

CHAPTER 3. PHARMACOLOGICAL TREATMENT

3.1 Pharmacological treatment of alcohol and drug use disorders

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The broad context of treatment

Treatment of substance use disorders works and is cost-effective (Cartwright, 2000; Simoens et al., 2002). For instance, Gerstein & Harwood (1994) examined the effects of treatment, the costs of providing treatment and the economic value of treatment in the United States. They found that the cost of providing the treatment was approximately US\$ 209 million, while the benefits society received during and after treatment were worth approximately US\$ 1.5 billion. A number of studies in other countries have confirmed that treatment works and that there is a net return on investment to the community (e.g. Simpson & Sells, 1982; Hubbard et al., 1997; Gossop, Marsden & Stewart, 1998).

O'Brien and McLellan (1996) compared drug dependence with adult onset diabetes, hypertension and asthma. For example, asthma is also a chronic relapsing condition with multiple etiologies, including a genetic component, personality and environment. Asthma, like substance use disorders, involves choice in the development of the condition (e.g. smoking) and requires significant behaviour changes. Continuing care across a person's lifespan is necessary. Relapse rates for asthma are in the order of 30–50%. These features are similar to drug dependence, yet no one argues about the benefit of providing treatment for asthma. The treatment of substance use disorders is as successful as the treatment of these medical conditions.

Governance can be described as the institutions, processes, policies and laws affecting the way people direct, control and administer treatment. Governance is an important component of the safety and quality of health care as poor treatment outcomes are often the result of failures of the health care system. Without proper governance systems, treatment services become vulnerable to abuse.

Simpson (2000) found that interactions between individual needs, motivation factors, social pressures and aspects of the treatment programme itself influence individuals to enter and remain in treatment. Drawing on research about how clients become engaged in treatment, Simpson (2000) conceptualized treatment as phases of outreach, induction, engagement, treatment and aftercare. The goals of treatment include reducing or stopping drug use, improving physical and emotional health, improving social functioning and relationships, and making meaningful contributions to the community, such as employment.

Maintenance of behaviour change requires substantial time and emotional commitment. Relapse prevention and managing cravings are central behaviour change requirements. In addition, individuals may need to learn to deal with emotions differently, acquire new or altered social skills, manage time effectively, and deal with interpersonal conflict in an

assertive manner. Financial management, employment skills and educational opportunities are also important components of establishing a drug-free and productive life.

Withdrawal treatment

The primary goal of withdrawal treatment (also called detoxification) is neuroadaptation reversal. Drug withdrawal treatment can be provided in a variety of settings – acute hospital, community residential unit, or as an outpatient service. The essential factors in effective withdrawal are a supportive environment and supportive counseling, provision of appropriate symptom management (usually pharmacotherapy), and development of a plan for further treatment after withdrawal (neuroadaptation) has been completed. It is important to note that withdrawal management is not a treatment in and of itself, and does not result in the substantial behavioural changes required for an individual to maintain a drug-free lifestyle. It is, however, the first step in attaining abstinence.

A meta-analysis of studies of pharmacological therapies for alcohol withdrawal (Mayo-Smith, 1997) suggested that benzodiazepines are effective in reducing withdrawal severity, incidence of delirium and seizures with a greater margin of safety and lower abuse potential compared to other therapies. A more recent systematic review (Holbrook et al., 1999) of randomized controlled trials reached a similar conclusion.

Most research into opioid agonists has focused on their use in maintenance treatment. However, the Cochrane review of opioid withdrawal compared 22 studies involving 1736 participants (Gowing, Ali & White, 2009). The major comparisons were between buprenorphine, methadone and clonidine or lofexidine. Severity of withdrawal was similar for withdrawal managed with either buprenorphine or methadone, but withdrawal symptoms may resolve more quickly with buprenorphine. Methadone is cheaper than buprenorphine and its administration in withdrawal management has no risk of precipitated withdrawal. Relative to clonidine or lofexidine, buprenorphine could be more effective in ameliorating withdrawal symptoms, and patients treated with buprenorphine or methadone are more likely to complete withdrawal treatment. At the same time there is no significant difference in the incidence of adverse effects, but drop-out due to adverse effects may be more likely with clonidine.

Opioid agonist pharmacotherapy (OAP)

There are three main medications for the treatment of heroin dependence, namely methadone, buprenorphine and naltrexone. Methadone and buprenorphine work by eliminating withdrawal symptoms, reducing or eliminating cravings and blocking euphoric effects from any additional heroin use. These three mechanisms are important and an adequate dose is required for these effects to occur. This dose may exceed the dose requirement just to eliminate withdrawal. The longer a person is in treatment, the greater the gains and benefits that accrue from opioid agonist pharmacotherapy. Methadone treatment has repeatedly been found to reduce substantially and, in many cases, completely eliminate heroin use. It also protects against HIV/AIDS and reduces HIV risk-taking behaviour. There are also benefits of reducing the risk of death from heroin overdose death as well as of criminal behaviour.

Opioid agonist pharmacotherapy treatment has been found in Cochrane reviews to be more effective than no treatment in terms of reducing heroin use, imprisonment and retention in treatment. It has also been found to be more effective than detoxification or outpatient drug treatment counselling in terms of reducing heroin use, criminal behaviour

and risky sexual behaviour. Finally, opioid agonist pharmacotherapy has been found to be more effective in terms of retention in treatment than therapeutic communities, outpatient drug-free treatment and naltrexone treatment.

WHO conducted a study in China, Indonesia, Iran, Lithuania, Poland, Thailand and Ukraine which found that treatment outcomes in terms of retention, drug use, HIV risk, health, criminal behaviour and employment were comparable to those found in studies conducted in Australia, the United Kingdom and the United States (Lawrinson et al., 2008).

