Italy.
[b] All double blind, one adequate allocation concealment, the others not described.
[c] High heterogeneity $P = 0.04$.
[d] Random effect model.
[e] Length of treatment.
[f] All outpatient and all conducted in the United States.
[g] Based on urinalysis.
[h] Three double blind, one with adequate allocation concealment, the others not stated.
[i] Outpatient, conducted in the United States.
[j] Double blind, allocation concealment not stated.
[k] Only one study, few patients, result not statistically significant.

Recommendation

For opioid agonist maintenance treatment, most patients should be advised to use methadone in adequate doses in preference to buprenorphine.

- Strength of recommendation – strong
- Quality of evidence – high
- Remarks – Although the general preference may be for methadone over buprenorphine, some patients may do better with buprenorphine. Reasons for use of buprenorphine may include previous response to buprenorphine or lack of response to methadone, short duration of action of methadone (i.e. withdrawal symptoms between doses), interaction between methadone and other medications taken, specific adverse effects of methadone, treatment availability and patient preference for subjective effects of buprenorphine compared to methadone. Reasons not to use buprenorphine include a history of buprenorphine injection, buprenorphine-specific adverse effects and failure of buprenorphine treatment in the past.

A1.5 What maintenance doses of methadone should be used?

GRADE evidence profile

Author(s): Amato L, Minozzi S
Date: 24 March 2006
Question: Should methadone maintenance (40–59 mg/day) versus methadone maintenance (1–39 mg/day) be used for opioid dependence?
Patient or population: Opioid dependents
Settings: Outpatient
Systematic review: Faggiano F et al. *Methadone maintenance at different dosages for heroin dependence* (CLIB 3, 2003)[140]

Quality assessment						Summary of findings					
						No of patients		Effect		Quality	Importance
No. studies	Design	Limitations	Consistency	Directness	Other considerations	Methadone maintenance medium doses (40–59 mg/day)	Methadone maintenance low doses (1–39 mg/day)	Relative risk (RR) (95% CI)	Absolute risk (AR) (95% CI)		
Retention in treatment [7–26] (objective follow-up: 20 weeks)											
1[a]	Randomized trial	No limitations[b]	No important inconsistency	No uncertainty	Imprecise or sparse data (–1)[c]	44/84 (52.4%)	34/82 (41.5%)	RR 1.26[d] (0.91 to 1.75)	110/1000 more (40 less to 260 more)	⊕⊕⊕○ Moderate	7
Mortality [7–26] (objective follow-up: 6 years)											
1[e]	Observational studies[f]	No limitations[f]	No important inconsistency	No uncertainty	Imprecise or sparse data (–1)[g]	1/262 (0.3%)	4/822 (0.5%)	RR 0.57[d] (0.06 to 5.06)	2/1000 less/20 less to 5 more)	⊕○○○ Very low	9

[a] Outpatient, conducted in the United States.
[b] Double blind, allocation concealment unclear.
[c] Only one study.
[d] Fixed effect model.
[e] One CPS, outpatient, conducted in Dutch; for CPS medium doses = 55–70 mg/day, low doses = 5–55 mg/day.
[f] One CPS of moderate quality.
[g] Large confidence interval.
[h] CPS.

GRADE evidence profile

Author(s): Amato L, Minozzi S
Date: 24 March 2006
Question: Should methadone maintenance (60–120 mg/day) versus methadone maintenance (1–39 mg/day) be used for opioid dependence?
Patient or population: Opioid dependents
Settings: Outpatient
Systematic review: Faggiano F et al. *Methadone maintenance at different dosages for heroin dependence* (CLIB 3, 2003)[140]

