

Substance Use Disorders, Chronic Disease & Medication Safety



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Quality use of Medicines (QUM)



QUM: National Strategy Definitions

- Selecting management options wisely: consider “role” for medicines vs other options
- Choosing suitable Medicines (if medicine is necessary): disease, individual, risk vs benefit, cost etc
- Using Medicines Safely & Effectively: monitoring outcomes, minimise “misuse” etc

Example: Risk Evaluation & Monitoring System
(REMS)

Approved Risk Evaluation and Mitigation Strategies (REMS)

The Food and Drug Administration Amendments Act of 2007 gave FDA the authority to require a Risk Evaluation and Mitigation Strategy (REMS) from manufacturers to ensure that the benefits of a drug or biological product outweigh its risks. The table below provides a list of REMS that have been approved by FDA....

ADR & ADE : Definitions



- **Side Effects:** *unwanted but anticipated problems occurring in addition to a drug's therapeutic effects; usually dose related e.g. opioid induced constipation*
- **Toxicity:** *degree to which a drug (any dose) can cause harm humans/animals; acute/chronic e.g. chemotherapy*
- **Adverse Drug Reactions:** *any harmful reaction related to use of drug, need stop drug/treatment etc. (Ref: WHO Adverse Reaction Terminology & ICD)*
- **Adverse Drug Events:** *harm caused by the use of a drug e.g.. Adverse drug reactions, OD, medication errors, etc*

***An ADR requires causal link between drug & event**

ADE's & ADR's: Prevalence



ADR's :

~5% hospital admissions

~ 5% inpatient episodes (daily)

0.4% GP attendances

1:1000 hospital deaths

~ 50% “***preventable***”

*(Aust Qual Health Care Study : Day R, '95; Improving Med Safety Aust : '02
DoHA; Austr MRPs in Pharmacoepi: '04, Roughead, E.)*

Risks for an ADR



- Increased age
- Polypharmacy
- Comorbidity
- Past History of ADR
- Pharmacogenetics
- Psychosocial factors (*borrow, swop & sharing meds, > older, NESB, etc*)

Why Report an ADE/ADR ?



- Our job to look after patients
- To avoid risk of recurrence (RED Alert Card)
- Document event for future reference
(eg. re-exposure and outcomes)
- To better “monitor” in hospital drug related complications
(e.g. process/batch/prescriber errors etc)
- To add to drug knowledge database:
Pharmacoepidemiology & Pharmacovigilance

Substance Abuse Definitions



- ***Substance Use Disorder*** (ICD : WHO) & ***Substance Abuse*** (DSM IV) = drug use + problems.
- ***Tolerance*** = more drug to get same effect
- ***Substance Dependence*** = Daily physical need for the drug = homeostasis (*neuroadaptation*)
- ***Addiction*** = Dependent/compulsive use despite harm.
- ***Withdrawal*** = Illness after stopping Dependent use (*neuroadaptation reversal*)
- ***Intoxication*** = Impairment associated with high dosage

Neurobiology of Addiction

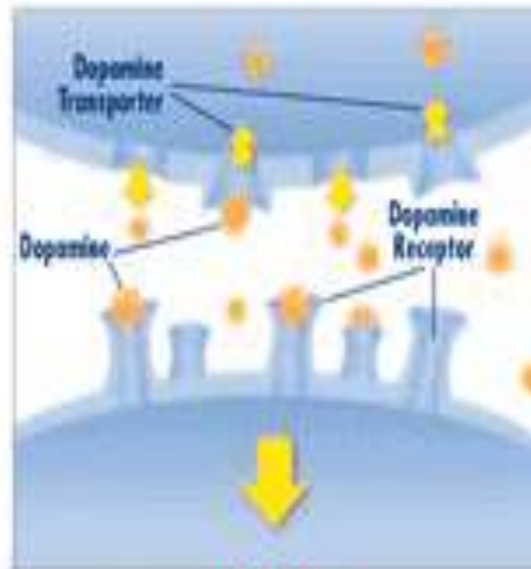
ALL DRUGS OF ABUSE TARGET THE BRAIN'S PLEASURE CENTER

Brain reward (dopamine) pathways

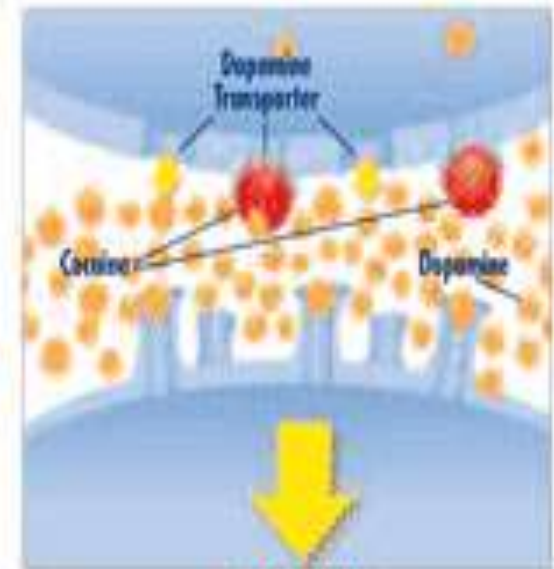


These brain circuits are important for natural rewards such as food, music, and art.

All drugs of abuse increase dopamine



FOOD



COCAINE

Typically, dopamine increases in response to natural rewards such as food. When cocaine is taken, dopamine increases are exaggerated, and communication is altered.

