Outcomes from the Malaysian Arm of The International Survey Informing Greater Insights in Opioid Dependence Treatment (INSIGHT) Project

Parikial George, MBBS

International Medical University, Clinical School, Jalan Rasah, 70300 Seremban, Negeri Sembilan, Malaysia

SUMMARY

Background: Opioid dependence (OD) is a chronic, relapsing condition representing a significant societal burden in Asia. Opioid maintenance treatment (OMT) in combination with psychosocial treatment is considered to be the most effective strategy to treat opioid dependence. In Malaysia, about 52,000 patients reported receiving OMT in December 2012.

Objective: The International Survey Informing Greater Insights in Opioid Dependence Treatment (INSIGHT) project aimed to assess aspects of OMT access and quality of care by surveying patients and users with opioid dependence, and healthcare professionals treating opioid-dependent patients.

Materials and Methods: Using a structured questionnaire, 50 patients who were currently receiving OMT (or had received OMT in the past 3 months) and 77 physicians were surveyed in Malaysia regarding the provision and quality of OMT.

Results: Patients were predominately male and in their thirties. Nearly all patients (98%) reported currently receiving methadone liquid; almost half (48%) reported ever having received psychosocial counselling and only 14% had ever received buprenorphine−naloxone in the past. Most physicians reported they were treating their patients with OMT (77% on methadone and 15% on buprenorphine−naloxone), and 3% used psychosocial counselling alone. Although methadone maintenance doses were close to levels recommended by WHO guidelines, induction doses of methadone, and both induction and maintenance doses of buprenorphine were well below these levels in Malaysia.

Conclusions: The findings suggest that OMT implementation in Malaysia can be improved by providing patients with more education on treatment options, better access to available treatments, including abuse-deterrent formulations, and psychosocial support.

KEY WORDS:
Methadone, buprenorphine, opiate substitution treatment, Malaysia, humans, heroin dependence

INTRODUCTION

The United Nations Office on Drugs and Crime (UNODC) estimated that there were approximately 16.5 million heroin and opium users in the world in 2013. [1] The cost of opioid dependence to society is significant and results in unemployment, homelessness, family disruption, loss of economic productivity, social instability and criminal activities. [2]

More than half of the world's estimated opioid users live in Asia [3] and opioid use in most parts of Asia has increased since 2009. [1] As a consequence, many countries in East and Southeast Asia have concentrated human immunodeficiency virus (HIV) and hepatitis C virus (HCV) epidemics driven in large part by sharing of contaminated needles and syringes among injecting drug users. [3] In Malaysia, with a population of 29.2 million, [4] there are an estimated 400,000 to 800,000 drugs users, 5 170,000 of whom are injecting drug users; [6] an estimated 234,000 people use heroin. 7 The estimated prevalence of HIV among injecting drug users in Malaysia was 22.1% in 2009 [6] and HCV prevalence among this population is currently 67.1%. [1]

Opioid maintenance treatment (OMT) is recognised as being highly effective [8, 9] and cost-effective [10] in the treatment of opioid dependence but its implementation varies internationally. In response to the HIV epidemic in Malaysia, the government introduced a harm-reduction approach into the National Strategic Plan on HIV and AIDS. This initiative was based on the recognition that, for many drug users, total abstinence from psychoactive substances is not a practical option. [11] The aim of this strategy was to reduce high-risk behaviours associated with drug injection through introduction of a needle and syringe exchange programme. [12] As of December 2012, a total of 52,080 patients were reported to be on OMT at either government or private facilities, [13] with a prediction that 75,000 individuals will be on OMT by the end of 2015. [13] There are currently an estimated 350 medical practitioners providing OMT services in the community [13] and approximately 352 sites are distributing sterile needles and injecting equipment through 267 outreach contact points, 73 government clinics and 12 centres. [14] While most OMT provision in Malaysia is based on methadone, buprenorphine is also a significant component of the public

This article was accepted: 15 April 2015
Corresponding Author: Philip George, International Medical University, Clinical School, Jalan Rasah, Seremban, 70300, Malaysia
Email: drphilgeorge@gmail.com

health strategy to reduce problems associated with heroin dependence in Malaysia.[15] Buprenorphine–naloxone is the only form of buprenorphine approved for use in Malaysia and is an abuse-deterrent formulation with reduced likelihood of misuse by injection compared with buprenorphine alone.[16]

Rationale for the Insight Project

The International Survey Informing Greater Insights in Opioid Dependence Treatment (INSIGHT) project was designed to assess the real-world experience of opioid-dependence treatment in many parts of the world. The INSIGHT project was the most recent of a series of surveys conducted globally, initially in Germany (the Project Improve survey)[17] and subsequently in wider Europe (the European Quality Audit of Opioid Treatment [EQUA TOR] project),[18–23] to assess key questions in terms of treatment provision and outcomes for people with opioid dependence. As part of the INSIGHT study, data were collected from nine countries: Croatia, Czech Republic, Indonesia, Israel, Malaysia, Poland, Romania, Slovenia and South Africa. Here, we present INSIGHT data specific to Malaysia with a view to assessing the impact of current practice on treatment access, quality of care and patient outcomes in the country. Key questions regarding treatment of opioid dependence in Malaysia are addressed, including whether current practices are effectively drawing users into treatment, whether they are ensuring compliance among patients, and whether desired outcomes are being achieved. Permission was obtained to publish this portion of the project from the overall INSIGHT project.

