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Guidelines in the treatment of opiate addiction: a review and recommendation

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Summary

Guidelines assist practitioners in the management of opioid dependence, however, important day-to-day issues in the field must be addressed, such as "Which medication to use, how to start, how to dose, when to stop, how to manage complications and comorbidities?". The workshop aimed to define the approach to managing the gap between guidelines for opioid dependence management and the real life clinical situations. 6 expert speakers in the field of opioid dependence management presented detailed guidelines examination, the evidence for the guidelines, and expert clinical experience highlighting the practical needs for prescribers in opioid dependence management for individualised patient care and comorbidities. Results: Sufficient evidence supports the treatment of opioid dependence, but evidence gaps remain which are likely to be important in guiding specific decisions about individual patient care. Clinical experience is vital to bridge the gaps between Guidelines advice, effective individual patient tailored care in the treatment of opioid dependence. Conclusions: It is important to tailor care to individual patient needs under the consideration of evidence based facts. Initial recommendations for treatment directed by a system based on tolerance to opioids, level of existing psychopathology, and abuse of other substances could bridge the gap between Guidelines and the real life clinical setting.

*Key Words:*Opiate dependence management; guidelines; patient needs

1. Introduction

Opioid maintenance treatment with opioid agonists is widely used for the pharmacological management of opioid dependence. Moving from a previous era when the question was, "Should we treat?", the relevant questions are now focused on, "How should we treat?". The present discussion aims to define evidence, experience and gaps for day-to-day treatment decisions in opioid dependence.

Not all treatment decision processes are adequately directed by Guidelines for the management of opioid dependence. It is important to tailor care to specific individual patient needs. The following questions should be asked when considering the value of Guidelines and applying their advice in day-to-day care: What is the basis of the guidance? What is the evidence? What are the gaps? What is the underlying psychiatric comorbidity?

The discussion is informed by a detailed analysis of Guidelines creation and also with experiences of clinical experts managing the real life clinical situations, individualised care and comorbidities in opioid dependence.

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Table 1 Outstanding research questions: Decision making in opioid dependence management

Area of focus	Key question
Opioid maintenance vs. opioid withdrawal (+/- antagonist)	• What is the impact on quality of life? • What is evidence for maintenance versus detox and long acting antagonist? • How to manage patient selection?
Opioid maintenance – how to provide treatment?	• Which opioid agonist to choose, in which situation? (Buprenorphine versus buprenorphine/naloxone) • Supervised versus unsupervised – very little data on unsupervised • High dose versus low dose – little data on higher doses of buprenorphine (>8mg) • +/- Psychosocial support – little data on social support/web based interventions
Opioid withdrawal – how to manage?	• What medication to manage opioid withdrawal (what to use when methadone/ buprenorphine/ clonidine are not available)? • Withdrawal from maintenance treatment and prescription opioids • +/- Psychosocial support – role of residential rehabilitation • +/- Antagonist for relapse prevention – long acting antagonists
Opioid overdose prevention	• Distribution of naloxone • Use of opioids in chronic non-malignant pain

2. Discussion

2.1. Evidence for Guidelines in opioid management: account of World Health Organisation (WHO) experience

The WHO ATLAS on Drug & Alcohol Treatment Service [17] identifies opioid dependence as the most common reason for seeking help for addiction. This need was in part the drive for development of WHO Guidelines, which met the needs of experts in a broad range of settings trying to manage opioid dependence. The WHO Guidelines for psychosocially assisted pharmacological treatment of opioid dependence [3] were published in 2009.

These Guidelines were developed according to WHO process for clinical Guidelines [16] and are based on systematic reviews of the literature using the GRADE process to determine the quality of the evidence with support of procedural and content experts. The work assessed treatment modalities with use of Opioid agonists, antagonists and other medicines. The approach used "PICO" format [1]: for this Population (opioid dependent), does Intervention A (i.e. methadone), Compared to intervention B (i.e. opioid withdrawal) result in better Outcomes of interest (i.e. mortality, quality of life)?

