Patients that benefit from buprenorphine-naloxone on medically assisted treatment for opioid dependence in Malaysia

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SUMMARY

Introduction: Opioid dependence is recorded as the most common drug of abuse in Malaysia. Currently, the preferred substitution therapy for most Government treatment centres is methadone used as substitution therapy for opioid dependence. There are, however patients who may benefit from being on the combined buprenorphine-naloxone formulation as substitution therapy instead.

We discuss six cases of opioid dependence of varied backgrounds that were treated with buprenorphine-naloxone therapy and their outcomes.

Discussion: All of the reported patients improved after the induction of buprenorphine- naloxone. Two of the cases highlighted the transfer of patients on methadone to buprenorphine-naloxone due to the adverse effect and interactions of methadone with other medications. During the transfer there were no major adverse reactions noted, and patients were safely able to continue with the maintenance therapy of buprenorphine- naloxone.

Conclusion: Buprenorphine-naloxone is a safe and effective drug substitution therapy for opioid dependence. It has fewer interactions with other medications, and has similar efficacy to methadone. Being a partial agonist, it has a less sedating effect making patients more functional.

KEY WORDS:
Medication assisted treatment, opioid, buprenorphine-naloxone, benefits

INTRODUCTION

There are currently 400,000 estimated drugs users in Malaysia, 170,000 of who are reported as injecting drug users (IDU). Opioid dependence remains the main addiction in the country, and can be due to recreational use or prescription opioid use. Medication assisted treatment (MAT) for opioid dependence was introduced in 1996 in Malaysia with naltrexone, an opioid antagonist.[1] Buprenorphine (a partial opioid agonist) maintenance therapy was subsequently introduced in 2003, followed by methadone (a full opioid agonist) maintenance therapy in 2005.

The co-formulation of buprenorphine with naloxone (an opioid antagonist) was introduced in 2006, to reduce the abuse potential of intravenous buprenorphine. Despite having a similar general efficacy as methadone, the use of buprenorphine-naloxone has been limited to private practice in Malaysia.[2] The government public health programmes still prefer to use methadone maintenance therapy only.

However, buprenorphine has some advantages in comparison to methadone, in that it is potentially safer than methadone in the situation of an overdose and that it may produce less physical dependence compared to methadone.[3] Treating heroin dependent patients with methadone substitution therapy runs the potential risk of drug interactions which can cause QTc prolongation leading to cardiac arrhythmias.[4] The long duration of action also allows buprenorphine to be administered every other day or every third day as opposed to a daily regimen.

In this paper, six cases of patients of varied backgrounds who have been treated with buprenorphine-naloxone are presented to demonstrate the efficacy of using this as a modality in the treatment of opioid dependence. The case series registration and permission to publish was obtained from the National Medical Research Register.

MATERIALS AND METHODS

Selection of case

Being a case series, there was no selection or sampling process for patients and they were chosen among those that were already on follow-up with the first three authors. They were identified for being on high-dose methadone or being treated for opioid pain medication dependence. All six patients are on follow-up and treatment by the first three authors. The chosen six patients are from local private and public hospital settings.

The authors ensured that no personal identification information was gathered or compiled. Every effort was taken to avoid identification of the patient including not reporting name, ID details, place of receiving treatment or address. Gender and age are the only identifying features reported. This follows the process of a case series write up.

This article was accepted: 21 June 2015
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Demographics
Table I gives a brief overview of the demographics of the six patients and their comorbid conditions, as well as the duration of opioid dependence and the days it to took to stabilise after initiation of buprenorphine-naloxone therapy.

DISCUSSIONS

Patient A
A 45-year-old lady divorcee and single parent was admitted to the ward for history of seizure. This was the second time she had a seizure and investigations done showed a normal EEG and CT-brain. Four years ago she had a surgery done to her right knee with partial knee replacement and ensuing complications leading to chronic pain ever since. She was prescribed several different opioid pain medications and before admission was taking intramuscular morphine 5 mg twice a day for the last 1 and ½ years. This provided some relief but it was not complete. She also was prescribed zolpidem for insomnia and had developed tolerance as she was taking 5 to 6 tablets every night.

She used to work as a senior executive but for the last one year she was unemployed and spent most of her time at home. Her 16-year-old son was concerned about her condition and he too had to miss school and was unable to focus on his studies for the last one year as he had to often look after her and bring her to hospital.

