Clinical Update Oct/Nov 2013

Welcome to the latest Clinical Update from SMMGP. Highlights include:

- Sofosbuvir and ledipasvir fixed-dose combination with and without ribavirin in treatment-naive and previously treated patients with genotype 1 hepatitis C virus infection (LONESTAR)
- Tobacco-stained fingers: a clue for smoking-related disease or harmful alcohol use? A case-control study
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- Views and experiences of hepatitis C testing and diagnosis among people who inject drugs: Systematic review of qualitative research
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Sofosbuvir and ledipasvir fixed-dose combination with and without ribavirin in treatment-naive and previously treated patients with genotype 1 hepatitis C virus infection (LONESTAR): an open-label, randomised, phase 2 trial.

Lawitz E, Poordad FF, Pang PS, et al. Lancet Published Online First: 1 November 2013. doi:10.1016/S0140-6736(13)62121-2

This open-label study enrolled 100 patients with HCV infection from a liver centre in Texas, USA. They all had chronic genotype-1 hepatitis C infection. They excluded people with any hepatic decompensation, a BMI of less than 18, or co-infection with hepatitis B or HIV. They were then split into two cohorts. The people in *cohort A* had no cirrhosis and had never been treated. They were randomly assigned to three possible treatment options and they all received sofosbuvir + ledipasvir. One group for 8 weeks, another group for 12 weeks, and a third group for just 8 weeks but with the addition of ribavirin. People in *cohort B* had been unsuccessfully treated in the past. The study design meant that about 50% of those in cohort B could have compensated cirrhosis. This was determined by liver biopsy. They were then split into two groups. Again, both groups got sofosbuvir + ledipasvir with one group being treated for 12 weeks and the other group for 8 weeks with the addition of ribavirin.

The primary outcome was sustained virological response 12 weeks after treatment (SVR12). In total, 60 were allocated to cohort A and 40 to cohort B. The results can be summarised fairly easily as 97 out of 100 achieved SVR12. All 97 of these patients also went on to achieve SVR 24. One of these patients was lost to follow up so in the intention-to-treat analysis is regarded as a treatment

failure. The other two did show virological breakthrough during study treatment (they were in groups who didn't receive ribavirin). The patients in the two groups who were also getting ribavirin had the highest rates of adverse events. In the non-ribavirin groups there was no anaemia. Overall, just under half of the patients had at least one adverse event during the study but all the adverse events were generally rated as mild - nausea, URTI, and headache for example.

Commentary: The results from LONESTAR are impressive. Anyone familiar with current HCV treatment regimes will know about the daily ribavirin and the weekly pegylated interferon needed for weeks and months. The weekly injections of interferon are a tough proposition with numerous side effects and a commitment to treatment for up to 48 weeks in genotype-1 infections. This study used a regime of tablets that requires a quarter of the time, seems to have tolerable side effects, and looks like it could achieve far better SVRs. One simply couldn't ask for much better than that.

There weren't enough patients in this study to distinguish between the treatment groups but the response rates were high even in the face of previous treatment failure, cirrhosis and *IL28B* genotype. There is an ongoing phase 3 study with nearly 2000 people and a lot will depend on the results of this as other factors still need to be considered. What will it cost? Will people who inject drugs be included in these studies? Will the SVRs hold to the 12-month point? It will be a few years before these all shake out but, in the meantime, this is a genuinely remarkable study that raises the possibility of spectacular reductions in the HCV infection burden.

Tobacco-stained fingers: a clue for smoking-related disease or harmful alcohol use? A case-control study. *John G, Pasche S, Rothen et al. BMJ Open 2013:3:e003304.*

This study was based in a Swiss community hospital of 180 beds. They found 49 adults who presented with staining from tobacco on the fingers. They were then matched to 49 control smokers by age, gender, height and pack-year (PY). The outcomes they looked at included: smoking-related carcinoma, ischaemic heart disease, peripheral arterial disease, stroke and COPD (determined by lung function). The association between harmful alcohol use, mental disorder or unemployment with the tobacco-staining was adjusted for smoking behaviour through logistic regression.