Quality assessment						Summary of findings					
						No of patients		Effect		Quality	Importance
No. studies	Design	Limitations	Consistency	Directness	Other considerations	Methadone maintenance (60–120 mg/day)	Methadone maintenance (1–39 mg/day)	Relative risk (RR) (95% CI)	Absolute risk (AR) (95% CI)		
Retention in treatment at 7–26 weeks (objective follow-up: 7–26 weeks)											
5	Randomized trials	No limitations	No important inconsistency	No uncertainty	None	138/247 (55.9%)	102/249 (41.0%)	RR 1.36 (1.13 to 1.63)	150/1000 more (50 to 260)	⊕⊕⊕⊕ High	7
Opioid abstinence (proportion of negative urine samples over 12 weeks)											
1	Randomized trials	No limitations	No important inconsistency	No uncertainty	Very imprecise or sparse data (–2)	55	55	—	WMD –2.0 (–4.8 to –0.8)	⊕⊕○○ Low	7
Opioid abstinence at 3–4 weeks (urinalysis)											
3	Randomized trials	No limitations	Inconsistent findings (–1)[a]	No uncertainty	Imprecise or sparse data (–1)	55/118	34/119	—	RR 1.59 (1.16 to 2.18)	⊕⊕○○ Low	7
Cocaine abstinence at 3–4 weeks (urinalysis)											
2	Randomized trials	No limitations	No important inconsistency	No uncertainty	Imprecise or sparse data (–1)	35/83	20/85	—	RR 1.81 (1.15 to 2.85)	⊕⊕⊕○ Moderate	6

[a] Significant heterogeneity.

Author(s): Amato L, Minozzi S
Date: 24 March 2006
Question: Should methadone maintenance (60–120 mg/day) versus methadone maintenance (40–59 mg/day) be used for opioid dependence?
Patient or population: Opioid dependents
Settings: Outpatient
Systematic review: Faggiano F et al. *Methadone maintenance at different dosages for heroin dependence* (CLIB 3, 2003)[140].

Quality assessment						Summary of findings					
						No of patients		Effect		Quality	Importance
No. studies	Design	Limitations	Consistency	Directness	Other considerations	Methadone maintenance (60–120 mg/day)	Methadone maintenance (40–59 mg/day)	Relative risk (RR) (95% CI)	Absolute risk (AR) (95% CI)		
Retention in treatment at 7-13 weeks [211,212] (Objective follow-up: 7–13 weeks)											
2[a]	Randomized trials	No limitations[b]	No important inconsistency	No uncertainty	Imprecise or sparse data (-1)	138/173 (79,8%)	137/174 (78,7%)	RR 1.01[c] (0.91 to 1.12)	10 more/1 000 (80 less to 90 more)	⊕⊕⊕○ Moderate	7
Retention in treatment at 27- 40 weeks[211,213,214] (Objective follow-up: 27–40 weeks)											
3[d]	Randomized trials	No limitations[e]	No important inconsistency	No uncertainty	None	157/277 (56,7%)	130/283 (45,9%)	RR 1.23[c] (1.05 to 1.45)	100/1 000 more (30 more to 190 more)	⊕⊕⊕⊕ High	7
Opioid abstinence[212] (Objective[f]- follow-up: 3–4 weeks)											
1[f]	Randomized trials	No limitations[b]	No important inconsistency	No uncertainty	Very imprecise or sparse data (-2)[g]	10/31 (32,3%)	6/28 (21,4%)	RR 1.51[c] (0.63 to 3.61)	110/1 000 more (120 less to 330 more)	⊕⊕○○ Low	7
Criminal activity[212] (Objective and subjective[i]- Range: to . Better indicated by: lower scores)											
1[h]	Randomized trials	No limitations[b]	No important inconsistency	No uncertainty	Very imprecise or sparse data (-2)[g]	31	28	-	WMD 0.05 (-0.03 to 0.13)	⊕⊕○○ Low	6
Mortality[215] (Objective follow-up: 6 years)											
1[m]	Observational studies[n]	No limitations[o]	No important inconsistency	No uncertainty	Very imprecise or sparse data (-2)[p]	0/316 (0%)	1/362 (0,3%)	RR 0.38[q] (0.02 to 9.34)	0/1 000 (10 less to 10 more)	⊕○○○ Very low	9

