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The extent of diversion of fentanyl for non-medical purposes in Australia: What do we know?

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THE EXTENT OF DIVERSION OF FENTANYL FOR NON-MEDICAL PURPOSES IN AUSTRALIA: WHAT DO WE KNOW?

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TABLE OF CONTENTS

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EXECUTIVE SUMMARY

Background:

Fentanyl is a potent synthetically produced opioid agonist with an important role in the treatment of strong chronic pain, such as cancer pain. However, the drug does carry the risk of fatal opioid overdose if used inappropriately. In Australia, the most common forms of commercially available fentanyl include a transdermal patch, a lozenge or injection.

Small numbers of fentanyl overdose deaths have occurred from medically prescribed fentanyl patches, usually when the medication was not used as prescribed, or was used by someone other than to whom it had been prescribed. In the United States prior to 1996, reports of fentanyl abuse through the Drug Abuse Warning Network were typically low, although increases in fentanyl emergency department mentions and fentanyl-related deaths were reported by 2002 and 2003.

Clandestinely produced fentanyl, though currently generating some concern in the United States, is not a new phenomenon. Fentanyl and several potent analogues have been produced and sold as "synthetic heroin" at least as early as 1979. Deaths involving clandestinely produced fentanyl have been reported since then from the United States, Sweden, the Ukraine, Russia, and Denmark. The most recent report is a series of 272 fentanyl overdose deaths in Detroit, Chicago and New Jersey occurring over a period of a few months in the United States (Boddiger 2006). Fentanyl was either sold separately or added to street heroin or cocaine, and laboratories producing fentanyl have been discovered in both the United States and Mexico.

Triggered by this most recent report of US fentanyl fatalities, this report considers the likelihood of fentanyl misuse by Australian injecting drug users (IDU). We aim to present a summary of what is known about the extent of diversion and clandestine production of fentanyl among IDU, and any harms associated with its use in this context.

Method:

Data sources consulted included: fentanyl prescription data from the Australian Government Department of Health and Ageing; the Illicit Drug Reporting System (IDRS); the Australian Needle and Syringe Program (NSP) survey; and the National Coroners Information System (NCIS).

Results:

Low numbers of transdermal fentanyl have been prescribed in Australia since the drug was listed on the Pharmaceutical Benefits Scheme (PBS) in 1999, with only gradual increases over time.

There were no mentions of fentanyl use by the injecting drug users interviewed as a part of the 2005 IDRS or NSP surveys. There were also no mentions of fentanyl diversion or misuse by the key informants in the 2005 IDRS.

Since 2004, two fentanyl-related deaths have been recorded in the NCIS. The first was a case of acute fentanyl overdose in an ambulance officer who died after injecting a vial of fentanyl intranasal spray, presumably obtained from his workplace. The second fatality had limited information available, but fentanyl was detected at lethal levels in post-mortem toxicology in addition to other drugs in toxic concentrations.

Conclusions:

Despite recent reports of a number of deaths in the United States involving clandestinely produced fentanyl (Boddiger 2006), diverted or clandestinely produced fentanyl does not yet appear to pose a major threat to IDU in Australia. Fentanyl continues to have an important use in the treatment of chronic pain, and this must not be put under threat by, as yet, unfounded concerns of fentanyl misuse in Australia. However, drug markets are dynamic, and continued monitoring of the harms associated with injecting drug use, as well as drug use patterns among sentinel groups of IDU, is essential.

1. INTRODUCTION

Fentanyl is a synthetically produced opioid agonist and is one of the most potent opioids in medical use; it is estimated to be 100 times more potent than morphine (Gutstein and Akil 2006). Fentanyl is also used to treat cancer pain and other forms of chronic pain that cannot be managed by less potent treatments, among people who are tolerant to the effects of opioids (Marier, Lor et al. 2006).