Questions addressed include: benefits of opioid maintenance compared to opioid withdrawal with possible antagonist, benefits of opioid maintenance including choice of opioid (methadone, buprenorphine), supervised or unsupervised dosing, high dose or low dose treatment, and value of psychosocial support. Opioid withdrawal was assessed to determine medication choice in opioid withdrawal (methadone, buprenorphine, others) with or without psychosocial support and/or antagonists for relapse prevention.

The guidance aimed to define evidence for practical questions. The systematic review identified a set of studies meeting key criteria.

The process identified that there was relatively strong evidence to compare buprenorphine versus methadone; there was little data to compare supervised and unsupervised dosing. There was limited data defining best practice on impact on quality of life, for maintenance therapy versus withdrawal.

Important questions are outstanding for management of prescription opioid dependence: the predominant form of opioid dependence. Strong prescription opioids have similar mortality to heroin dependence, but in a different population of patients and with different interventions needed.

Of the thousands of "hits" in the systematic search fewer than 1 in 100 sources were relevant to the development of Guidelines. There are a number of reasons why the process identified so little evidence for important questions: studies were limited to small numbers of patients, often lacking intention to treat analysis and follow up. Often studies showed poor adherence to CONSORT for their design.

To improve the understanding of opioid dependence management and to better inform clinical decisions, there is a need for international collaborations to deliver larger overpowered studies to generate more data. There is need for consensus building in the research community on what research questions need answers (table 1),

which trials are needed. Consensus building on trial design and outcome measurement issues to drive international collaboration on clinical research via clinical trials network would be of great value.

2.2. *Australian Guidelines for the treatment of opiate addiction*

The treatment for opioid dependence in Australia has a well-defined basis. Since the Dole and Nyswander studies in 1964 and the introduction of Opioid Agonist Therapy in Australia in 1969, there is recognition of the need for programmed intervention in opioid dependence. Treatment was endorsed nationally in 1985 and there were 46,697 pharmacotherapy clients by 2012. The unmet need for heroin dependence is around 40,000 cases [2].

The basis of the Guidelines come from the 1990's: the noted growth in heroin use and related 'crises' such as overdose, risk of viral infection (HIV, HCV) presented a challenge to expand treatment numbers quickly. To deliver the increase in care needed it was necessary to expand into private sector involving GPs & pharmacies.

The evolution of treatment in Australia includes the introduction of Naltrexone, registered in 1999 and addition of buprenorphine, which was introduced in 2002. The use of buprenorphine was modelled on methadone treatment in Australia but was preferred by some clinicians over methadone because of the inherently lower risk profile medication. Early concerns of misuse (injecting of tablets) led to the introduction of the combination product, Suboxone® (2005) as strategy to reduce misuse [8].

The recent revision of Guidelines in Australia aimed to combine different existing guidance documents into an integrated resource, more clearly evidence-based and reflecting new experience. The process aimed to provide broad policy context and framework for Medication Assisted Treatment for opioid dependence while promoting national consistency with jurisdictional responsibilities.

The Guidelines are based on a review of evidence using the NHMRC [9] systematic approach. Not all evidence is graded by the standard approach: the Guidelines include evidence that is based on the standard of care, clinical experience consensus or regulatory requirement.

The Guidelines reflect agreement on areas including induction doses, stabilisation regimes, maintenance doses, role of urine drug screening, and treatment in pregnancy. Areas where evidence is evolving include: use of take away doses, withdrawal regimes from maintenance treatment, prescription opioid dependence treatment, and methadone to buprenorphine transfer.

For takeaway doses and unsupervised dosing the evidence base is limited. Most studies have been conducted in the context of supervised dosing. It is important to differentiate takeaway doses from unsupervised dosing. In the family context where there is a responsible adult, this can enable a takeaway dose to be supervised in many cases. When defining the access to medicines with takeaway doses and unsupervised dosing, policy must strike a balance between patient rights and access to safe and effective treatment, against medication diversion concerns.

Takeaway dosing is not usually available in the first 3 months of treatment after which it may be appropriate for 1 to 6 consecutive doses; number of consecutive days offered as takeaway doses is dependent on jurisdictional regulations and a patient risk assessment. This type of dosing is suitable for clients assessed as stable. The risk assessment is based on: regular attendance at appointments, urine drug screens provided when requested, no or infrequent additional opioid use, benzodiazepine use absent or low levels and stable, no alcohol abuse, no or infrequent use of stimulants, no recent intoxicated presentations or overdoses (in prior 3 months) and no recent missed doses.