Opioid agonist pharmacotherapy has consistently been found to reduce injecting drug use in terms of both the proportion of participants who continue injecting and the frequency of injecting for those who continue to inject. The interaction between these two components is important in terms of HIV risk-taking behaviour. Several studies have also shown lower rates of HIV seroconversion or of acquiring HIV when in treatment. HIV-infected drug users are more likely to take up treatment for their HIV and are also more likely to adhere to that HIV treatment when on opioid agonist pharmacotherapy. Health care costs and HIV-related medical complications are also significantly lower.

Training needs for opioid agonist pharmacotherapy

Until recently opioid agonist pharmacotherapy was largely restricted to specialist, clinic-based programmes that were heavily regulated and marginalized from mainstream health services. Changes in understanding the role of opioid agonist pharmacotherapy programmes, along with a shift towards a public health model of intervention, has seen the development in some countries of community-based programmes that are incorporated in other health and welfare services.

Further expansion of opioid agonist pharmacotherapy programmes to meet unmet demand brings with it the need to train the workforce in the use of this pharmacotherapy. This requires the development of clinical guidelines and procedures specifically tailored to community-based programmes. It also requires specialist services to provide clinical consultancy and treatment back-up for more complex clients.

Any training programme in opioid agonist pharmacotherapy will need to address attitudes and knowledge as well as skills. Training should combine didactic teaching, interactive learning, clinical case scenarios, assessment role plays and the opportunity for feedback and discussion. The use of learning objectives and competency-based training models is also required (Allsop et al., 1997). The assessment procedure can be used to determine whether the medical practitioner meets the learning objectives and can be authorized to prescribe. The assessment procedure will also assist practitioners in identifying their own training needs as well as providing the community and patients with confidence in the standards of treatment.

Duration and comprehensiveness of treatment

Duration of treatment is important. Longer length of treatment has been demonstrated to be associated with improved outcomes (e.g. Magura et al., 1999; Ball & Ross, 1991; Kang & De Leon, 1993). In addition, imposing arbitrary time limits on treatment does not enhance treatment outcomes (Ward, Mattick & Hall, 1998). A meta-analysis of treatment outcomes has confirmed the relationship between length of treatment and treatment outcomes (Brewer et al., 1998).

3.2 Policy framework and guidelines for the pharmacological treatment of substance use disorders

(Figures 3.1–3.4)

Background

- Policy documents and guidelines on the pharmacological treatment of substance use disorders may assist in regulating the context in which pharmacological treatment is provided, thus ensuring the optimal availability and use of different medicines in the treatment of substance use disorders.
- A policy framework is often needed to guide the regulation of medicines which have the potential for abuse, a number of which are useful for the treatment of substance use disorders – including opioids and benzodiazepines.
- Nominated focal points were asked about the presence of policy documents on the pharmacological treatment of substance use disorders, and were requested to indicate whether guidelines on the pharmacological treatment of these disorders exist in their countries.

Salient findings

Policy documents on pharmacological treatment

- Policy documents on the pharmacological treatment of substance use disorders were reported by 40.2% of countries.
- The region reporting the highest proportion of policy documents on the pharmacological treatment of substance use disorders was Europe (70.4%).
- There is some variation according to country income group. The lowest proportion of countries reporting policy document was in the lower middle-income countries (22.5%). In 73.5% of high-income countries, policy documents were reported.

Guidelines on pharmacological treatment

- Guidelines on the pharmacological treatment of substance use disorders were reported by approximately half of the surveyed countries (51.8%).
- The European and Western Pacific regions reported having the highest proportions of countries with pharmacological guidelines for substance use disorders (76.8% and 71.4% respectively). The lowest proportion of countries with pharmacological guidelines was reported from the African Region (21.0%).
- There is an effect of country income level on the presence of guidelines regulating pharmacological treatment of substance use disorders between low-income/lower middle-income countries (31.7% and 37.5% respectively) and higher middle-income/high-income countries (69.2% and 79.4% respectively).

Notes and comments

- Policy documents and guidelines on the pharmacological treatment of substance use disorders appear to be absent in a significant proportion of surveyed countries, especially in low-income and middle-income countries. This may reflect the difficulties that lower-income countries have in developing such policies, or the perceived lack of need for such policies. This in turn may affect the capacity to regulate the use of medicines with abuse potential, such as benzodiazepines and opioids.
- Guidelines for the pharmacological treatment of substance use disorders are common in high-income and upper middle-income countries, but much less so in low-income and lower middle-income countries. Again, this may reflect the difficulties that low-income and lower middle-income countries have in developing guidelines, or the lack of priority given to such guidelines. This may affect the capacity to ensure that the most cost-effective medicines are used.

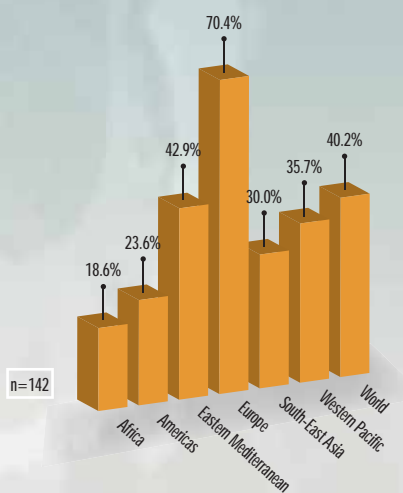


FIGURE 3.1
PROPORTION OF COUNTRIES
WITH POLICY DOCUMENTS
ON THE PHARMACOLOGICAL
TREATMENT OF SUBSTANCE USE
DISORDERS, BY REGION, 2008

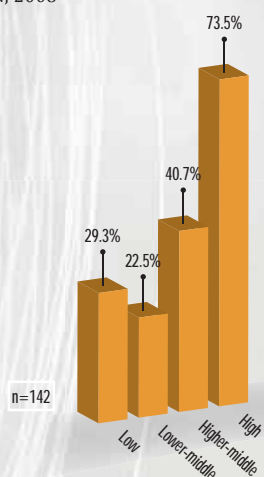


FIGURE 3.2
PROPORTION OF COUNTRIES
WITH POLICY DOCUMENTS
ON THE PHARMACOLOGICAL
TREATMENT OF SUBSTANCE
USE DISORDERS, BY INCOME
GROUP, 2008