[a] Both outpatient and both conducted in USA
[b] Both double blind, allocation concealment unclear
[c] Fixed effect model
[d] All outpatient and all conducted in USA
[e] adequate allocation concealment, 2 unclear; 2 double blind, 1 single blind
[f] Outpatient, conducted in USA
[g] Based on urinalysis
[h] Double blind, allocation concealment unclear
[i] only 1 study, few participants
[l] During the treatment
[m] Outpatient, conducted in USA
[n] Medium number/week of criminal activities
[o] 1 CPS, outpatient, conducted in Dutch. For CPS high doses = >75 mg/day, medium dose = 55–70 mg/day
[p] 1 CPS of moderate quality
[q] Few events

Recommendation

On average, methadone maintenance doses should be in the range of 60–120 mg per day.

- Strength of recommendation – strong
- Quality of evidence – low

Strength of recommendation

The degree of confidence that the desirable effects of adherence to a recommendation outweigh the undesirable effects.

Desirable effects
- health benefits
- less burden
- savings

Undesirable effects
- Harms
- more burden
- costs

Strength of recommendation

strong recommendations are those for which:

- **most individuals should receive the intervention, assuming that they have been informed about and understand its benefits, harms and burdens**

- **most individuals would want the recommended course of action and only a small proportion would not**

- **the recommendation could unequivocally be used for policy making**

Strength of recommendation

standard recommendations are those for which:

- **most individuals would want the suggested course of action, but an appreciable proportion would not**
- **values and preferences vary widely**
- **policy making will require extensive debates and involvement of many stakeholders.**

Reasons for a standard recommendation

- absence of high quality evidence
- imprecise estimates
- uncertainty or variation in how different individuals value the outcomes
- small net benefits
- uncertainty whether the net benefits are worth the costs (including the costs of implementing the recommendation)

Recommendations for treatment of the individual patient			
		Strength of recommendation	Quality of evidence
Choice of treatment	For the pharmacological treatment of opioid dependence, clinicians should offer opioid withdrawal, opioid agonist maintenance and opioid antagonist (naltrexone) treatment, but most patients should be advised to use opioid agonist maintenance treatment.	Strong	Low to moderate
	For opioid-dependent patients not commencing opioid agonist maintenance treatment, consider antagonist pharmacotherapy using naltrexone following the completion of opioid withdrawal.	Standard	Low
Opioid agonist maintenance treatment	For opioid agonist maintenance treatment, most patients should be advised to use methadone in adequate doses in preference to buprenorphine.	Strong	High
	During methadone induction, the initial daily dose should depend on the level of neuroadaptation; it should generally not be more than 20 mg, and certainly not more than 30mg.	Strong	Very low
	On average, methadone maintenance doses should be in the range of 60–120 mg per day.	Strong	Low
	Average buprenorphine maintenance doses should be at least 8 mg per day.	Standard	Very low
	Methadone and buprenorphine doses should be directly supervised in the early phase of treatment.	Strong	Very low
	Take-away doses may be provided for patients when the benefits of reduced frequency of attendance are considered to outweigh the risk of diversion, subject to regular review.	Standard	Very low
	Psychosocial support should be offered routinely in association with pharmacological treatment for opioid dependence.	Strong	High
Management of opioid withdrawal	For the management of opioid withdrawal, tapered doses of opioid agonists should generally be used, although alpha-2 adrenergic agonists may also be used.	Standard	Moderate
	Clinicians should not routinely use the combination of opioid antagonists and minimal sedation in the management of opioid withdrawal.	Standard	Very low
	Clinicians should not use the combination of opioid antagonists with heavy sedation in the management of opioid withdrawal.	Strong	Low
	Psychosocial services should be routinely offered in combination with pharmacological treatment of opioid withdrawal.	Standard	Moderate
Pregnancy	Opioid agonist maintenance treatment should be used for the treatment of opioid dependence in pregnancy.	Strong	Very low
	Methadone maintenance should be used in pregnancy in preference to buprenorphine maintenance for the treatment of opioid dependence; although there is less evidence about the safety of buprenorphine, it might also be offered.	Standard	Very low

