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Title: Global opioid agonist treatment: A review of clinical practices by country

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Abstract

Aims

We assessed how opioid agonist treatment (OAT) for opioid use disorder (OUD), specifically methadone and buprenorphine, including buprenorphine-naloxone, is delivered in routine clinical practice, with a focus on factors that affect access to and delivery of these services. The aims of this review were to summarize eligibility criteria for entry to OAT, doses in routine clinical practice, access to and eligibility for unsupervised dosing, and urine drug screening practices in OAT programs globally.

Methods

We completed searches of PubMed, Embase, and grey literature databases for cross-sectional or observational cohort studies of OAT using either methadone or buprenorphine. Dose data extracted from eligible studies were compared with guidelines provided by WHO.

Results

We found 140 reports from 41 countries that contained data for at least one of the relevant indicators. A diagnosis of opioid dependence or opioid use disorder was the most common eligibility requirement for OAT (13 or 17 countries). Reported mean or median doses for methadone ranged from 16 to 131 mg while range for buprenorphine was 2.5 – 19 mg. Access to unsupervised dosing under some conditions was reported in 18 of 27 countries. Frequency of regular urine drug screenings (UDS) ranged from several times a week to eight times per year (methadone) or as clinically indicated.

Conclusions

Opioid agonist treatment practices, including doses prescribed, vary greatly both within and across countries. Of particular concern is the persistence of lower dose prescribing practices, in which patients may be prescribed doses below those proven to yield significant clinical benefits.

Keywords: Opioid use disorder; opioid agonist treatment; methadone; buprenorphine; dosing; clinical practice

1. Introduction

Opioid use disorder (OUD) is an important public health issue, affecting an estimated 40.5 million people globally in 2017.[1] OUD is characterized by physical dependence and/or continued self-administration of opioids (illicit or pharmaceutical) with loss of control over use, including use despite adverse consequences, and craving.[2] Opioid agonist treatment (OAT; e.g. methadone or buprenorphine prescribed over an extended period of time) is effective in managing OUD, improving physical, behavioral, and psychological health of individuals with OUD,[3, 4] reducing the risk of infectious disease transmission due to unsafe injection practices,[5, 6] and reducing risk of mortality.[7] OAT prevents withdrawal, provides opioid receptor blockade, and helps reduce or eliminate cravings to use opioids.

The number of countries in which OAT is available is rising. A 2017 systematic review of HIV prevention interventions for people who inject drugs (PWID) found that OAT was available in 86 countries, including methadone in 81 countries and buprenorphine in 56,[8] compared to what was available in 2010 – methadone in 61 countries and buprenorphine in 41 countries.[9] Information regarding the implementation and uptake of OAT has become more readily available since the first systematic review of global OAT coverage was published in 2010;[9] however, to the best of our knowledge, there are no published systematic reviews that focus on the characteristics of delivery of OAT worldwide.

The World Health Organization (WHO) published guidelines in 2009 for the delivery of psychologically assisted pharmacological treatment of people with OUD based on published literature and the expertise of content experts.[10] These guidelines included dosing recommendations for both methadone and buprenorphine, outlining recommended initial and continued dose ranges. The guidelines for methadone recommend an initial dose of less than 20 mg/day and an ongoing treatment dose of 60 -120 mg/day, and the guidelines for buprenorphine recommend an initial dose from 2 – 8 mg/day and an ongoing treatment dose of at least 8 mg/day.

The WHO guidelines also recommended that methadone and buprenorphine consumption be supervised in the early stages of treatment to maximize treatment adherence and minimize risks such as diversion to other persons and non-prescribed use by injection. There is less guidance regarding ongoing supervision throughout treatment. Supervised dosing throughout treatment aims to maximize treatment adherence and minimize diversion of medications to the unregulated market. However, daily supervised dosing for all patients receiving OAT is resource-intensive and can be onerous for patients.[11] In some settings, unsupervised dosing (i.e., “take-away” or “take-home” doses) may be provided at the discretion of the prescribing doctor to patients who demonstrate “stability”, but there has been little research to inform this clinical decision.[12] Balancing patient safety with the need for more flexible treatment with less supervision is a complex task with critical implications for patient and community safety.