MATERIALS AND METHODS

Design and participants

Specific information on the treatment of patients with opioid dependence was collected using responses to questionnaires from opioid-dependent patients and treating physicians. Potential participants were identified through local knowledge from key treatment experts in OMT in Malaysia and through market-research fieldwork agencies. Physicians were initially recruited using target lists and then by referrals from those already recruited in order to reach the target sample size, predominantly from towns and cities across Malaysia. To be included in the study, physicians must have been in practice 2–35 years, treated a minimum of five opioid-dependent patients per month, and had no professional involvement with healthcare companies. Patients were included if they had long-term opioid dependence and were currently receiving OMT or had received OMT within the past 3 months. A list of screening questions was used to identify physicians and patients who met the inclusion criteria. Participation was voluntary and all participants were informed about the study and provided verbal consent prior to participating. Sample sizes were chosen to allow statistical comparison with other countries included in the INSIGHT programme. In three of the nine countries in the wider INSIGHT programme, healthcare professionals (HCPs) comprised physicians and nurses therefore HCP-reported data for the overall INSIGHT data include physicians and nurses combined, whereas HCP-reported data from Malaysia consisted of physicians only.

Questionnaires

Questionnaires were adapted from those used in Project Improve[17] and EQUATOR[21, 22] which were developed in conjunction with local treatment experts. Physician questionnaires (in English) included 42 questions and focused on physician demographics, prescribing behaviours (including reasons for treatment behaviours), treatment goals, patient outcomes, specific prescribing information, attitudes to OMT, and perspectives on misuse and diversion. Patient questionnaires included 56 questions and focused on patient demographics, medical background, current experience with OMT medication, treatment goals, treatment awareness, therapy options, attitudes to OMT (including key influences), misuse and diversion, and prison experience. Most questions required categorical responses. Patient questionnaires were available in English and in Bahasa Malaysia (the Bahasa Malaysia versions were translated and back-translated by the key treatment expert/lead author).

Survey procedure

Physician questionnaires were completed through telephone and online interviews undertaken in English. Patient questionnaires were completed using self-completion forms filled in by the patient in the presence of someone to aid completion if needed (e.g., a physician or field-agency employee). Physicians and patients received reimbursement for their participation (121 RM and 20 RM, respectively). Fieldwork was conducted between August and October 2012.

Statistical analysis

Questionnaires were collated and data analysed by a market-research agency. Survey responses were primarily analysed with descriptive statistics (response frequencies and percentages) in order to characterise attitudinal patterns.

RESULTS

Patient and physician demographics and background information

Fifty patients and 77 physicians took part in the survey. Patients (mean age 38.3 years) were predominantly male and 88% were in full- or part-time employment (Table I). A small proportion of patients (12%) reported receiving treatment for conditions other than substance abuse; the most common being HCV (6%) and respiratory disease (4%) (Table I). Over three-quarters of patients described their current health status as good or very good based on mental health (76%) or physical health (78%) and 96% considered their life situation to be very or fairly stable (Figure 1).

Physicians (mean age 40.6 years) were predominantly male (60%) (Table 1). The primary medical specialty of most physicians was general/family practice and most worked in the public/government-funded sector (Table I). Of the physicians recruited, most were practicing in Kuala Lumpur (31%) or Johor Bahru (17%), with just 5% from Seremban, 3% from Penang, and the remaining 44% from other areas. The median population size served by the participating physicians was 452,900, with only 28% serving populations of less than 50,000.

Access to treatment

Among the patients surveyed, 76% reported receiving treatment in a practice specialising in addiction medicine; 16% received treatment in a doctor's private office and 8% in an outpatient clinic. While 62% of patients surveyed reported it was very or fairly easy to find a physician, 18% reported finding it very or fairly difficult. The most frequently cited factor that would have encouraged patients to start OMT earlier in Malaysia was fewer conditions or requirements to start treatment (36% of patients), followed by better availability of treatment (28%) (Figure 2).

Quality of care

Mode of treatment

On average, physicians in Malaysia (N=77) reported that 18% of their patients were treated with medical withdrawal/detoxification (compared with 27% of patients according to HCPs in the overall INSIGHT survey; N=448) and 82% were treated with maintenance therapy (compared with 73% according to HCPs in the overall INSIGHT survey).

Patient knowledge of treatment options

The majority of patients in Malaysia (66%; N=50) had heard of methadone before starting treatment, although this figure was lower than the proportion across the whole INSIGHT survey (82%; N=474). Less than half (48%) of patients had heard of buprenorphine–naloxone before starting treatment compared with 43% in the INSIGHT survey. Just over half (56%) of patients in Malaysia reported asking for a specific medication and their request was granted in all cases. Similarly, 49% of patients across the INSIGHT survey reported asking for a specific medication and 92% of these were granted their request.