Unsupervised dosing improves client's reintegration into daily activities, reduces cost of treatment, reduces stigma. There are risks to manage; risk depends on frequency and number of consecutive takeaways. In approving single occasion takeaways, the prescriber needs to place emphasis on safety of client and family.

The Guidelines are informed by evidence, clinical experience and patient expectations. It is important to reflect jurisdictional differences and resource or capability limits, size and nature of problem and Regulatory control. The Guidelines are an advance but there are areas where evidence is still required. The picture of need is changing: prescribed medicines containing opioids are now the source of dependence for the majority of new clients entering treatment.

2.3. *Recognising the clinical problems in opioid maintenance treatment and expert recommendations for clinical management*

The impact of opioid dependence is well described. In Europe, there are 1.4 million users as de-

Table 2 Comparison of care models in opioid dependence management

Type of care model	Advantages	Disadvantages
General practitioner based care	• "Family doctor"- prevention & early treatment initiation • May be cost effective • Integration into mainstream medicine is possible due to general nature of the general practitioner-based service • Decentralized, possible greater access • More capacity to treat, offer services in addiction • Low threshold for acceptance to treatment • Drug-drug interaction can be carefully managed from holistic picture	• Limited psychiatry education in some cases – comorbidity may be difficult to manage • Time for education may be limited in the busy GP setting • Lack of multi-professional support through specialised clinics which cannot be offered
Specialist care setting	• Multidisciplinary setting • Pharmacist with specialist skills available • Psychiatrist available to consult on comorbidities • Nurses, specialist trained • Psychologist available • Social worker available	• High threshold - selected group • Often by nature of clinical service, centralized in large cities • Limited capacity may be a problem • Often expensive • "Stigma-addiction" clinic attendance may be a problem for patients/ clients

fined according to EMCDDA definition; Opioid dependence is related to 90% of drug related overdoses in Europe with a high mortality [15]. The Mortality rate is increased compared to age matched group in predominantly young men, with overdose deaths [5] and suicide rate 14 times higher than the general population [7]. HIV and Hepatitis C infections are well known somatic comorbidities in this population (The prevalence of hepatitis C virus antibodies among injecting drug users is varying between 22% and 83% across European countries according to EMCDDA evidence).

Treatment options are well defined for detoxification and maintenance. For detoxification, treatment with methadone or buprenorphine is more effective than detoxification with α2 adrenergic agonists. Detoxification should always be followed by planned relapse prevention as detoxification increases mortality risk.

For opioid maintenance therapy the two mainstays of medication are oral methadone and sublingual buprenorphine including the combination product buprenorphine/ naloxone. Other medication, such as slow release oral morphine (SROM) show efficacy but use is limited to some countries [18,19]. Evidence shows that methadone reduces heroin use, injection and needle sharing, and is more effective at 60-120 mg/ day dose [2]. Buprenorphine or Buprenorphine/ Naloxone are safe and effective in maintenance treatment as an alternative to methadone; clinical practice determines that higher doses (> 8 mg) are more effective. Combination products have advantages when misuse is a concern.

Based on the knowledge of effective treatment, individualised care should be prepared for all patients based on best outcomes predictors. These include: higher versus lower dosages of opioid medication, matching services to patient needs (range of services, individualised care program, special care for comorbidity and poly-drug dependence), flexibility of regimes (intake, controls) with appropriate staff attitudes and competence.

There are different care models in Europe; Guidelines do not clarify which approach is optimal. In Austria, France, Germany, UK care is mainly general practitioner provided. In Denmark, France, Italy, Netherlands, Portugal, Spain care is provided in specialist centres, and in Finland, Greece, Sweden, Norway care is provided in a small number of dedicated specialist centres. There are advantages of both systems as set out in table 2. An integrated model of both central and local services has many benefits – it avoids stigma of going to the specialist services but provides opportunity to escalate input if needed. The care model in opioid dependence should be reconsidered so it is less restrictive and is similar to other chronic disease: Guidelines should assist in this area. An optimal combination of a mix of services for dependence management can be set up for each individual patient. This can range from self-care in stable situations through to the need for complex, expert input in the residential setting. The frequency of need

for care and input along with the costs of service will vary for each patient, over time. Special populations such as people at risk of misuse and worsening outcomes have a need for individualised care. Special tailoring of care should also be provided to patients within the criminal justice system [4], and to pregnant women [14].