The results showed that 84% of the case group had cigarette-related disease compared with 80% of the control group (not statistically significant at all.) Symptomatic peripheral arterial disease was more frequent (OR 3.5, CI 95% 1.1 to 14.6) in the tobacco-stained group. There was no statistical difference for ischaemic heart disease, stroke and COPD. There was a strong association between harmful alcohol use and tar stains - and this persisted even when adjusted for unfiltered cigarettes, more than one pack per day and age at smoking onset.

Commentary: This is a little gem of a paper. Such a simple and obvious clinical sign and one that we see innumerable times in clinics, yet it seems it can have meaning beyond the blindingly obvious that the person in front of you is smoking like the proverbial chimney. One underlying message from this paper is that smokers with staining seemed to present with markers of more addictive behaviour - they are the ones using more alcohol, who started smoking earlier, who smoke the most with fewest breaks. Basically, if you see someone with tobacco-staining on his fingers this paper provides the rather compelling and not altogether intuitive finding that alcohol use should be explored. An AUDIT questionnaire for anyone with tobacco-stained fingers perhaps?

'Surfing the Silk Road': A study of users' experiences. *Hout MCV, Bingham T. Int J Drug Policy Published Online First: 8 September 2013. doi:10.1016/j.drugpo.2013.08.011*

This study reported on the online drug marketplace called 'Silk Road' which has operated since 2011. The dark internet is an area of the internet where anonymity and privacy is fundamental - it cannot be accessed via usual browsers. Users download software, Tor, to maintain security. Payments are made by Bit Coin, an online currency indexed to the US dollar. This study reported on the authors' systematic online observations, monitoring of discussion threads on the site and analysis of 20 anonymous online interviews with a convenience sample of 'Silk Road' users.

Most of the participants were male in either professional employment or in tertiary education. Favourite drugs included MDMA, 2C-B, ephedrine, nitrous oxide, ketamine, cannabis and cocaine. Reasons reported for using the site were: curiosity, concerns about street drug quality and personal safety, the variety of products, ease of product delivery, and the anonymity of the process. The time and technical expertise needed to use 'Silk Road' was noted and there was great appreciation for the 'Silk Road' online community:

"The community here is awesome. There is a 'Drug Safety Forum'. The whole philosophy behind the place is that if you want to put heroin in your body, go ahead. But hey, if you want to get off that nasty drug, we're here to help you too. It's not like real life where street dealers might coerce you into keeping your addiction."

Commentary: We all know how apparently easy it is to buy certain pharmaceuticals off the internet. The 'Silk Road' website takes this to a different level. The FBI shut down the original 'Silk Road' in October 2013. Within a month or so 'Silk Road 2.0' was up and running. It seems likely that this kind of website may come and go but it will remain an option for many people to access their drugs.

Tor (The Onion Router) was originally invented by the US Navy to allow secure communications and is used by dissidents in oppressive regimes to gain access to censored material and to organise political activity. There are also some evil uses for this kind of 'deep internet'. Child

pornography is the most obvious example and a flourishing market for the online buying and selling of drugs will cause alarm in law enforcement agencies. At present, a high level of technical ability is required and vulnerable populations such as the homeless and opiate dependent are likely to be excluded. It may not necessarily be all bad news when it comes to sites like 'Silk Road'. If one accepts that people are going to use substances then it simply changes where they source them. Arguably, it cuts out the middleman and it is with these middlemen that much of the violence can occur in many communities. In addition, it cuts the lengthening supply chain that generally increases the risk of cutting and contamination. There are those who will be anxious about the challenges of law enforcement in these dark corners of the internet but there might be also be some harm reduction value in sites like 'Silk Road'. This paper offers a unique insight into this emerging phenomenon.