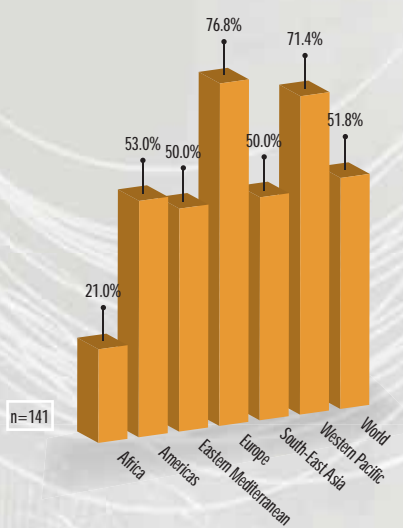


FIGURE 3.3
PROPORTION OF COUNTRIES
WITH GUIDELINES ON THE
PHARMACOLOGICAL TREATMENT
OF SUBSTANCE USE DISORDERS,
BY REGION, 2008

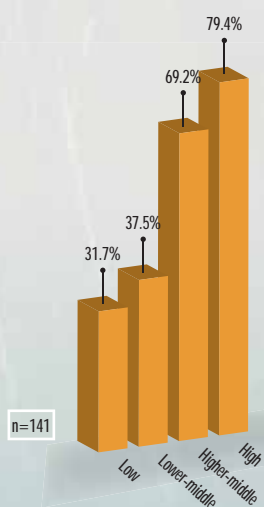


FIGURE 3.4
PROPORTION OF COUNTRIES
WITH GUIDELINES ON
THE PHARMACOLOGICAL
TREATMENT OF SUBSTANCE
USE DISORDERS, BY INCOME
GROUP, 2008

3.3 Availability of therapeutic drugs for alcohol and drug use disorders

(Figures 3.5–3.9)

Background

- Nominated focal points were asked about the use of different medications for the treatment of alcohol withdrawal in their countries.
- Focal points were requested to indicate the availability of opioid agonist pharmacotherapy for the treatment of opioid dependence – such as the availability of methadone, buprenorphine and buprenorphine/naloxone.
- On the treatment of opioid dependence, countries were asked which opioid agonists would be used for the treatment of opioid withdrawal and which for the maintenance of opioid dependence.
- WHO recommends the use of benzodiazepines for the management of alcohol withdrawal. The Organization recommends methadone for the treatment of opioid dependence as it is more cost-effective than buprenorphine, but also recommends that both methadone and buprenorphine should be available, if possible, and that the syrup/solution formulations of methadone should be used since it is easier to supervise their dispensing effectively. WHO does not have recommendations on the use of buprenorphine/naloxone as it was not considered in the most recent WHO guidelines on the treatment of opioid dependence.

Salient findings

Pharmacological treatment of alcohol withdrawal

- In 90.9% of countries, benzodiazepines were reported to be used for the management of alcohol withdrawal. Chlorpromazine and new antipsychotics were identified for the management of alcohol withdrawal in 55.9% and 49.2% of countries respectively.
- The use of chlorpromazine in countries appears to decrease with increasing country income.
- The use of acamprosate for the management of alcohol withdrawal was reported to be highest among countries in the high-income group (41.9%), compared to countries in the lower income groups (low-income = 5.3%).

Pharmacological treatment of opioid dependence

- For the treatment of opioid dependence, availability of methadone was reported by 41.6% of countries that responded to this question in the survey, buprenorphine by 27.7%, and buprenorphine/naloxone by 20.8% of countries in the survey.
- The highest proportion of countries reporting availability of methadone (88.6%), buprenorphine (59.1%) and buprenorphine/naloxone (50.0%) was in Europe. Africa was the region reporting the lowest proportion of countries having methadone and buprenorphine (9.3%). No country in the Eastern Mediterranean Region reported having buprenorphine/naloxone formulation.

- There is an effect of income level on the availability of opioid agonists for the treatment of opioid dependence across different income groups of countries. This income effect is strongest for methadone. The proportion of countries using methadone increases across different income groups of countries (i.e. 12.2% of low-income countries reported methadone, compared to 88.6% of high-income countries).