2.4. The influence of diagnosing and treating psychiatric comorbidities on successful outcomes in management of opioid dependence

It is important to recognise the presence of other psychiatric comorbidities in the tailoring of individual treatment in opioid dependence management because these increase the severity of psychopathology (i.e. number of emergency admissions, suicides…), frequency of risk behaviour and related infections (i.e. HIV, HCV), psychosocial impairment, and tendency to criminal behaviours compared to opioid dependent subjects without these comorbid disorders.

Epidemiological evidence shows psychiatric comorbidities are common. Most frequent are depression, anxiety and personality disorder. Although psychiatric comorbidity occurs in females and males, it is more frequent in females [12]. Women are twice as likely to have a mood or anxiety disorder and more likely to have a borderline personality disorder and men are more likely to have an antisocial personality disorder [6].

Lifetime prevalence of mood disorders in those with opioid dependence is higher than in the general population [12]. Independent major depression disorders are more frequent than substance-induced disorders and more frequent in women than in men. The occurrence of independent major depression disorders is almost three times higher in opioid dependent women than in the general female population.

The presence of major depression at treatment intake or during follow-up in opioid dependence results in a worse clinical outcome compared to the treatment of opioid dependence without depression. This means a greater risk of relapse in both drug use and psychiatric disorders. The main clinical differences between induced and primary depression in opioid users are described in table 3.

Due to the clinical relevance of comorbid depression there is a need for specific treatment of depression as a comorbidity in opioid dependence. Figure 1 defines a joined up approach to the management of depression in opioid dependence [10, 13]. Psychological and pharmacological interventions

Figure 1. Management of depression coexisting with substance misuse: a joined up approach of psychological and pharmacological intervention