ADDICTION: a chronic disease



The New Science of Addiction: Genetics and the Brain

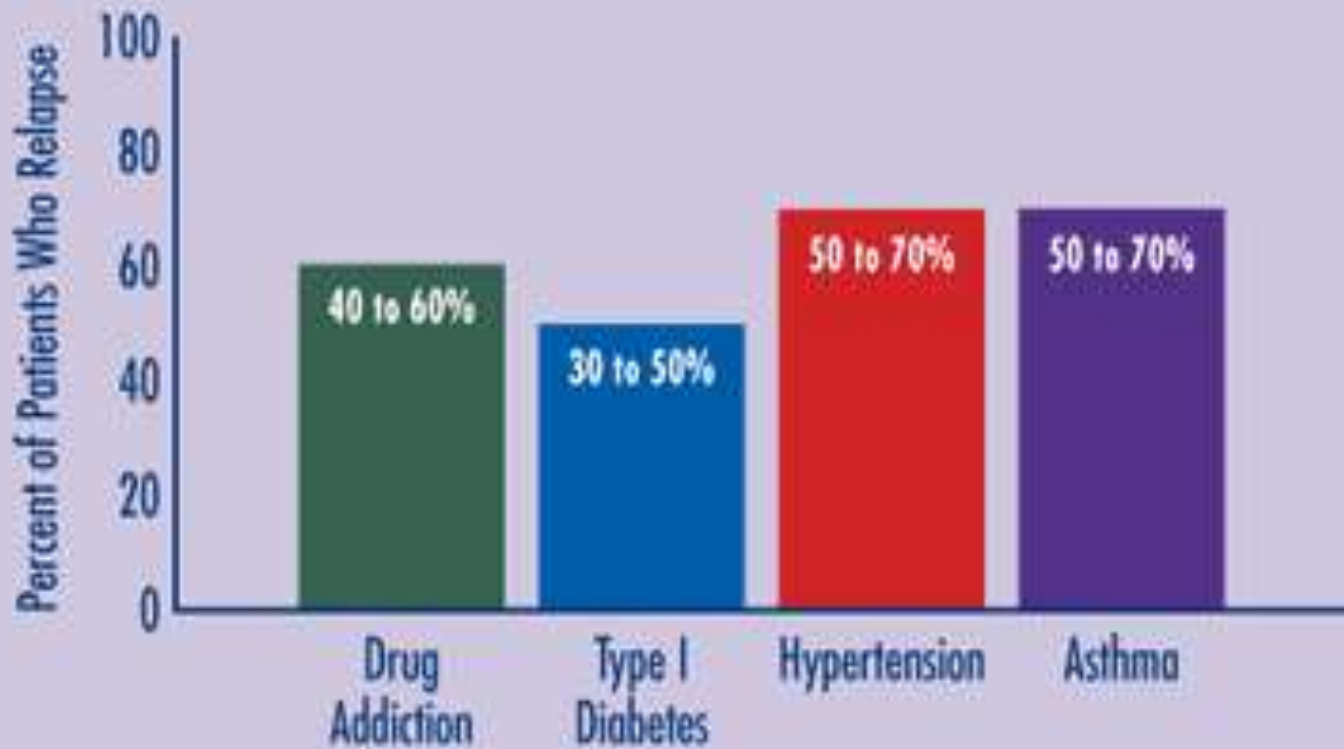
Drug addiction is a chronic disease



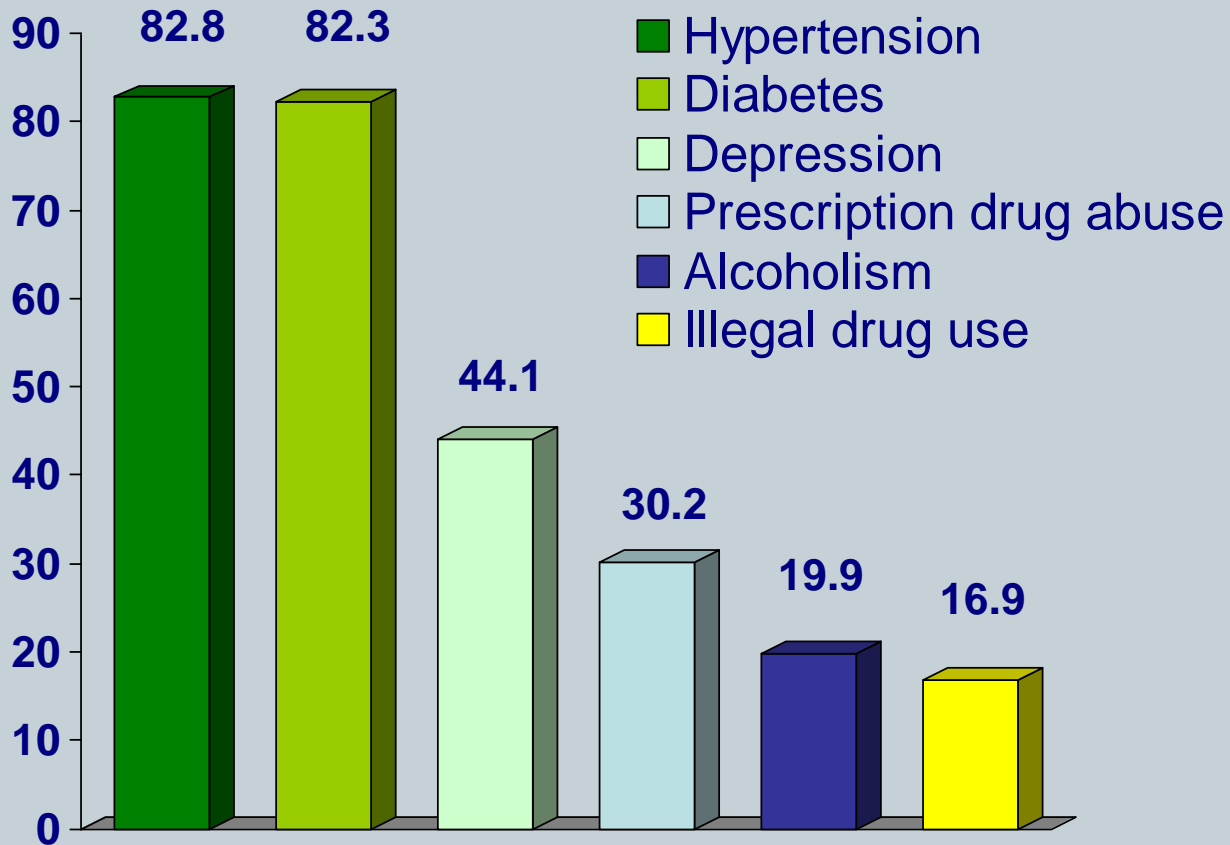
Chronic Disease & “Relapse”



