Deep vein thromboses in users of opioid drugs.

Cornford CS, Mason JM, Inns F. British Journal of General Practice 2011; DOI: 10.3399/bjgp11X613115

This study was a retrospective analysis of deep vein thrombosis (DVT) prevalence and incidence. They used the data from 734 patients in treatment for opioid dependence who were registered to a single specialised primary care practice in Middlesborough. They added data from the Treatment Outcomes Profile (TOP), data from the National Drug Treatment Monitoring System form, and data extracted from the GP records. The practice records looked at DVT frequency, location, timing, scan confirmation, management and complications.

There was a history of ≥1 DVT in 102 people in the sample and this gave a prevalence of DVT of 13.9% (95% CI=11.5-16.6). There was an annual incidence rate of 3.2% (95 CI=2.6-3.7). There was an increase in this incidence rate with age, for females and in crack cocaine users. The independent risk factors that predicted DVT were increasing age, female sex (x1.7), sex-worker status (x3.1) and intravenous drug use. Those who had had previous DVT reported lower health and wellbeing scores.

All the patients were treated with heparin rather than warfarin. Data were available for 85 out of 102 patients who had either completed treatment with anticoagulants or who were currently receiving treatment - their compliance was 74%. The usual risk of pulmonary embolism in anyone admitted to hospital with a DVT is around 7% (up to 10% with proximal clots) but in this sample a prevalence of 2-6% was found. Leg ulcers were recorded in 15.7% of those who had past DVT.

SMMGP comment: This is a great paper. Based in general practice in England it's a topic that is long overdue for investigation. The issue of DVTs in users has received a desperately poor amount of attention. The long-term sequelae, often leading to chronic venous insufficiency with all its morbidity, can be horrifying. The authors point out that in the under 40s, injecting drug-related DVTs account for over half of hospital cases. (It's worth mentioning here that NICE don't have guidance on acute management of thromboembolism - but they do have guidance on reducing the risk for general hospital admissions. Scandalously, injecting drug use doesn't merit a single mention - not even in the risk factors section.)

The annual incidence of 3.2% is 100 times greater than the age-comparable general population. But what can be done about it? There seem few specific measures and this is perhaps part of the reason this topic has remained unexplored; good overall treatment (with appropriate access to opiate substitution therapy and detoxification services), reduction of injecting, reduction of frequency of injection with solid harm reduction advice would seem to be appropriate. Finally, it was worth noting the finding in this study that the mean age of DVT was, on average, eight years after the start of heroin use. So, as for HCV infection, there is a window of opportunity.

Comparison of methadone and buprenorphine for opiate detoxification (LEEDS trial): a randomised controlled trial.

Wright NM, Sheard L, Adams CE, Rushforth BJ, Harrison W, Bound N, et al. British Journal of General Practice. 2011; DOI: 10.3399/bjgp11X613106

This study was an open label pragmatic randomised controlled trial in three prison primary healthcare departments in the north of England. They recruited 306 prisoners who were using illicit opiates and they were given daily buprenorphine or methadone. This was given as a standard reducing regime over a maximum of 20 days. The primary outcome was abstinence from illicit opiates at 8 days post-detoxification. They used, where possible, the objective measure of urine testing but self-report and clinical notes were also used where this was not feasible.

The results showed that abstinence was achieved for just under 74% at eight days post detoxification. There was no statistically significant difference between methadone and buprenorphine (OR 1.69: 95% CI=0.81 to 3.51). The only association with abstinence was whether or not the individual was still in prison - although this had a hefty OR of 15.22 (95% CI=4.2 to 55.3) there were quite wide confidence intervals. None of the other variables such as mean daily use, length of use, administration route, previous successful detoxifications, or length of previous abstinences was associated with achieving abstinence.

New approaches to dealing with opioid drug dependence. *Rushforth B, Wright NM. British Journal of General Practice. 2011; DOI:bjgp11X612927*

This editorial set out the 'new approaches' to dealing with drug dependence but really sets out to clarify some of the concepts of recovery and where they sit within general practice. They give a briefing on the new drug strategy with its tagline 'supporting people to live a drug-free life' and highlight the shift away from the harm-reduction approach. They go on to discuss some of the broader definitions of recovery and emphasise the importance of the concept of wellbeing rather than 'cure'.

