Clinical Update – March 2015

Welcome to the SMMGP Clinical Update (March 2015). Papers discussed include:

- Solving the problem of non-attendance in substance abuse services.
- Experiences of UK patients with hepatitis C virus infection accessing phlebotomy: A qualitative analysis
- HCV treatment rates and sustained viral response among people who inject drugs in seven UK sites: real world results and modelling of treatment impact.
- Addressing liver disease in the UK: a blueprint for attaining excellence in health care and reducing premature mortality from lifestyle issues of excess consumption of alcohol, obesity, and viral hepatitis.
- Mother's little helper? Contrasting accounts of benzodiazepine and methadone use among drug-dependent parents in the UK.
- Mortality and cause of death in a cohort of people who had ever injected drugs in Glasgow: 1982-2012.
- Methadone dose in heroin-dependent patients: role of clinical factors, co-medications, genetic polymorphisms and enzyme activity.
- E-cigarette knowledge, attitudes, and use in opioid dependent smokers.

Solving the problem of non-attendance in substance abuse services. *Milward J, Lynskey M, Strang J. Drug Alcohol Rev 2014, Nov;33(6):625-36.*

This narrative review draws together research on the people who 'did not attend' (DNA) for appointments in addiction services. It also pulls in evidence from the broader healthcare literature to suggest interventions that may be worth considering. The areas covered in their review include:

Accelerated intake. Services that offer appointments on the same day, next day or within two days significantly improve attendance at the initial treatment session.
Motivational interviewing. Attendance has been used as an outcome in groups receiving motivational interviewing but the results have been mixed and no clear conclusions can be drawn about its effect.
Contingency management (CM). This is one of the areas that has been most studied. Meta-analyses have suggested that CM, compared to other psychosocial interventions, is one of the more effective options for achieving abstinence and retention but CM for attendance in people on methadone has not been looked at in detail. A couple of different models of CM are considered - the fixed value reward (usually vouchers) and 'intermittent reinforcement' where participants are entered into a draw for a prize. The studies looking at these were generally small and this hampers the conclusions that can be drawn.

Appointment reminders including SMS reminders. The most common reason cited for missing appointments is forgetfulness - cited by 27% of patients in one study for patients attending psychiatric clinics. RCTs looking at postal and telephone call reminders have been conducted.

Standard letters were found to have no effect on attendance. In another study telephone calls did show a small effect and in a third study a personalised letter was more effective than no contact at all. Further studies have shown benefit of telephone reminders one to three days before initial appointments. SMS appointment reminders have been shown, in more general out-patient settings, to be effective at reducing non-attendance.

Commentary: There can't be many clinics across the country where the topic of DNAs isn't discussed on a more or less weekly, if not daily, basis. Despite the promise of the title of this paper there isn't much that is a great revelation in this study; perhaps the most surprising thing is just how little research there is into this area given its monumental impact on the daily routine of clinics. My major concern about the discussion of DNAs is when it morphs into a blame game and with that mindset it's a small step to the imposition of punitive measures. I have grave reservations about local policies where reductions and discharges quickly follow DNAs. Perhaps the most important point from this paper is the introductory comments by the authors emphasising that we know people who miss appointments have worse outcomes. Clearly we need to strike a balance with clinical safety but the lack of a clear answer to the problem of DNAs is worth remembering. It seems probable to me there will never be a complete answer and we need to frame services and policies with that simple fact in mind.

Telephone and SMS reminders look favourite strategies at present - ideally within 1-3 days and with some personalised content as well. So do people who attend substance misuse services have access to mobile phones? Personal experience would suggest that they do and the authors reported on one USA study that showed 91% had mobile phones. However, nearly a quarter changed their number more than three times per year and that also rings true with clinical experience in the UK.

Experiences of UK patients with hepatitis C virus infection accessing phlebotomy: A qualitative analysis. *Clements A, Grose J, Skirton H. Nurs Health Sci 2014, Dec 11.*

This qualitative study aimed to provide "an understanding of the experiences and perceptions" of people with hepatitis C virus (HCV) who have blood taken but who have venous damage. Interviews took place with ten people who were attending an acute Trust in the south-west of England (the authors are based in Plymouth). Interviews were transcribed and thematically analysed with field notes and the researcher's reflective diary supplementing the transcription.