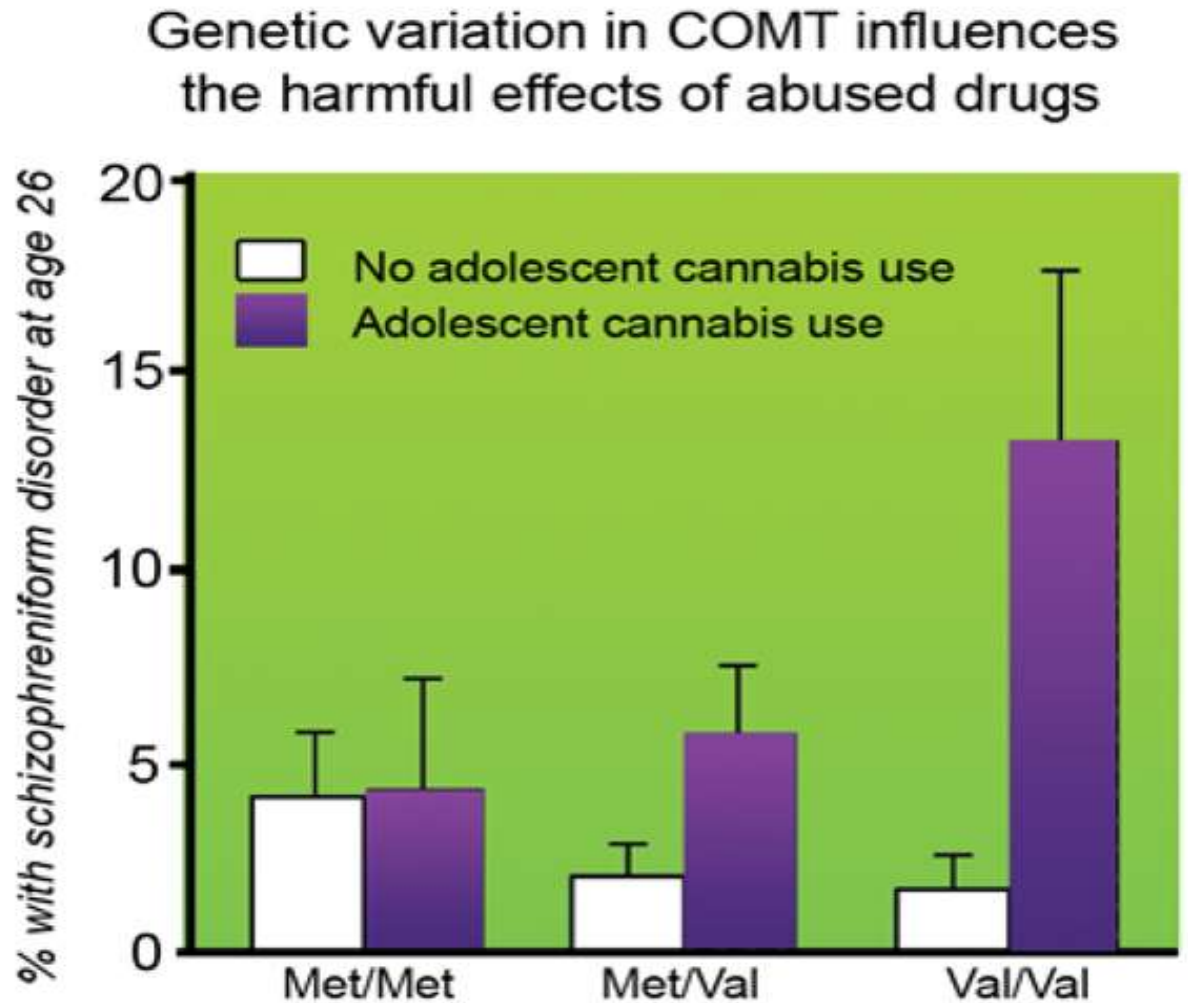
COMPARISON OF RELAPSE RATES BETWEEN DRUG ADDICTION AND OTHER CHRONIC ILLNESSES



GP “confidence” to treat

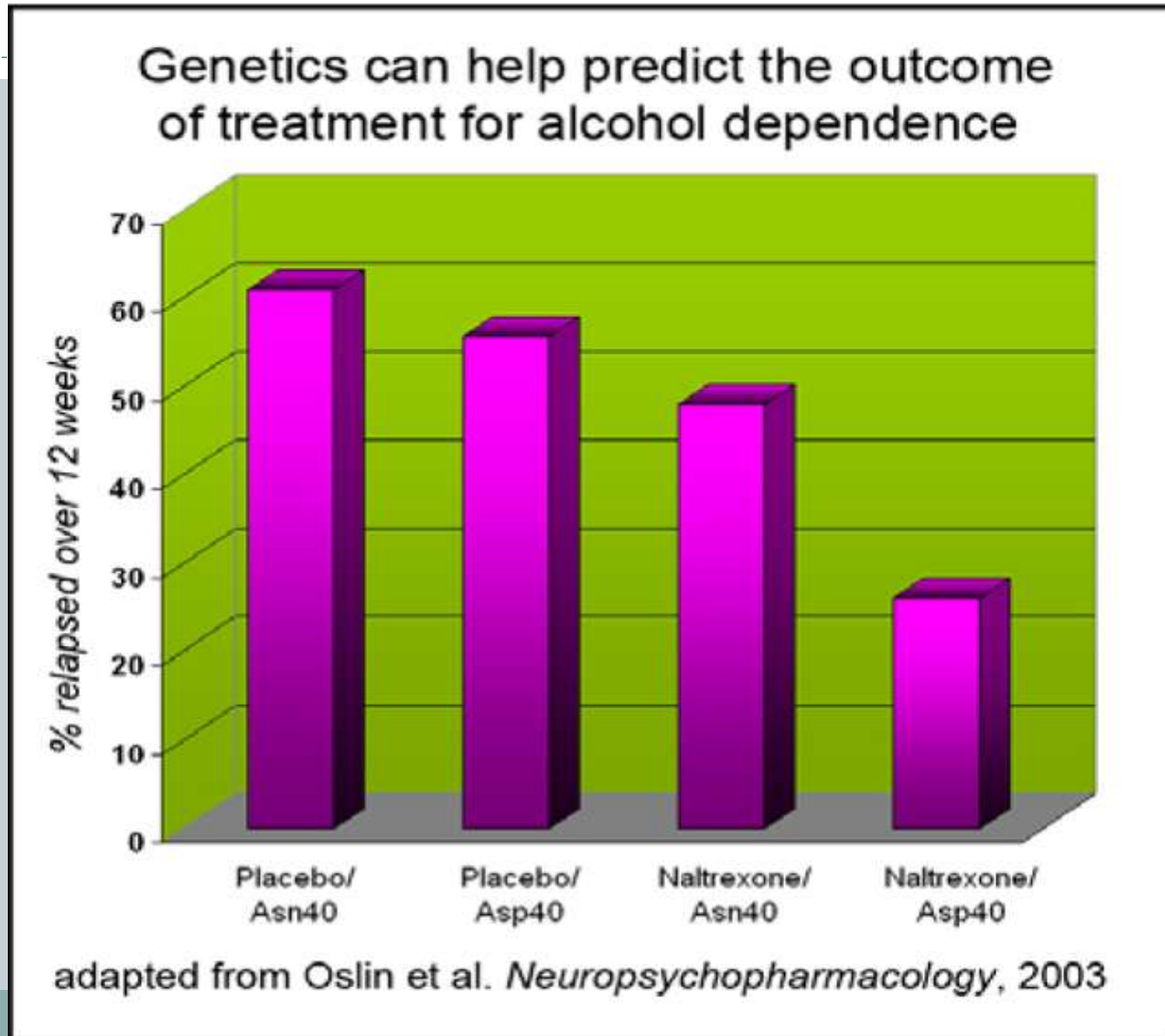


Genes & vulnerability...

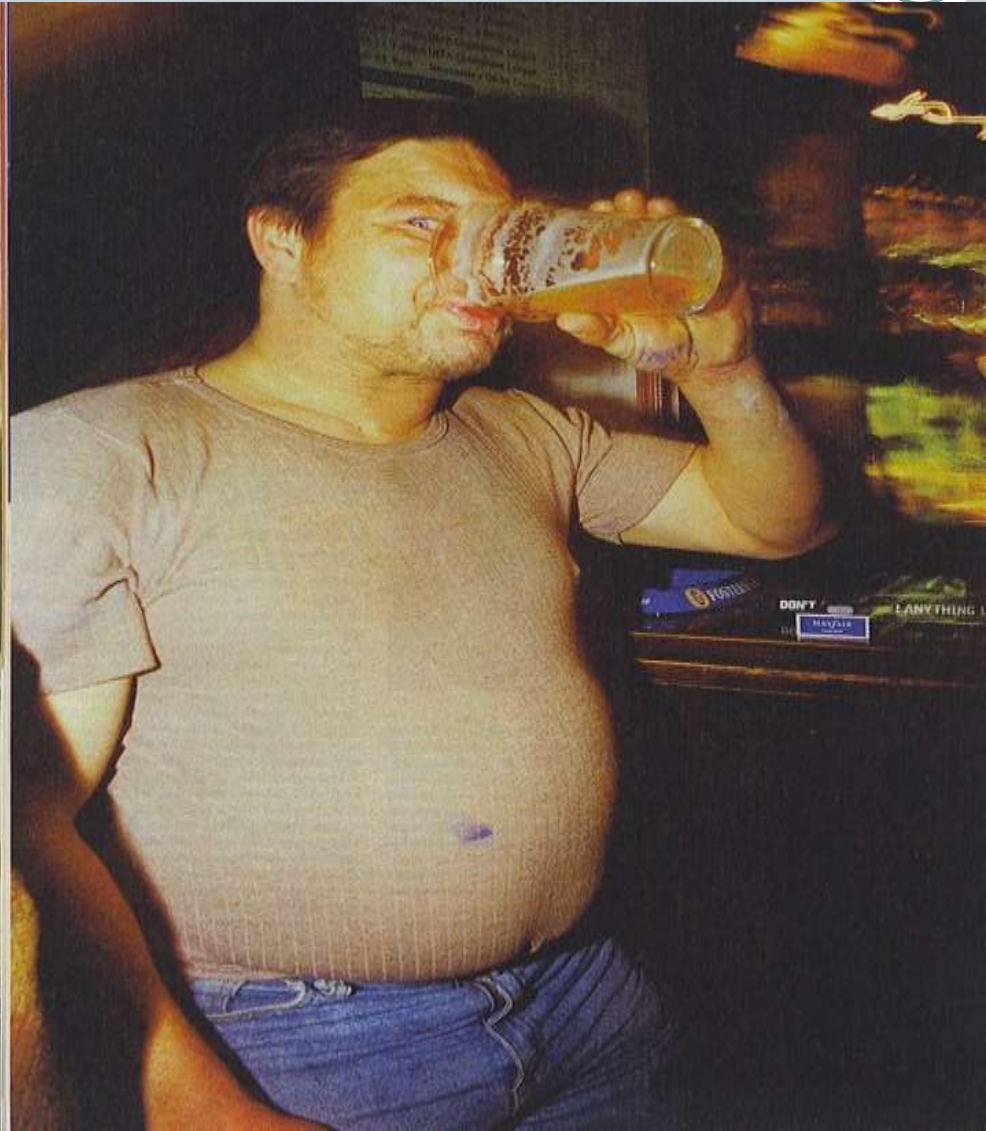


adapted from Caspi et.al. *Biol. Psych*, May 2005.

Genes & Treatment Response...



Co-morbidity: genes + environment



Chronic
cardiovascular,
liver, renal and
airways disease
(*Metabolic Syndrome*)

Increased Opioids Prescribing in Australia...