Used as prescribed, fentanyl serves an important role. For instance, cancer pain can be severe and ongoing, but is sometimes punctuated by transient increases in pain intensity, termed "breakthrough pain" (Zeppetella and Ribeiro 2006). Untreated breakthrough pain contributes to impaired functioning and psychological distress (Portenoy, Payne et al. 1999), so its effective treatment is essential for the comfort and wellbeing of people suffering chronic pain. So far, fentanyl is the only opioid that has been shown to be effective by systematic review for the management of breakthrough cancer pain (Zeppetella and Ribeiro 2006).

Due to its high potency, fentanyl is potentially fatal at very low doses that can be difficult to detect by standard toxin screening tests (Kramer and Tawney 1998). When fentanyl was first introduced in Europe in the 1960s and the United States in the 1970s, indications for its use included the relief of postoperative pain (Smialek, Levine et al. 1994). These labelling instructions were revised in the US after several deaths involving fentanyl use after minor operations, and fentanyl is no longer indicated for this purpose (McCarthy 1994).

In Australia, fentanyl is available in a number of different preparations, including: Durogesic® (transdermal patch), Actiq® (lozenge), Sublimaze® (injection), or in combination with anaesthetic drugs. All fentanyl preparations are only available under the highest level of restrictions (Schedule 8). Fentanyl transdermal patches were registered in Australia in 1997 for the management of chronic cancer pain requiring opioid analgesia, and in 1999 the patches were listed on the PBS for this indication. In 2006 the PBS listing was expanded to include treatment of chronic pain of all causes (National Prescribing Service 2006).

As with many strong opioids, we need to balance the need for effective analgesia against the risks of diversion and non-prescribed use. Fentanyl has a euphoric effect and this has

led to generally isolated cases of misuse of fentanyl obtained through employment, such as anaesthesiology (Berens, Voets et al. 1996; Gold, Melker et al. 2006). A more concerning development is clandestine production of fentanyl which has been most recently reported in the United States and Europe (Boddiger 2006). These reports have sparked concerns about the possible misuse of fentanyl among injecting drug users (IDU) in Australia. This report aims to summarise the literature on the risks of diverted and clandestinely manufactured fentanyl, and consider the likelihood of fentanyl misuse by Australian IDU.

1.1 Fentanyl diversion

Prescription medications can be "diverted" from the normal drug distribution system when individuals obtain medication inappropriately through their profession (e.g. healthcare professionals), when individuals use their own prescribed medication recreationally for a non-medically intended purpose, or when individuals use medication prescribed to another person (Fudala and Johnson 2006). Opioid analgesics may be obtained from a number of sources including medication theft, purchase through patients or the internet, prescription forgery or obtaining a number of prescriptions from several doctors or "doctor shopping" (Joranson and Gilson 2006).

Diverted opioid analgesics can be used for intoxication, to relieve the effects of opiate withdrawal, as a substitute for illicit heroin, or as a form of treatment for heroin dependence where other pharmacotherapies such as methadone or buprenorphine are less available (Degenhardt, Black et al. 2006). Diversion of opioid analgesics is likely to be influenced by a number of different factors, including the availability of heroin and other 'desirable opioids', jurisdictional prescribing policies (Degenhardt, Black et al. 2006), availability of the diverted medication and marketing from the pharmaceutical company.

In 2004, the United States Food and Drug Administration (FDA) objected to advertising claims made by the manufacturer of fentanyl patches that they had a lower abuse potential than other opioid products. The FDA stated that while there were fewer mentions of fentanyl abuse by the Drug Abuse Warning Network in comparison to other opioid products, this was most likely to be due to the fact that fentanyl patches were not as widely prescribed as other fentanyl products, rather than being indicative of the abuse potential of the patches per se. (Medscape Medical News 2004). After continued reports of adverse events, both the United States FDA and Health Canada reiterated warnings

concerning the risks of inappropriate use of fentanyl patches (World Health Organisation 2005b; World Health Organisation 2005a).