Table 2. Recommendations by strength and quality of evidence

	Strength of recommendation		total
Quality of evidence	strong	standard	
High/moderate	3	1	4
Low/very low	3	3	6
No evidence	3	2	5
Total	9	6	15

Problems

1. Absence of evidence

SR did not consider critical outcomes

OR

Primary studies did not consider critical outcomes or did not report them in an homogeneous way

2. Low quality of evidence

Grading: advantages and limits

- Explicit valuation of the quality of evidence of the single studies
- Do not permit the valutation of clinical relevance of the information given by the single studies
- Penalize areas where is difficult/impossible to conduct RCTs

Dipartimento di Epidemiologia
del Servizio Sanitario Regionale
Regione Lazio

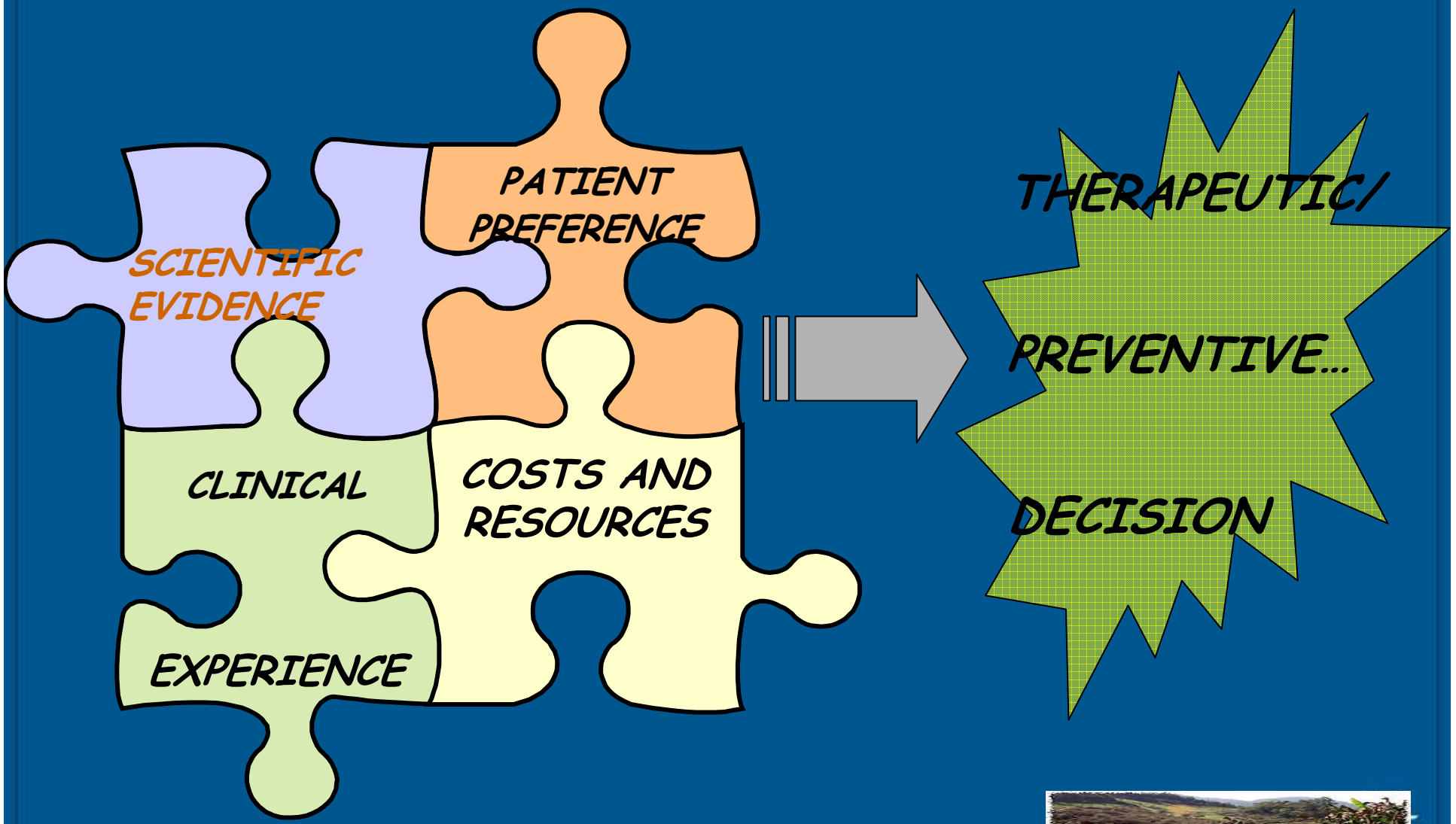
Conclusions (about guidelines)

