Singapore's Experience With Buprenorphine (Subutex)

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Buprenorphine (Subutex) has been used to treat opioid dependency in the past 16 years. Subutex (or buprenorphine hydrochloride) was approved by the Singapore's Ministry of Health (MOH) in 2000 as a substitution treatment for opiate-dependent drug abusers within the framework of medical, social and psychological treatments. It was subsequently introduced into the Singapore market in 2002. In spite of the promise of improvement in the lives of addicts with medical care, a distinct trend of buprenorphine abuse has occurred. A cascade of events from 2002 to 2006 led to discontinuation of Subutex treatment programs in the country. In this paper, firstly reports on morbidity and mortality caused by Subutex IV abuse will be reviewed and secondly, the MOH response to the situation will be outlined and finally, implications of Singapore's experience with Subutex will be discussed.

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Introduction

Buprenorphine (Subutex) has been used to treat opioid dependency in the past 16 years. This drug was introduced in New Zealand (1) in 1991 and in France (2) in 1995, and was approved by the American Food and Drug Association (FDA), in order to be used by qualified doctors in certified offices (3). In October 2002 Subutex (buprenorphine hydrochloride) was approved by Singapore's Ministry of Health in 2000 for treatment of opioid dependency, in a medical, social and psychological framework and it came to the market in the same year. From then on, Subutex became an alternative for methadone to treat opioid dependency in Singapore(4). It is believed that in comparison with other agonist prescriptions, buprenorphine has a low abuse potential and with better side effects profile (5). Subutex, which was introduced to the Singapore's market, was in the form of the sublingual tablet.

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Buprenorphine Abuse

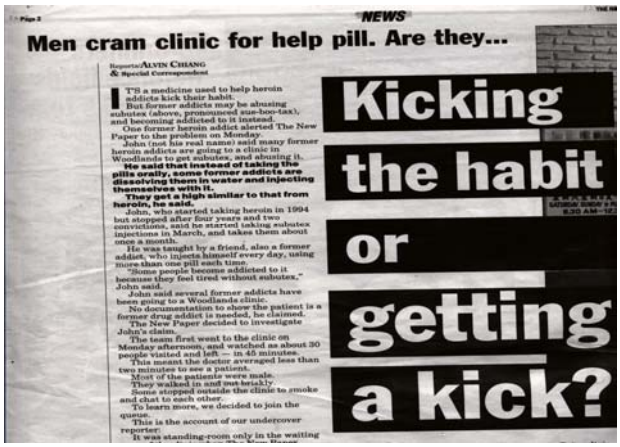
Although it was expected that buprenorphine would have a good profile, many opioid dependent patients misused it by injecting to achieve a 'high'. In spite of the promise of improvement in the lives of addicts with medical care, a distinct trend of buprenorphine abuse has occurred from 2004 to 2006. The intravenous injection of pulverized buprenorphine tablets may produced various physical complications, such as abscesses, human immunodeficiency virus (HIV) infection, hepatitis B or C infections, optic neuritis secondary to infection with Candida albicans, respiratory depression, and tricuspid or pulmonary valve endocarditis. Both intravenous and intra-arterial injections of pulverized buprenorphine may cause peripheral limb ischemia.

Though, prior to the introduction of Buprenorphine, the injection culture wasn't prevalent in Singapore, during a four-year period, at least 3,800 people were known who misused the buprenorphine through IV route. The patients misused buprenorphine alone or with other drugs. Complications of parental drug abuse were increasingly noted by clinicians. These complications included infections of varying severity and vascular complications: cellulitis, abscesses, gangrene, necrotizing fasciitis, compartment syndrome,

and distal limb ischemia associated with multiple injection sites (including the femoral vein/artery and neck vein regions), limb amputations and infective endocarditis (4,6). There was not any formal published data on the incidence, but some reports showed that patients, who were admitted to the hospital with side effects of IV drug use in the year 2005, were more than those of previous year. In one study, Loo et al reported four cases of severe upper limb complications from the parental abuse of Subutex (4). These patients were hospitalized in the first three months of 2005, while there were no such documented cases in the preceding three years. In another study (6), 53 buprenorphine IV abusers were reported, who were hospitalized in 2005. Thirty one had surgical complications, while 22 presented with medical ones. Of the surgical patients, 12 had cellulitis and thrombophlebitis, six developed abscesses of the limbs, 10 were patients with ischemia and gangrene of the digits and limbs, one had septic arthritis, one had necrotizing fasciitis, and one had a pseudo aneurysm of the femoral artery. There were no reported cases of mortalities. Only 9 patients needed surgical interventions.