There is some evidence to suggest that fentanyl is not a preferred opioid by American IDU. Butler and colleagues developed the Opioid Attractiveness Scale (OAS) in order to understand the features of a product that make one preparation more 'attractive' than another to potential abusers (Butler, Benoit et al. 2006). 'Attractiveness' is likely to be affected by: (i) positive features of the drug preparation (e.g. speed of onset, duration of effect, extractability); (ii) negative features of the preparation (e.g. presence of impurities, antagonist combination, messiness); and (iii) extrinsic factors such as the availability, availability of alternatives, cost, and social stigma of use. The authors used the OAS to measure the 'attractiveness' of 14 opioid analgesic products.[1] OxyContin® (oxycodone) was considered the most attractive of the products rated, Durogesic® (fentanyl reservoir patch) was considered the least attractive and Actiq® (fentanyl lozenge) was rated approximately half way between the two extremes in terms of attractiveness (Butler, Benoit et al. 2006). It should be noted that this study received unspecified support from Janssen Pharmaceutica Inc., the company involved in the production of Durogesic®.

1.1.1 Deaths attributed to diverted fentanyl

Small numbers of fentanyl overdose deaths have occurred from medically prescribed fentanyl patches, usually when the medication was not used as prescribed, or was used by someone other than to whom it had been prescribed. Fentanyl patches have been misused by applying more than one patch at the one time, applying heat to the patch (so speeding up drug release), chewing the patch, using a discarded patch, and/or extracting fentanyl from the patch for the purposes of injecting, ingesting or inhaling (Flannagan, Butts et al. 1996; Arvanitis and Satonik 2002; Reeves and Ginifer 2002; Liappas, Dimopoulos et al. 2004; Lilleng, Mehlum et al. 2004). Other deaths have occurred when fentanyl was used to control less severe or postoperative pain, or in children or adolescents (McCarthy 1994) (Raymond and Morawiecka 2004).

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[1] Vicodin® (hydrocodone), OxyContin® (oxycodone), TalwinNX® (pentazocine-naloxone), MS Contin® (morphine), Methadone, Dilaudid® (hydromorphone), Actiq® (fentanyl), Avinza® (morphine), Kadian® (morphine), Percocet® (oxycodone), Suboxone® (buprenorphine-naloxone), Fentanyl matrix patch®, Stadol Nasal Spray® (butorphanol), and Durogesic® (fentanyl reservoir patch).

During the period 1990 to 1996, the United States recorded a 1168% increase in the prescription use of fentanyl. At the same time, there was a 59% decrease in reports of fentanyl abuse on the Drug Abuse Warning Network (DAWN) databases. Abuse mentions for fentanyl were typically less than 200 cases per year and accounted for a small proportion of drugs of abuse monitored by the DAWN system. Abuse mentions remained low and stable throughout this period, despite the increasing medical use of fentanyl (Joranson, Ryan et al. 2000). In 2002, the situation was markedly different: emergency department mentions for fentanyl increased more than 50-fold from 1994 to 2002, while the number of fentanyl prescriptions increased only 7.2-fold during the same period (Compton and Volkow 2006).

In Virginia (US), in particular, there were increasing reports of fentanyl-related deaths in 2002 and 2003. Of the 23 deaths reported from 2002, 19 were attributed to the misuse of fentanyl transdermal patches. This area of the US is also known for high levels of oxycodone and methadone abuse and the US authors suggest that fentanyl may also be becoming more desirable among opioid users (Kuhlman, McCaulley et al. 2003).