They identified four main themes:
Conflicts associated with phlebotomy. This came up in a number of ways - the use of hazard warning labels on blood forms was associated with stigma on the part of the user. There was a perceived sense of a negative attitude from staff. When users gave advice on good locations to get

blood this was often ignored and caused more pain. Multiple attempts to get blood were painful and distressing. Participants who wished to take their own blood met with a mixed response. They noted that staff could be "blaming or punitive and exhibit shock and disgust". It was also noted that some users were referred to secondary care if primary care clinicians couldn't get bloods.

Emotional responses to phlebotomy. Some participants felt guilty if a doctor had to be called to them to take bloods. Many felt unable to complain because of the perceived self-inflicted nature of the HCV infection. One participant in the study did describe a positive experience when he was able to take blood himself from his own femoral vein.

Patient as expert. All the participants felt that they were the best judge of their own venous access and they knew which damaged veins to avoid.

Offering solutions. The participants did describe important differences in the HCV services they attended - they found the staff easier to talk to and felt their concerns about phlebotomy were listened to. The need for communication was recognised as vital.

Commentary: I have yet to see a published study that explores the experience of injecting drug users and phlebotomy - this study is as close as it gets, though it does concentrate on people with HCV infection. They are, of course, a particularly important group as the testing and subsequent monitoring of HCV treatment will require some degree of access to bloods even if the initial screening has become simpler in recent years with widespread access to dried blood spot testing.

And although this paper related to HCV treatment I suspect the same lessons can be taken for the management of any chronic disease in an ageing drug user. This is an area where it is easy to unintentionally promote stigma and we need to approach phlebotomy with sensitivity. The answer to this is curiously simple and entirely predictable - communication. As one participant said:

"You can't just treat the patient as a patient without taking into consideration what their past or present needle activity is going to have done to their body."

HCV treatment rates and sustained viral response among people who inject drugs in seven UK sites: real world results and modelling of treatment impact. *Martin NK, Foster GR, Vilar J, Ryder S, E Cramp M, Gordon F, et al. J Viral Hepat 2014, Oct 7.*

This study uses a mathematical model to estimate the likely consequences of HCV treatment in the UK – both at current levels and if treatment rates were scaled up. They focus in on specific UK sites: Bristol, East London, Manchester, Nottingham, Plymouth, Dundee and North Wales.

There is a wealth of data in this study. They found that treatment rates across the sites varied from <5 to over 25 per 1000 PWID. It also analyses the use of the new HCV treatments that are soon to arrive: the interferon-free direct acting antivirals (IFN-free DAAs). They noted that scaling up of treatment to 26/1000 PWID annually (which had already been achieved in two sites) using the new

IFN-free DAAs could result in a reduction in chronic HCV prevalence of at least 15% at all sites. In Plymouth, Dundee and North Wales this scaling up was predicted to halve chronic HCV within a decade.

Addressing liver disease in the UK: a blueprint for attaining excellence in health care and reducing premature mortality from lifestyle issues of excess consumption of alcohol, obesity, and viral hepatitis. *Williams R, Aspinall R, Bellis M, Camps-Walsh G, Cramp M, Dhawan A, et al. The Lancet 2014, Nov;384(9958):1953-97.*

This detailed report covers all the facets of liver disease in the UK. Here are a few key facts to give a flavour:

- Liver disease is the only chronic disease that has been rising in the past 40-50 years. The standardised mortality ratios have increased 400% since 1970.
- In England and Wales 60,000 people have cirrhosis leading to 10,948 deaths in 2012.
- Most of this is related to alcohol consumption. We have overtaken most of Europe in liver disease - and only Finland, where they have the same liberalised approach to alcohol, can match us.
- Two panel recommendations on addressing viral hepatitis B and C stand out:
  The highly effective DAA drugs for HCV should lead to a national strategy to identify more with HCV and those most likely to transmit infection, such as injecting drug users and prisoners, should be prioritised.
  Ambitious targets should be set to eradicate liver disease caused by HBV and HCV in the next 20-30 years.