Due to the increased health complications of Subutex IV abuse, at the end of 2005, Ministry of Health decided to limit the Subutex usage by introducing some guidelines (7). They include limiting number of patients a single doctor can treat, making mandatory for doctors, prescribing the medication to attend an eight-hour course in the treatment of opioid dependence, and creating an online central database, making the notification of these patients compulsory. Most of the opioid dependent patients were treated in an office/clinic setting, but those who abused the Subutex were inflicted by side effects, consequently needing to receive care in the hospital for surgical or orthopedical complications.

The Center for Forensic Medicine reported 50 cases of buprenorphine-related deaths (8), with an incidence rate nearly doubling from 9 per 1000 to 17 per 1000 autopsies during a period of 20 months from September 2003 to August 2005. The postmortem blood samples taken were positive for buprenorphine with or without other substances. There were 44 cases out of 50 (88%) showing concurrent use of benzodiazepines, such as midazolam, diazepam and nitrazpam. The media reports had also highlighted indiscriminate disposal of contaminated needles and syringes, sometimes blatantly, in public places. These reports coupled with the congregation of Subutex users in some "hotspots", including medical clinics, caused significant public concern. For several weeks in August 2006, newspaper headlines took a tougher stance with addiction medical practitioners. Newspapers reported to the Singaporean public that some physicians inappropriately were selling buprenorphine (used to help rehabilitate drug addicts) to patients just for profit (Figure 1).


NEWS

Men cram clinic for help pill. Are they...

Reporter/ALVIN CHIANG
& Special Correspondent

IT'S a medicine used to help heroin addicts kick their habit.
But former addicts may be abusing subutex (above, pronounced sue-boo-tax), and becoming addicted to it instead.
One former heroin addict alerted The New Paper to the problem on Monday.
John (not his real name) said many former heroin addicts are going to a clinic in Woodlands to get subutex, and abusing it.
He said that instead of taking the pills orally, some former addicts are dissolving them in water and injecting themselves with it.
They get a high similar to that from heroin, he said.
John, who started taking heroin in 1994 but stopped after four years and two convictions, said he started taking subutex injections in March, and takes them about once a month.
He was taught by a friend, also a former addict, who injects himself every day, using more than one pill each time.
"Some people become addicted to it because they feel tired without subutex," John said.
John said several former addicts have been going to a Woodlands clinic.
No documentation to show the patient is a former drug addict is needed, he claimed.
The New Paper decided to investigate John's claim.
The team first went to the clinic on Monday afternoon, and watched as about 30 people visited and left — in 45 minutes.
This meant the doctor averaged less than two minutes to see a patient.
Most of the patients were male.
They walked in and out briskly.
Some stopped outside the clinic to smoke and chat to each other.
To learn more, we decided to join the queue.
This is the account of our undercover reporter:
It was standing-room only in the waiting

Kicking the habit or getting a kick?

Figure 1. Singaporean newspapers against physicians

There was a significant demand on healthcare practitioners to treat and rehabilitate patients with the above mentioned medical and surgical complications, and also a high social cost attached to the issue. Another important issue was the high degree of buprenorphine diverted to the black market. A study assessed 120 buprenorphine abusers, all of them fulfilling the diagnostic criteria for opiate dependence (9). The study revealed while 60% of those taking buprenorphine obtained it from doctors, 40% obtained it from "friends" or the black

market. This is an indication of a fairly large-scale diversion and abuse, in part due to the medical profession not being adequately familiar with the treatment of chronic opiate dependent patients, especially those with long histories of multiple incarcerations, antisocial behaviors and personality disorders. The study also showed that 53.3% of subjects only started intravenous drug use, after the introduction of buprenorphine. Since it is well documented that the injection of medications designed for oral consumption puts the abuser at a risk of harm from the rapid onset of drug effect, local injury and vascular injury, these findings are of concern, as buprenorphine is prescribed only for sublingual use (Figure 2).