1.2 Deaths attributed to clandestinely produced fentanyl

Despite concern generated by the most recent reports of fatalities from clandestinely produced fentanyl (Boddiger 2006), this is not a new phenomenon. Fentanyl has been clandestinely manufactured and sold as "synthetic heroin" or "China White" as early as 1979 (Henderson 1991). These compounds can include several illicit fentanyl analogues including α-methylfentanyl and 3-methylfentanyl, the latter of which is even more potent than fentanyl and has been estimated to be 6,000 times as potent as morphine (Berens, Voets et al. 1996). While clandestine production of fentanyl is difficult, it is possible with an experienced chemist. This form of fentanyl is generally a white or greenish powder (J.Maxwell, personal communication, August 2006).

Between 1980 and 1988, 112 coronial cases involving fentanyl as a suspected cause of death were identified from post-mortem toxicology samples sent to a Californian laboratory. While this was not a random sample of toxicology reports, fentanyl death cases were distributed over 44 cities in California and some neighbouring states. Less than 2% of the fentanyl deaths were from the larger cities, Los Angeles and San Francisco, cities that accounted for 30% of heroin-related deaths over the eight year period (Henderson 1991). The demographic profile of individuals who had died from

fentanyl was very similar to the profile for persons entering heroin-dependence treatment in California. The fentanyl involved in the majority of these cases was thought to be clandestinely manufactured as it was commonly contaminated with benzylfentanyl, a precursor used in illicit fentanyl synthesis (Henderson 1991). Bronchopneumonia or aspiration of stomach contents was not commonly found, indicating that the fentanyl deaths occurred rapidly.

In 1994 and 1995, nine fentanyl-related deaths were reported in Sweden in a 16-month period among substance-dependent people. The drug samples in these cases included fentanyl as an additive in low concentration amphetamine powders with caffeine, phenazone and sugar as cutting agents. Seven of these deaths were from acute fentanyl toxicity and the fentanyl powder mixtures were thought to be clandestinely produced (Kronstrand, Druid et al. 1997).

A lab producing clandestine fentanyl was discovered in Belgium in 1995 when the manufacturer experienced production problems and presented at hospital suffering from fentanyl withdrawal and extreme agitation. In this case, fentanyl was taken as an oral liquid (Berens, Voets et al. 1996). Reports of fentanyl-related deaths have also come from the Ukraine, Russia, and Denmark (The Drug Enforcement Administration 2006).

There were also deaths occurring in the 1990s in the US, with 30 deaths where fentanyl was detected post-mortem being reported in Maryland over a three month period. Twenty-five of these deaths were from the one city, and 28 deaths had drugs other than fentanyl detected post-mortem. All deaths were attributed to alcohol and drug intoxication. Street samples of fentanyl associated with the deaths contained fentanyl hydrochloride with varying degrees of impurities, indicating that the fentanyl was clandestinely produced. Nine individuals were later found guilty of charges relating to the sale and distribution of fentanyl (Smialek, Levine et al. 1994).

In late 2005, the United States authorities began to notice an increase in opioid overdose deaths involving fentanyl. The deaths appeared localised to several cities; including 130 fentanyl overdose deaths in Detroit and 100 in Chicago over a period of a few months, and 42 in one weekend in New Jersey. These deaths involved fentanyl that appears to have been clandestinely produced, and either sold separately or added to street heroin or cocaine. The size of the problem caused pressure on ambulance services, having to attend to multiple overdoses in the same location (Boddiger 2006). The numerous

incidents pointed to the rapid and widespread introduction of fentanyl into the heroin market in several US states, and the publication of the report in The Lancet drew significant attention.

The DEA discovered one laboratory producing fentanyl in Mexico in May 2006, and five have been discovered in the US since 2000 (The Drug Enforcement Administration 2006). The most recent US fentanyl laboratory discovery in late 2005 was producing fentanyl in both powder and tablet form. Some tablets were green and were small replicas of OxyContin tablets, and others contained a combination of MDA, fentanyl and caffeine (The Drug Enforcement Administration 2006). There is some speculation in the US that fentanyl is being added to heroin to increase the opioid effect, and there are reports of opioid-dependent people seeking out the drug specifically (J. Maxwell, personal communication, August 2006).