Views and experiences of hepatitis C testing and diagnosis among people who inject drugs: Systematic review of qualitative research. *L. Jones A, Atkinson G, Bates E, et al. Int J Drug Pol 2013. doi: 10.1016/jdrugpo.2013.11.004. Published online ahead of print.*

This study found 28 qualitative research studies after they searched 14 databases and hand searched selected journals, as well as relevant websites. They included any study of a qualitative design that examined the views and experiences of, as well as the attitudes toward, HCV testing and diagnosis among people who inject drugs (PWID) and those involved in providing care. Three major themes emerged in the analysis and were as follows:

Missed opportunities for the provision of information and knowledge. This cropped up repeatedly as a theme. The limited provision of information by healthcare professionals was one factor and also individual's awareness that they had incomplete or only partial knowledge. Many people were unclear on the meaning of a diagnosis and a policy of not informing people who inject drugs of the outcomes of testing was noted to cause anxiety. *Shifting priorities between HCV testing and other needs.* Some studies described a trivialisation of a positive HCV diagnosis but this was relative when compared to a HIV diagnosis and arose as a consequence of joint testing procedures. PWID perceived themselves as never being completely safe from HCV, however, many felt their own risk was low due to a belief they were minimising the risk within their own injecting network. Obtaining drugs was prioritised over healthcare but for those who did get a positive diagnosis this did lead some to seek treatment. Others expressed anxiety that a positive diagnosis would reduce their chances of finding a long-term partner, it would affect sexual relations, and their hopes of starting a family. *Testing as unexpected and routine.* Many people had experienced testing as part of routine health assessments but when consent for testing was not explicitly obtained then this worsened anxiety and confusion over a positive diagnosis.

Positive experiences of testing were rare but important motivators of testing were noted to be trust and rapport from staff in drug services as well as support and encouragement.

Commentary: The work of the clinician is grounded in the individual and presenting themes will often feel much harder to reconcile with definite changes of practice. That said, this is a good overview of the key areas to consider when consulting with people who inject drugs. Most of these factors can be addressed - they are not insurmountable and small changes in consultations alongside small changes in service provision can have large impacts for the individuals.

Interventions to prevent the initiation of injection drug use: A systematic review.

Werb D, Buxton J, Shoveller J, et al. Drug Alcohol Depend 2013;133:669–76.

This systematic review evaluated the effectiveness of any intervention that stopped people from initiating injecting. In the initial search they found 384 papers but only eight studies met the inclusion criteria. There were able to categorise these into four different types of intervention: social marketing, peer-based behaviour modification, treatment, and drug law enforcement.

Four studies found a significant effect and peer-based behaviour modification and addiction treatment interventions were found to be the most effective. *Social marketing* was considered in a single study that used posters to communicate messages about injection related harm to Montreal street youth. Most of the results were qualitative but they were viewed as effective in preventing young people from initiating injection. Two of the *peer-based behaviour modification* studies were known as ‘Break the Cycle’ and were conducted in the UK, Uzbekistan and Krygystan. The UK study included 86 participants and involved getting peer injectors to provide education around the harms of injecting. The injecting drug users themselves had a reduction in injecting in front of non-injectors and requests to initiate non-injectors dropped from 36 to 15 after exposure to the intervention. The number of initiates dropped from six to two. *Treatment* was examined in a single study looking at injection initiation amongst intra-nasal heroin users. Overall the results suggested that increased number of times in treatment was associated with a decreased chance of injecting. There were three *drug law enforcement* studies and two found no impact with the results being inconclusive in the other.

Commentary: How can we stop people from starting to inject? It is a common clinical scenario to be sat with a patient who is smoking heroin but hasn’t perhaps achieved complete abstinence. Maybe you know that their partner injects or you know that their associates inject. It would be nice to know what could be done to help ensure they don’t start injecting. Keeping them in treatment is an obvious measure and this study bears that out. There is something of a lack of evidence for other measures but the peer-based approach seems to hold promise to tackle this specific problem.

Prudent use of voluntary workers and other peer-based initiatives, particularly with those who have been service users themselves in the past, might be the best resource.

