

Abuse of Prescription Buprenorphine, Regulatory Controls and the Role of the Primary Physician

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Abstract

Introduction: Buprenorphine is an opioid partial agonist approved in several countries for the treatment of opioid dependence. It was approved in Singapore in 2002 for this indication, and is more widely available in the primary care setting and can be prescribed by all licensed physicians who have undergone designated training. There is limited literature addressing the risk of its illicit abuse via intravenous self-administration. **Clinical Picture:** We report 2 such cases of the abuse of prescription buprenorphine in the psychiatric consultation-liaison service of a general teaching hospital, the treatment approaches and outcomes. **Conclusion:** We also briefly review the indications, uses and abuses of buprenorphine in Singapore, and as reported in other countries, and the roles of primary care physicians, in order to stimulate greater awareness and understanding among specialists and general practitioners, who would encounter these patients in various settings.

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Key words: Opioid dependence, Partial agonist, Primary care setting

Introduction

Buprenorphine is an opiate partial agonist that has been used for pain management, and in the past few years has been approved for the treatment of opioid dependence in Singapore and other countries. Buprenorphine is available in primary care clinics and can be prescribed by all licensed physicians who have undergone designated training. While there is growing alarm at the illicit diversion and abuse of buprenorphine via intravenous administration, there is limited literature addressing this problem in the local context. The authors, a psychiatry resident who was on the consultation-liaison service in a teaching-general hospital in Singapore and a visiting clinical fellow from the US (who has buprenorphine prescription privileges with the US Drug Enforcement Agency), noted substantial numbers of patients abusing prescription buprenorphine obtained from their primary care physicians or through illicit means. In a 3-month period on the psychiatric consultation-liaison service, one author personally saw over 25 patients who abused buprenorphine intravenously, usually with a benzodiazepine. Two cases are briefly presented below for illustration.

The main contact between the opioid-dependent patient and medical services remains at the primary physician or general practitioner (GP) level. However, all physicians will encounter these patients in hospitals and specialist clinic settings as these patients present with various medical problems. Moreover, various guidelines and regulations mandate that the primary care physicians provide counseling and non-pharmacologic treatments or refer them to appropriate settings. As the main contact point, the role of primary care physicians is pivotal and requires further clarification for implementation.

Uses and Abuses of Buprenorphine

The evidence base for buprenorphine's efficacy in the treatment of opioid dependence has been growing.^{1,2} It has been shown to enable patients to discontinue the misuse of opioids without experiencing severe withdrawal symptoms and has been seen as a new paradigm for office-based treatment for patients with opioid dependence.^{3,4} Hence it has been used for both detoxification and maintenance. It should be clarified, however, that this is a "treatment" for dependence and does not imply a cure for opioid

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dependence. The purpose of prescription buprenorphine is harm reduction, by minimising opioid withdrawal symptoms, and thereby reducing the need for the continued illicit acquisition and use of heroin and other opioids. While there is the possibility of eventually tapering the patients off buprenorphine, this is still under investigation. For many patients, they will be on maintenance buprenorphine for a long time, if not indefinitely.

Buprenorphine is a semi-synthetic opioid derived from thebaine, a naturally occurring alkaloid of the opium poppy. It is a partial agonist at the opioid μ receptor. Its sublingual bioavailability is extensive enough to be a feasible route of administration.⁵ Its maximal effects are less than those of full agonists like heroin and methadone, and the agonist effects increase linearly with increasing doses until moderate doses, where they reach a plateau called the “ceiling effect”. Theoretically, it carries a lower risk of abuse, dependence and side effects compared to full opioid agonists. However, the potential of buprenorphine to produce euphoria and opioid-like effects results in its abuse via the intravenous route.⁵ As take-home medications in the ambulatory setting, there is greater likelihood for illicit and risky intravenous self-administration.

If administered intravenously, complications such as infectious endocarditis, blood-borne infections, limb gangrene and even death may result. Deaths have been reported in association with concomitant administration with benzodiazepines, alcohol and other opioids. Available literature on its abuse is mostly from France, where it has been used since 1996.⁶⁻⁹ One study showed that the risk of its abuse appears to be higher with increased prescribed dosages, in contrast to methadone.⁶ In Australia, Jenkinson et al¹⁰ reported that in their study sample of opioid-dependent patients, 37% reported having illicitly injected buprenorphine in their lifetime.