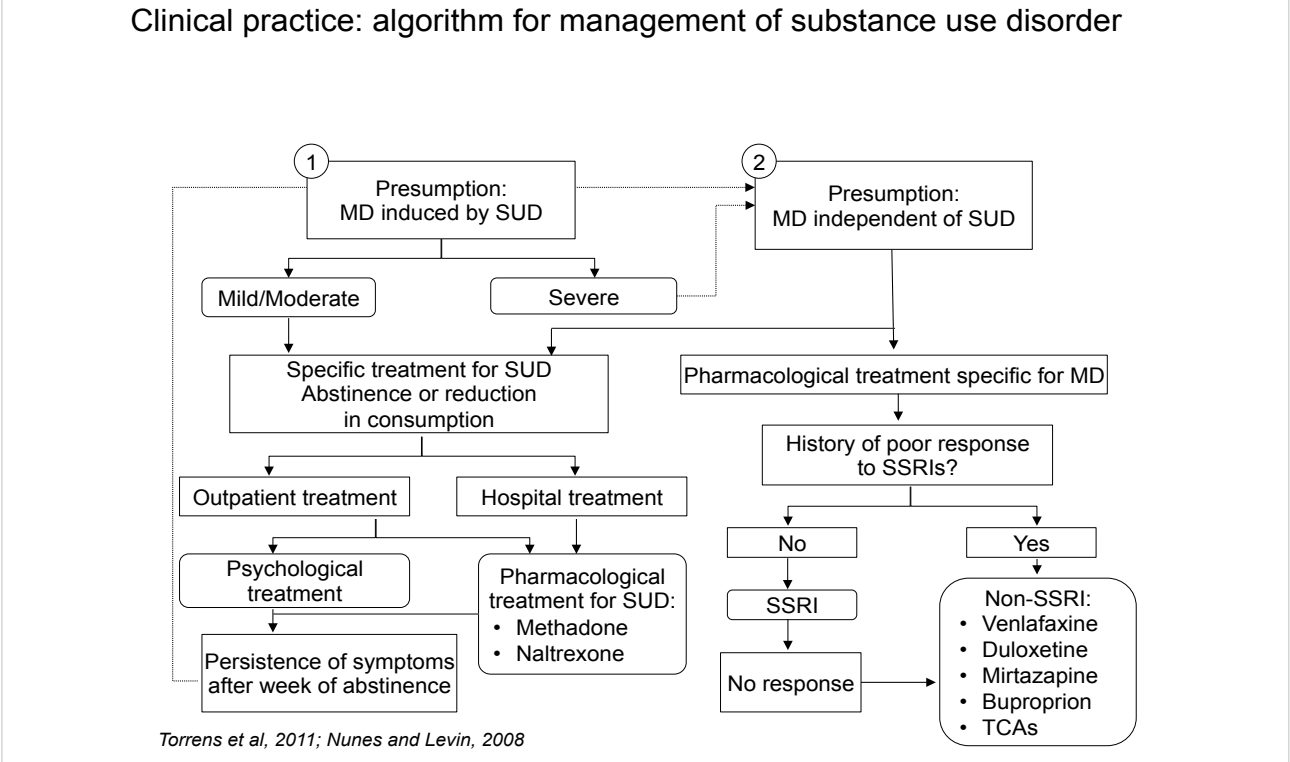

Table 3 Criteria for diagnosis of depression as a comorbidity with opioid dependence

Type	Patient profile	Frequently associated symptoms	Prognostic indicators
Depression induced by substance use disorder (SUD)	• Men • Young people	• Emergence of depressive symptoms: • During an escalation of SUD consumption, or • During a significant drop in SUD consumption	• History of alcoholism in the family • SUD due to illegal drugs (not alcohol)
Depression independent of SUD	• Women • White or Hispanic • Elderly	• History of depression independent of SUD • History of good response to antidepressant treatment for previous episodes • Family history of depression • Emergence of depressive symptoms	• Suicide attempts • Antisocial personality • Alcohol dependence
Depression concurrent with SUD	• Elderly		• Increase in depressive symptoms throughout life • History of suicide attempts • Comorbid anxiety

may have beneficial impact on depression and opioid dependence, however the evidence is not strong. It is important to understand the safety and efficacy profiles of pharmacological interventions for depression and opioid dependence.

A major analysis of pooled evidence [11] determined there was low evidence supporting the clinical use of antidepressants for the treatment of depressed opioid addicts in treatment with opioid agonists (methadone). This analysis considered both the possible "Improvement of depressive symptoms by antidepressants" and "Improvement of opioid use by antidepressants". This meta-analysis did not demonstrate a positive benefit for either.

It is important to consider medication safety when treating depression and opioid dependence. Specific interactions of antidepressant medications such as Tricyclic antidepressants are well described and include increased adverse events and risk of overdose, with potential for abnormalities of cardiac rhythm in some cases. There is a further need for evidence to guide treatment of both conditions: opioid dependence and comorbidities, such as depression.

5. Conclusions

There are important gaps in the evidence to be filled, which might direct specific decisions about individual care for each patient. There is sufficient evidence supporting the treatment of opioid dependence; clinical experience is essential to complete the gaps between advice in Guidelines and successful care of individual patients. In the practical setting a simple system may be of use to clinicians. A system based on tolerance to opioids, level of existing psychopathology (how strong is the dependence?) and abuse of other substances can be used to make initial recommendations for treatment in maintenance. The system and potential recommendations in model cases are defined in table 4.

This system and potentially other similar approaches are useful starting points for tailoring care to the needs of individual patients and moving from the Guidelines to the real life in the clinical setting.

Table 4 A proposed treatment system and potential recommendations, to bridge the gaps between Guidelines and successful patients in the treatment of opioid dependence.

Example	Tolerance to opioids	Severity of psychopathology	Abuse of other substances	Recommendation for maintenance
Patient 1	Low	Low level of existing psychopathology	Use of cocaine	Buprenorphine products
Patient 2	Medium	High level of existing psychopathology	Use of alcohol	Buprenorphine products
Patient 3	High	High level of existing psychopathology	Use of benzodiazepines	Methadone