Commentary: The first thing that occurred to me from the Martin *et al* study is the astonishing low baseline we currently have for treatment of HCV. I'd have guessed around 1-2% with some hope that it had improved in recent years. In some centres it is better but on others the treatment rates are <5 per 1000. I almost thought there was a zero misprinted here. It really is less than 1 in 200.

The Lancet Commission report is 45 or so pages and covers a lot of ground. Obesity, alcohol and viral hepatitis make up the triumvirate that loom over the UK's liver health to such devastating effect and this report considers all three. Obesity will not be as great an immediate concern to the primary care physician working with a substance misuse population - but the other two, alcohol and viral hepatitis, are major concerns so there is plenty here for us to consider.

From the perspective of the boots-on-the-ground clinician one of the most worrying recent experiences has been an apparent tailing off of HCV treatment we've seen in the past few months. Everyone is now hanging on for the new IFN-free DAAs. The long-term future on a war against HCV may be promising, with hopes of total victory in the decades to come, but at the moment we're stuck

in a phoney war where nothing is happening. We'd be interested to hear if others across the country are having a similar experience - send a tweet to **@SMMGP**.

Mother's little helper? Contrasting accounts of benzodiazepine and methadone use among drug-dependent parents in the UK. *Chandler A, Whittaker A, Williams N, McGorm K, Cunningham-Burley S, Mathews G. Drugs 2014, Dec;21(6):470-5.*

This study involved longitudinal qualitative interviews (45 in total) with 19 opioid-dependent parents in Scotland during the antenatal and postnatal period. It explored their use of benzodiazepines and the interviews were analysed using a narrative informed thematic analysis.

They found that most of the parents described using benzos in addition to opioids. One theme identified was that while they all expressed a desire to cut down or stop using opioids, which were considered to be stigmatising, this was rarely considered with their use of benzos. They normalised their benzodiazepine use and it was framed as therapeutic and unproblematic.

The authors described how many parents used drugs to help them in their attempts to live a normal daily life. In this regard opiate substitution therapy (OST) attracted some positive feelings. However, the challenges of OST were also highlighted with the difficulties of dispensing restrictions such as daily supervision being noted. These were regarded as being especially problematic for parents - with some of them acutely aware of the difficulties of taking their methadone in the chemist with their children present.

Overall, the accounts of benzodiazepines tended to be presented far more positively and constructively as parents used them to manage anxiety or as mood enhancers. This then allowed them to go about their daily routine as parents and these functional benefits were emphasised to people like GPs. The authors recognised these divergent views towards methadone and benzos - and they were most obvious in people who were dependent on both.

There was also suggestion in the themes that there was a gendered view of benzodiazepine use. In woman and mothers there was some acceptance, the "mother's little helper" of the title, but in males the use of benzodiazepines was regarded as dangerous.

Commentary: When it comes to consultations with people on OST who are also dependent on benzodiazepines these are useful and important findings. The framing of benzos as a therapeutic option needs to be appreciated. The views that some forms of drug use are deemed more acceptable than others will be recognised and one comment will be familiar to all GPs:

“I said to him I’m not taking them to get out of my face. I said I just take two at night to help me get to sleep.”

Neither will it come as a surprise that one of the key themes was that parents were more likely to want to reduce OST than benzos. The authors go on to suggest a different approach to benzos may be needed in light of this. This may strike some as rather typical of throwaway comments sometimes found in academic papers – as a clinician faced with repeated demands to prescribe benzodiazepines it's challenging to see what this approach might be. And no suggestions are offered here, but given the use of benzos as 'therapy' perhaps we need to find other supportive, probably psychosocial, if not outright social, interventions that can fill the therapeutic gaps benzos currently fill for many people.