The WHO guidelines omit any specific recommendations on urine drug screening (UDS) for the purposes of treatment monitoring, although an initial screen for opioids is recommended as part of assessment and treatment induction. Health care providers may use UDS to assess how a patient’s treatment is progressing. For example, a positive UDS for extra-medically consumed opioids may indicate a need to review a patient’s dose or adjust the frequency of clinical visits to improve the assurance of regular medication adherence. The

few published papers that have evaluated the effectiveness of mandatory UDS on patient health outcomes did not find clear benefits of this practice on patient outcomes.[13]

In this review we assess how OAT for OUD (specifically methadone and buprenorphine, including buprenorphine-naloxone) is delivered in routine clinical practice, with a focus on factors that affect access to and delivery of these services. The aims of this review are to document and summarize at a country level:

1. Eligibility criteria for entry to OAT
2. Doses of methadone and buprenorphine as prescribed in routine clinical practice
3. Access to unsupervised dosing and eligibility to receive unsupervised doses
4. Urine drug screening practices in OAT programs, including indications for UDS and outcomes/consequences for OAT recipients following positive and negative UDS findings

2. Methods

Search terms

There has been considerable debate in recent years over appropriate terminology to describe the use of methadone and buprenorphine to treat OUD.[14-16] Prior to the introduction of buprenorphine, 'methadone maintenance treatment' was a widely used term, which remains in use in some parts of the world (e.g. China). 'Opioid substitution treatment' is used by the WHO and other UN agencies to refer to treatment with methadone or buprenorphine.[14-17] 'Opioid agonist treatment' is increasingly used with the argument that it is more precise and less open to misinterpretation than its predecessors.[15] We therefore use the terminology 'opioid agonist treatment' and the abbreviation OAT in this review but included all previous descriptor terms in conducting our literature search.

Studies of OAT using either methadone or buprenorphine for OUD were included (with any of the above terminologies). Where buprenorphine is referred to, this includes buprenorphine-naloxone coformulation. This review does not include other opioids used for treatment of OUD in relatively few countries (e.g. slow-release oral morphine; tincture of opium; injectable diamorphine; injectable hydromorphone), recently approved depot and implant forms of buprenorphine, or opioid antagonists (e.g. naltrexone).

Search strategy and study selection

This review included searches of peer-reviewed and grey literatures. This review is reported in line with the PRISMA guidelines for reporting of systematic reviews. We searched PubMed and Embase in July 2018 to identify relevant peer-reviewed literature. As many of the indicators of interest are not typically used as study outcomes, but may be reported incidentally in a paper's background or methods, our search strategy had to balance comprehensiveness (identifying as many potentially relevant studies as possible) with capacity to screen the resulting list of studies. Search terms are provided in the Supplementary Materials. Searches were limited to papers published from 2010 onwards to ensure that data reflected recent clinical practice.

Eligible reports were cross-sectional or observational cohort studies of people receiving OAT, or papers describing an OAT program, presenting information relevant to at least one of the selected indicators. Where longitudinal studies were included, baseline data were extracted. Reports of clinical trials were excluded as these may not reflect standard treatment practices (e.g. strict eligibility criteria; pre-specified dosing protocols; frequent UDS to measure trial outcomes). Studies were excluded from dose analyses if the study design focused on a subset of patients receiving OAT (e.g. a specific race/ethnic group) as the reported data may not reflect data for all patients in that program or area; however, if such reports included other information relevant to the indicators of interest (e.g. unsupervised dosing policies), the report was included for that indicator. We did not include assessments of clinical guidelines for OAT, as these may not be indicative of actual clinical practice.

Initial search results were screened on the basis of title and abstract by a team including SL, HJ, and four research assistants. The full-text of studies shortlisted on this basis were double-screened independently by the same team, with conflicts resolved through discussion with SL.

In addition to peer-reviewed literature, a database of grey literature on HIV prevention interventions for PWID, including OAT, assembled for a previous systematic review,[8] was searched for additional reports containing relevant data. This database was screened by one research assistant, then SL identified relevant reports from the shortlisted studies. Five further reports were identified by co-authors at the data extraction stage and added to the shortlisted studies.

We identified during data extraction that many papers reported data from substantially earlier time periods, potentially limiting the relevance of the information to current clinical practice. We therefore elected to include only data relating to clinical practices from 2010 onwards (i.e. data collection for the study occurred during the past decade). Where data were collected over a period of several years, we included the data if the time period encompassed 2010. Where year of data collection was not reported, we assumed data were collected two years prior to the publication year.

Data extraction

Data were extracted into a spreadsheet by the search team. All data points were checked against the original report for accuracy by the senior author. Information extracted on eligibility criteria to commence OAT included any reported requirement for treatment entry, such as patient age, diagnosis, assessments to be completed, or requirements to be non-responsive to other treatment modalities prior to OAT. For methadone and buprenorphine doses, we extracted mean or median doses and their associated measures of dispersion. Where reports provided the proportion of patients receiving doses above 60mg of methadone or 8mg of buprenorphine, this information was also extracted.