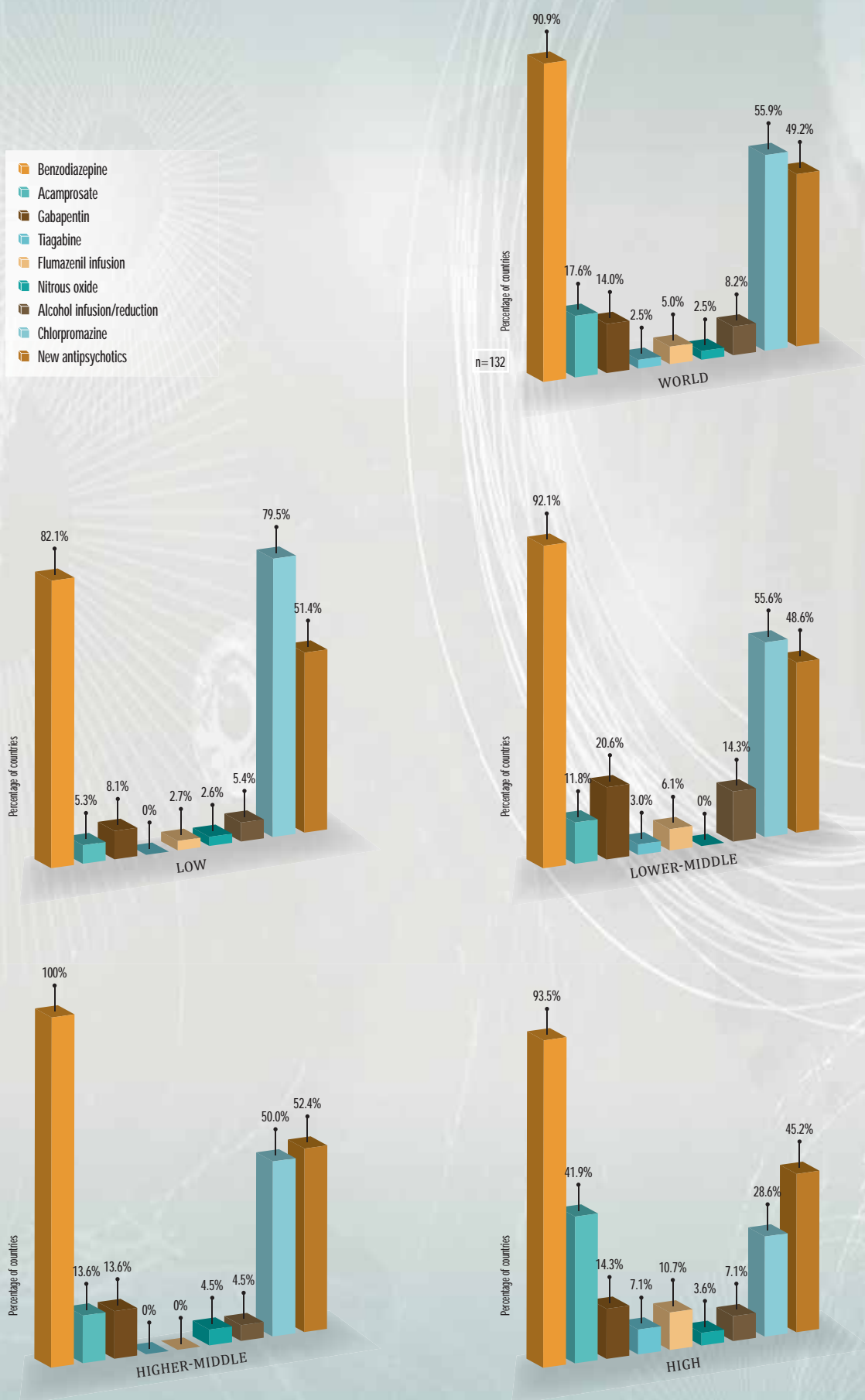
Pharmacological treatment of opioid withdrawal and maintenance of opioid dependence

- Approximately a third of countries reported using methadone for detoxification and maintenance of opioid dependence. For maintenance of opioid dependence, methadone solution/syrup seems to be used more often than methadone tablets. For opioid withdrawal and maintenance, buprenorphine was reported to be used by approximately 25% of countries.

Notes and comments

- The situation with availability of medications may change over a relatively short time. This, as well as the number of countries from which the relevant information was collected in the survey, should be taken into consideration when interpreting the data presented.
- The reported use of medications other than benzodiazepines for alcohol withdrawal suggests that there is considerable variation in practice in the management of alcohol withdrawal. The high rate of use of chlorpromazine is a concern since chlorpromazine is specifically not recommended by WHO as it may increase the risk of seizures during alcohol withdrawal.
- The fact that alcohol and drug medication is available in countries does not imply there is information on the coverage of the population in need of pharmacological treatment. As described in chapter 2, coverage of opioid-dependent persons with agonist maintenance appears to be low.
- Availability of opioid agonist pharmacotherapy for the treatment of opioid dependence appears to be low, especially in low-income and lower middle-income countries.
- The use of buprenorphine and buprenorphine/naloxone is effectively limited to high-income countries and approximately 10% of lower-income countries. This is consistent with its higher cost. Methadone is more available in lower middle-income and upper middle-income countries, presumably due to a greater sensitivity to cost in these countries.
- The reported use by two countries of buprenorphine patches for opioid agonist maintenance is noteworthy.
- While 42% of countries report the availability of methadone, only 31% report the availability of the methadone syrup formulation. The remaining 15 countries are presumably using methadone tablets for opioid agonist maintenance treatment. It is difficult to supervise the dispensing of methadone in tablet form. Take-home doses are also easily sold or injected, which can result in problems, including diversion to the street market.

FIGURE 3.5
MEDICATIONS USED IN COUNTRIES FOR THE MANAGEMENT OF ALCOHOL WITHDRAWAL, BY INCOME GROUP, 2008



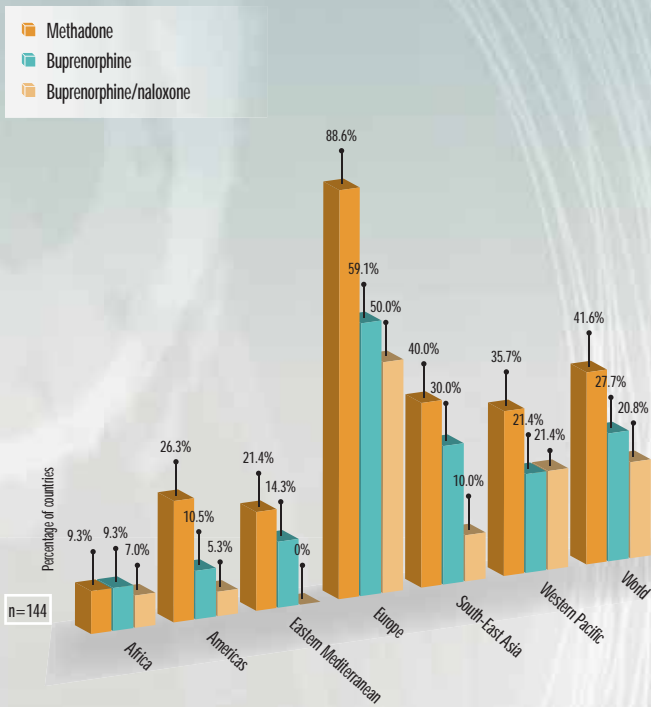


FIGURE 3.6
AVAILABILITY IN COUNTRIES OF OPIOID AGONIST PHARMACOTHERAPY FOR THE TREATMENT OF OPIOID DEPENDENCE, BY REGION, 2008