The expert panel formulated strong recommendations even if in presence of lack of evidence (3/9) or low quality of evidence (3/9)

The use of GRADE allowed the transparency of the process

The reader is informed that some recommendations are based on expert opinions.

Evidence based health care



DECIDE

Developing and Evaluating Communication strategies to support Informed Decisions and practice based on Evidence

DECIDE

Developing and Evaluating Communication Strategies to Support Informed Decisions and Practice Based on Evidence

is a 5-year project (running from January 2011 to 2015) co-funded by the European Commission under the Seventh Framework Programme.

Project Objective

"To improve the dissemination of evidence-based recommendations by building on the work of the GRADE Working Group to develop and evaluate methods that address the targeted dissemination of guidelines."

Background

Healthcare decision makers face challenges in understanding guidelines, including the quality of the evidence upon which recommendations are made, which often is not clear.

Guidelines are also typically developed as a one-size-fits-all package.

By developing and evaluating targeted dissemination strategies, DECIDE aims to increase the use of evidence-based interventions in a sustainable way and to reduce the use of interventions where benefits are uncertain.

Methods

GRADE is a systematic approach towards assessing and communicating the quality of evidence and the strength of recommendations.
It has been developed to address the weaknesses of other grading systems and is now widely used internationally. The DECIDE consortium, which is composed of members of the GRADE Working Group, will further develop this approach to ensure effective dissemination of evidence-based recommendations targeted at the key stakeholders (healthcare professionals; policymakers and managers; patients and the general public) who determine what happens in clinical practice.
We will collect stakeholder input from advisory groups, consultations and user testing.
This will be done across a wide range of health systems in Europe.
The targeted dissemination strategies that are developed will be evaluated in randomized trials, refined and used and evaluated with real guidelines developed by the DECIDE partners and other guideline developers that we support.

Expected results

Dissemination strategies for recommendations that have been rigorously evaluated in diverse settings, support the transfer of research into practice, and are adapted to real-world healthcare systems.

The DECIDE Project: Policy Makers and Managers focused strategies to go from Evidence to Coverage Decision

Davoli M, Pregno S, Parmelli E, Amato L, Brunetti M,
DePalma R, Magrini N, Nonino F, Saitto C

The **EU DECIDE project**, has the objective to develop and evaluate communication strategies to support evidence-informed decisions for different stakeholders, by building on the work of the GRADE Working Group. As part of this project we are developing frameworks to provide available evidence to policymakers to support coverage decisions. We conducted stakeholders consultations: through a semi-structured questionnaire 1) to finalise a survey instrument exploring perceptions regarding current practices for guidelines dissemination methods and strategies and 2) to collect input regarding specific frameworks about different coverage scenarios. The following dimensions were included in the frameworks: seriousness of the problem, quality of available evidence, benefits and harms, costs, cost-effectiveness, feasibility, equity and value. Major comments and criticisms are summarized below:

The consultations included 101 people met during two international and two Italian conferences. The majority of them (96 %) stated that the frameworks presented could have been useful for taking coverage decisions.
The survey and frameworks built upon these comments will be sent to policy makers and managers across Europe. The results will be used to develop/refine a specific tool for going from evidence to coverage decisions.