Treatments received by patients

Nearly all patients (98%) reported having ever received methadone liquid and the same proportion reported currently receiving this treatment; almost half (48%) of patients reported having ever received psychosocial counselling whereas only 14% reported ever having received buprenorphine–naloxone (Figure 3). Based on physicians' reports, the mean proportion of patients receiving methadone was 77% and the mean proportion receiving buprenorphine–naloxone was 15% (Figure 4).

Medication dosing

According to physicians, median methadone induction doses were lower in patients in Malaysia than recommended by WHO guidelines but median maintenance doses were broadly in line with the recommendation (24) (Figure 5). For buprenorphine, both induction and maintenance doses (Figure 5) were lower and dose escalation was slower than recommended in WHO guidelines (24). Australian guidelines recommend achieving 12 to 16 mg/day by Day 3 for buprenorphine (25) and higher doses (16–32 mg/day) have been associated with better retention and reduced opioid use versus doses <16 mg/day (26). Median time to buprenorphine maintenance dose was 8.5 days in Malaysia compared with mean of 11.1 days in INSIGHT overall.

Table I: Patient and physician demographics

Patient demographics	
Number of patients	50
Age (mean years ± SE)	38.3 ± 1.4
Sex (% male)	96
Employment status (% patients)	
Full-time	48
Part-time	40
Unemployed and looking for work	10
Not working	2
Comorbidities for which patients reported receiving treatment (% patients)	
HCV	6
Respiratory disease	4
Cardiovascular disease	2
Depression	2
HIV	2
Physician demographics	
Number of physicians	77
Age (mean years ± SE)	40.6 ± 1.1
Sex (% male)	60
Medical specialty* (%)	
General/family practice	64
Psychiatry/psychology	16
Addiction medicine	12
Other†	9
Practice setting (%)	
Private	36
Public/government funded	64

Experience with opioid-dependent patients (mean years ± SE) 5.1 ± 0.4
*The total percentage exceeds 100% due to rounding
†Other included: emergency medicine, internal medicine, pain management, addiction psychiatry, primary care and occupational medicine, and orthopaedics

Treatment outcomes

Continuing use of opioids

Only 4% of patients in Malaysia reported that they continued to use opioids at least once per week compared with 18% in the INSIGHT survey overall. In addition, only 2% of patients in Malaysia reported that they continued to use opioids daily versus 10% in the INSIGHT survey overall (Figure 6).

Misuse and diversion of medication

The proportion of patients reporting that they had ever misused (i.e., injected and/or snorted) or diverted (i.e., sold and/or given away) their OMT medication was lower in Malaysia (misused: N=1/50, 2%; diverted: N=4/50, 8%) than in the overall INSIGHT survey (misused: N=115/474, 24%; diverted: N=140/474, 30%) (Figure 7).

DISCUSSION

The best outcomes for opioid dependence are achieved with long-term OMT at adequate doses.[24] This survey of OMT in Malaysia highlights the benefits of appropriate OMT provision and suggests opportunities for continued improvement of outcomes in this country.

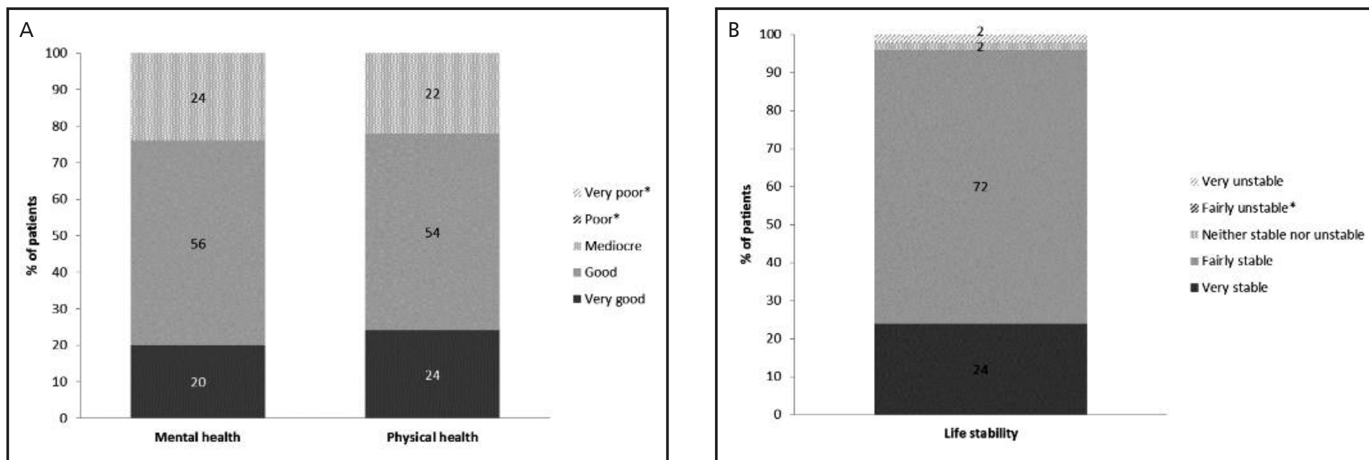

Fig. 1: Patient-reported current health status (A) and life stability (B).
(A) Quality of mental health and of physical health reported by participating patients (N=50). *No patients reported their mental or physical health to be 'Very poor' or 'Poor'; 76% reported their mental health to be 'Good' or 'Very good', and 78% reported their physical health to be 'Good' or 'Very good'. (B) Stability of life situation reported by patients (N=50). *No patients reported their life situation to be 'Fairly Unstable' and 96% reported their life situation to be 'Fairly stable' or 'Very stable'.