She was diagnosed to have opioid analgesic dependence with non-benzodiazepine abuse. The seizures were thought to be due to withdrawals from her opioid use. She was started on buprenorphine-naloxone combination therapy at 2 mg daily and diazepam equivalent of zolpidem dose (25 mg a day). The diazepam was gradually tapered down and after two months she is now on 5 mg at night. She continues her buprenorphine-naloxone therapy at 2 mg daily and is now well. She resumed work as an executive manager and feels her pain is under control and has had no episodes of seizure or sleep difficulty. Her son remarks that he feels he finally has his mother back. The choice of buprenorphine-naloxone therapy over methadone as a substitution treatment helped her to stay alert and function in her current position.

Patient B
A 47-year-old man was referred for the management of chronic pain issues. He had an orthopaedic problem which required a major surgery four years ago and since then has been regularly taking tramadol about 200 to 300 mg in divided doses. During this period he had been experiencing increasing fainting spells for which he was extensively investigated without any positive findings.

The tramadol was prescribed legally in the beginning for pain but later he obtained it illegally and the dosing became erratic. The fainting spell had been there intermittently even before the accidental fall causing the orthopaedic problem. He was diagnosed to have Opioid Analgesic Dependence with chronic pain disorder. He was started on a non-steroidal anti-inflammatory for acute pain. He had tried to stop tramadol in the past but experienced mild discomfort, mild (atypical) opioid withdrawal like symptoms, worsening pain, sleep disturbance and some difficulty in daily functioning.

MAT using buprenorphine-naloxone regime was commenced at 2mg a day in view of his mild withdrawal symptoms. Eventually the patient experienced total pain relief and was able to go back to normal function; therefore a collective decision was made that he may need to be on buprenorphine-naloxone maintenance therapy in view of risk factors based on long term abuse of tramadol analgesic, dependence, repeated fainting spells (due to erratic abuse of tramadol) and poor quality of life.

Currently, he is stable on the treatment and has been able to return to his normal routine and functioning for past one year without complications. There were no fainting spells or the use of additional opioid analgesics during this period.
Patient C

A 40-year-old man was referred for medical stabilization prior to a surgical procedure. He had been suffering from multiple pain issues and was self-medicating with pethidine and benzodiazepines.
He met with a motor vehicle accident during his younger days but recovered from the poly trauma completely. He started experiencing excruciating pain a few years ago, especially at the shoulders and back. The pain was relieved by intramuscular injection of pethidine. He underwent a major surgery at the lumbar region four years prior and had felt some relief after the surgery. One year ago he had a fall in the house and suffered a closed fracture dislocation of left ankle joint but refused any treatment because of fear of pain. He had been intermittently given pethidine injection for pain by his general practitioner as all the other analgesic medications do not work anymore.

In the past few years, he had trouble sleeping because of the pain, therefore he had tried various sleeping tablets. He also realized that the use of pethidine had gone out of control when he self- administered the drug intravenously 4 to 5 times per day. He combined it with sleeping tablet cocktails to help ease the pain and sleep. Because of his high pethidine dose, mode of use (intravenous) and concomitant abuse of benzodiazepine, he repeatedly experienced withdrawal seizures and overdose effects. He also had serious cognitive impairment, especially memory problem which was probably due to the effect of the drugs or due to hypoxic brain damage.

He was diagnosed to have Opioid Analgesic Dependence with concomitant benzodiazepine abuse and underlying chronic pain. The aim of the treatment was to medically stabilize the patient so that he could undergo the necessary surgery for the fracture dislocation of ankle joint. He was started on MAT using the buprenorphine-naloxone regime. A rapid dose escalation was done up to 12 mg by the third day, and later gradually increased further to 20 mg daily dosing. He was given another NSAID for the "acute on chronic pain" and was also on daily physiotherapy as complimentary treatment for chronic pain management. The pain symptoms were manageable but there were intermittent exacerbations of pain symptoms precipitated by emotional stressors. He still had difficulty with sleep. In view of long standing abuse of benzodiazepine the patient was started on long acting benzodiazepine to help improve his sleeping pattern and prevent from abusing sleeping tablet cocktails. He underwent