References

1. Akobeng A.K. (2005). Principles of evidence based medicine. *Arch Dis Child* 90 (8): 837-840.
2. Australian Institute of Health and Welfare. (2012). National opioid pharmacotherapy statistics annual data collection: 2011 report. AIHW Press: Canberra. Cat. No. PHE 161.
3. Department of Mental Health and Substance Abuse, WHO. (2009): Guidelines for the psychosocially assisted pharmacological treatment of opioid dependence. WHO Press ISBN 978 92 4 154754 3
4. European Monitoring Centre for Drugs and Drug Addiction (2002). 2002 Annual report on the state of the drugs problem in the European Union and Norway. Luxembourg: Office for Official Publications of the European Communities 2002. ISBN 9209168-129-6.
5. European Monitoring Centre for Drugs and Drug Addiction (2013). European Drug Report 2013: Trends and Developments. Luxembourg: Office for Official Publications of the European Communities 2013. ISBN 978-92-9168-611-7.
6. Grella C.E., Karno M.P., Warda U.S., Niv N., Moore A.A. (2009). Gender and Comorbidity Among Individuals with Opioid Use Disorders in the NESARC Study. *Addict Behav* 34(6-7): 498–504.
7. Harris E.C., Barraclough B. (1997). Suicide as an outcome for mental disorders. A meta-analysis. *Br J Psychiatry* 170: 205–228.
8. Larance B.K., Degenhardt L.J., Lintzeris N., Bell J.R., Winstock A., Dietze P., Mattick R.P., Ali R.L., Horyniak D. (2011): Post-marketing surveillance of buprenorphine-naloxone in Australia: diversion, injection and adherence with supervised administration. *Drug Alcohol Depend* 118: 2-3, 265-273.
9. National Health and Medical Research council, Australian Government. (2009): Levels of evidence and grades for recommendations for developers of guidelines.Accessed online at: http://www.nhmrc.gov.au/_files_nhmrc/file/guidelines/developers/nhmrc_levels_grades_evidence_120423.pdf
10. Nunes E., Levin F. (2008). Treatment of co-occurring depression and substance dependence: using meta-analysis to clinical recommendations. *Psychiatr Ann* 38: 730–738.
11. Pani P.P., Vacca R., Trogu E., Amato L., Davoli M. (2010): Pharmacological treatment for depression during opioid agonist treatment for opioid dependence. *Cochrane Database System Review* (9): CD008373.
12. Torrens M., Gilchrist G., Domingo-Salvany A., (2011). Psychiatric comorbidity in illicit drug users: Substance-induced versus independent disorders. *Drug Alcohol Depend* 113: 147-156.
13. Torrens M., Martínez-Sanvisens D., Martínez-Riera R., Bulbena A., Szerman N., Ruiz P. (2011). Dual Diagnosis: Focusing on Depression and Recommendations for Treatment. *Addictive Disorders & Their Treatment* 10(2): 50-59.
14. Unger A., Jagsch R., Jones H., Arria A., Leitich H., Rohrmeister K., Aschauer C., Winklbauer B., Bawert A., Fischer G. (2011): Randomized Controlled Trials in Pregnancy: Scientific and Ethical Aspects Exposure to different opioid medications during pregnancy in an intra-individual comparison. *Addiction* 106 (7): 1355 – 1362.
15. United Nations Office on Drugs and Crime. (2011): World Drug Report 2011. United Nations Publication E.11.XI.10.
16. World Health Organisation. (2010): WHO Handbook for Guideline development. WHO Press ISBN 978 92 4 154844 1. (NLM classification: WA 39).
17. World Health Organization. (2010): ATLAS on substance use: Resources for the prevention and treatment of substance use disorders. WHO Press ISBN 978 92 4 150061 6. (NLM classification: WM 270).
18. Ferri M, Minozzi S, Bo A, Amato L. (2013) Slow-release oral morphine as maintenance therapy for opioid dependence.Cochrane Database Syst Rev. Jun 5;6
19. Beck, T., Haasen, C., Verthein, U., Walcher, S., Schuler, C., Backmund, M., Ruckes, C. and Reimer, J. (2014), Maintenance treatment for opioid dependence with slow-release oral morphine: a randomized cross-over, non-inferiority study versus methadone. *Addiction.* doi: 10.1111/add.12440.

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Conflict of interest

IM served as Board Member for Reckitt Benckiser Pharmaceuticals, Mundipharma, D&A Pharma, and Lundbeck. No conflict of interest for other authors

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