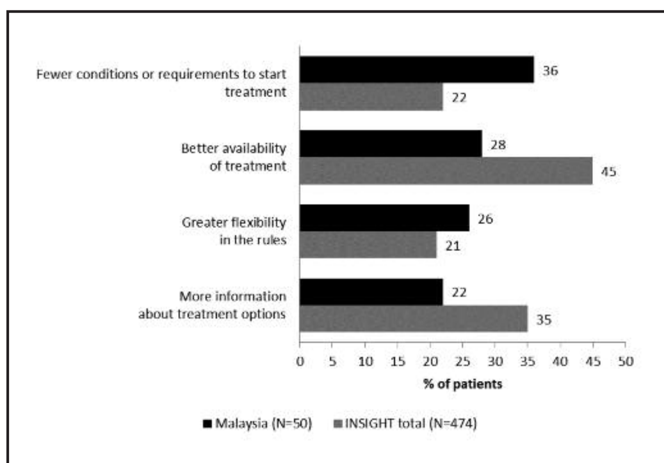

Fig. 2: Patient-reported factors that might have encouraged them to start treatment earlier.
Top 4 factors reported by patients that might have encouraged them to start treatment earlier. Results for the Malaysian population are in black (N=50) and for the total survey population in grey (N=474).

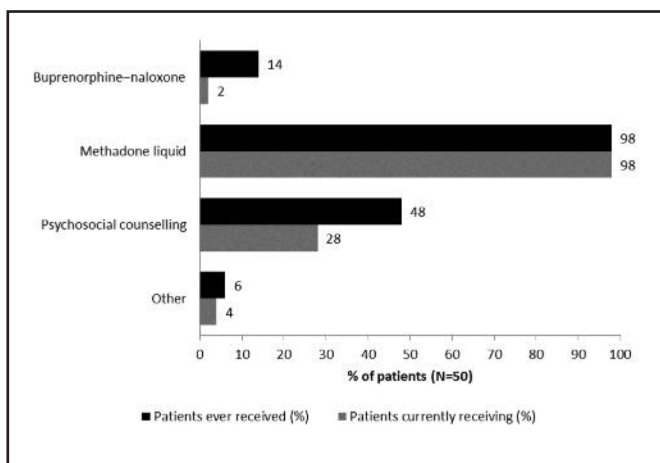

Fig. 3: Patient-reported OMT experience.
Patient-reported experience of opioid maintenance treatment (OMT), shown as percentage of patients who had ever received (black) or were currently receiving (grey) each treatment. 'Other' treatments included traditional/herbal therapies.

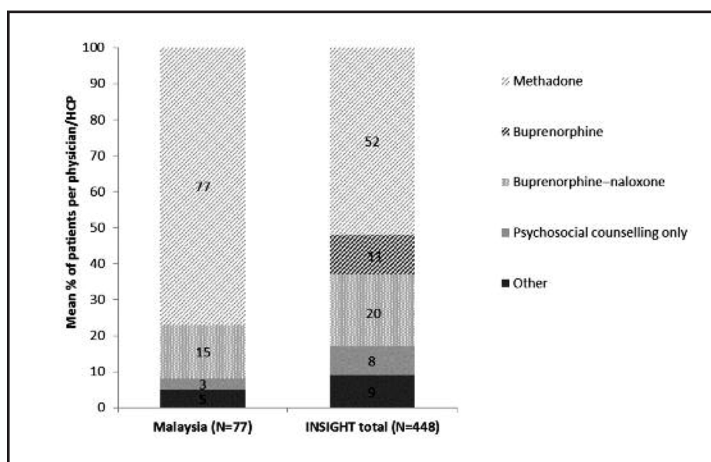

Fig. 4: Physician-reported treatment frequency.
Mean proportion of patients treated with specific treatments according to physicians in the Malaysian arm of INSIGHT (N=77) and in the overall survey (N=448). 'Other' included naloxone and other unspecified treatments.