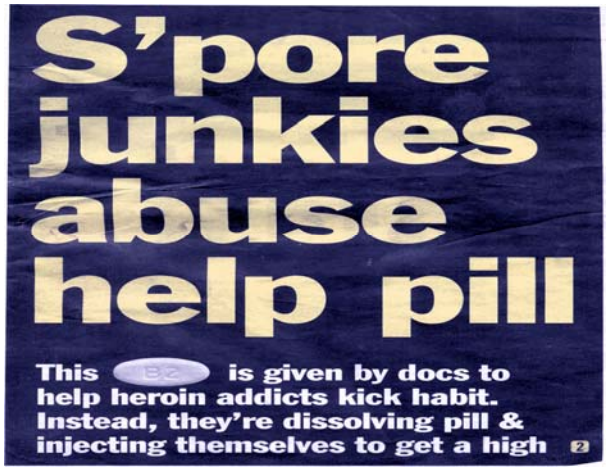


Figure 2. Singaporean newspapers against buprenorphine

Singapore's Ministry of Health Response to the Situation

To tighten control on Subutex prescription, the ministry of health introduced a Clinical Practice Guideline for treatment of opioid dependency in November of 2005(7). This clinical guideline also described the principles of how to prescribe buprenorphine. Furthermore, ministry of Health (MOH) introduced a Central Addiction Registry for Drugs, Singapore (CARDS)-a web-based system which monitors the prescription of by doctors and enables them to identify patients who obtain additional supplies from different doctors. In addition, MOH required Subutex-prescribing doctors to attend a mandatory eight-hour training course on managing opiate dependents. Anecdotally, these measures were effective in significantly reducing the incidence of obtaining buprenorphine from multiple prescriptions. Unfortunately, the Subutex abuse situation on the ground persisted. The decision was thus made by Singapore's MOH to eradicate the problem and nip it in the bud from causing further harm. The two main priorities of MOH were to prevent new addicts to this drug and to help the current users wean off this drug. A three-pronged approach was adopted (10).

Buprenorphine Controlled Drug

In 14th of August of 2006, according to the Drug Control Law, buprenorphine was introduced as a controlled drug class A. Imports, distribution, possession and using buprenorphine became illegal except in case of medical use in the framework of the regulations. The buprenorphine users, who were arrested for the first and second time, were sent for compulsory treatment in rehabilitation centers. Those who were arrested more than two times were sentenced to severe punishments such as long-term imprisonment (LTI). Under long-term incarceration, third-time or more abusers could face a maximum of the cane if convicted. If they commit a subsequent offence of consumption after their conviction for a LTI, they could face a maximum sentence of 13 years imprisonment and 12 strokes of the cane. Those arrested for trafficking or possession of buprenorphine will face even stiffer penalties. If convicted, traffickers will face a minimum sentence of five years imprisonment and five strokes of the cane, and a maximum sentence of 20 years imprisonment and 15 strokes of the cane. Those convicted for possession of buprenorphine will face up to 10 years imprisonment, $20,000 fine, or both. To deter proliferation of a needle culture among drug abusers, those found in possession of syringes, stained or otherwise, will face up to three years imprisonment, $10,000 fine, or both(10).

Subutex Voluntary Rehabilitation Program (SVRP)

The Subutex Voluntary Rehabilitation Program (SVRP) was the second step of MOH to tackle the problem. With the assistance of a group of skillful Psychiatrists, SURP was introduced. This program was consisted of medical and rehabilitation components. This program was launched for all the Subutex abusers including those who were not registered in CARSDS. The medical component consists of a detoxification regime of sublingual buprenorphine (under daily supervised dosing) in gradual tapering dose reduction from the current dose, usually within five to seven days. In the case if the withdrawal symptoms lasted longer, the duration of treatment will be increased. The treatment of most patients was preformed in an outpatient setting, however some patients may require inpatient detoxification, such as those with high potential for complicated withdrawal (e.g. patients with concurrent poly-substance abuse or patients with history of complications during previous withdrawal experiences), presence of other co-morbid medical conditions (e.g. uncontrolled diabetes, infections) and those with a history of depression or psychosis. The medical component is being carried out at the Institute of Mental Health (IMH). Subutex is only prescribed in medical centers and under supervision; however, symptomatic medications for withdrawal symptoms are also available and allowed for take home.