SMMGP comment: The LEEDS study has shown that methadone and buprenorphine are equally effective in achieving abstinence from opiates at 8 days. There have only been six previous studies comparing these two for detoxification – and they were all outside prison with an average of just 36 participants per study. One interesting wrinkle from the results is the finding that there was only a single factor associated with abstinence – this could be an important lesson for clinicians who may be tempted to pre-judge the likely success of detoxifications and that almost no one should be discouraged. However, the authors highlight the limitations themselves: detoxification is just a single step and the high risk of drug-related death on release from prison points to the need for good ongoing care.

Perhaps most importantly this study is an important proof of concept. This was the first clinical trial in a UK prison for over ten years. The call of 'more research needed' is almost a cliché, and potentially self-serving, but in this case is utterly justified. We need better data on how detoxification in prison translates into long-term outcomes to help stave off knee-jerk political interventions. Recent policy has had a strong political edge and that has had the effect of steering some healthcare providers away from opiate substitution therapy. This may well be the right approach - but given the devastating effect, also highlighted by the authors, of drug-related deaths after release it is crucial policy makers have an evidence base to which they can turn.

The BJGP editorial title trumpets a 'new approach' and this always makes for good copy in the journals but there is no revolution here. The editorial dampens these expectations and places the drug strategy in a more pragmatic, GP-friendly context where wellbeing is placed well above an ideological drive to 'cure' people.

Mortality of those who attended drug services in Scotland 1996–2006: Record-linkage study. *Merrall ELC, Bird SM, Hutchinson SJ. International Journal of Drug Policy. 2012 Jan. 1;23(1):24–32.*

This study looked at the causes of death amongst a cohort of people in contact with drug-treatment services in Scotland from April 1996 until March 2006. They looked at their treatment records and linked them to national registers of deaths and hepatitis C virus diagnoses. They calculated cause-specific death-rates and standardised mortality ratios (SMRs). They split the results into two eras - 1996/7 to 2000/01 and 2001/2 until 2005/06.

The cohort comprised of 69,456 individuals and this amounted to 350,315 patient-years. There were 2590 deaths. There were five major causes of death: drug-related, homicide and infectious diseases all had high SMRs of >5; the second and third most frequent causes of death were suicide and digestive-system diseases. These five causes accounted for 2028 (78%) of the 2590 deaths.

The SMR went from 6.4 (95% CI: 6.0-6.9) for the first era to 4.8 (95% CI: 4.6-5.0). An HCV diagnosis doubled the risk of cause-specific mortality. The increase in drug-related deaths in older people (>34 years) was also specific to HCV-diagnosed individuals. Stimulant misuse increased suicide risk and the adjusted hazard ratio was 1.91 (95% CI: 1.35-2.60). Alcohol misuse also increased hazard ratios for drug-related deaths and deaths from digestive system disease.

SMMGP comment: It is encouraging that there has been a decline in the deaths between the two periods. The data also confirm what has been shown in other studies - infection with hepatitis C virus leaves people particularly vulnerable, and likely to die even younger. Not all of this is simply due to the effects of the hepatitis virus on body systems (though this is undoubtedly important). It is less easy to see how the increased homicide risk would tie in with the biological ageing associated with HCV - but it does highlight the important of HCV status as an important marker for those who need the greatest support to reduce mortality risks.

The finding of stimulant misuse being associated with increased suicide risk has, the authors suggested, never been demonstrated before. There may be some reverse causation here - i.e. those with depressive or suicidal ideation are turning to stimulants to self-medicate. There may also be an issue with the 'come-down' after the euphoria from the stimulants. It's an area to watch.

Intervention against excessive alcohol consumption in primary health care: A survey of GPs' attitudes and practices in England 10 years on. *Wilson GB, Lock CA, Heather N, Cassidy P, Christie MM, Kaner EF. Alcohol and Alcoholism. 2011 Aug. 12;46(5):570–577.*

This study wanted to ascertain the views of general practitioners regarding the prevention and management of alcohol-related problems. There was a similar study conducted in 1999 with which to compare the results. They surveyed 282 GPs in the East Midlands using a postal questionnaire that measured practices and attitudes, including the Shortened Alcohol and Alcohol Problems Perception Questionnaire (SAAPPQ).