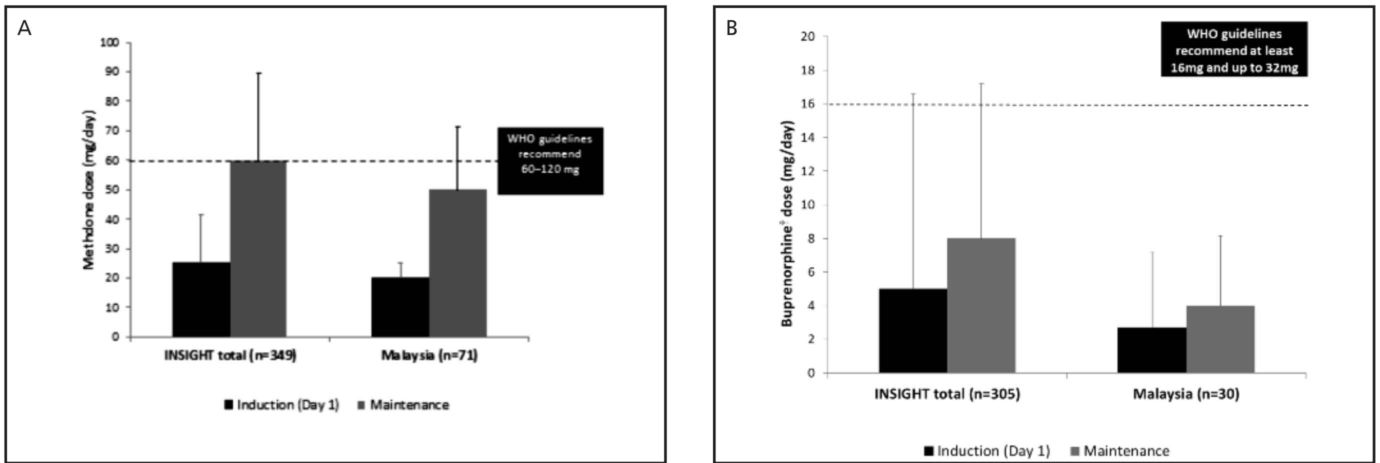

Fig. 5: Induction and maintenance doses prescribed by physicians.
Median induction dose (black) and maintenance dose (grey) of (A) methadone and (B) Buprenorphine prescribed by healthcare providers (HCPs) in the overall INSIGHT population and by Malaysian HCPs. Error bars show standard deviations. Dotted lines show the maintenance doses recommended by the World Health Organisation (24). †Data for buprenorphine include Mono-buprenorphine and buprenorphine–naloxone.

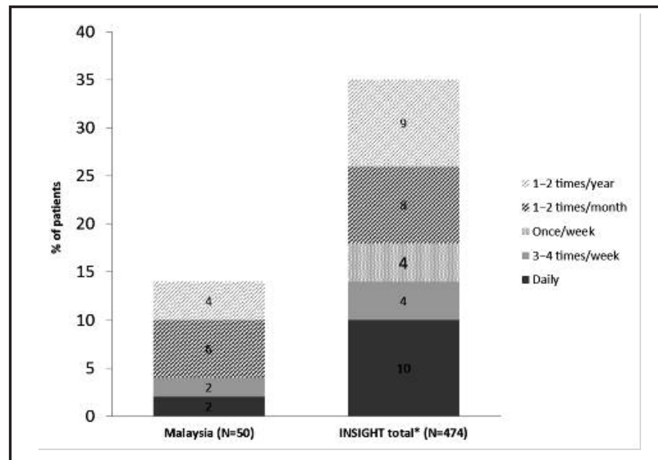

Fig. 6: Patient-reported frequency of opioid use in addition to or instead of OMT medication.
Frequency of opioid use in addition to, or instead of, opioid maintenance treatment (OMT) reported by patients in the Malaysian arm of the survey and in the overall INSIGHT population. Of the 50 Malaysian patients, 14% reported still using opioids, and 84% reported never using opioids in addition to or instead of OMT.