Regulatory Control in Different Countries

Buprenorphine is a semi-synthetic opioid that has been used for pain management for decades. As for the treatment of opioid dependence, there are 2 versions currently on the market, both administered sublingually. Buprenorphine as monotherapy is marketed under the name Subutex[®], and buprenorphine in combination with naloxone is marketed as Suboxone[®] (both manufactured by Reckitt Benckiser Healthcare, UK). Subutex[®] was first approved in France in 1996, in the United Kingdom in 1998 and Australia in 2001. However, Suboxone[®] had not yet gained approval in these countries. The US Food and Drug Administration simultaneously approved both Subutex[®] and Suboxone[®] in October 2002,¹¹ making the US the first country to do so. In Singapore, Subutex[®] was approved for the treatment of opioid dependence in 2002, but Suboxone[®] is still pending approval.

In the US, buprenorphine for opioid dependence comes under the strict aegis of the Drug Addiction Treatment Act of 2000 (DATA 2000), which only permits physicians who meet certain qualifications to treat opioid addiction with such medications in treatment settings other than the traditional methadone clinic. In short, the law mandates that physicians be granted the privilege of prescribing buprenorphine only if they meet certain training requirements (e.g., specified certifications in addiction medicine or psychiatry, or an approved training course). In addition, the physician has a 30-patient-per-physician limit for such treatment and has the “capacity to refer such addiction therapy patients for appropriate counseling and other non-pharmacologic therapies”. If these requirements can be attested to, the Drug Enforcement Agency (DEA) assigns each qualifying physician a special identification number.¹¹ As a result of the new legal framework, primary care physicians are now actively involved in the office-based treatment of opioid dependence.

Along similar lines, the Ministry of Health, Singapore, issued guidelines on the Prescription and Use of Buprenorphine (Subutex[®]) on 3 November 2005.¹² The stated purpose of the guidelines were to “stem the illicit use and diversion” of buprenorphine, and to “lay out good clinical practices and administrative controls” for all physicians. Moreover the guidelines stated that doctors should have the training or resources to “adequately counsel and manage” their patients and each physician must have attended an 8-hour training programme conducted by the Community Addictions Management Programme. In addition, all prescriptions have to be logged into cross-reference checking systems to prevent the patients from going to multiple clinics for their supply.

Brief Description of 2 Cases in Singapore

Case 1

A single man in his mid-twenties with active intravenous buprenorphine and benzodiazepine abuse presented to the emergency room for pain and swelling secondary to possible left thigh cellulitis and was admitted to the general medical ward. His medical history was significant for longstanding heroin and benzodiazepine dependence. He had been getting Subutex[®] from GPs and instead of taking them sublingually as prescribed, had been grinding them up with Dormicum[®] (midazolam) and injecting the combination intravenously.

On the second day of admission, he complained of withdrawal symptoms, with myalgia, tremors and chills, and demanded Subutex[®] and Dormicum[®] from the treating physicians. He turned abusive when his demands were not met. A referral was made to the consultation-liaison psychiatry service with the suggestion that the patient be transferred to the inpatient psychiatric unit since the cellulitis required only antibiotic treatment. During the psychiatric

interview, the patient calmed down but expressed anger that the physicians did not seem sympathetic towards his medical problems. He was counseled on the risks of intravenous Subutex[®] abuse. Upon his request for discharge, he was assessed to be medically stable, neither in acute withdrawal, nor a risk to himself or others. He was discharged to be followed up at an outpatient addiction programme. However, the patient defaulted substance abuse treatment and was admitted twice to the same hospital for different medical complaints over the next 2 months. Each admission was preceded by heavy intravenous self-administration of buprenorphine with or without benzodiazepines.