1.3 Concerns regarding fentanyl abuse in Australia

While the report of the recent series of US fentanyl fatalities (Boddiger 2006) has generated some concern, these concerns are best placed in the light of the existing data. Fentanyl has important and legitimate medical uses (Zeppetella and Ribeiro 2006) so we must first be aware of the size of the problem of diverted and clandestinely produced fentanyl in Australia before declaring fentanyl a threat in this country.

Australia is fortunate to have existing drug monitoring systems that have been running, at least in NSW, for over a decade (Stafford, Degenhardt et al. 2006). These monitoring systems are able to provide data from IDU and those people who work closely with them. Another important monitoring system is the National Coroners Information System (NCIS), a database containing the majority of coronial cases occurring since 2000.

1.4 Aims of this study

In this paper, our general aim is to present a summary of what is known about the extent of diversion and clandestine production of fentanyl among IDU, and any harms associated with its use in this context. More specifically, this paper aims to:

1. examine trends in fentanyl prescriptions across Australia;
2. present data from IDU sampled in routine monitoring systems (IDRS and NSP survey);
3. present data from key experts working with IDU on the extent of fentanyl diversion; and
4. present data from the NCIS on fentanyl-related overdoses.

2. METHOD

2.1 Prescription data

Prescription data of fentanyl transdermal preparations from 1999 to 2005 were obtained from the Drug Monitoring System (DRUMS) run by the Australian Government Department of Health and Ageing and the Drug Utilisation Subcommittee (DUSC) of the Pharmaceutical Benefits Advisory Committee. The data is presented from 1999, the year that fentanyl transdermal patches were first listed on the PBS for the management of chronic cancer pain requiring opioid analgesia.

2.2 IDU surveys

There are two Australian studies that routinely monitor illicit drug use and related harms through annual cross-sectional surveys of injecting drug users (IDU): the Illicit Drug Reporting System (IDRS) and the Australian Needle and Syringe Program (NSP) survey. These surveys are conducted each year in all jurisdictions in Australia.

2.2.1 IDRS

The IDRS surveys regular injecting drug users (IDU) in each capital city who are actively engaged in illicit drug markets. The IDU sample is considered a sentinel group of drug users within which emerging trends may be seen before spreading to other groups of drug users. The IDRS also interviews 'key experts' (KE) who have regular contact with IDU (e.g. health professionals) or have knowledge about drug classes, drug manufacturing, or the diversion of drugs (e.g. law enforcement personnel or pharmacists). Each jurisdiction obtains ethics approval to conduct the study from the appropriate ethics committees in their state or territory. Further information about the IDRS methodology has been published elsewhere (Stafford, Degenhardt et al. 2006). A total of 943 IDU and 274 KEs were surveyed nationally in the 2005 IDRS.

2.2.2 NSP survey

The Australian NSP survey forms the basis of human immunodeficiency virus (HIV) and hepatitis C surveillance among IDU in Australia (National Centre in HIV Epidemiology and Clinical Research 2006). It is an annual national survey of all clients attending selected NSPs during the designated survey week. All NSP clients are asked to complete

a brief, anonymous questionnaire and to provide a capillary blood sample for HIV and hepatitis C virus (HCV) antibody testing. The questionnaire includes a range of demographic characteristics and behavioural data, including IDU reports of the 'last drug injected'. More information on the Australian NSP survey methodology and questionnaire can be found in the National Data Report 2001–2005 (National Centre in HIV Epidemiology and Clinical Research 2006). In 2005, 1,800 IDU completed the survey.