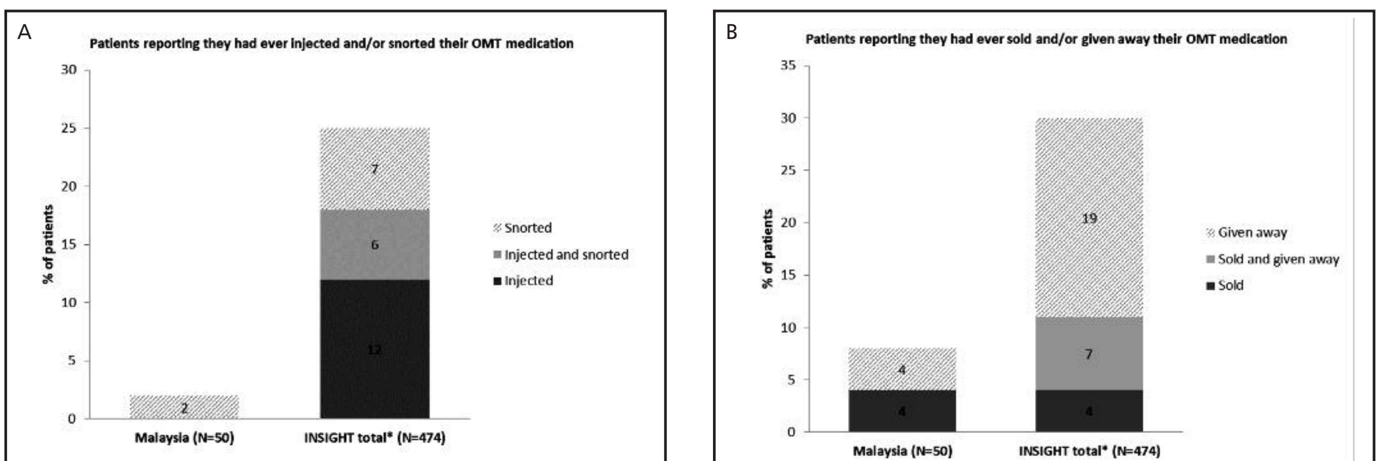

Fig. 7: Misuse (A) and diversion (B) of OMT medication.
Proportion of patients reporting (A) misuse (snorting and/or injecting) and (B) diversion (giving away and/or selling) of their opioid maintenance treatment (OMT). Of the 50 Malaysian patients, 1% did not answer the question.

Treatment access

Although over half of patients surveyed found it very or fairly easy to find a physician to prescribe OMT, over a quarter indicated that better availability of therapy could have encouraged them to start treatment earlier. In reality, access to treatment may be lower than detected here: firstly, many of the surveyed patients were from large cities where access to treatment is likely better than in rural areas; secondly, patients were already in treatment which necessarily defines a population who successfully accessed treatment. Even among this population, reducing the barriers to access (fewer conditions or requirements to start treatment) would have encouraged earlier treatment-seeking. Most patients (76%) received treatment in specialised addiction clinics. Providing OMT in the primary care setting, as in other countries, is one cost-effective way to improve access to treatment. Improving access to OMT in Malaysia requires both political and practical changes: governments and decision-making organisations need to recognise the benefits of providing fully reimbursed OMT to all who need it.

Quality of care

OMT use is associated with a greater reduction in opioid use, HIV risk behaviours and transmission, mortality, and criminal activity than detoxification/withdrawal. [24] Although it is encouraging that detoxification/withdrawal treatment in Malaysia is lower than the overall INSIGHT population, it is still used in almost 20% of patients. This may be financially motivated, as a more affordable alternative to OMT; however, patients in Malaysia were frequently unaware of all OMT options available, with only 66% and 48% having heard of methadone and buprenorphine–naloxone, respectively, before starting treatment. Despite this lack of awareness, over half of patients requested specific OMT medications and all requests were granted. As therapeutic outcomes and treatment retention are influenced by the knowledge and attitudes of opioid users towards OMT, [27] it is important that patients are given accurate information from credible sources about the condition and all available treatment options.

Methadone liquid was the most widely used OMT in this sample; physicians report use in 77% of patients, and buprenorphine–naloxone use in only 15%. This pattern may reflect the predominance of government clinics, in which methadone is fully government-funded, whilst buprenorphine–naloxone is paid for by patients themselves. Limited awareness of buprenorphine–naloxone among patients and physicians, or a perceived high cost of this treatment compared with methadone liquid may also contribute. Economic assessments in other countries have demonstrated high cost-effectiveness of both methadone and buprenorphine treatment. [10, 28] Furthermore, with buprenorphine–naloxone, unobserved dosing has been shown to be significantly more cost-effective than observed dosing; [29] as well as reducing staffing costs, unsupervised dosing may permit patients to continue working. It should be noted that the survey took place before the film formulation of buprenorphine–naloxone was available in Malaysia. Buprenorphine–naloxone film takes significantly less time to dissolve than tablets [30] and relies on a mucoadhesive delivery, possibly further reducing the abuse potential. The reduced requirement for supervision of buprenorphine–naloxone and its lower potential for abuse compared with methadone should be considered when making decisions about treatment.

Adequate doses of OMT medication are vital to good outcomes, and in this respect practice in Malaysia seems to deviate from recommendations. [24] Both induction and maintenance doses of buprenorphine were lower than recommended in guidelines (8–32 mg), and buprenorphine induction appeared to take longer on average than recommended. [24] This slow escalation may result from lack of familiarity with recommended dosing schedules and a mistaken belief that the ‘start low, go slow’ principles of methadone escalation apply to buprenorphine, from infrequent appointments and limited opportunities to increase the dose, or from reluctance or inability of patients to pay for optimal doses.

Although studies and recommendations recognise the utility of psychosocial support, [24, 31, 32] only 28% of this Malaysian population were currently receiving it. Limited uptake of psychosocial support may be due to the costs involved, lack of trained professionals to deliver it, the treatment system currently in place, or lack of patient engagement.

Patient outcomes

The stabilising effect of OMT on patients’ lives in Malaysia highlights the benefit of OMT treatment provision –most patients reported that their life situation was very or fairly stable once they were receiving OMT, and 88% of patients were in employment. For those patients who continue to use opioids, suboptimal OMT medication dosing, misuse and diversion of medication and lack of psychosocial support may be contributing factors, and these need to be minimised through appropriate supervision and abuse-deterrent formulations.

LIMITATIONS

Limitations of the Malaysian arm of the INSIGHT survey are similar to those of EQUATOR. [21] Comparatively small samples were surveyed (50 patients; 77 physicians), which allowed only descriptive comparisons to be made. However, nearly a quarter of all physicians who treat opioid dependence in Malaysia were included in this survey, and patient demographics were consistent with a previous study, [33] and in line with the ‘average’ profile of opioid-dependent individuals.