We defined 'unsupervised dosing' as doses of methadone or buprenorphine that patients were permitted to take away from and consume outside of a healthcare facility or dispensing location. Information extracted for this indicator included whether unsupervised dosing was permitted, and eligibility criteria for unsupervised dosing. For UDS indicators, we extracted information on the frequency of UDS and implications for patients of a positive (or negative) UDS.

Risk of bias

Risk of bias assessments give an indication of how study design and conduct may have influenced an outcome. Given the nature of this review in searching for data that are frequently reported incidentally rather than as part of study design or outcomes, we did not complete a risk of bias assessment.

Data analysis

We had planned to undertake a meta-analysis of mean methadone and buprenorphine doses reported in the included studies. However, much of the extracted dose data was missing standard deviations, or reported medians rather than means. Rather, dose data are reported as minimum and maximum mean and/or median doses identified both within and across all reports identified for that country. The minimum and maximum proportions of people prescribed >=60mg methadone, or >=8mg of buprenorphine, are also presented by country.

For the remaining indicators (treatment eligibility, access to unsupervised dosing, and use of UDS), data for each indicator were first grouped by country. For each indicator, data for each country were qualitatively synthesized to produce a summary for that country. For some indicators (e.g. access to unsupervised dosing), this was relatively straightforward as for the most part only yes/no information was available. For others (e.g. use of UDS), different studies provided different information, reflecting varying practices between treatment sites. In these instances, the resulting summary captured the range of practices reported. Data management was conducted in Excel and meta-analysis synthesis was conducted using a random effects model using STATA. This analysis was not pre-registered on a publicly available platform and the results should be considered exploratory.

3. Results

The peer-reviewed literature search returned 7,415 results for screening, and the grey literature database provided 137 reports for screening. After screening and exclusions, 140 reports from 41 countries contained data for at least one of the relevant indicators (Figure 1).

Eligibility for OAT

We identified 32 reports from 17 countries that described eligibility criteria and restrictions to entry for OAT. Findings are summarized in Table 1 and complete data are provided in Supplementary Table 1. As expected, a diagnosis of opioid dependence or opioid use disorder (DSM-IV or ICD) was required to be eligible for OAT in most countries (13/17 = 76%). Assessment by specialists (e.g. psychiatrists) or confirmation of OUD diagnosis by multiple physicians or multidisciplinary teams were required in some instances. A minimum age requirement (usually 18) was mentioned for 6 . Other treatment entry criteria included prior attempts at non-pharmacological treatment for OUD (Armenia and Kyrgyzstan),[18, 19] an "unsuccessful" detoxification attempt (Finland[20] and Iran) or evidence of recent use by an opioid positive urine test (Israel, Macao, Tanzania). Requirements for people to have completed detention in a compulsory detoxification centre prior to OAT entry were removed in China in 2006.[21] Requirements that people entering OAT have their details reported to law enforcement registries were identified in Armenia, Azerbaijan and China.

Methadone and buprenorphine doses prescribed in routine clinical practice

There were 101 reports from 34 countries providing data on prescribed doses of methadone or buprenorphine. Findings are summarised in Tables 2 and 3, with countries ordered by doses prescribed, and complete data are provided in Supplementary Tables 2 and 3.

The first nine countries listed report prescribing high mean doses of 73-131 mg and an additional country (Malaysia) reports a high percentage maintained on doses $\geq$80 mg The next group of 13 countries report a wide range of doses that encompass 48-119 mg and includes Ireland that reports a substantial percentage on >=60mg. The final group of 10 countries report lower doses with a range that encompasses mean doses as low as 16 mg (Nepal) and as high as 69 mg (China). The percentage of patients receiving doses >=60mg generally corresponds to mean dose ranges where this data is available.

Considerably fewer data were identified for buprenorphine dose levels. Table 3 shows data for 15 countries where data were available. The first 6 countries listed report high mean buprenorphine dose ranges that encompass 10-19 mg. the next group of 7 countries report mean doses from 5.8 - 9.2 mg. Only Nepal reports using very low doses.

Availability of unsupervised dosing

Information on availability of unsupervised dosing was extracted from 52 reports from 27 countries (results summarized in Table 4 and complete data provided in Supplementary Table 4 Unsupervised dosing was permitted in 18 of 27 countries (67%) at least under some conditions. Typically this practice was implemented at the discretion of the prescribing physician for patients considered suitable. Some reports noted objective indicators that were used to determine suitability for unsupervised dosing, including compliance with program rules or negative UDS.