Health Care

Australian trends in opioid prescribing for chronic non-cancer pain, 1986-1996

James R Bell

There is evidence that the use of opioids is increasing worldwide,¹ and the increasing use of slow release morphine in Queensland has recently been reported.² In recent years there has been a cautious reappraisal of the role of opioids in chronic non-cancer pain.^{3,4} A recent survey of members of the Australian Pain Society found that 85% of respondents felt that opioid drugs could be used in patients with chronic pain.⁵ However, it is well recognised that benefits of opioid use in terms of improved pain control and sense of well-being need to be weighed against the risk of an increase in drug dependence.

The aims of this study were to describe trends in opioid prescribing for chronic non-cancer pain, to investigate whether a person who begins taking oral opioids regularly will continue to do so in the long-term, and to assess the extent to which opioid treatment is associated with dose escalation over time.

Methods

Three data sources were used:

- Records from the Commonwealth Department of Health, Housing and Community Services. This organisation maintains records of drugs consumed in each State, and officers of the department provided data on national and State consumption of Schedule 8 (S8) opioid drugs for the years 1984-1995. Figures on oral opioid consumption obtained from the Commonwealth give a State by State breakdown on all morphine preparations except morphine mixtures. For the years 1986-1988 use of these morphine mixtures in each State was documented State by State, and NSW accounted for 50%-66% of national consumption; after 1988 only figures for national consumption are available. For the purposes of this study, NSW consumption of morphine mixtures after 1988 was estimated to be 55% of national consumption. By 1995 morphine mixtures accounted for less than 20% of total oral morphine consumption, so inaccuracy in this estimate is unlikely to alter greatly the overall trend in oral morphine use.
- Monthly summaries of authorities to prescribe S8 drugs from the Pharmaceutical Services Branch (PSB) of the NSW Department of Health. It is a legal requirement in

Abstract

Objective: To identify trends in the use of opioid drugs for chronic non-cancer pain.

Design: Review of three sets of official records — the record of Schedule 8 (S8) opioid drugs used in Australia, 1984-1995, from the national Department of Health, Housing and Community Services; New South Wales Department of Health statistical summaries of the number of authorities to prescribe S8 drugs for cancer pain and non-cancer pain for each June from 1990 to 1996, and NSW Department of Health patient records for a cohort of patients first prescribed S8 drugs in 1991.

Main outcome measures: Total quantities of opioids used in Australia; numbers of S8 authorities issued in NSW. Outcome measures for the cohort study were the proportion of patients remaining on opioids long-term, the proportion for whom dose escalated over time, and the diagnoses for which opioids were being prescribed.

Results: Between 1986 and 1995, the amount of oral morphine used in Australia rose from 117 to 578 kg. Use of all other oral S8 opioids combined increased from 93 to 149 kg in NSW, the number of authorities to prescribe for non-cancer pain rose from 3326 in June 1990 to 5743 in June 1996 (73% increase), while cancer pain authorities rose from 2652 to 4631 (82% increase). Sixty-nine of the 102 patients ceased to receive drugs on authority over the five year follow-up. These subjects received opioids for a mean of 19 months. Among the remaining 33 subjects, dose escalation was common. Diagnostic information indicated that many patients had significant psychological and social problems.

Conclusions: There has been a dramatic increase in opioid prescribing, a substantial proportion of which is for non-cancer pain. In a sample of patients being treated for non-cancer pain, long term use and dose escalation occurred in one third of cases.

MJA 1997; 167: 26-29

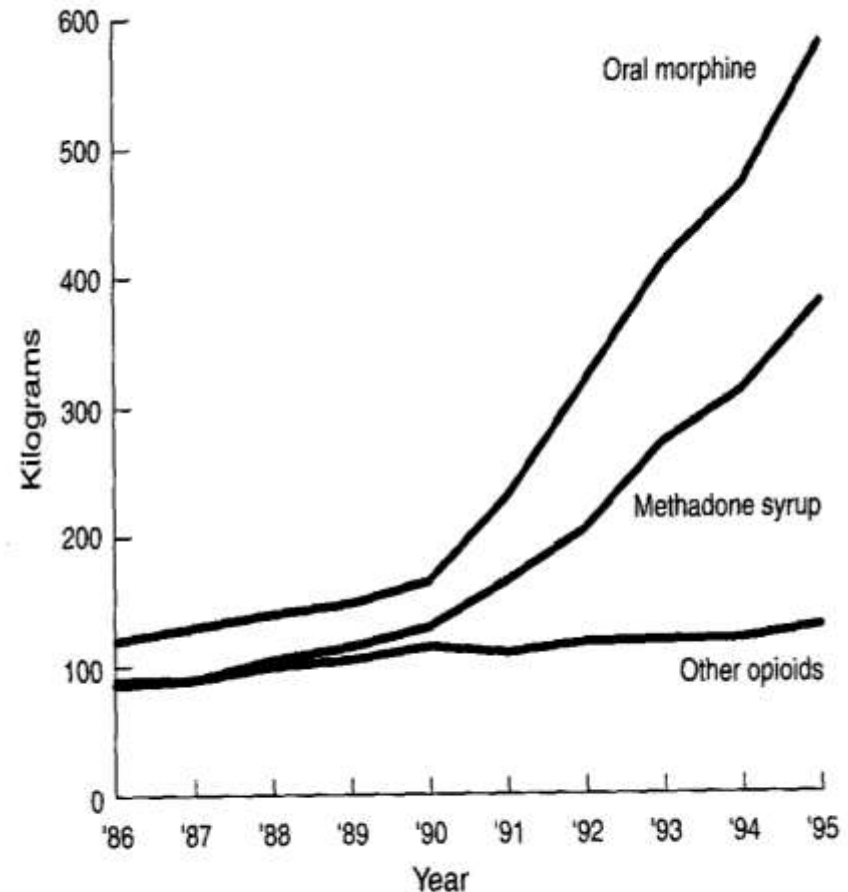
all Australian States that regular prescribing of S8 drugs to any individual patient beyond a certain minimum period requires an authority. The issued authorities specify whether opioids are prescribed for cancer pain or non-cancer pain, and trends in the issuing of authorities provide an indication of whether there has been an increase in prescribing for non-cancer pain. In NSW, the PSB issues these authorities, and since 1990 the department has prepared a monthly summary of all current authorities. Summaries for the month of June each year were used to estimate trends in the point prevalence of authorities to prescribe opioid drugs from 1990 to 1996.

For editorial comment, see page 9; see also page 30

Drugs and Alcohol Unit, Prince of Wales Hospital, Sydney, NSW.