Mortality and cause of death in a cohort of people who had ever injected drugs in Glasgow: 1982-2012. *Nambiar D, Weir A, Aspinall EJ, Stoové M, Hutchinson S, Dietze P, et al. Drug Alcohol Depend 2014, Nov 27.*

This paper reports on a 30-year follow up of a cohort in Glasgow. Initially they started with 456 people who injected drugs and they report that 139 (30.5%) had died during the 9024 person-years of follow up. This is a nine times greater mortality than the general population. This was most keenly felt in the 15-24 years age group who had a standardised mortality ratio (SMR) of 31.6 (95% CI 21.2-47.1).

Commentary: It is also worth noting that liver-related mortality has become more of an issue as the years have gone by - not a new finding but it bears re-iteration. They found that nearly half of liver-related deaths involved alcoholic liver disease and the impact of HCV in this cohort hasn't been fully realised either.

Despite the ageing of the general population and the recognition of older drug users the main finding from this study was that the highest mortalities (more than 30 times greater than the general population) were seen in the youngest users across the cohort. This for me is a key finding and reinforces that the need to treat older users shouldn't diminish the importance of interventions that keep younger users alive.

Methadone dose in heroin-dependent patients: role of clinical factors, comedications, genetic polymorphisms and enzyme activity. *Mouly S, Bloch V, Peoc'h K, Houze P, Labat L, Ksouda K, et al. Br J Clin Pharmacol 2014, Dec 30.*

This study took 81 patients who were stable on methadone and they then underwent a series of tests including: clinical examination, treatment history, liver/intestinal cytochrome P450 (CYP) 3A4 activity, *R,S*-methadone trough concentration and also a number of significant polymorphism genes.

They found that methadone dose was correlated to the highest dose ever used. Other factors that were independently associated with high dose methadone were: body weight (OR 1.57, 95% CI 1.01-2.44), history of cocaine dependence, and ethnicity (Asian>Caucasian>African). They also noted a moderate correlation between liver/intestinal CYP 3A4 activity and methadone dose with steady state dose - but not highest ever dose. None of the genetic polymorphisms were predictive of methadone dose.

Commentary: The conclusion of this study was that:

Methadone maintenance dose was predicted by sociodemographic and clinical variables rather than genetic polymorphisms or liver/intestinal CYP3A4 activity in stable patients.

Previous experience seems to be just about the most useful marker when it comes to methadone dosage and one we all fall back on - but I've also assumed, given the variation in individual metabolism, that anything more prescriptive was likely to be inaccurate. I've certainly never used body weight as a gauge - this paper suggests body weight is associated with higher dose but I noted that the confidence intervals are a whisker off insignificance. The final point I'd make from this study is the author's introduction that 30% to 80% of people are *under-dosed* on their methadone. Measures like the Clinical Opiate Withdrawal Scale do not take into account global clinical improvement or craving suppression and careful personalised titration remains the best approach.

E-cigarette knowledge, attitudes, and use in opioid dependent smokers. *Stein MD, Caviness CM, Grimone K, Audet D, Borges A, Anderson BJ. J Subst Abuse Treat 2014, Nov 20.*

The 315 participants in this study were recruited from a treatment programme in Massachusetts. They were on either methadone or buprenorphine, they were all smokers and they completed a brief 10-minute questionnaire. In total 98.7% had heard of e-cigs, 73% had ever tried them and just over a third (33.8%) had used e-cigs in the past 30 days. The most common reason for using was curiosity (41%) but just over a quarter (26%) had used e-cigs to help quit nicotine. Significant numbers of them believed that e-cigs could help people quit smoking (74%) and that they could help reduce the use of regular cigarettes (79%).

Commentary: This study showed a significantly higher proportion of the opioid-dependent population had used e-cigs than is found in the general population. The debate about e-cigs has become a common discussion in public health but their role as harm reduction in what we might call 'can't-stop-won't-stop' groups is less considered. Whatever one's individual views I suspect this study reflects a typical pattern – while doctors and policymakers bicker and discuss the merits and demerits of e-cigs the people who are opioid-dependent have already got there and are trying it for themselves. It could be a good topic for discussion in the next consultation with someone who has COPD.