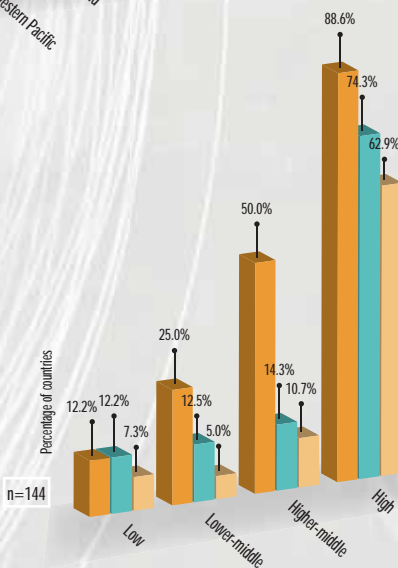


FIGURE 3.7
AVAILABILITY IN COUNTRIES OF OPIOID AGONIST PHARMACOTHERAPY FOR THE TREATMENT OF OPIOID DEPENDENCE, BY INCOME GROUP, 2008

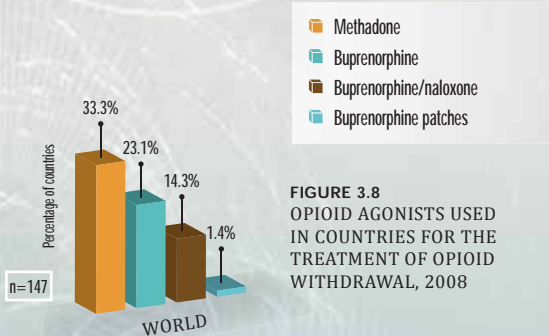


FIGURE 3.8
OPIOID AGONISTS USED IN COUNTRIES FOR THE TREATMENT OF OPIOID WITHDRAWAL, 2008

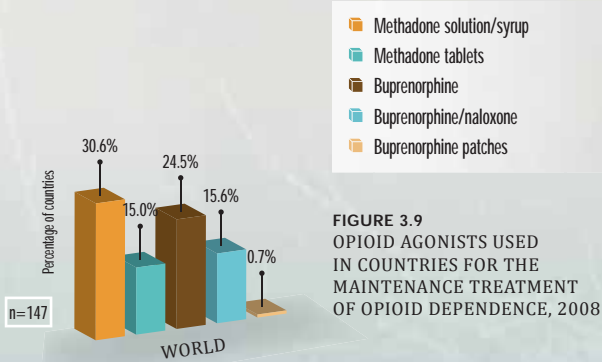


FIGURE 3.9
OPIOID AGONISTS USED IN COUNTRIES FOR THE MAINTENANCE TREATMENT OF OPIOID DEPENDENCE, 2008

3.4 Administration of opioid agonist pharmacotherapy

(Figures 3.10–3.14)

Background

- Nominated focal points were requested to indicate the duration of opioid agonist treatment, and were asked whether such treatment would be provided in a time-limited or an open-ended manner. WHO recommends open-ended treatment.
- Questions were asked on the formulation of methadone which is used for the treatment of opioid dependence. Focal points were requested to indicate whether methadone would generally be provided in tablet form or in syrup/solution. WHO recommends the use of the syrup/solution formulations as they are easier to supervise when being dispensed and, when diluted, they are not easily diverted to the black market for injection.
- Focal points were asked about the use of inpatient facilities for the commencement of methadone, buprenorphine and buprenorphine/naloxone, and were asked specifically whether treatment would normally be started as an outpatient or as an inpatient in their countries. WHO recommends that outpatient commencement should mainly be used.
- The following figures (Figs. 3.10–3.14) apply to countries in which opioid agonist treatment is available.

Salient findings

Duration of opioid agonist treatment

- Treatment with opioid agonist pharmacotherapy was reported to be open-ended in the majority of countries, with 74.1% of countries reporting no time-limit for opioid agonist pharmacotherapy. Across different income groups, the lower middle-income group of countries seems to have the highest proportion of countries with a time-limited opioid agonist treatment approach (45.5%).

Formulation of methadone

- Over 55% of countries in the survey (countries having opioid agonist pharmacotherapy available) reported using methadone syrup/solution for the treatment of opioid dependence. Approximately 25% of countries reported using methadone tablets only, while another 20% of countries reported using both oral solution and tablets.