Urine drug screening practices in OAT programs

We identified 51 reports from 17 countries that provided information on UDS practices in OAT settings (results summarized in Table 5; complete data are provided in Supplementary Table 5). The information presented was typically limited to frequency of screening with minimal details regarding rationale for or events that may trigger UDS.

The frequency of UDS varied from several times a week (e.g. some reports from Israel;[18, 19] one report from the US[20]) to once a month (e.g. patients receiving buprenorphine after stabilisation in some US settings[21]), while others stated that UDS was undertaken as clinically indicated. Several reports indicated that the collection of urine samples was supervised; for example, via one-way mirror.[22] In Hong Kong, UDS was undertaken for program monitoring purposes only, and was entirely voluntary.[23] Some reports from the United States noted that the frequency of UDS was dictated by the patient's insurance company[24] or parole terms,[25] rather than clinical factors.

Reported implications of a positive UDS for the patient included decreased access to unsupervised dosing and increased clinical visits. Positive UDS results could also lead to removal from treatment, although most reports noted that this occurred only if clinical interventions (e.g. increased physician visits or counselling) in response to the positive result did not lead to a negative UDS.

4. Discussion

In this global systematic review, we found wide variation between, and sometimes within, countries in the way OAT is delivered. Our findings suggest that there are considerable opportunities to improve clinical practice in the delivery of OAT.

Opioid use disorder/opioid dependence was the main treatment eligibility criterion in most settings which seems appropriate. However, restrictive entry criteria for OAT were sometimes reported, including prior attempts at non-pharmacological treatment. Additionally, several countries require that the details of patients who receive OAT are provided to law enforcement agencies. The reasoning behind such registration was not made explicit in the identified reports but does not appear to have any clinical purpose and likely acts as a barrier to treatment entry. Satisfactorily addressing the concerns of communities and law enforcement is a key challenge in scaling up OAT in many settings and may require changes in the legal and cultural landscape in such countries. Strict laws and aggressive policing have also made it difficult for public health agencies to implement and expand evidence-based interventions to treat OUD.[26-28] There are published accounts of law enforcement targeting PWID at treatment facilities,[29] intimidating health care providers,[29, 30] and confiscating sterile syringes.[31] These practices actively deter PWID from seeking treatment and prevent providers from serving their patients. Encouragingly, a study in Kyrgyzstan that examined the effects of integrating police training with public health education has shown promise and may serve as a feasible model for law enforcement agencies in countries with similar epidemics.[32]

Importantly, our data indicate that many people prescribed OAT are prescribed doses below those that are considered optimal for clinical benefit. A 2003 systematic review that evaluated the efficacy of different doses of methadone found that doses ranging from 60 - 100 mg/day were more effective in retaining patients in treatment and reducing substance use during treatment compared to lower doses (1-39 mg/day).[33] A review of the literature regarding buprenorphine dosing noted that doses above 16 mg resulted in greater clinical benefit than doses between 8-16 mg.[34] Only 2 of 12 countries had doses of 16 mg or high in our data (Table 3). Additionally, there is some evidence that higher doses of OAT may reduce non-opioid use among patients receiving OAT. Two RCTs found that patients who received higher doses of OAT had a greater probability of abstaining from cocaine compared to those who received lower doses.[35, 36] For several countries, multiple data sources confirmed low dosing to be a concern. Our results suggest that a large proportion of patients receiving OAT are not prescribed doses high enough to promote cessation of extra-medical opioid use, which may undermine the clinical and public health benefits of OAT. Our finding that many OAT patients are prescribed doses below those that are considered minimal for producing clinical benefit has also been reported in other studies.[37, 38]

Unsupervised dosing was not permitted at all in several settings. Lack of access to unsupervised dosing has been identified as an important barrier to OAT entry and retention, as daily attendance for dosing can be onerous, time-consuming, and expensive.[39, 40] Requiring daily supervised dosing is also resource-intensive for treatment providers, potentially limiting treatment capacity.[41] That said, in countries where unsupervised dosing is widespread, the introduction of higher levels of supervised methadone dosing was followed by a reduction in methadone overdose deaths.[42] Models of care that require limited

supervision can be implemented safely, particularly in relation to buprenorphine prescribing, and are already in use in some settings.[41, 43, 44] Research to identify patients most suited to lower levels of supervision, and those in need of higher levels of supervision, is still needed.

