Editorial

Medicalising the Treatment of Opioid Dependence

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Traditionally the treatment of opioid dependence in Singapore has not been viewed as a public health problem, but rather as a social problem that necessitated custodial and other punitive approaches. The turning point came in 1996, when, after a pilot programme in the Prisons Department, naltrexone was introduced as an option in management of heroin dependence.[1] However, because of long-standing attitudes and perceptions held by both the public and the medical profession, ambivalence persisted towards the addict as a patient.

Recent advances in neuroscience have increased our understanding of substance-use disorders, and the new insights have important implications for clinical practice. Neural pathways and major receptors have been identified for most drugs of abuse. Many of the biochemical cascades within the brain cell that follow the drug activation of cell membrane receptors have been elucidated.[2]

Almost all substances of abuse have common effects on the dopaminergic mesolimbic reward system, which extends from the ventral tegmentum to the nucleus accumbens, with projections to the limbic system and the orbitofrontal cortex. Contrary to the view that addicts are weak or bad people lacking will or morals, addiction is now known to be a chronic, relapsing brain disorder characterised by compulsive drug seeking and use.[3] In short, prolonged drug use causes pervasive brain changes at the molecular, cellular, structural and functional levels, which persist long after the addict stops taking the drug. Hence, the cue-induced craving and the propensity to relapse.[4]

There are three medications – apart from adjunctive ones – that are widely used in the treatment of heroin dependence, namely naltrexone, methadone, and buprenorphine. Naltrexone is an opioid receptor antagonist, while methadone is an agonist, and buprenorphine is a partial opioid agonist at the mu opioid receptor and also an antagonist at the kappa opioid receptor. There is insufficient evidence for routine maintenance treatment using naltrexone in opioid dependence.[5] Both methadone and buprenorphine are equally efficacious, but methadone maintenance requires high doses to prevent relapses, whereas buprenorphine has a better retention rate.[6] Methadone is hardly prescribed locally except for a few elderly opium addicts, because of the concern about its street value as a drug of abuse.

Readers should note that, apart from their use for detoxification, neither buprenorphine nor methadone is a "cure" for opioid dependence: both these drugs are substitution agents. However, as maintenance treatment the drugs can help the addict to function better socially and occupationally.[7]

In spite of the promise of improvement in the lives of addicts with medical care, a distinct trend of buprenorphine abuse has occurred over the past 2 years. Buprenorphine in tablet formulation [proprietary name Subutex (Schering-Plough)] was marketed in Singapore in 2002 as a prescription-only medicine for sublingual administration. Soon afterwards, cases began to appear of the intravenous abuse of Subutex tablets. The intravenous injection of pulverised buprenorphine tablets may produce various physical complications, such as abscesses, human immunodeficiency virus (HIV) infection and 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 pulverised buprenorphine may cause peripheral limb ischaemia.

The consequences of intravascular Subutex abuse are clearly described in 2 papers in this issue of *Annals*.[8,9] Other descriptions of similar complications have been published in local journals of medicine and of epidemiology.[10,11]

There is a high social cost attached, and a significant demand on healthcare resources to treat and rehabilitate patients with these medical or surgical complications. An additional drawback of buprenorphine is the high degree of drug diversion, as described in the paper by Winslow et al.[12] The detailed study by Winslow et al[12] is most interesting, as it profiles buprenorphine abusers who seek medical help to escape their situation. It provides strong evidence that the proper selection of patients is one of the most important factors promoting the successful treatment of opioid abuse using buprenorphine substitution.

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In the Australian National Clinical Guidelines and Procedures for the Use of Buprenorphine in the Treatment of Heroin Dependence,[13] it is clearly stated that buprenorphine is only indicated for those who are opioid-dependent, and that particular caution should be exercised when assessing the suitability of buprenorphine treatment for anyone with polydrug use.[13] The abusers profiled[11,13] included 39.2% of subjects who initiated buprenorphine use to stop heroin abuse, and a slightly lower proportion who did so "out of curiosity". Polysubstance abuse was reported by 81.7% of those profiled.