Case 2

A married female in her mid-thirties presented while 6 months pregnant for viral gastroenteritis. She had been abusing Subutex[®] by injecting it intravenously for a year and had no prior antenatal care. She had obtained Subutex[®] from her husband, who was also abusing it. Both of them had previously been remanded in governmental drug rehabilitation centres for opioid dependence. She was referred to the psychiatry consultation liaison service and counseled on the risks of illicit substance abuse and especially with regard to her pregnancy. She was referred to the local substance abuse programme. She was also followed up by a social worker to ensure compliance with treatment and antenatal care.

The Role of the Primary Care Physician

The above cases illustrate the difficult nature of treating patients with opioid dependence using a prescription opiate agonist. In addition to the laws and guidelines issued by each jurisdiction on the prescribing of buprenorphine, a review of the literature shows that despite the high prevalence and substantial socioeconomic burden of substance abuse and their co-morbid substance-related disorders, many physicians are unprepared to treat such patients.¹³ This is in spite of the fact that most, if not all, health professionals have contact with patients with substance abuse problems, and should be able to assess risks, and provide brief interventions, harm reduction advice or referral to appropriate services.

However, McGillion et al¹⁴ argue that in general, physicians are often not keen to be involved with patients with substance abuse problems. They view these patients as being difficult to work with, manipulative, poorly motivated, and time-consuming. Moreover, some may have encountered physical or verbal threats and abuse from these patients. Miller et al¹³ further identified many factors which serve as barriers to the effective treatment of substance abuse and their related disorders. The 5 major categories are (1) lack of acceptance of the medical model for

addictions; (2) lack of faculty and physician role models for the training of future physicians; (3) lack of curricula time spent on these disorders in medical education, which is disproportionate to the socioeconomic burden of this disease; (4) lack of parity and physician advocacy; and (5) personal and family history of addictions in physicians. They advocated for clearer roles for the physician in the diagnosis and treatment of substance-related disorders, developing curricula in medical education, residency training and continuing medical education.

Buprenorphine is not currently listed as a controlled drug under the Misuse of Drug Act, Singapore. It is also the first opiate agonist to be used on a wider scale by GPs in Singapore. Methadone, introduced far earlier, is a controlled drug under the Act and is not commonly used in the primary setting. Primary care has been proposed as the ideal setting for the treatment of substance abuse, with many potential advantages.¹⁵ In many GP surveys, despite the negative views held about these patients, most physicians still acknowledged the appropriateness of their setting and the importance of their own role in the treatment.^{13,16,17} By linking primary care to substance abuse care providers, treatment outcomes could be improved and the patient would receive better overall holistic care, including the treatment of comorbid medical problems. There would also be a reduction in perceived stigmatisation and allow substance abuse to be part of the training loop for physicians. From the economic perspective, overall healthcare costs would drop by reducing duplication of services. Moreover, a study of patients with substance abuse problems and their perceptions of GP care showed that the majority of patients believed their GPs had positive views about them in contrast to those attending specialist treatment centres.¹⁸ A high proportion of drug users had sought treatment from GPs known to be sympathetic to their treatment.

Discussion

The combination of buprenorphine and naloxone, marketed as Suboxone[®], is designed to decrease the potential for abuse by injection because it leads to acute withdrawal symptoms.³ In the US, it is reported that over 90% of the buprenorphine prescriptions are for Suboxone[®] because of the much lower abuse potential.¹⁹ Therefore, buprenorphine monotherapy (Subutex[®]) is reserved for pregnant women who need to be maintained on opioids and risks of naloxone to the fetus are still unknown, as in Case 2. This is consistent with the view of the National Institute of Drug Abuse (NIDA) that Suboxone[®] would be the dominant medication prescribed because the effects of the opiate antagonist naloxone predominate when injected illicitly. The NIDA expects that Suboxone[®] will have a relatively low street value as compared to all other forms of prescription opiates.²⁰

While this combined buprenorphine-naloxone formulation may ameliorate the problem of diversion with illicit and risky use, and is being considered for licensing in several of the above-named jurisdictions, the fundamental problem of opioid dependence remains. Substance abuse and dependence are common problems that are potentially manageable, if not curable, with the goal of harm reduction. Integrated programmes of substance abuse treatment involving primary care physicians or GPs, addiction/substance abuse psychiatrists, clinicians and social workers are likely to provide the best outcomes. For the present, we recommend that the primary care physicians take on more proactive roles in terms of providing counselling and/or involve the ancillary services and addiction psychiatrists in the ordinary course of treating their patients with substance abuse problems.