This research project has received funding from the European Union Seventh Framework Programme (FP7-HEALTH.2010.3.1-1 – two stage) under grant agreement n° 258550

GRADE DECIDE Evidence to coverage decision framework

Prepared by: Silvia Pregno May 13,2012

Patients: people with opioid dependence

Intervention: buprenorphine

Comparison: methadone

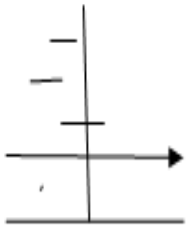
Should buprenorphine be covered for maintenance treatment in opioid dependent persons?

Background. Opioid dependence is characterized by a cluster of cognitive, behavioral and physiological features. The *International Classification of Diseases, 10th edition* (ICD-10) identifies six such features: a strong desire or sense of compulsion to take opioids, difficulties in controlling opioid use, a physiological withdrawal state, tolerance, progressive neglect of alternative pleasures or interests because of opioid use persisting with opioid use despite clear evidence of overtly harmful consequences. ICD-10 defines opioid dependence as the "presence of three of more [of these features] present simultaneously at any one time in the preceding year". Opioid dependence does not develop without a period of regular use, although regular use alone is not sufficient to induce dependence. Opioid dependence is a worldwide health problem that has enormous economic, personal and public health consequences.

There are an estimated 15.6 million illicit opioid users in the world, of whom 11 million use heroin. Opioids are the main drugs of abuse in Asia, Europe and much of Oceania, and it is estimated that globally the consumption of the opioid class of drugs is increasing. The neurological changes that occur with opioid dependence constitute a brain disorder. Therefore, opioid dependence can be considered as a medical condition, with complex sociological and individual determinants. Opioid dependence is characterized by a series of symptoms that have long-term prognostic implications, and for which a treatment set of pharmacological and psychosocial interventions exist aimed at reducing or ceasing opioid use, preventing future harms associated with opioid use, improving quality of life and well-being of the opioid-dependent patient.

Broadly speaking, there are two pharmacological approaches to opioid dependence treatment – those based on opioid withdrawal and those based on agonist maintenance that is matter of our question. The agonist maintenance treatment usually consists of daily administration of an opioid agonist (e.g. methadone) or a partial agonist (e.g. buprenorphine). The resulting stable level of opioid effect is experienced by the dependent user as neither intoxication nor withdrawal, but more as "normal". The aims of agonist maintenance treatment include: reduction or cessation of illicit opioids, reduction or cessation of injecting and associated risk of blood borne virus transmission, reduction of overdose risk reduction of criminal activity and improvement in psychological and physical health.