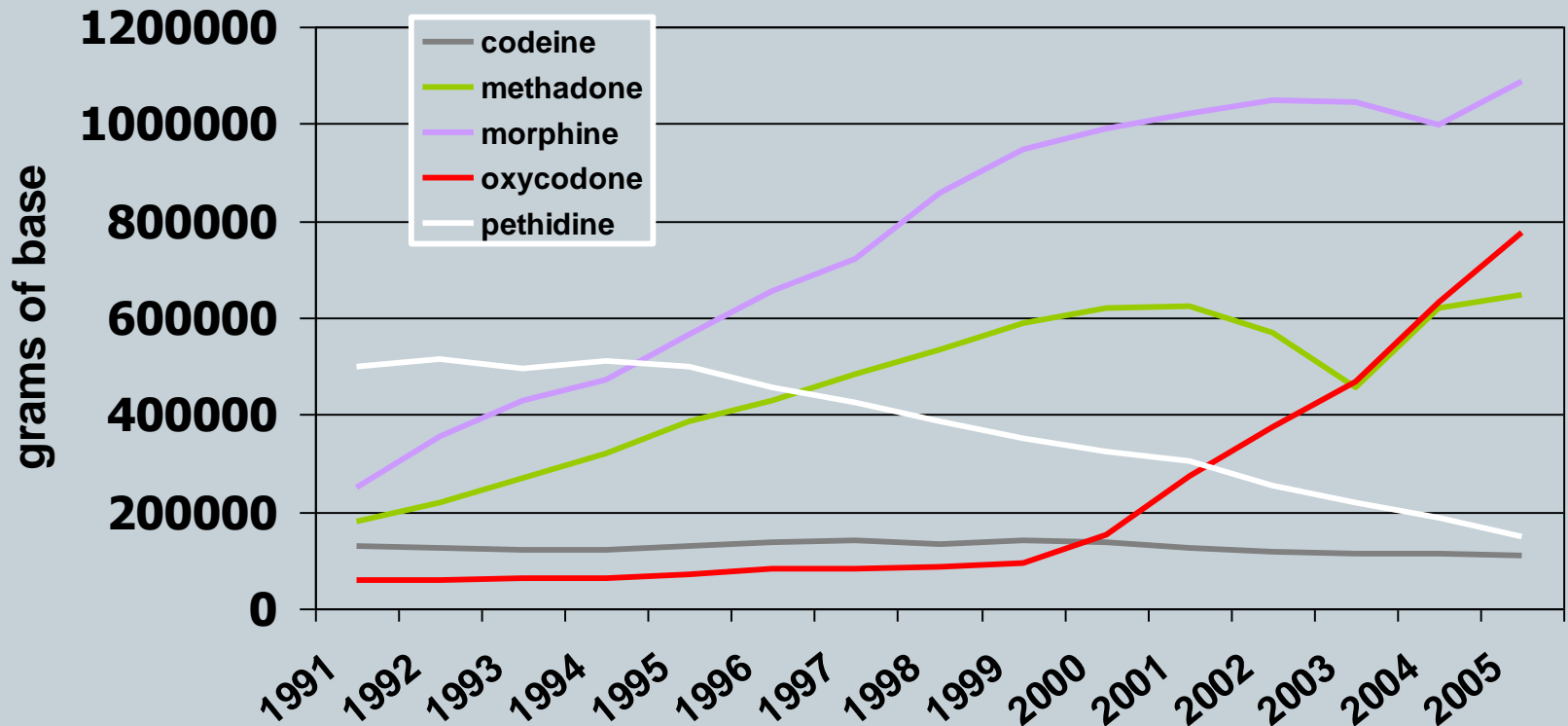
James R Bell, BA, FRACP, Director

No reprints will be available. Correspondence: Dr J R Bell, Drugs and Alcohol Unit, Prince of Wales Hospital, High Street, Randwick, NSW 2031. E-mail: james.bell@nsw.edu.au



Australian consumption of opioids, 1986-1995.