Table I: Opioid Analgesic Dependence Heroin Dependence

	Opioid Analgesic Dependence				Heroin Dependence	
Patient	**A**	**B**	**C**	**E**	**D**	**F**
Age	45	47	40	52	38	46
Gender	Female	Male	Male	Female	Male	Male
Comorbid Condition	Non-benzodiazepine abuse	Chronic pain	Benzodiazepine abuse and chronic pain	Benzodiazepine dependence	Major Depressive disorder	Human Immunodeficiency Virus
Duration of opioid dependence (years)	4	4	4	2	More than 10	10
Stabilisation (number of days it took)	2	3	14	3	4	7

the surgery successfully and was continued on buprenorphine-naloxone maintenance therapy and long acting benzodiazepine. The discharge plan was gradual tapering of long acting benzodiazepine and referring to pain management team for long term follow up and intervention.

Patient D

A 38-year-old single male security guard with a longstanding history of heroin dependence had been stabilised on 65mg of methadone for the past 2 months. He was inducted into the methadone substitution program 6 months ago with presentation of heroin dependence, mainly intravenous use for more than ten years. He also frequented the services of the needle and syringe exchange program for fresh supply of injecting needles and syringes. However in the past four months, after induction into the methadone program, he maintained total abstinence from heroin. On a routine blood examination, he was found to have contracted Hepatitis C from his injecting habit but remained retroviral negative.

He consulted the Psychiatry department presenting with a month's history of pervasively low mood associated with a loss of interest and motivation in activities. He had stopped work a few days prior to his visit due to complaints of lethargy and tiredness. It was the suicidal urges secondary to feelings of hopelessness that compelled him to seek help. A comprehensive evaluation revealed that he was suffering from a Major Depressive Disorder. He was appropriately initiated and optimized on selective serotonin reuptake inhibitors (SSRI) antidepressant, fluvoxamine at 200mg daily for his disorder. After two weeks on the antidepressant, the patient started complaining of severe headache, nausea and vomiting. He was reviewed at the A&E where he presented himself with an altered conscious level. Urine toxicology for other substances was negative. Upon questioning his dose of methadone had also not changed and had been constant and regular since the past two months. Examination revealed shallow breathing and pinpoint pupils. He was assessed to have opioid overdose and was immediately treated with naloxone (opioid antagonist), which spontaneously improved his situation.

Collaborating clinical findings and history, it was decided that the sudden increase in the methadone levels was due to interaction of the antidepressant, fluvoxamine with liver enzymes, leading to a decrease in methadone breakdown. This phenomenon had directly caused the sudden increase of methadone levels causing overdose symptoms.

After discussion with the patient, he was switched to buprenorphine-naloxone combination, stabilizing to a dose of 10mg daily. He continues with the same dose of his antidepressant with no interaction with the current buprenorphine-naloxone regime.

Patient E

A 52-year-old lady was brought by her friends after they discovered she had been taking rather high doses of tramadol and alprazolam daily and was showing behaviour changes. She was previously diagnosed with Major Depression and was on an antidepressant. She started follow- up for her depression after coming to Malaysia two years ago and also complained of chronic knee pain and insomnia. Her doctor started her on tramadol and alprazolam and she eventually developed tolerance and dependence to both. She tried stopping the tramadol on her own but got very sick and could not tolerate more than a day without it.

Her husband was employed as a senior executive and she was a housewife with three teenage children. Her husband was frequently away overseas on official work and her children were her constant concern. She was diagnosed to have opioid analgesic dependence with benzodiazepine dependence. She was started on buprenorphine-naloxone combination therapy at 2mg daily and diazepam equivalent of her alprozolam dose (20mg a day). The diazepam was gradually tapered down and now after six months she is on 7.5mg at night.

Her buprenorphine-naloxone dose was reduced after 4 months to 1mg daily and 1 month ago she stopped it all together. She had some mild withdrawal symptoms such as irritability, insomnia and restlessness but they subsided after 2 to 3 weeks. Her knee pain is managed with NSAID medication given when necessary. Emotionally she feels better and her friends find her more stable. The choice of buprenorphine-naloxone combination therapy over methadone as a substitution treatment helped her to overcome the withdrawals that she would have experienced when stopping the tramadol and also to come off being on the substitution therapy early and easily.

Patient F
A 46-year-old male security guard with diagnosed problems with Heroin Use Disorder on a stable dose of methadone of 120mg daily was brought to the A&E after a fall from his motorbike. Detailed history from the patient (once recovered) revealed that he had a sudden episode of loss of consciousness right before the fall. Urine toxicology done at the A&E for drugs of abuse was negative.