	CRITERIA	JUDGEMENT	EVIDENCE	COMMENTS
Severity	**What is the severity of the condition?**	Very low ☐ Low ☐ Uncertain ☐ Moderate ☐ High ☐	Injecting drug use has been strongly associated with HIV, accounting for 30% of HIV infections outside sub-Saharan Africa, and up to 80% of cases in some countries in eastern Europe and central Asia and accounting for an estimated 90% of new hepatitis C infections(an estimated 130 million people are infected with hepatitis C, with 3–4 million people newly infected each year). In countries with a low prevalence of HIV, opioid dependent individuals have been found to have been found to have an annual mortality of 2–4% per annum, or 13 times that of their peers. This increased mortality is primarily due to overdoses, violence, suicide, and smoking and alcohol-related causes In countries with high HIV prevalence, acquired immunodeficiency syndrome (AIDS)also makes a significant contribution to mortality. Opioid dependence per se is associated with a significant reduction in quality of life as meaningful activities become replaced by time spent intoxicated or seeking opioids. In addition they have high rates of psychiatric comorbidity, particularly depression and post-traumatic stress disorder.	
Equity	**What would be the impact on health inequities?**	Increased ☐ Probably Increased ☐ Little or uncertain ☐ Probably reduced ☐ Reduced ☐	Opioid agonist maintenance treatment, combined with psychosocial assistance, was found to be the most effective. Oral methadone liquid and sublingual buprenorphine tablets are the medications most widely used for opioid agonist maintenance treatment. In the context of high-quality, supervised and well-organized treatment services, these medications interrupt the cycle of intoxication and withdrawal, greatly reducing heroin and other illicit opioid use, crime and the risk of death through overdose.	
Approriate use	**Is inappropriate use likely to be an important problem?**	Yes ☐ Probably ☐ Uncertain ☐ Probablynot ☐ No ☐	In planning treatment systems, resources should be in a way that delivers effective treatment to as many people as possible. Opioid agonist maintenance treatment appears to be the most cost-effective treatment, and should therefore form the backbone of the treatment system for opioid dependence. Countries with established opioid agonist maintenance treatments usually attract 40–50% of dependent opioid users into such treatments, with higher rates in some urban environments. Because of their cost, inpatient facilities should be reserved for those with specific needs, and most patients wanting to withdraw from opioids should be encouraged to attempt opioid withdrawal as outpatients.	

	CRITERIA	JUDGEMENT	EVIDENCE	COMMENTS
Benefits and Harm	Overall, are the anticipated desirable effects large?	Favour methadone ☐ Favour buprenorphine ☐ Uncertain ☐	***Summary of overall results for each considered critical outcome***	Death:
	Overall, are the anticipated undesirable effects small?	Favour methadone ☐ Favour buprenorphine ☐ Uncertain ☐	**Death (9)***: not measured in the RCTs included (see Comments)	
	Overall, what is the certainty of the anticipated effects (in our setting)?	Favour methadone ☐ Favour buprenorphine ☐ Uncertain ☐	**Retention in treatment (9)*** — Risk Ratio 95% CI — Certainty of the effect Flexible buprenorphine vs flexible methadone: RR 0.84 (95%CI 0.74 to 0.95) — ⊕⊕⊕◯ Moderate Low dose buprenorphine vs low dose methadone: RR 0.67 (95%CI 0.52 to 0.87) — ⊕⊕⊕◯ Moderate Medium dose buprenorphine vs medium dose methadone: RR 0.87 (95%CI 0.69 to 1.10) — ⊕⊕◯◯ Low High dose buprenorphine vs high dose methadone: RR 0.79 (95%CI 0.20 to 3.16) — ⊕◯◯◯ Very Low  **Use of opioids (urinanalysis) (7)*** — Rule of thumb for effect size — Certainty of the effect Flexible buprenorphine vs flexible methadone: SMD -0.11 (95%CI -0.23 to 0.02) — no difference — ⊕⊕⊕⊕ High Low dose buprenorphine vs low dose methadone: SMD - 0.35 (95%CI -0.87 to 0.16) — no difference — ⊕⊕⊕◯ Moderate Medium dose buprenorphine vs medium dose methadone: SMD 0.26 (95%CI 0.08 to 0.44) — buprenorphine less able to suppress heroin use — ⊕⊕⊕◯ Moderate High dose buprenorphine vs high dose methadone: SMD 0.10 (95%CI -0.80 to 1.01) — no difference — ⊕⊕◯◯ Low	
Value	Would patients feel that the benefits outweigh the harms?	Favour methadone ☐ Favour buprenorphine ☐ Uncertain ☐	No data available about the quality adjusted life expectancy or this specific question. Cohort studies of dependent illicit opioid users show that although a significant proportion (10–40%) are abstinent at follow-up, most continue to use illicit opioids. Contact with treatment is one factor associated with recovery from opioid dependence; other factors include personal motivation, religion, spirituality family and employment	