All patients enlisted are offered basic psycho-education. The rehabilitation components included naltrexone, structured substance abuse counseling (non-residential), and half-way house (residential) placement. For continuity of care, patients could be referred for further addiction follow-up, when indicated or to the relevant specialist clinics for further management of co morbid mental or medical conditions detected. The importance of compliance with the prescribed program was strongly emphasized as the patient must play their part if they wish to overcome their dependence. Patients who default their appointments, are non-compliant with the treatment regime and/or are found to be abusing opiates, benzodiazepines or any other controlled/ illicit drugs will be disqualified from SVRP. Family and society support was also strongly encouraged.

The Transitional Period

The third response of the MOH to the situation was provision of a transitional period. In August 14, 2006 beginning treatment for new patients with buprenorphine was banned. The take-home doses of patients, who were treated with Subutex before, should be omitted from next appointment and all patients should come daily and use Subutex sublingually under direct supervision (i.e. daily observed therapy or DOT) of their doctor or treatment staff. The doctors and the treatment team should assure that sublingual Subutex is completely dissolved before letting the patients leave the office/clinic. If the treatment centre was closed on weekends or on public holidays, the clinic is required to provide a private prescription slip for their patients to collect their daily dose of Subutex from IMH Pharmacy.

Subutex users were given a two-week period (to sign up for the SVRP. They could do so through existing doctors, managing their opiate dependence. GPs were requested to encourage their patients to sign up for SVRP. It was proposed that when the patients were on DOT, there were ample opportunities for GPs to counsel their patients on their treatment options. Subutex users could also sign up through the MOH hotline. Some also chose to walk in directly to IMH concerning their appointments. The latter two groups were mainly patients who were not registered in CARDS. Patients who consented for the SVRP were contacted by MOH for their appointment details. GPs and emergency departments were also advised of the treatment options for patients when experiencing withdrawal symptoms. IMH also set up a Detoxification Clinical Advisory Service, facilitated by addiction medicine specialists, to assist doctors managing such patients (10).

Implementation of Subutex Voluntarily Rehabilitation Program (SVRP)

There were over 3,000 patients who registered in the SVRP. This program began August 21, 2006 (one week earlier of the due time) to treat patients who were not under coverage of general physicians. Medical component of SVRP was completed in September 30,2006 and 2,269 out of all registered patients in the program were detoxified in the Institute of Mental Health (75% of all registered patients). About 68% of patients entered into detoxification completed the program. SVRP has been a massive logistical exercise. The scale of the medical detoxification phase is unprecedented not only in Singapore, but also in other countries. Additional medical and paramedical staff from IMH and restructured general hospitals, as well as locums were mobilized by MOH and trained by IMH to assist with the patient load.

Additional security personnel and support staff were also employed to enable the SVRP Clinics to run morning, afternoon, and evening clinics (including weekend morning and afternoon sessions). The implementation of SVRP occurred in context of a multi-agency approach with IMH anchoring the treatment aspects, with the Central Narcotics Bureau and the Singapore Police Force providing assistance to ensure security and safety (10).

Conclusion

As it has been demonstrated briefly, a cascade of events has led to a discontinuation of buprenorphine treatment programs in Singapore since December of 2006. What can we learn from Singapore's experience with Subutex (Buprenorphine)? One simple way is criticizing Singapore's health system for implementation of buprenorphine treatment programs in their country without building necessary capacities and to consider our programs immune from such negative adverse consequences. Another suggestion is recognizing blind spots and vulnerability factors of Singapore's Subutex program and to learn how to avoid such obstacles in health system development. Singapore's experience with introduction of Subutex as a treatment option in opioid dependence showed that how launching a new treatment modality without appropriate capacities, knowledge and skill for applying of that would cause various side effects at individual and social level. Physicians of addiction medicine did not lose only a treatment modality, but most importantly, they lost society's general trust to medical solutions for a challenge of community's health system. Press attacking addiction physicians, is a serious threat for professionalism and its negative adverse effects on future of addiction medicine is expected. If patients feel physicians are only thinking about their own profits, they will lose their trust in physicians. As patients lose faith with their physicians, who will act in their own best interests, thus, their respect for the profession fades. Without respect and trust, caring for patients becomes more challenging and less enjoyable. Patients may reject treatments that are in their best interest, or demand therapies of little benefit and potential harm to them. Professionalism is the most significant factor to the entire field of medicine. We have much to lose if the public questions our professionalism. The time spent working on professionalism may not seem to improve daily clinical productivity, but the rewards can be greater than imagined: better care for your patients and an even more satisfying practice for yourself.

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