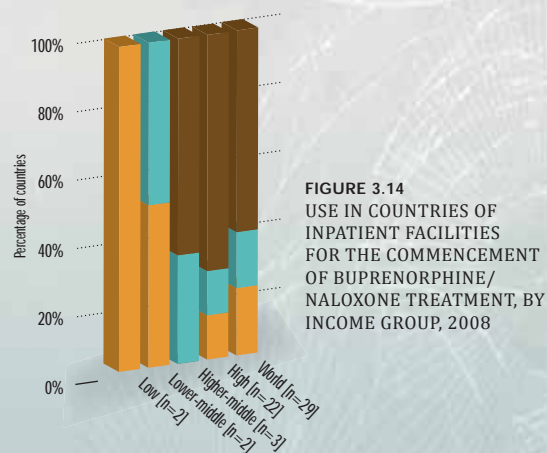
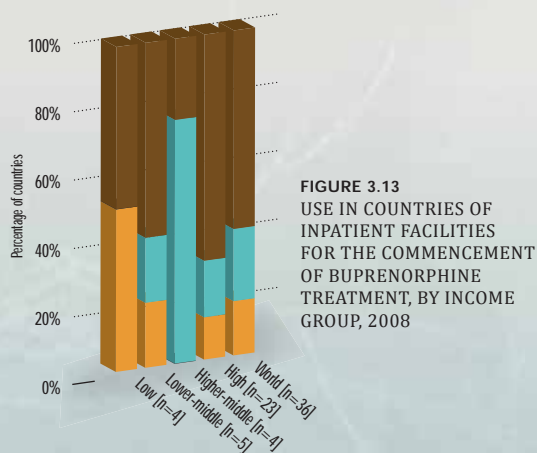
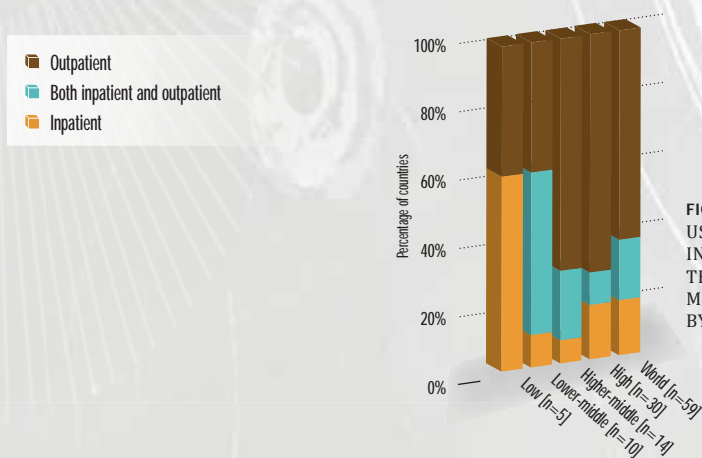
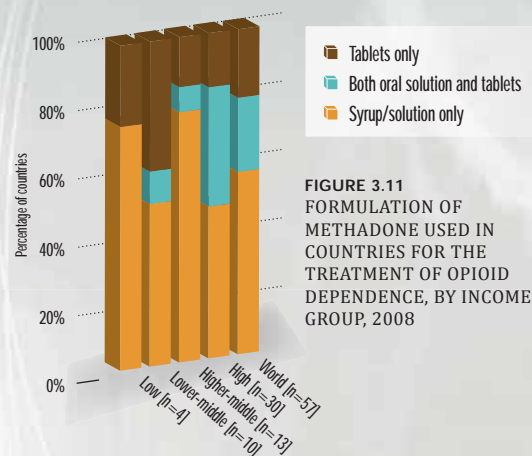
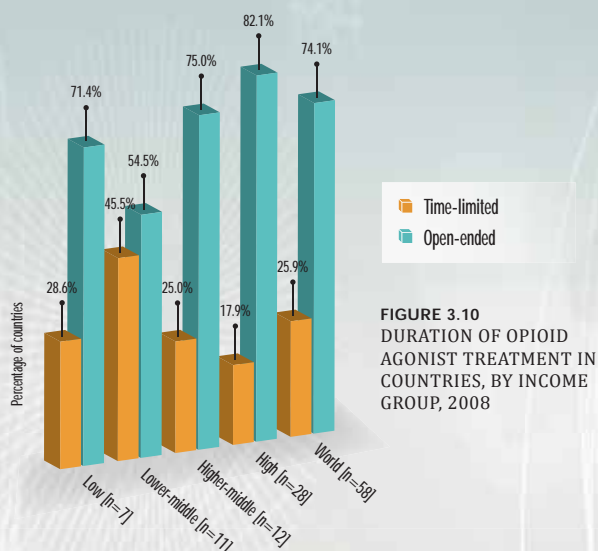
Inpatient facilities for the commencement of opioid agonists

- Opioid agonist pharmacotherapy such as treatment with methadone, buprenorphine, and buprenorphine/naloxone is commenced on an outpatient basis in approximately 60% of countries in the survey. Approximately 20% of countries reported commencing treatment with methadone, buprenorphine and buprenorphine/naloxone as an inpatient. An additional 20% of countries reported commencement of opioid agonist pharmacotherapy on both an inpatient and outpatient basis.

- Compared to high-income countries in which outpatient treatment with opioid agonists seems to be common, there is a tendency for fewer countries in the low-income and lower middle-income groups to commence treatment with methadone and with buprenorphine/naloxone on an outpatient basis.

Notes and comments

- Availability of opioid agonist pharmacotherapy such as treatment with methadone, buprenorphine or buprenorphine/naloxone appears to be limited, especially in lower-income groups of countries. Thus the overall number of countries in the respective groups are low.
- Outpatient treatment for opioid agonist pharmacotherapy appears to be a common treatment approach in high-income countries. Outpatient treatment for the pharmacological treatment of opioid dependence might be less expensive for countries, and may improve the capacity of inpatient services to deal with more complicated patients.
- As mentioned in section 3.3, the use of methadone tablets for opioid agonist maintenance treatment can result in difficulties in the capacity to effectively supervise the dispensing of methadone. The data in this section indicate that some countries have both tablet and solution formulations of methadone available and use both formulations in the treatment of opioid dependence.



3.5 Supervision and prescription requirements for opioid agonist pharmacotherapy

(Figures 3.15–3.23)

Background

- Nominated focal points were asked whether supervision of opioid agonist pharmacotherapy such as pharmacological treatment with methadone, buprenorphine, and buprenorphine/naloxone was required in their countries. WHO guidelines recommend that the administration of both methadone and buprenorphine should be directly supervised, at least early in treatment, to reduce misuse and diversion to the illicit market.
- Focal points were requested to indicate whether the level of supervision of methadone, buprenorphine and buprenorphine/naloxone would be individually determined by the treating doctor, or whether it was determined by a universally applied standard. WHO guidelines recommend that the level of supervision be individually determined.
- Focal points were asked about the minimum training requirements for health care staff responsible for the prescription of opioid agonists, and what kind of health care staff in their countries would have the authority to prescribe methadone, buprenorphine or buprenorphine/naloxone.