Where unsupervised dosing is available, the proportion of patients receiving any unsupervised doses was rarely reported, so we were unable to assess the extent to which policies permitting unsupervised dosing are put into practice. In determining access to unsupervised dosing, mention was often made of physician discretion in determining 'stability' or other indicators of suitability; however, given there are no universally agreed upon criteria for stability, there is likely variation and subjectivity (allowing for bias) in defining and measuring 'stability', and in practice there may be little relationship between indicators of treatment adherence and access to unsupervised dosing.[12] A recent study reported no association between adherence to the treatment regimen and the number of unsupervised doses prescribed, and suggested that system-level factors (e.g., location, what type of OAT is available, if the prescriber worked in a public or private practice), and not patient behaviors, are more likely to dictate who would be eligible for take-home doses.[12] Paradoxically, one study in London found that patients receiving OAT who were less adherent to their treatment regimen were more likely to be prescribed take-home doses compared to those who fully adhered.[45] Research comparing the effects of supervised to unsupervised dosing is lacking,[46] though there have been a small number of randomized controlled trials comparing the effects of these two strategies. Two trials, one conducted in Australia[47] and another Scotland,[48] reported no differences in treatment retention nor medication adherence between patients who were and were not prescribed take-home doses. However, another trial conducted in Italy found that patients receiving OAT who were assigned supervised daily consumption had a higher retention rate than those who were assigned take-home doses.[49] A qualitative study found that patients recognized the value of supervised dosing at the beginning of treatment as it may help establish a daily routine and were accepting of supervised dosing with the potential of modification at a later time.[42] However, there is also concern that supervised dosing may jeopardize patient privacy and may lead to increased stigma.[50, 51]

Frequent urine drug screening was mandated in many of the settings reviewed here. In some reports from the United States, it was noted that insurance companies or parole officers determined the frequency of UDS rather than clinicians. A recent systematic review identified only one evaluation of the impact of UDS on OAT outcomes, finding that providing take-home doses, contingent on negative UDS results, increased treatment retention.[52] This study did not examine the impact of UDS on treatment retention or other outcomes directly. The review concluded that there is very little evidence on the effectiveness of UDS in OAT on clinical or public health outcomes.[52] Given that UDS has cost implications, is potentially embarrassing and invasive for patients, may perpetuate substance-use stigma, and is currently implemented in a highly variable way with little evidence-based guidance, there is a clear need for methodologically rigorous research that establishes whether UDS improves OUD treatment outcomes, and the frequency of testing and other aspects (e.g., direct observation) of how UDS is implemented that are required to achieve this.

This study has several imitations. Our review only included clinical practices that were published in English in academic journals and in grey literature. Our results reflect the

clinical practices of facilities that have contributed to the literature which may not reflect overall practices within a country. Further, the number of clinics represented in the literature in relation to the total number operating in each country is unknown. We are unable to comment on practices in countries that lacked reports; we identified reports relating to 41 countries, but there are at least 86 countries where OAT is implemented to some extent.[8] We used a comprehensive search strategy, but it is possible that papers relevant to our study's objectives may have been overlooked or mistakenly excluded.

We restricted the data included in this analysis to those reported in peer-reviewed publications and grey literature. We chose not to review clinical guidelines or treatment policies as these may not be translated into clinical practices, since our focus was on reporting what happens in routine clinical care. National guidelines may provide broader, and possibly, more comprehensive protocols for OAT entry and clinical care. Additional research examining national guidelines may be warranted. Similarly, research examining OAT legal and policy environments globally may shed light on how practices may vary between countries, and opportunities to improve care.

Clearly there is a need to collate and pool observational data from OAT across countries to improve the evidence base and motivate cross-country comparisons and studies on OAT delivery and drug related harms. We did not evaluate all aspects of OAT care, such as whether patients have access to counselling or other psychosocial support, whether treatment is accessed in specialty or primary care settings, or availability of OAT dispensing in community pharmacy settings.[53] We cannot assume that the studies that we identified are reflective of all clinical practice in a given country and have noted where variation was observed between studies from one country.

Despite these limitations, our study provides a comprehensive overview of OAT in clinical practice. The data provided by peer-reviewed articles that describe OAT in practice reported that doses prescribed to patients varied greatly within countries and globally, and that a large proportion of patients may be prescribed doses below those proven to yield significant clinical benefits. Further research is necessary to understand why there is such variability in clinical practice and how to best provide care for patients with OAT globally.

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