The GPs reported lower levels of postgraduate education or training on alcohol-related issues than in 1999 but this did not quite reach significance. Most GPs felt that it was legitimate to manage problem or dependent drinkers and that it could be done adequately in general practice. However, they had low levels of motivation, task-related self-esteem and job satisfaction. Key barriers were 'busyness' (63%), lack of training (57%) and contractual incentives (48%).

SMMGP Comment: The conclusion of the authors in this study was that there continues to be a gap between actual practice and the potential work related to alcohol problems. In a decade where the rising tide of alcohol-related conditions threatens to swamp services there has been little apparent change in the perspective of GPs. It seems unsurprising that GPs will highlight being too busy as a barrier - and it is difficult to imagine a time when GPs won't be busy. It's really a matter of prioritisation. Inevitably, some GPs will raise 'contractual incentives' when asked to do more work. The insidious effect of a QOF culture is to ask for payment for any work – one may argue over the importance of alcohol-related illness but it's simply not practical to dangle carrots over each and every clinical condition. Ultimately, if GPs have the training, then when they are presented with the patients in front of them, they'll do the right thing. It's really all about education and the 57% who feel they lack training are the most concerning.

It's worth commenting on the timing - this postal survey was conducted in 2009 and the *RCGP Certificate in the management of alcohol problems in primary care* was launched in September 2009 so will have had no impact on the results of this survey. The majority of GPs in the survey had had less than four hours of training. Since its launch more than 1500 healthcare professionals have done the RCGP alcohol certificate. SMMGP will continue to get involved in improving education around alcohol issues in primary care.

A prospective, randomized, multi-center acceptability and safety study of direct buprenorphine/naloxone induction in heroin-dependent individuals. *Amass L, Pukeleviciene V, Subata E, et al. Addiction 2012;107:142-151*

This study consisted of a two-day double-blind, double-dummy induction phase followed by 26 days of open-label treatment with buprenorphine-naloxone. They used nineteen sites in ten European countries from March 2008 to December 2009. They recruited 187 opioid-dependent men and women ≥15 years of age.

The aim of the study was simply to see if individuals could go straight on to buprenorphine-naloxone ('direct') rather than first starting on buprenorphine and converting a later date ('indirect'). The primary outcome was the patient response to direct and indirect buprenorphine-naloxone induction.

The power calculation suggested that the study would need a sample size of 310 patients to have an 80% probability of establishing non-inferiority. They didn't recruit this many - they had 187 opioid-dependent men and women ≥15 years of age. The results showed that 178 out of 187 (95%) completed the first two days consisting of the double-blind induction phase and 138 (72%) completed the open label phase from days 3-28.

SMMGP comment: It's difficult to see why this study was quite so complex; it ranged across ten countries just to recruit 187 opioid-dependent patients. The argument for buprenorphine-naloxone versus buprenorphine has never really been convincing. Unless there is a significant risk of diversion *for injection* of the buprenorphine (something that seems to be less of an issue in the UK compared with diversion for snorting) then there seems little mileage in buprenorphine-naloxone – and if diversion is really a major concern then perhaps supervision may be appropriate.

The busy clinician may skim this paper, perhaps read the abstract, and subliminally absorb the idea of prescribing buprenorphine-naloxone. Ultimately, all this study does, at best, is prove the *equivalence* of buprenorphine-naloxone. In the UK, what would be useful to see is a genuinely good reason why we should prescribe buprenorphine-naloxone over generic buprenorphine. This study has successfully demonstrated that adding naloxone to a buprenorphine

tablet in the first two days makes no difference. That will come as little surprise.

It will also come as little surprise that this study was heavily sponsored by the manufacturer. The best reason for using buprenorphine-naloxone is when there is a real and significant concern around diversion for intravenous use. Other than that, unless you happen to be determined to have a lemon-flavoured tablet, there is little demonstrable advantage.