Salient Findings

Supervision of opioid agonist pharmacotherapy

- Supervision of methadone for the treatment of opioid dependence was required by 85.4% of countries in the survey. In 60.6% of countries buprenorphine supervision was required, and in 71.4% of countries buprenorphine/naloxone supervision was required.
- There seems to be no effect of country income level on the supervision requirements of opioid agonist pharmacotherapy.
- Approximately three quarters of countries in the survey (74.1% for methadone, 74.3% for buprenorphine, 69.0% for buprenorphine/naloxone) reported that the level of supervision with the respective opioid agonists would be individually determined by the treating doctor.
- Compared to high-income countries, a higher proportion of countries in the low-income and lower middle-income groups reported that the level of methadone and buprenorphine supervision would be individually determined by the treating doctor.

Training requirements for health care staff for the prescription of opioid agonists

- Almost every country in the survey reported that doctors require some additional training to prescribe methadone (98.2%), buprenorphine (97.4%) and buprenorphine/naloxone (96.4%). In approximately one third of countries surveyed, methadone, buprenorphine and buprenorphine/naloxone may be prescribed by any doctor, without additional training.
- In approximately 10% of countries surveyed, it was reported that non-doctors are given the authority to prescribe opioid agonists. The proportion of countries in which non-doctors may prescribe methadone, buprenorphine and buprenorphine/naloxone seems to be highest in the low-income group.

Notes and comments

- Most countries have been shown to use a supervised system of delivering methadone and buprenorphine, despite the increased cost that this entails. It is worth noting that the proportion of countries requiring supervision of buprenorphine/naloxone is not markedly different from the proportion of those requiring supervision of methadone or buprenorphine.
- In approximately 30% of countries in the survey, the level of methadone, buprenorphine or buprenorphine/naloxone supervision is not individually determined by the treating doctor.
- The question on additional training requirements demonstrates that in most countries the routine training of medical staff is not considered sufficient for the treatment of opioid dependence with methadone or buprenorphine. The fact that more than 20% of countries which use methadone allow prescription by any doctor without special training implies that it is possible to integrate methadone and buprenorphine into primary care services.
- Some focal points in the survey reported that non-doctors may prescribe opioid agonist pharmacotherapy. This has happened in both high-income and low-income countries.

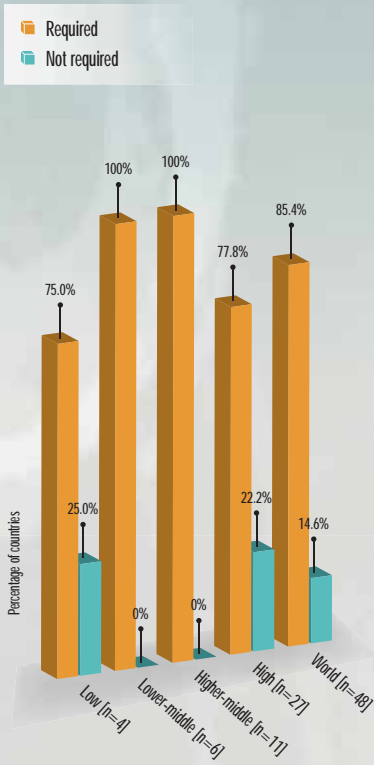


FIGURE 3.15
SUPERVISION OF
METHADONE TREATMENT
IN COUNTRIES, BY INCOME
GROUP, 2008

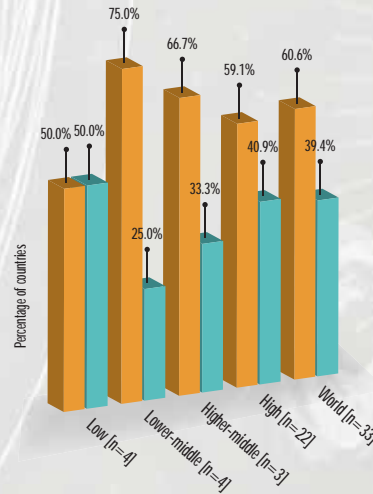


FIGURE 3.16
SUPERVISION OF
BUPRENORPHINE
TREATMENT IN COUNTRIES,
BY INCOME GROUP, 2008

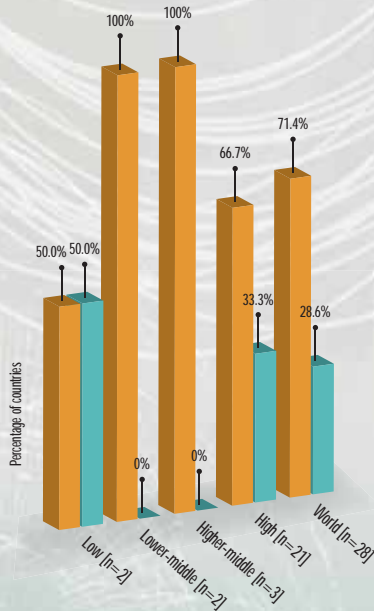


FIGURE 3.17
SUPERVISION OF
BUPRENORPHINE/NALOXONE
TREATMENT IN COUNTRIES
BY INCOME GROUP, 2008

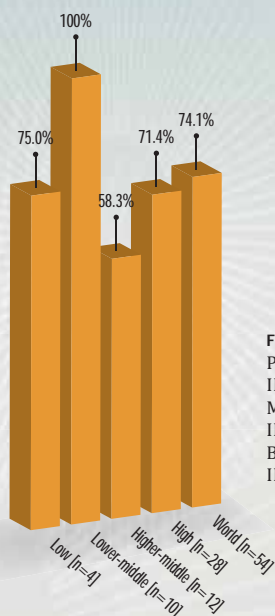


FIGURE 3.18
PROPORTION OF COUNTRIES
IN WHICH THE LEVEL OF
METHADONE SUPERVISION IS
INDIVIDUALLY DETERMINED
BY THE TREATING DOCTOR, BY
INCOME GROUP, 2008