Some bias was inherent in the survey. The questionnaire design, although similar to others, [21, 33] relied on self-reported data that individuals could, or were willing to, recall. The focus on large geographical centres means the results may not reflect circumstances in more rural areas; only patients already accessing treatment were surveyed, perhaps under-estimating problems with treatment access; and individuals with literacy problems were unlikely to participate, potentially skewing the results towards higher-achieving, less marginalised individuals. Lastly, the majority of physicians practised in government clinics where methadone is fully funded, therefore the results may not reflect treatment patterns in private practices, where the distribution of buprenorphine–naloxone may differ from government clinics.

CONCLUSIONS

The Malaysian arm of the INSIGHT survey provides real-world data on the treatment of opioid dependence in Malaysia from the perspectives of patients and physicians. Although the small sample size and urban focus means that these survey results cannot be generalised to the entire Malaysian population, some conclusions can be drawn. Implementation of OMT in Malaysia appears to have a positive impact on patients with opioid dependence who are able to access treatment, but additional steps need to be taken to improve treatment access and to optimise treatment quality. These steps could include better education of patients with regard to treatment options, more appropriate OMT medication dosing, wider use of abuse-deterrent formulations, and greater provision of psychosocial support. Changes such as these could work towards improved outcomes at both individual and societal levels.

ACKNOWLEDGEMENTS

The authors would like to thank the physicians, patients and treatment centres who participated. The questionnaires were based on those created by Professor Dr Heino Stöver, with additional input from the authors and Reckitt Benckiser Pharmaceuticals. The survey was funded by Reckitt Benckiser Pharmaceuticals. Chive Insight and Planning provided market research consultancy assistance. Market research was conducted by Central Force and data were analysed by PSL.

Disclosures and conflicts of interest

Dr Philip George is a member of speaker bureaux for several pharmaceutical companies including Reckitt Benckiser Pharmaceuticals, Lundbeck, Eli Lilly, Solvay Pharma, GlaxoSmithKline, Astra Zeneca, and has taken part in research funded by Reckitt Benckiser Pharmaceuticals Ltd and Eli Lilly; received honoraria as a speaker from the Malaysian Psychiatric Association, Addiction Medicine Association of Malaysia, and Malaysian Healthy Ageing Society.

Financial support for the medical writing of this manuscript was provided by Reckitt Benckiser Pharmaceuticals; medical writing support was provided by Tim Mitchell at Real Science Communications. The author had editorial control, contributed to writing and review of the article, and had final responsibility for the decision to submit it for publication.