Association of CIPRAMIL (citalopram hydrochloride) with dose-dependent QT interval prolongation. *Lundbeck Limited UK and MHRA. Letter to healthcare professionals. 24th October 2011.*

This letter was sent out to all healthcare professionals giving further details on citalopram and concerns associated with the QT interval. The maximum recommended dose of citalopram is now 40mg as there is believed to be a dose-dependent effect causing prolongation of the QT interval and putting patients at risk of torsades de pointes. No one should be on 60mg and those with a known QT interval prolongation, congenital long QT syndrome or use of other QT prolonging medications should not be on citalopram at all. A further letter was issued by Lundbeck in December extending similar advice to the prescribing of escitalopram.

SMMGP comment: This might seem slightly peripheral to work in substance misuse but it is worth highlighting given that most clinicians working in these settings will be aware of the problems with QTc prolongation. This is clearly an important issue for all practitioners but is particularly pertinent to anyone involved in prescribing methadone. Crucially the wording of this document is important. It specifically states that the 'use of citalopram with other medicinal products know to prolong the QT interval is contraindicated'. This seems clear and unambiguous. One would imagine that the prescribing of citalopram and methadone together would be extremely difficult to defend now.

The letter gives some indication of the size of the effect - compared to placebo the mean change from baseline in QTc was 7.5 msec at the 20mg daily dose and 16.7 msec at the 60mg daily dose. (Typically a QTc above 450msec would be considered as prolonged and one about 500msec would represent a significant risk of arrhythmia.) One also wonders if this change in recommendations could have an impact on other medications. All the other SSRIs have been associated with QT prolongation in the past and methadone has been known to increase the QTc interval by as much as 10msec for every 50mg increase in dose.

See also the discussion on the SMMGP forums **http://tinyurl.com/citalopram-QC**

Quantitative assessment of time dependent drug-use trends by the analysis of drugs and related metabolites in raw sewage. *Reid MJ, Langford KH, Mørland J, Thomas KV. Drug Alcohol Depend. 2011 Dec. 15;119(3):179–186.*

This paper presented the findings of a study that involved the comprehensive sampling of sewage in Norway. A total of 104 sewage samples were collected from a plant that served around half a million people in Oslo. They analysed the sewage for methamphetamine, cocaine and cocaine metabolites (benzoylecgonine). The consumption profiles of cocaine and methamphetamine were found to vary in terms of frequency and timing of use. Most cocaine was consumed during the evening hours and 45% of the consumption occurred in weekend periods. The flow of methamphetamine was more evenly spread throughout the week.

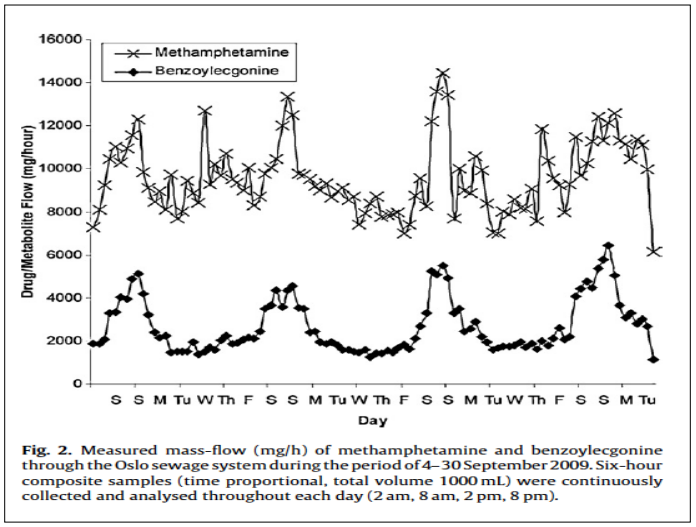

Fig. 2. Measured mass-flow (mg/h) of methamphetamine and benzoylecgonine through the Oslo sewage system during the period of 4–30 September 2009. Six-hour composite samples (time proportional, total volume 1000 mL) were continuously collected and analysed throughout each day (2 am, 8 am, 2 pm, 8 pm).

SMMGP comment: Perhaps much of the information that will be gained through sewage analysis could, arguably, be obtained by talking to folk rather than seeking the answer at the tail end. However, it does add objective data and quantitative weight to the findings of other types of survey. The results do seem to suggest that methamphetamine is perhaps more likely to be used on a daily basis - this could have clinical implications and it is may mean that methamphetamine users will come to the attention of the drug-treatment services if daily use either leads to, or is indicative of, dependent use.