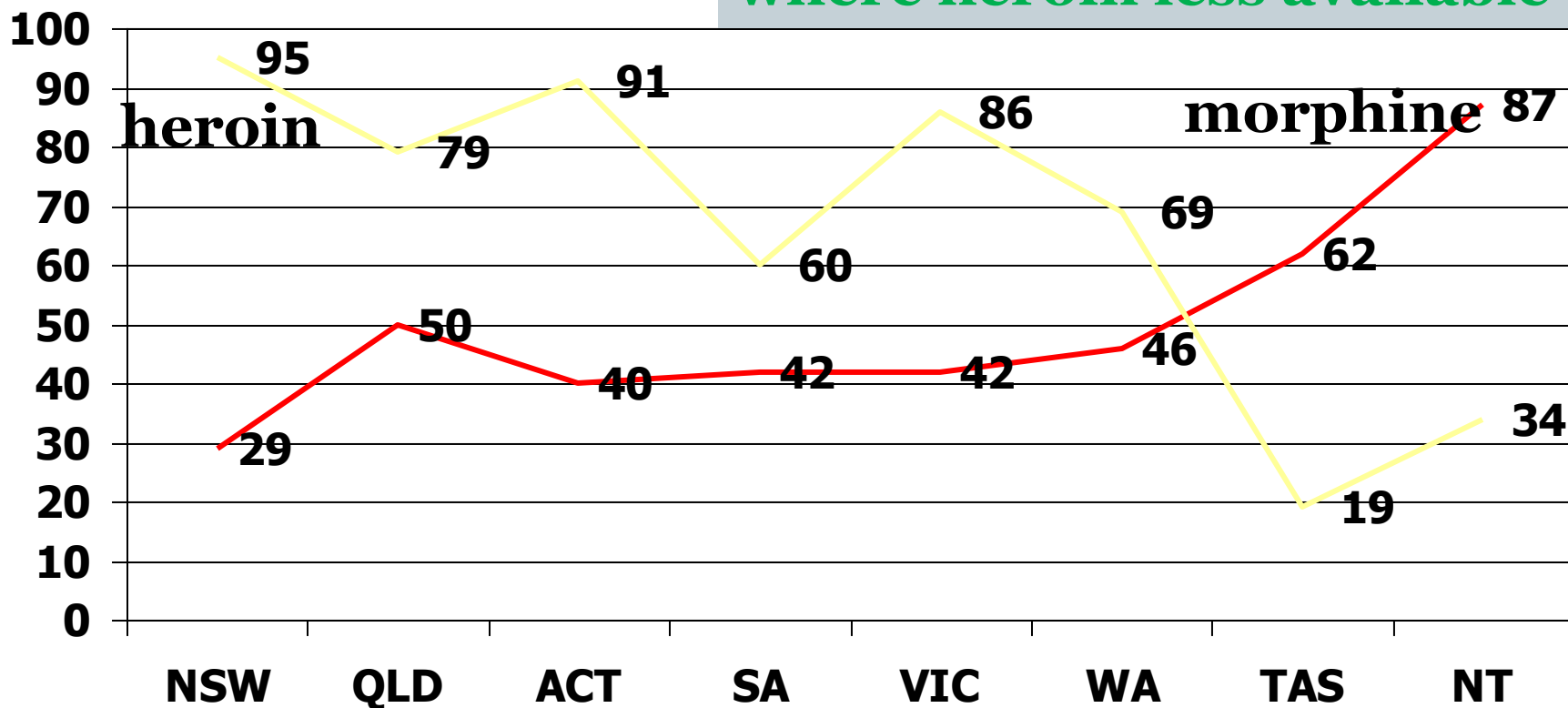
Opioid Supply in Australia



Recent Morphine and Heroin use by jurisdiction: IDRS 2004



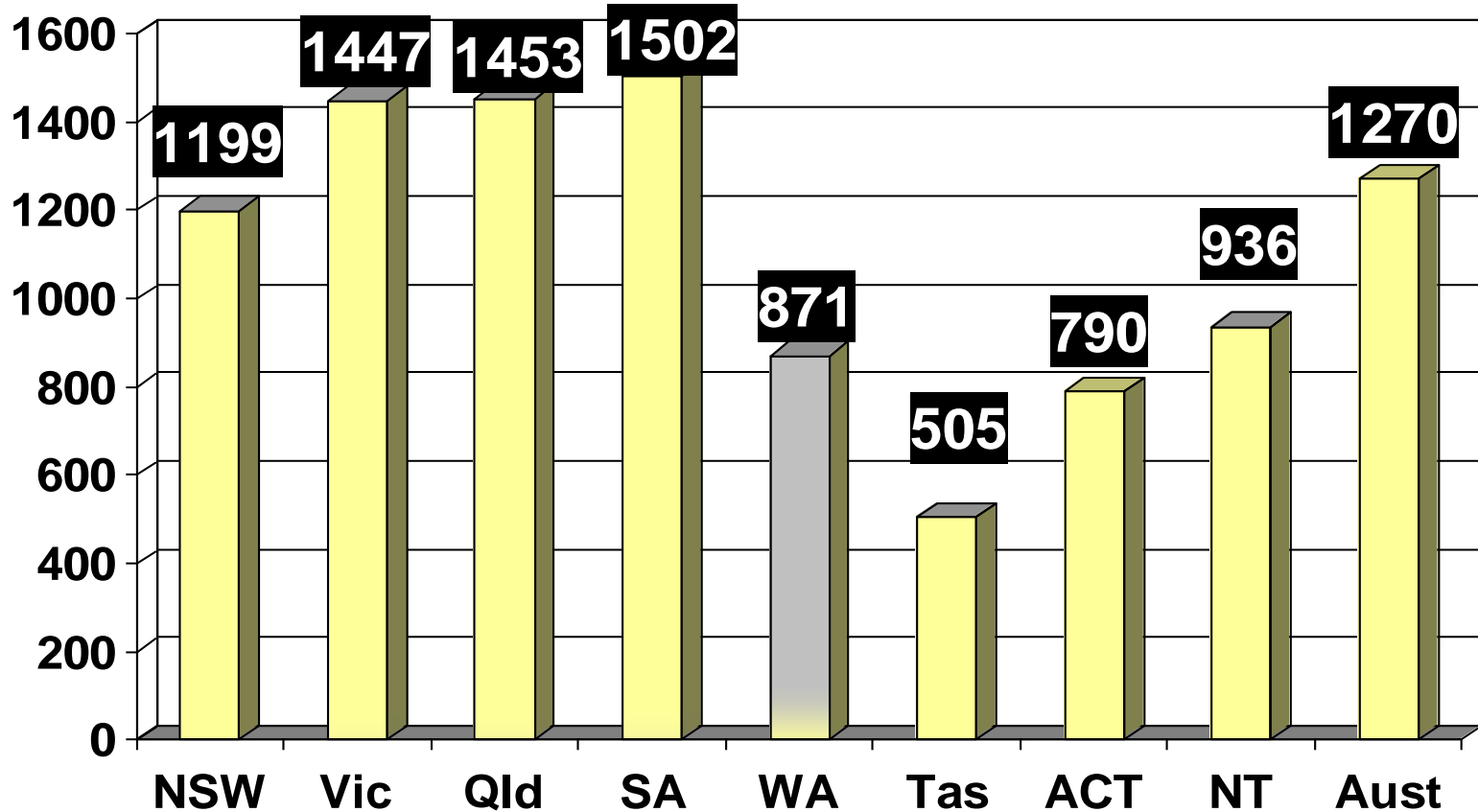
Morphine use prevalent where heroin less available



* Last 6 months

Illicit Drug Reporting System (IDRS)

HIC 'Doctor shoppers'*/1000 GPs 1997



*15+ different GPs, 30+ Medicare consultations, PBS drugs > than clinically necessary

Consequences of increased supply



- **“...very strong correlation between therapeutic exposure to opioid analgesics.....and their abuse”**
 - (Cicero TJ et al. Relationship between therapeutic use and abuse of opioid analgesics in rural, suburban and urban locations in the United States. *Pharmacoepidemiol Drug Saf* 2007;16(8):827-40)
- **“...linear relationship between total opioid analgesic sales and drug poisoning mortality.”**
 - (Paulozzi LJ, Ryan GW. Opioid analgesics and rates of fatal drug poisoning in the United States. *Am J Prev Med* 2006;31(6):506-11.
- **“..statistically significant association between ...total Kg and (DAWN morbidity).**
 - Dasgupta N et al, Association between non-medical use and prescriptive usage of opioids. *Drug Alc Dep* 2006;82:135-42.

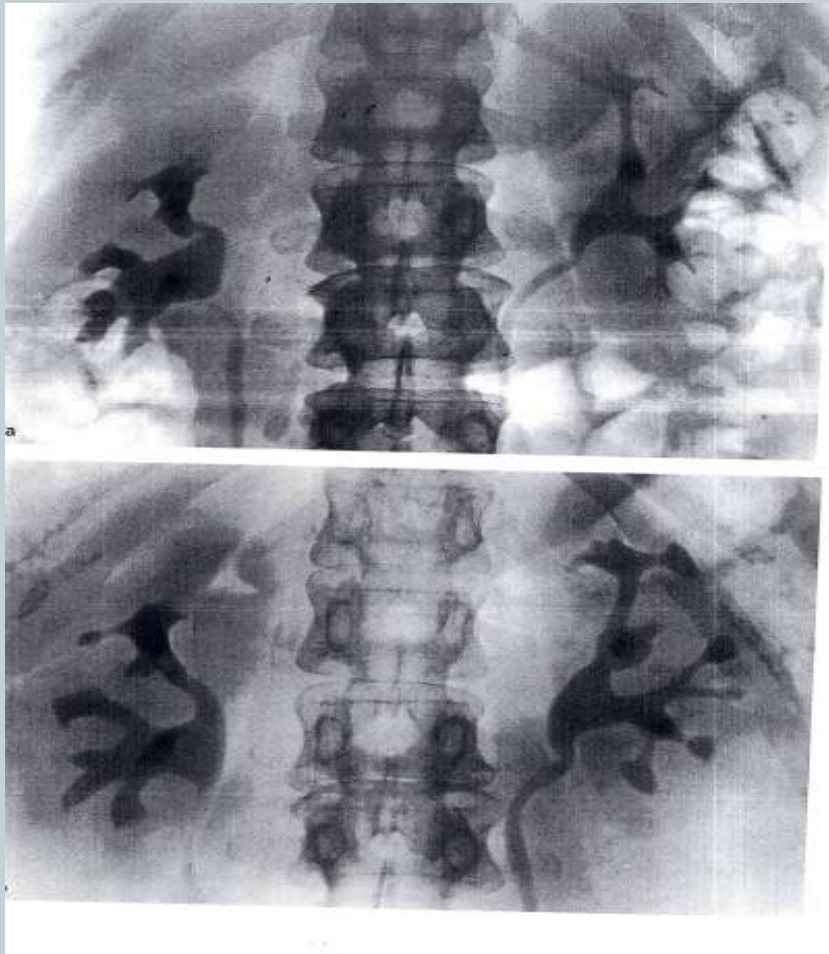
Pharmacy robbery



OxyContin in time-delay safe



“Analgesic Abuse” History:



- ‘53: Zollinger & Spuhler describe “Syndrome” : Interstitial Nephritis.
- 70-80’s... Phenacetin?
- Prof. P. Kincaid-Smith: ‘66 Syn: AA, PU, IHD, PD, CRF; ‘71 seasonal variation; ‘73 rat medulla & PG’s..
- *Robinson G et al “Misuse OTC codeine-containing analgesics” NZMJ vol 123 June 2010.*
- *Frei, M et al “Serious Morbidity assoc misuse OTC codeine-ibuprofen” MJA vol 193 (5) Sept 2010.*

Temazepam IV & Digital Infarction



..& Unisom Sleep-gels..

Drug dealers flood cities with 'jellies'

The black market in the sleeping tablet drug, temazepam, has become a multi-million-pound business for drug dealers and is causing a new epidemic in cities throughout the country.

The number of deaths caused by temazepam is unknown, largely because it is mixed with other substances in drug cocktails. However, it has been linked to 50 deaths last year in Glasgow alone. Leslie Sharp, the chief constable of Strathclyde Police, has estimated that there are about 10,000 drug abusers in Glasgow, of whom two-thirds are thought to be addicted to temazepam.

The trade in prescription-only drugs is concentrated in Scottish cities, particularly Glasgow and Edinburgh, and cities in the North-west and North-east of England. It is also becoming increasingly popular in the more remote in the South-east and the North.

Potential profits from illegal sales of the drug are vast. Costing less than 1p each to buy from a wholesale pharmaceutical company, capsules retail at 41c to 55c each—more than a 1,000 per cent mark-up.

The scale of the problem was exposed in recent police operations. In April, a drugs wholesaler licensed by the Home Office was jailed for four-and-a-half years for flooding Scottish cities with 1.8 million capsules of temazepam which were then sold on the streets.

Sturges Amin, of New Malden, Surrey, had legitimately bought the haul for £24,000. The judge said his value on the black market ranged from £3.8m to £11.4m.