Patient is a known case of HIV since the past 10 years and had been initiated on HAART in the past year due to his deteriorating immunity status and cell (CD4) counts. Since the initiation of the HAART regime he claimed that his methadone dose had also been gradually titrated up due to inadequate efficacy. He has been adherent to his methadone treatment regime and has also been abstinent from all drugs of abuse. In the past few days he had been admitted to the General Hospital after intense skin rashes that were thought to be due to the adverse effects of one of the HAART medication. In view of a switch of regimes, his HAART medications were withheld. He was discharged home upon cessation of the rashes with an appointment to the Infectious Disease clinic the following week. He had maintained on the same dose of methadone without any alterations throughout his admission and discharge period. The incident of the fall occurred two days after his discharge from the hospital.

An ECG done at the A&E showed a prolonged QT interval. With no past history of cardiac problems, the pathology was attributed to high Methadone dose which then most likely caused the syncopal attack.

In view of the interactions between the HAART medications and methadone, he was initiated on Buprenorphine-naloxone combination. He is currently stabilized on a daily buprenorphine- naloxone dose of 12mg. He continues his HAART regime along with the buprenorphine- naloxone combination without any interactions or complications. Serial ECG after the switch has been within normal limits.

DISCUSSION

In the above cases, the patients were managed with buprenorphine-naloxone combination for their opioid dependence. The patient maintenance dose of buprenorphine-naloxone varied according to the individual patient and their needs. All of the reported patients improved after the induction of buprenorphine-naloxone, and only two still suffered from withdrawal effects during the initiation of the medication. Most of the patients stabilised within a week, except for patient C who took two weeks to stabilise. The reason for the long duration of the stabilisation was due to poly-substance dependence history and because he was suffering from ongoing chronic pain.

Two of the cases highlighted the transfer of patients on methadone to buprenorphine-naloxone due to the adverse effect and interactions of methadone with other medications. During the transfer there were no major adverse reactions noted, and patients were safely able to continue with the maintenance therapy of Buprenorphine-naloxone.

In Malaysia, Human Immunodeficiency Virus is mainly associated with intravenous drug Use (IDU). Despite this, only a minority of IDU HIV patients received HAART treatment.5 Few HIV patients in drug rehabilitation centres in Malaysia receive HIV-related care or treatment.6 Research also shows that drug-drug interactions can result in decreased methadone blood levels when administered with anti-retroviral regimen.7 As Patient F demonstrated, buprenorphine- naloxone can be a safe and effective alternative drug substitution therapy for patients on HAART. However, further studies regarding this need to be conducted.

HIV injecting risk is markedly reduced for patients on MAT.[8] A study demonstrated that buprenorphine-naloxone maintenance therapy is effective in reducing some of the adverse effects and maintaining the quality of life for HIV-infected patients who are opioid dependent.[9]

Methadone maintenance therapy is still the preferential treatment in many government hospitals. However, studies have found that buprenorphine can be an important alternative and is cost- effective in countries around the world, including Malaysia.[10] In the United States of America, buprenorphine-naloxone was also found effective when prescribed in the primary care setting.[11]

Buprenorphine-naloxone treatment has also been associated with better preservation of cognitive function in comparison to methadone, especially when the patient is co-treated with benzodiazepine.[12] It has also shown to have a less sedating effect making patients perform and engage much better. Methadone exerts additive effects to both anxiolytics and antidepressants, which can increase the risk of mortality, respiratory depression and coma. There have been cases of serotonin toxicity with monoamine oxidase inhibitors when combined with methadone.[13]

CONCLUSION

Buprenorphine-naloxone is a safe and effective drug substitution therapy for opioid dependence. It has a lower abuse potential compared to buprenorphine alone, and has similar efficacy to methadone. It is also less sedating than methadone making it less disabling in those who are functional. This case series highlights some benefits of using buprenorphine-naloxone formulation in treating patients with opioid dependence. A newer formulation of buprenorphine-naloxone is available as a film, which further reduces the risk of diversion and misuse.[14] A market research in Malaysia identified that buprenorphine-naloxone film was thought to be superior by practitioners compared to existing treatment options.[16]

ACKNOWLEDGEMENTS

We would like to thank the Director General of Health, Malaysia for permission to publish this paper.

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