It is well known that the prognosis for substance abusers receiving treatment is better in those abusers who have a stable family, occupational, financial and educational background. In the Singaporean abusers profiled, only 52.5% were currently employed, and a third had debts. Almost 80% had a past history of imprisonment, not counting Drug Rehabilitation Centre (DRC) admissions (indicating possible anti-social personalities).[11] Half of abusers had primary school education only. With a monthly income of less than $500 in 55.8% of abusers, we wonder how carefully they were selected (if at all) for maintenance treatment with buprenorphine – which is not inexpensive – in the first place.*

Some of these intravenous Subutex abusers may have adopted this behaviour because a smaller (and thus cheaper) amount of pulverised buprenorphine, injected together with pulverised midazolam, can create a more intense euphoria than a larger amount of buprenorphine taken sublingually.

What went wrong locally (as well as in various other countries)? Several factors have contributed to this new behaviour. Heroin addicts were previously managed and rehabilitated at DRCs and prisons; doctors are thus generally inexperienced in treating these addicts and their condition. The number of general practitioners, physicians, and psychiatrists trained in addiction medicine is grossly inadequate for our population. The preparation of doctors to deal with clinical problems arising after the market launch of Subutex was less than ideal.

Compounding the situation is the fact that midazolam in its oral formulation is available as a prescription-only hypnotic for patients in Singapore, in contrast to Europe and the USA, where midazolam is only available for use as an anaesthetic agent, as a solution for intravenous injection. The Subutex abusers often crush midazolam tablets and add the powder to crushed Subutex tablets before injecting the mixture. A number of drug overdoses causing deaths have been reported in the local press in association with the intravenous abuse of buprenorphine both with and without the concomitant injection of high doses of benzodiazepines. Regulatory controls have been revised several times, but they did not solve the problem of diversion and abuse. While these control measures are being reviewed, it should be kept in mind that buprenorphine is effective in the maintenance treatment of heroin dependence for many addicts, who would otherwise end up with a 'revolving-door syndrome' of relapses of compulsive heroin seeking and use.

Suboxone (Schering-Plough), which is a buprenorphine-naloxone combination product, has been touted as an answer to Subutex intravenous abuse and diversion. The tablet is to be taken sublingually. Naloxone is an opioid antagonist commonly given to reverse the overdose toxicity of opiates. Addicts who abuse Suboxone intravenously are likely to experience a very unpleasant and painful opioid withdrawal syndrome due to the effect of naloxone. Suboxone is expected to have a lower street value compared to Subutex and other forms of prescription opioids.

However, it pays to remember that ultimately, the successful treatment of substance use disorders lies with effective psychosocial and behavioural treatments. No medical programme with Subutex or Suboxone should be initiated if the patient or physician does not have such resources, or access to them. The nature of addiction and the treatment programme should be properly explained to the patient and family members or caregivers.[14] Physician training and continued education in this area are necessary as there is constant review of best practices.[15]

In the USA, the abuse of and dependence on the synthetic opioid analgesic OxyContin, a proprietary sustained-release formulation of oxycodone, is rapidly spreading. The changing profile of heroin users, and the phenomenon of OxyContin abuse, both demonstrate that legal opioids can be and are being abused. This fact underscores the need for vigilance among all doctors, and for use of appropriate therapeutic interventions by trained experts.

Editor's note:-

According to the 101st edition of the Singapore Index of Medical Specialties (MIMS, published in 2005 by CMPMedical Asia Pte Ltd), Subutex 2 mg tablets cost $5.33 each, and Subutex 4 mg tablets cost $16.00 each. Schering-Plough also manufactures an older version (Temgesic) of sublingual buprenorphine. Temgesic 10 mg tablets cost $0.59 each, and Temgesic 30 mg tablets cost $1.63 each.

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