In February, detectives seized 1.5 million tablets from a locked garage in north London. They believed these were destined for cases in Scotland, although they were supposed to have been for export. Last August, police seized 350,000 capsules from a Surrey warehouse. The police believe that the distribution network is now well

With 1,000% mark-up, the 3p prescription pills offer profits of millions. Jason Bennetto reports

the drugs from the wholesalers. Detective Chief Inspector Neil Kingman, of the South East Regional Crime Squad, said: "It is extremely easy to forge documents and there is no monitoring of the drug once it has left the factory, which makes it easy for the tablets to end up in the hands of drug dealers."

There is also a thriving black market fed by forging or stealing prescriptions, leading to thousands of deaths with legitimate users. Doctors who are willing to prescribe temazepam without asking too many questions are targeted by addicts.

Known as "cobby eggs"—because of the drunken appearance of the user—or "jellies", the drug comes in capsules and tablets. As a Category C

The pills injected by heating it up in a microwave, with water or simply from the warmth of the hand. Once in a vein the solution can return to a gel and clog up the blood system, causing large clots. This can lead to gangrene in the legs, arms, fingers, toes and testicles. Unless the extremities affected are amputated the clot can break off and infect the lungs, resulting in death.

Addicts who inject regularly often have to freeze into their groin because they destroy most of the veins on their arm, but they also use their hands and neck. Injecting into the groin is particularly dangerous because it is easy accidentally to pierce an artery, which can cause clots.

Injecting is a major problem in Glasgow, Edinburgh, Liverpool and Manchester.

In the North-east, particularly in Newcastle, the tablets are popular with young people who chew them, often combining them with alcohol and cannabis as a cheap way of "getting out of your head". In November, a 10-year-old boy was suspended from school after he was caught administering to temazepam while in class at a school in Hamilton, near Glasgow.

The third group to abuse the sleeping tablet are users, who use temazepam as a method of coming down and sleeping after a night of dancing while on ecstasy or speed.

Dr Sue Ruben, clinical director of the drugs and HIV prevention department at the North West Community NHS Trust, said: "One of the biggest sources of the drug is from local warehouses. Patients have told us there are known drug houses in Liverpool where thousands of tablets are for sale."

She said that the drug's use



Anti-temazepam campaigner Sarah, a mother-of-four who lost an arm four years ago when she injected a liquidified version of the drug. Photograph: Howard Barker

BY JASON BENNETTO

Four times each day, Sarah used to take the medicine that her doctor had prescribed. But rather than swallow the sleeping capsules that were supposed to give her a peaceful night, she would heat them up on a spoon, using a syringe, and would draw up the warm liquid and inject it into her veins.

At first she used her arm, but the veins became difficult to find. Later she would plunge the needle into her head, groin or neck. "The drug gave me such a nice feeling, it would make me feel bold and brave, I felt I could face anyone, deal with any situation — it gave me courage."

Sometimes she would inject the temazepam six times daily. Then one day four years ago, the mother-of-four awoke to find pain almost immediately. "My friend said I shouldn't worry."

She went down and went to sleep but woke several hours later in terrible pain. "I called an ambulance and went to hospital. My arm started to turn black and there was no pulse in my wrist at all. They told me the hand was dead."

Sleeping capsules gave mother courage but cost her an arm

elbow. "I felt so ashamed at what had happened, but my children were just glad I was still alive," she said.

Sarah, 44, who lives in Liverpool, was first introduced to the capsules by her doctor while in her twenties. At the time, she was smoking heroin and found it difficult to sleep. Even after losing her arm, her doctor continued to prescribe temazepam. Now she is fiercely opposed to anyone using the drug. "There's no need to use it — there are lots of alternatives, but temazepam is so easy to get hold of, it's killing people all the time," she said.

Further evidence of the terrible effects

for to get her monthly methadone prescriptions. He talks about temazepam which he had been injecting for several years. "It's piss easy to get hold of, it's £3 a tablet, I use about 60 every week."

"It gets you speed. It gives the methadone a rush and gets you high. The doctor started giving it to me to help me sleep and someone told me I could inject it. I know it can be dangerous but everything's a risk." Mark says he buys the tablets from "middle-aged people" who are prescribed them but don't use them, or from dealers.

One of the advantages of temazepam is that the user cannot overdose on it.

that he knocked himself out while pumping the fluid into his body. He fell forward and stabbed himself in the eye with the needle. He has since died of a heart overdose.

Another addict has just come out of hospital where he had spent three weeks recovering from thrombosis after accidentally injecting an artery rather than vein. "You know what you're doing it because it stings terribly all down your leg. Injecting gives you a buzz and boosts the effects of the amphetamine — it lasts for about 20 seconds," he said.

Janet, 27, used the drug to keep her "steady" while taking a mixture of speed, cocaine and heroin. "It's dirt cheap and we all know where to get it."

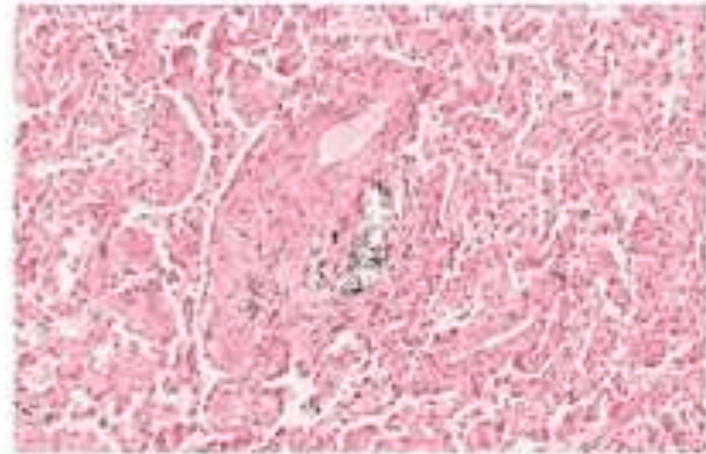
All the users questioned in Liverpool thought buying the gel capsules would not have any effect, claiming that it would just push up their reliance on the black market and make them more attractive.

A less dramatic use of the sleeping tablets can be found in the housing estates in Newcastle. Here some teenagers chew tablets or as they are known, "wobbly eggs", to get high. Simon, 15, said: "It's a cheap way of getting off your

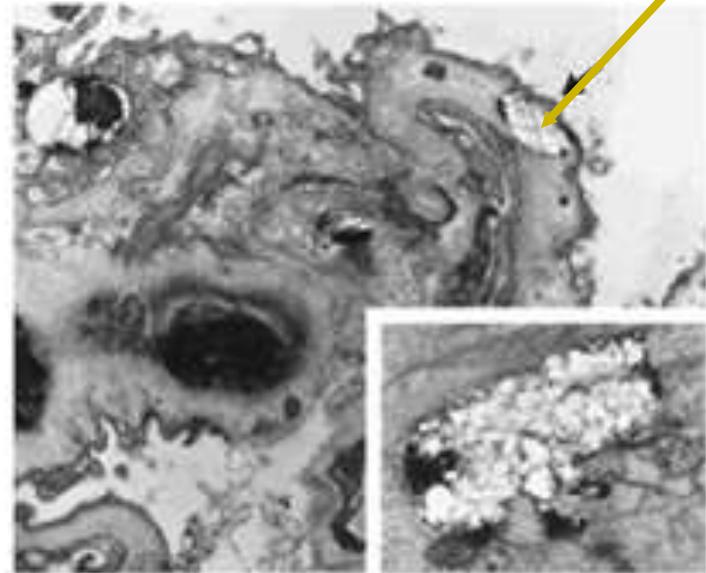
Talc pulmonary granulomatosis



A



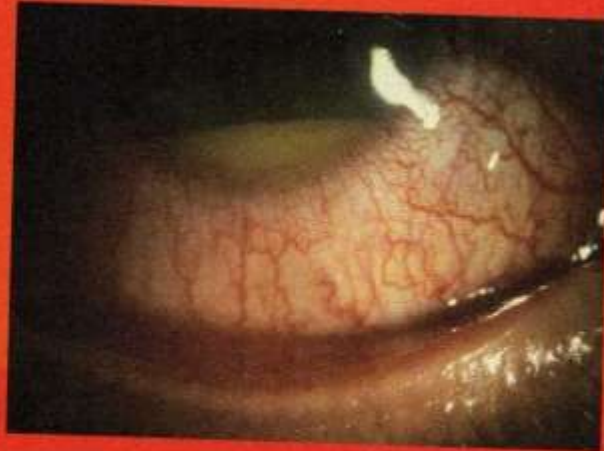
B



C

D

talc



INJECTING BUPRENORPHINE?