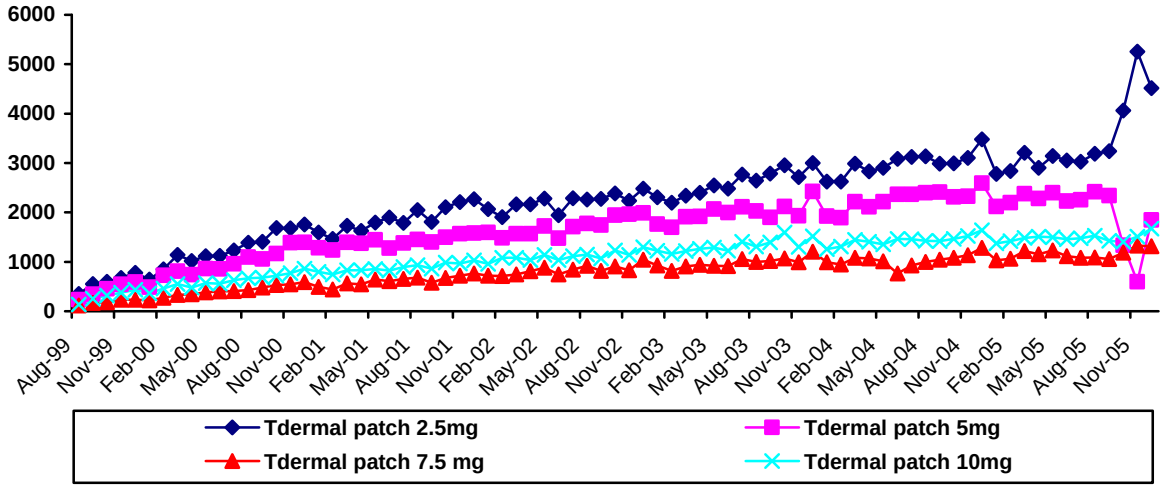
2.3 Coronial data

The National Coroners Information System (NCIS) is a regularly updated electronic database allowing access to all closed coronial cases in Australia. Coronial cases include deaths that are sudden and unexpected, or violent and unnatural. The NCIS is managed by the Monash University National Centre for Coronial Information (MUNCCI). Searches of this system were conducted on 14 September 2006 through the "Coroner's Screen" function, using the keyword "fentanyl" in coronial findings, autopsy, police and toxicology documents. Closed cases from all states from 2004 onwards were searched. These searches were approved by the relevant ethics committees.

3. RESULTS

3.1 Prescription data

Figure 1: Fentanyl scripts by preparation type: private and PBS 1999–2005



Since transdermal fentanyl was first listed on the PBS for the management of chronic cancer pain requiring opioid analgesia in 1999, there have been very low numbers of fentanyl transdermal patches being prescribed. The lowest dose (2.5mg) patch is the most commonly prescribed and in late 2005 it appears that the 2.5mg dose was being prescribed in preference to the 5mg patch.

3.2 IDU reports

Many IDU surveyed for the IDRS report heroin as their drug of choice, and this is the most commonly used opioid in Australia. When heroin is not available IDU tend to switch to other substitutes. The 2005 IDRS IDU sample (n=943) reported using illicitly obtained methadone syrup (24%), physeptone tablets (12%), buprenorphine (18%), and oxycodone (18%) in the six months prior to interview. Forty-four percent of participants reported using morphine, and 14% reported using 'other opioids' (including opium, codeine, dextropropoxyphene, pethidine, tramadol, Nurofen plus, Panadeine forte, and Deloxine) in the six months prior to interview (no distinction was made between licit and illicit methods of procurement for these products). There were no fentanyl mentions among the 2005 IDRS IDU sample.

The 2005 Australian NSP survey sample (1,800 IDU) also reported a range of prescription opioids as the 'last drug injected', including methadone (10%), buprenorphine (2%) and morphine (8%). There were no mentions of fentanyl as the 'last drug injected' among this sample of IDU (National Centre in HIV Epidemiology and Clinical Research 2006).

3.3 KE reports

The 2005 IDRS KEs (n=274) included general practitioners, pharmacists, drug dealers, staff of drug treatment agencies, NSP workers, researchers, user groups, law enforcement staff, youth workers, counselors, emergency workers, and general health workers. KEs did not mention fentanyl diversion or misuse among IDU.