Continuing care for patients with alcohol use disorders: a systematic review. *Lenaerts E, Mathei C, Matthys F, et al. Drug and Alcohol Dependence 2013. doi:10.1016/j.drugalcdep.2013.10.030. Published online ahead of print.*

This systematic review identified an initial 20 trials out of over 15,000 that met their inclusion criteria. Only six were felt to be strong enough in methodological terms to analyse further. Four trials suggested that an active intervention that empowered the patient on top of usual continuing care could lead to better drinking outcomes. Interventions included telephone calls, nurse follow-up, individual counselling and couples therapy.

Three trials used telephone calls in the experimental group. These varied from supportive calls every two weeks from the counsellor, to patient-initiated calls at predetermined times to empower the patient and which included more active counselling. In addition, home visits and acamprosate with physician review were included. *Psychotherapy* was used in a variety of forms - behavioural, motivational, twelve step facilitation, and interactional couples therapy have all been looked at. Relapse prevention and behavioural couple therapy seemed to show some effect. Twelve step facilitation did not show much effect and this fits with the overall evidence that doesn't show great effectiveness.

Commentary: After the dust has settled on an acute alcohol detoxification we need to think about the long-term care of people with alcohol problems. We know about the chronic nature of the disorder. It's worth noting that the percentage of patients who were continuously abstinent was low and ranged from 17% to 38.5% at 12 months follow-up. One of the challenges of this review was that it only included patients who had an alcohol use disorder and without any co-occurring substance misuse disorder. There is a risk that this study can seem unduly pessimistic and the authors do their best to wring out some positive conclusions. Largely, adding any intervention to 'usual care' seems to have some small effect. They also advocate a longitudinal approach with good continuity of care from GP or specialist. The authors are clear on the damaging consequences and so small differences in trials can make big differences to the individuals and their families.

Training family members to manage heroin overdose and administer naloxone: randomized trial of effects on knowledge and attitudes. *Williams AV, Marsden J, Strang J. Addiction 2013. doi:10.1111/add.12360 Published online ahead of print.*

The aim of this study was to evaluate a heroin overdose management training programme for family members. The take-home naloxone (THN) programme included an initial presentation on overdose

management and naloxone administration. There was then a practical session around management of an overdose situation and the administration of naloxone. Family members and carers involved were allocated to either the THN group or to a 'basic information' on opioid overdose management group that acted as the control group. The primary outcome measure was by self-completion of the Opioid Overdose Knowledge Scale (OOKS). The Opioid Overdose Attitudes Scale (OOAS) was used as a secondary outcome. They were assessed before the intervention and then again at three months.

In total 187 people were allocated - 95 to the THN training and 92 to the 'basic information' control group. The results showed that the group who had the THN training reported significantly greater overdose-related knowledge at three months. There were also more positive opioid overdose-related attitudes among the trained group. It was noted that 35% of the individuals in the trained group improved their knowledge; and 54% increased their attitude scores. This was compared to 11% and 30%, respectively, of the control group. During the follow-up period 13 participants witnessed an overdose and naloxone was administered on eight occasions. Five of these were in the THN group and three in the control group.

Commentary: This is really a study about education - and educational interventions are difficult to evaluate. The experimental design has many strengths over an observational study. The OOKS is a short MCQ based on some key facts around overdose and the use of naloxone and it was developed by the authors to assess educational interventions like these. There are also some weaknesses - the challenge with any sort of medical education is finding the hard, preferably clinical, endpoints. Inevitably, in a trial like this there are not going to be enough overdose events to set a clinical outcome (it would have to be an enormous study) and the authors acknowledge this. The authors state that because THN is superior to providing information it should now be rolled out to all family members 'routinely' in a bid to prevent fatal outcomes. There are lots of sound reasons why educating family members is a good idea - the authors quote a study where more than 1 in 5 family members or carers of illicit drug users had already witnessed an overdose. In their own study, two-thirds of the study group had daily contact with their 'drug-using relative' daily. I still think there are issues about 'routine' roll-out that need to be addressed – particularly how family members are recruited. In the end, it is the person who is in treatment and while the importance of social networks can't be under-estimated, the potential stigma should be considered alongside the economic costs of an intervention that had a modest effect on participants' completion of a short MCQ.