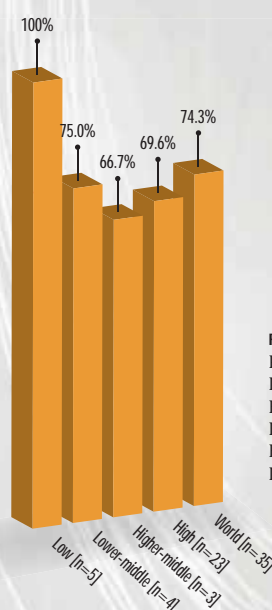


FIGURE 3.19
PROPORTION OF COUNTRIES
IN WHICH THE LEVEL OF
BUPRENORPHINE SUPERVISION
IS INDIVIDUALLY DETERMINED
BY THE TREATING DOCTOR, BY
INCOME GROUP, 2008

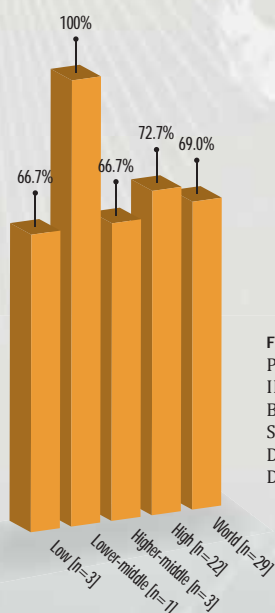


FIGURE 3.20
PROPORTION OF COUNTRIES
IN WHICH THE LEVEL OF
BUPRENORPHINE/NALOXONE
SUPERVISION IS INDIVIDUALLY
DETERMINED BY THE TREATING
DOCTOR, BY INCOME GROUP, 2008

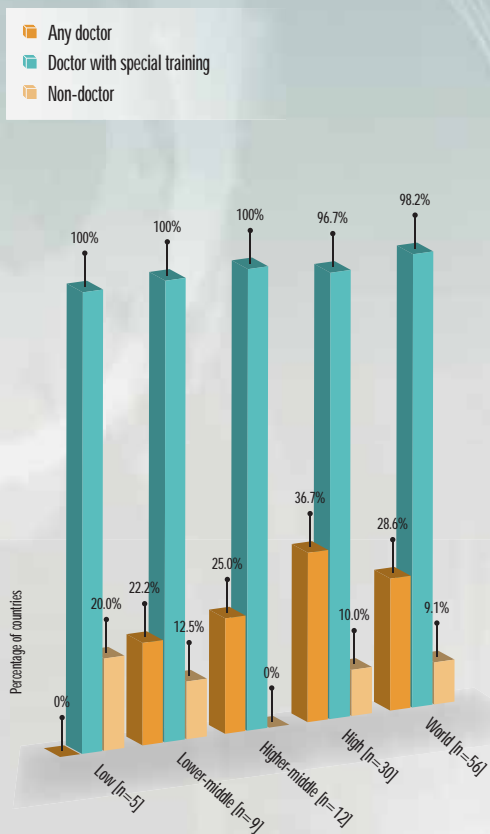


FIGURE 3.21
AUTHORITY OF HEALTH PROFESSIONALS IN COUNTRIES TO PRESCRIBE METHADONE, BY INCOME GROUP, 2008

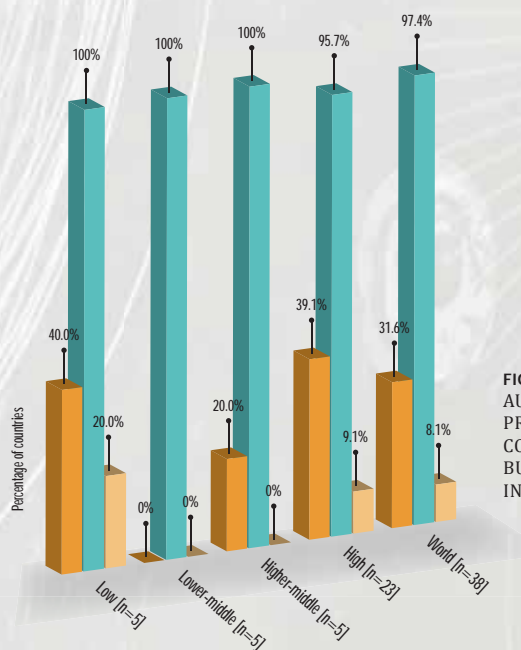


FIGURE 3.22
AUTHORITY OF HEALTH PROFESSIONALS IN COUNTRIES TO PRESCRIBE BUPRENORPHINE, BY INCOME GROUP, 2008

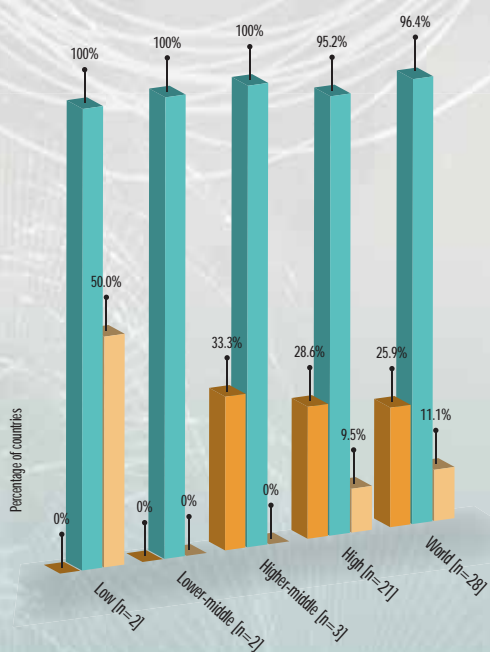


FIGURE 3.23
AUTHORITY OF HEALTH PROFESSIONALS IN COUNTRIES TO PRESCRIBE BUPRENORPHINE/NALOXONE, BY INCOME GROUP, 2008