DON'T BE BLIND
TO THE RISKS



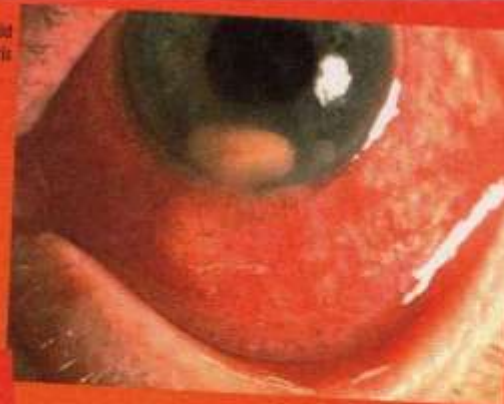
more info?

ask your doctor or pharmacist,
or call viviads on 1800 443 844



If drug use: fungal infection on
the iris and inside the eye, visible
through the pupil

Hypopyon: pus with a fluid
level in front of the iris



INJECTING BUPRENORPHINE?

DON'T BE BLIND
TO THE RISKS

And who can forget *Pethidine*?...



Substance Abuse Definitions



- ***Substance Use Disorder*** (ICD : WHO) & ***Substance Abuse*** (DSM IV)
- ***Tolerance*** = more drug to get same effect
- ***Substance Dependence*** = Daily physical need for the drug = homeostasis (*neuroadaptation*)
- ***Addiction*** =
Dependent/compulsive use despite harm.
- ***Withdrawal*** = Illness after stopping Dependent use (*neuroadaptation reversal*)
- ***Intoxication*** = Impairment associated with high dosage



06/11/2001

SUD's and Medication Safety Risk



- Co-morbidity (Liver disease, COPD, ABI, etc)
- Poor attendance at clinic/monitoring
- Poor medication adherence/compliance
- Likelihood “poly-pharmacy” (interactions)
- Overdose & Intoxication risk (driving, parenting...)
- Malnutrition & altered drug metabolism
- Diversion, sharing, swopping, hoarding etc



CORONERS COURT

Prescribing medication for long-term dual diagnosis patients

A coronial inquiry in Tasmania highlights the complexities of treating patients with a long-standing history of psychiatric illness who have seen different doctors. This case illustrates the need to be particularly cautious in prescribing medication and outlines preventative measures, writes Anjali Parbhoo.

Coroners must investigate all deaths where a person has died a violent, unnatural or unexpected death, or as a result of an injury or accident.

In late 2010 the Tasmanian Coroner investigated the death of a 38-year-old male with a history of Post Traumatic Stress Disorder (PTSD), depression and alcohol abuse. A post-mortem revealed that the deceased died as a result of multiple drug toxicity, including mocllobemide, venlafaxine, zopiclone, flunitrazepam and oxazepam. Toxicology testing revealed high levels of mocllobemide and venlafaxine. There was no alcohol found in the deceased's blood. The forensic pathologist who performed the post-mortem said that "mocllobemide...should never be taken in combination with venlafaxine... because the possibility of developing this potentially fatal drug reaction."

The deceased had received ongoing medical treatment from his general practitioner for PTSD, depression and alcohol dependence. He then sought treatment from two different psychiatrists.

In consultation with the first psychiatrist, the deceased was prescribed mocllobemide for his depression. The deceased did not see this psychiatrist again and chose to consult another psychiatrist. Accordingly, there was no formal handover of care between the two psychiatrists in relation to the deceased's management. The deceased then informed his general practitioner and the second psychiatrist that he was not currently taking any medication. The referral letter from the general practitioner to the second psychiatrist stated that the deceased was not taking any medication. The Coroner was satisfied that the deceased would have been aware that

he needed to disclose his medications to his treating practitioners.

The second psychiatrist prescribed the deceased with the anti-depressant venlafaxine, and oxazepam for treatment of his anxiety, insomnia and alcohol withdrawal symptoms. The second psychiatrist said the combination of these two drugs were safe in appropriate doses.

The Coroner determined that it was probable that the deceased "did not understand or appreciate the risks of mixing the particular medications". However, no information was provided to the deceased on these risks because the treating practitioners were not aware the deceased was taking these medications. The Coroner found that these practitioners acted reasonably given that the deceased had informed them that he was not taking any other medications.

In the words of the forensic pathologist, "this case highlights the difficulties of managing patients that consult multiple practitioners for complex medical problems as well as the dangers of mixing these two classes of medications".

Recommendations

Although the Tasmanian Coroner found the treating doctors acted reasonably in providing care to the deceased, the Coroner made the following preventative recommendations:

Medical practitioners should be cautious when treating patients with an extensive psychiatric history, who state that they are not taking any medications.	In such cases, medical practitioners should attempt to communicate with previous doctors or pharmacists to ascertain what medications have been prescribed.	Medical practitioners should inform and educate patients about the risks of combining different medications.
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The issue in this inquest was the absence of knowledge and communication by medical practitioners as to the involvement of other doctors.

This inquest highlights the difficulties faced by medical practitioners in treating dual diagnosis patients who have complex and multi-faceted conditions, including alcohol dependency and mental disorders. In certain circumstances, such as the case above, current treating medical practitioners may need to seek further information from past doctors in order to provide an appropriate and safe treatment plan for patients. Such information sharing may help to prevent such deaths in the future. *Y*

Doctors who require advice should contact AMA Victoria on (03) 9290 8722.

The content of this article is intended to provide a general guide only. Advice should be sought about a doctor's specific circumstances. AMA Victoria accepts no responsibility for any direct or indirect damage caused by the use of this article.

Medication Borrowing, Sharing & Swopping



Conditions facilitating “sharing” as identified in research:

- *More likely to share with a family member*
- *Share with someone else, if they had the same prescription*
- *Wanting to ‘help a friend’*
- *Had ‘leftover’ medicine – kept deliberately for ‘next time’*
- *Non-English speaking background*
- *More people in the house*
- *Single (not in a relationship)*
- *Wanting same medication as other family member*
- *Borrower had run out of prescription medicine in the short term*

(ref: Ellis, J in AFP Oct 2009)

Drug Diversion



- **Overseas Drug Diversion:**

PBS subsidised medicine is sometimes taken or sent from Australia for re-sale or for relatives and friends overseas who may not be able to get this medicine in their home country. Such activity is illegal and has potential health implications.

- **Illicit Diversion :** for street sale, etc

- **“*un-intended patient*” :** diversion associated with “accidental” exposure e.g. Methadone syrup

NB. Children!



“Abuse Deterrent Formulations”(ADF’s)

Categories of ADFs

Increasing Abuse Deterrence



Combination Mechanism

Pharmacologic and physical

Pharmacologic

Bioavailable agonist/sequestered antagonist
Prodrug

Aversive Component

Capsaicin (burning sensation)
Niacin (warmth, flushing)
Ipecac (emetic)

Physical

Difficult to crush
Difficult to extract

Packaging

Radio frequency identification (protection)
Tamper-proof (bottles)

SUD's & Medication Safety

Prescriber

- *One **ONLY**
- *Clarify **ALL** drugs/enviro;
- *Confirm;
- *Fax script;
- *Drug restriction & supervision strategies;
- *Adherence;
- *Monitor.



Pharmacy

- *One **ONLY**
- *ID patient
- *Observation
- *Monitor **ALL** drugs used;
- *Educate
- *Communicate
- Pseudoephedrine;*
- Codeine reg's.*



Patient

- *Restrict access
- *ID & family;
- *Comprehend;
- ***Consent** ;
- *Attendance;
- *Adherence ;
- *Contract

Thank you for your attention...