3.4 Searches of coronial data

Searches of coronial cases through the NCIS revealed 90 unique cases recorded since 2004 where fentanyl was mentioned somewhere in the findings, autopsy, police or toxicology documents. All but two of these cases involved fentanyl being used as medically indicated, for the treatment of chronic pain or used in combination with anaesthesia. One of the remaining cases was an ambulance officer who died of acute fentanyl toxicity after injecting the contents of a vial of fentanyl intranasal spray, presumably obtained from his workplace. The second case lacked both findings and autopsy documents, but fentanyl was detected at lethal levels in toxicology in addition to tramadol and venlafaxine in toxic concentrations. Both of these persons were found deceased at home.

4. DISCUSSION

Despite recent reports of a number of deaths in the United States involving clandestinely produced fentanyl (Boddiger 2006), this does not yet appear to pose a major concern in Australia. While the recent reports of fentanyl-related fatalities in the US have generated concern, the review of the literature concerning deaths from diverted and clandestinely produced fentanyl shows this is not a new phenomenon. Limited case series of fentanyl deaths have been reported from a number of North American and European countries from the late 1970s to the present day.

Previous reports have indicated that most misuse of prescription opioid analgesics is by street users and individuals with comorbid psychiatric conditions (Joranson and Gilson 2006), rather than by patients legitimately prescribed opioids for pain treatment. In Australia, there were no mentions of fentanyl use among the groups of IDU sampled in the 2005 IDRS and the 2005 NSP survey. Both IDU samples reported using a range of other prescription opioids, both prescribed and illicitly obtained. None of the KE interviewed for the IDRS mentioned the diversion and misuse of fentanyl as an emerging issue in Australia. Only two deaths where fentanyl was detected as playing a contributing role were reported in the NCIS from 2004 onwards. One was a case of diverted fentanyl and the other case was less clear as it lacked documentation. Neither case showed evidence of clandestinely produced fentanyl.

Fentanyl continues to have an effective and legitimate use in the treatment of cancer pain, breakthrough cancer pain and non-cancer-related chronic pain (Portenoy, Payne et al. 1999; Zeppetella and Ribeiro 2006). These indications, in properly selected patients, must not be put under threat by, as yet, unfounded concerns of fentanyl misuse in Australia.

Within the current context, and given the data presented on fentanyl in Australia, we feel that publication of material emphasising the risks or abuse liability of fentanyl (apart from that required by a prescribing doctor or the dispensing pharmacist as a part of routine clinical practice) is unwarranted. It has been observed by the Chicago police that publicising 'news alert' information concerning the presence of fentanyl on the streets had an appealing effect among IDU (The Drug Enforcement Administration 2006), so this approach should be avoided or used with great caution in Australia.

An effective public health approach to monitoring and responding to diversion and abuse of prescription opioids is warrented Such an approach would include routine monitoring of patterns of drug use and harms, guidelines/training regarding risk management for prescribers, and interventions targeting individuals who misuse prescription opioids. Effective targeting of interventions requires information about why prescription controlled drugs are misused, how they are diverted and who diverts them (Joranson and Gilson 2006). More research is needed in this area.

4.1 Conclusions

At the present time, diverted or clandestinely produced fentanyl does not appear to pose a major threat to IDU in Australia. Nevertheless, drug markets are dynamic, and illicit drug markets in Australia have undergone marked changes over the past five years (Day, Degenhardt et al. 2004; Roxburgh, Degenhardt et al. 2004; Degenhardt, Day et al. 2005). Continued monitoring of the harms associated with injecting drug use, as well as drug use patterns among sentinel groups of IDU, is essential. Both the IDRS and the National Illicit Drug Indicators Project (a national project that monitors routine data sources for drug-related harms) are important sources of information for detecting emerging trends, and patterns of harm over time.

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