*outcome rating scale: from 1-3 not important; from 4-6 important ; from 7-9 critical

	CRITERIA	JUDGEMENT	EVIDENCE	COMMENTS
Cost effectiveness	Is the cost small relative to the net benefits?	Favour methadone ☐ Favour buprenorphine ☐ Uncertain ☐	No cost effectiveness analysis available, using clinical effectiveness information presented above Cost difference Costs every 6 months (in AU $) Methadone (57 mg daily) / Buprenorphine (11 mg daily) Drugs*: 37 / 459 Other healthcare costs** 1,378 / 1,260 TOTAL COSTS 1,415 / 1,729	
Budget	Is the total cost (impact on budget) low?	Favour methadone ☐ Favour buprenorphine ☐ Uncertain ☐	Total yearly costs per 100.000 patients Methadone 283,000,000 AU $ Buprenorphine 345,800,000 AU $	

Balance of consequences	*Undesirable consequences clearly outweigh desirable consequences*	*Undesirable consequences probably outweigh desirable consequences*	*Desirable/undesirable consequences closely balanced or uncertain*	*Desirable consequences probably outweigh undesirable consequences*	*Desirable consequences clearly outweigh undesirable consequences*
	☐	☐	☐	☐	☐
Coverage decision	*Do not cover*	*Coverage with evidence development*			*Cover*
	☐		☐		☐
	We decided…				

Restrictions	
Justification	
Implementation	

Introduction to AGREE II

The AGREE instrument is a tool that assesses the methodological rigour and transparency in which a guideline is developed and it is used internationally. The Appraisal of Guidelines for Research & Evaluation (AGREE) Instrument was developed to address the issue of variability in the quality of practice guidelines. It is important to assess the methods used to develop practice guidelines in order to be confident of the resulting recommendations. The AGREE instrument is a tool that assesses the methodological rigour and transparency in which a guideline is developed and it is used internationally.

The AGREE instrument is a tool that assesses the methodological rigour and transparency in which a guideline is developed and it is used internationally.

Introduction to AGREE II

- The original AGREE Instrument, which was released in 2003, has been refined to improve the original tool's usability and methodological properties, namely its validity and reliability. These efforts have resulted in the new AGREE II tool that also includes a new User's Manual.

The AGREE II is both valid and reliable and comprises 23 items organized into the original 6 quality domains:
i) scope and purpose;
ii) stakeholder involvement;
iii) rigour of development;
iv) clarity of presentation;
v) applicability;
and vi) editorial independence.
Each of the 23 items targets various aspects of practice guideline quality.

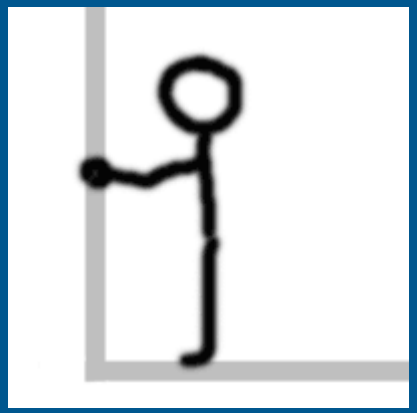
The AGREE II also includes 2 final overall assessment items that requires the appraiser to make overall judgments of the practice guideline and considering how they rated the 23 items.
The new User's Manual is designed to guide appraisers in the use of the AGREE II. The Manual is part of the complete AGREE II document or "package" and includes specific information and guidance for each of the 23 items and the 2 overall assessment items

European Commission

TAIEX

European Monitoring Centre for Drugs and Drug Addiction

Thanks



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