REFERENCES

1. United Nations Office on Drugs Crime. World Drug Report 2013 - May 2013, UNODC, Vienna, Austria. Available from: http://www.unodc.org/wdr/index.html (accessed January 2014).
2. World Health Organization, United Nations Office on Drugs and Crime, Joint United Nations Programme on HIV/AIDS. WHO/UNODC/UNAIDS position paper: Substitution maintenance therapy in the management of opioid dependence and HIV/AIDS prevention, 2004, Geneva, Switzerland. Available from: http://www.who.int/substance_abuse/publications/en/PositionPaper_English.pdf (accessed January 2014).
3. United Nations Office on Drugs Crime. World Drug Report 2011 - 2011, UNODC, Vienna, Austria. Available from: http://www.unodc.org/documents/data-and-analysis/WDR2011/World_Drug_Report_2011_ebook.pdf (accessed January 2014).
4. The World Bank. World Bank Total Population Data, 2012 . Available from: http://data.worldbank.org (accessed January 2014).
5. Ministry of Health, Malaysia. National clinical guidelines & procedures for the use of buprenorphine and buprenorphine/naloxone in the treatment of opioid dependence in Malaysia, 2006.
6. Ministry of Health, Malaysia. UNGASS country progress report: Malaysia. Kuala Lumpur AIDS/STD Section of the Disease Control Division, 2010.
7. Ruger JP, Chawarski M, Mazlan M, Luekens C, Ng N, Schottenfeld R. Costs of addressing heroin addiction in Malaysia and 32 comparable countries worldwide. Health Serv Res 2012; 47(2): 865-87.
8. Mattick RP, Breen C, Kimber J, Davoli M. Methadone maintenance therapy versus no opioid replacement therapy for opioid dependence. Cochrane Database Syst Rev 2009; (3): CD002209.
9. Mattick RP, Kimber J, Breen C, Davoli M. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. Cochrane Database Syst Rev 2008; (2): CD002207.
10. Connock M, Juarez-Garcia A, Jowett S, Frew E, Liu Z, Taylor RJ, *et al.* Methadone and buprenorphine for the management of opioid dependence: a systematic review and economic evaluation. Health Technol Assess 2007; 11(9): 1-171, iii-iv.
11. Ministry of Health. Malaysia: National Strategic Plan on HIV/AIDS, 2006 – 2010. Malaysia, 2006.
12. Ministry of Health. Malaysia: National Strategy Plan on HIV and AIDS, 2011 – 2015. Malaysia, 2011.
13. Ministry of Health, Malaysia. Revised national clinical guidelines & procedures for the use of buprenorphine and buprenorphine/naloxone in the treatment of opioid dependence in Malaysia - Third Edition, In preparation.
14. World Health Organization. Good practices in Asia: Effective paradigm shifts towards an improved national response to drugs and HIV/AIDS. Western Pacific Regional Office & Ministry of Health, Kuala Lumpur, Malaysia, 2011; ISBN 978 92 9061 519 4.
15. Schottenfeld RS, Chawarski MC, Mazlan M. Maintenance treatment with buprenorphine and naltrexone for heroin dependence in Malaysia: a randomised, double-blind, placebo-controlled trial. Lancet 2008; 371(9631): 2192-200.
16. Orman JS, Keating GM. Buprenorphine/naloxone: a review of its use in the treatment of opioid dependence. Drugs 2009; 69(5): 577-607.
17. Stöver H. Barriers to opioid substitution treatment access, entry and retention: a survey of opioid users, patients in treatment, and treating and non-treating physicians. Eur Addict Res 2011; 17(1): 44-54.
18. Benyamina A, Stöver H. Barriers to treatment access and informed patient choice in the treatment of opioid dependence in Europe. Heroin Addict Relat Clin Probl 2012; 14(1): 65-80.
19. Dale-Perera A, Goulão J, Stöver H. Quality of care provided to patients receiving Opioid Maintenance Treatment in Europe: Results from the EQUATOR analysis. Heroin Addict Relat Clin Probl 2012; 14(4): 23-38.
20. Fischer G, Nava F, Stöver H. Outcomes of opioid-dependence treatment across Europe: identifying opportunities for improvement. Heroin Addict Relat Clin Probl 2012; 14(4): 39-50.
21. Fischer G, Stöver H. Assessing the current state of opioid-dependence treatment across Europe: methodology of the European Quality Audit of Opioid Treatment (EQUATOR) project. Heroin Addict Relat Clin Probl 2012; 14(3): 5-70.
22. Goulão J, Stöver H. The profile of patients, out-of-treatment users and treating physicians involved in opioid maintenance treatment in Europe. Heroin Addict Relat Clin Probl 2012; 14(4): 7-22.
23. Stöver H. Assessing the current state of public-health-related outcomes in opioid dependence across Europe: data from the EQUATOR analysis. Heroin Addict Relat Clin Probl 2012; 14(4): 51-64.
24. World Health Organization, Department of Mental Health Substance Abuse. Guidelines for the psychosocially assisted pharmacological treatment of opioid dependence - 2009, WHO, Geneva, Switzerland. Available from: http://www.who.int/substance_abuse/publications/opioid_dependence_guidelines.pdf (accessed January 2014).
25. Lintzeris N, Clark N, Winstock A, Dunlop A, Muhleisen P, Gowing L, *et al.* National clinical guidelines and procedures for the use of buprenorphine in the treatment of opioid dependence - 2006, Department of Health and Ageing, Australia. Available from: http://www.health.gov.au/internet/drugstrategy/publishing.nsf/Content/472749A2E4A21AD4CA2575E3007E5595/$File/buprenabb.pdf (accessed January 2014).
26. Fareed A, Vayalapalli S, Casarella J, Drexler K. Effect of buprenorphine dose on treatment outcome. J Addict Dis 2012; 31(1): 8-18.
27. Alves P, Winstock A. Patients' knowledge about treatment for opiate dependence. The Psychiatrist 2011; 35(12): 448-53.
28. Doran CM, Shanahan M, Mattick RP, Ali R, White J, Bell J. Buprenorphine versus methadone maintenance: a cost-effectiveness analysis. Drug Alcohol Depend 2003; 71(3): 295-302.
29. Bell J, Shanahan M, Mutch C, Rea F, Ryan A, Batey R, *et al.* A randomized trial of effectiveness and cost-effectiveness of observed versus unobserved administration of buprenorphine-naloxone for heroin dependence. Addiction 2007; 102(12): 1899-907.
30. Lintzeris N, Leung SY, Dunlop AJ, Larance B, White N, Rivas GR, *et al.* A randomised controlled trial of sublingual buprenorphine-naloxone film versus tablets in the management of opioid dependence. Drug Alcohol Depend 2013; 131(1-2): 119-26.

31. National Institute for Health and Clinical Excellence. Drug misuse, Psychosocial interventions, NICE clinical guideline 51 - July 2007, NICE, UK. Available from: http://www.nice.org.uk/nicemedia/live/11812/35973/35973.pdf (accessed January 2014).
32. Ford C, Halliday K, Lawson E, Browne E. Guidance for the use of substitute prescribing in the treatment of opioid dependence in primary care - 2011, Royal College of General Practitioners, London, UK.
33. Lawrinson P, Ali R, Buavirat A, Chiamwongpaet S, Dvoryak S, Habrat B, *et al.* Key findings from the WHO collaborative study on substitution therapy for opioid dependence and HIV/AIDS. Addiction 2008; 103(9): 1484-92.