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REFERENCES

- Barnett PG, Rodgers JH, Bloch DA. A meta-analysis comparing buprenorphine to methadone for treatment of opiate dependence. *Addiction* 2001;96:683-90.
- Gerada C. Drug misuse: a review of treatments. *Clin Med* 2005;5:69-73.
- Fiellin DA, Rosenheck RA, Kosten TR. Office-based treatment for opioid dependence: reaching new patient populations. *Am J Psychiatry* 2001;158:1200-4.
- Kosten TR, Fiellin DA; US National Buprenorphine Implementation Program. Buprenorphine for office-based practice: consensus conference overview. *Am J Addict* 2004;13(Suppl):S1-S7.
- Elkader A, Sproule B. Buprenorphine. Clinical pharmacokinetics in the treatment of opioid dependence. *Clin Pharmacokinet* 2005;44:661-80.
- Guichard A, Lert F, Calderon C, Gaigi H, Maguet O, Soletti J, et al. Illicit drug use and injection practices among drug users on methadone and buprenorphine maintenance treatment in France. *Addiction* 2003; 98:1585-97.
- Varescon I, Vidal-Trecan G, Nabet N, Boissonnas A. Buprenorphine abuse: high dose intravenous administration of buprenorphine (French). *Encephale* 2002;28:397-402.
- Courty P. High dose buprenorphine and injection practices. A study of 303 patients (French). *Ann Med Interne (Paris)* 2003;154 Spec No 1:S35-45.
- Vidal-Trecan G, Varescon I, Nabet N, Boissonnas A. Intravenous use of prescribed sublingual buprenorphine tablets by drug users receiving maintenance therapy in France. *Drug Alcohol Depend* 2003;69:175-81.
- Jenkinson RA, Clark NC, Fry CL, Dobbin M. Buprenorphine diversion and injection in Melbourne, Australia: an emerging issue? *Addiction* 2005;100:197-205.
- Buprenorphine. Substance Abuse and Mental Health Administration, US Dept of Health and Human Services. Available at: <http://www.buprenorphine.samhsa.gov>. Accessed 12 December 2005.
- Ministry of Health Issues Guidelines on the Prescription and Use of Buprenorphine (Subutex); 3 November 2005. Ministry of Health, Singapore. Available at: http://www.moh.gov.sg/corp/about/newsroom/press_releases/details.do?id=34668568. Accessed 23 February 2006.
- Miller NS, Sheppard LM, Colenda CC, Magen J. Why physicians are unprepared to treat patients who have alcohol- and drug-related disorders. *Acad Med* 2001;76:410-8.
- McGillion J, Wanigaratne S, Feinmann C, Godden T, Byrne A. GPs' attitudes towards the treatment of drug misusers. *Br J Gen Pract* 2000;385-6.
- Samet JH, Friedmann P, Saitz R. Benefits of linking primary medical care and substance abuse services: patient, provider, and societal perspectives. *Arch Intern Med* 2001;161:85-91.
- Deehan A, Taylor C, Strang J. The general practitioner, the drug misuser, and the alcohol misuser: major differences in general practitioner activity, therapeutic commitment, and 'shared care' proposals. *Br J Gen Pract* 1997;47:705-9.
- Friedmann PD, McCullough D, Saitz R. Screening and intervention for illicit drug abuse: a national survey of primary care physicians and psychiatrists. *Arch Intern Med* 2001;161:248-51.
- Hindler C, King M, Nazareth I, Cohen J, Farmer R, Gerada C. Characteristics of drug misusers and their perceptions of general practitioner care. *Br J Gen Pract* 1996;46:149-52.
- Physician Buprenorphine Training, American Society of Addiction Medicine and the Massachusetts Society of Addiction Medicine; 3 Dec 2005; Boston, Massachusetts.
- Director's Report to the National Advisory Council on Drug Abuse; February 2003. Available at: <http://www.nida.nih.gov/DirReports/DirRep203/DirectorReport8.html>. Accessed 11 December 2005.