Clinical Update 2014-1

Welcome to our first Clinical Update this year. Highlights include:

- Sexual dysfunction among male patients receiving buprenorphine and naltrexone
- Prevalence of sexual dysfunction among male patients on methadone and buprenorphine
- Maintenance treatment for opioid dependence with slow-release oral morphine
- Not just 'Methadone Tracy': transformations of service-user identity
- General health of opioid substitution therapy clients
- Pharmacological interventions for drug-using offenders (Review)
- The diversion and injection of a buprenorphine-naloxone soluble film formulation
- The oral health of heroin drug users: case study in Bosnia and Herzegovina

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Sexual dysfunction among male patients receiving buprenorphine and naltrexone maintenance therapy for opioid dependence. *Ramdurg S, Ambekar A, Lal R. Journal of Sexual Medicine 2012;9:3198-3204*

This paper reported on a study in India that used a semi-structured questionnaire and the Brief Male Sexual Functioning Inventory (BMFSI) on 60 sexually active men - 30 were on buprenorphine and 30 were on naltrexone maintenance. Their main outcome measures were: prevalence of premature ejaculation; erectile dysfunction; low sexual desire; weakness due to semen loss; and overall satisfaction.

The results showed that 83% of men on buprenorphine and 90% on naltrexone reported at least one of the sexual dysfunction symptoms. These split down as follows: premature ejaculation (83% bup/87% nal); erectile dysfunction (43% bup/67% nal); and reduction or loss in sexual desire (33% bup/47% nal).

The prevalence of sexual dysfunction among male patients on methadone and buprenorphine treatments: a meta-analysis study. *Yee A, Seng Loh H et al. Journal of Sexual Medicine 2014;11:22-32*

This meta-analysis looked at papers up until December 2012. A total of 1,570 participants in 16 studies were included after all the searching, sifting and sorting. The authors employed quite a strict set of criteria to assess the methodological value of the prevalence

studies they found after their systematic search. Sexual dysfunction included erectile dysfunction, ejaculatory disturbances and lack of desire.

The prevalence estimate for sexual dysfunction with the pooled data was 52% (95% CI, 0.39-0.65). There were four studies that compared methadone and buprenorphine directly. There was a significantly higher odds ratio in the methadone group with a risk four times greater (OR=4.01, 95% CI 1.52-10.55, p=0.0049) for sexual dysfunction.

Commentary: Both of these studies examined the problem from the perspective of men. I'm sure most clinicians will have had consultations where the topic of methadone and erectile dysfunction has been discussed. The most obvious comment to make is on the high prevalences that the studies found. Now compare those numbers to the frequency of those consultations where erectile dysfunction has been raised as a topic. I'd wager there is a significant gap. One of the challenges is unpicking the underlying set of causes for sexual dysfunction and the first study makes some attempt to pick the bones out of the problem. Inevitably, methadone is held up as the guilty party - but, in this case, as suggested by the second study, there does seem to be some merit in the argument. The usual suggestion is to change people from methadone to buprenorphine. In practice, particularly if the man in question is on a half-decent dose, this is not always straightforward. This recommendation is often tossed about by the authors of papers (particularly anyone writing about QTc intervals) but one wonders how much experience they have of the challenges of a methadone conversion.

The first paper was based in India and there may be some cultural differences that should be borne in mind - this is most obvious in the outcome measure "weakness due to semen loss". This is a phenomenon reported in clinical practice in India but which remains under-researched and, in my experience at least, isn't a common complaint in UK practice.

Maintenance treatment for opioid dependence with slow-release oral morphine: a randomized cross-over, non-inferiority study versus methadone. *Beck T, Haasen C, Verthein U, et al. Addiction 2013. Published online ahead of print. doi: 10.1111/add.12440*

This paper compared slow-release oral morphine (SROM) to methadone in a study conducted over two 11-week periods with 157 patients. They were all in treatment in

Switzerland and Germany on doses of 50mg or greater of methadone for at least 26 weeks. As one would expect with a cross-over study the participants spent 11 weeks on either methadone or slow-release morphine before being swapped over to the other medication. The end-point was the proportion of heroin-positive urine samples per patient and period of treatment. Each week, two urine samples were collected. They set a non-inferiority boundary of 10% for difference in proportions using a two-sided 95% confidence interval.

The proportion of heroin-positive urine samples in the SROM group was 0.20. In the methadone treatment group it was 0.15. Hence a difference of 0.05 with a 95% CI range of 0.02 to 0.08 and as the 95% CI also fell within the 10% range the SROM was regarded as non-inferior. There was no significant difference in retention in treatment and safety outcomes were also similar.

The slow-release oral morphine was provided in capsules. Converting methadone to SROM was done in a ratio of 1:6 to 1:8. Conversely, SROM was switched back to methadone in a ratio of 8:1 to 6:1. During the treatment phases supervision was scheduled for at least 3 days per week.

Commentary: This is an important study as it adds to some existing evidence and could lead to greater use of SROM. These patients were well established on methadone - all of them had been on it for at least six months. One has to ask what advantage these people would gain from moving to slow-release oral morphine. Well, perhaps the sexual dysfunction problems highlighted in this update may be a factor. Or maybe they have a QTc problem and buprenorphine doesn't suit. SROM then presents an alternative and medications don't get much more generic or cheaper than oral morphine. In practice it is harder to see all that much use of SROM - substance misuse services are locked in an embrace with methadone and buprenorphine and fear of diversion often pushes other options to the very margins.

This is a robust study and the authors were quick to point out its 'real world' setting. The stability of the participants is a key feature needed for a cross-over study and there is clearly some real world applicability here.

People who have been on methadone for years may well feel limited in their options - I

hesitate to use the word 'parked' given the pejorative use of that term in the past. SROM offers a further option that may be worth considering - and this study adds to some evidence that the outcomes are equivalent to methadone.

Not just ‘Methadone Tracy': transformations of service-user identity following the introduction of hepatitis C treatment into Australian opiate substitution settings.
Rance J, Treloar C. Addiction. Available online ahead of print. doi:10.1111/add.12392

This qualitative study was part of the Australian ETHOS (Enhancing Treatment for Hepatitis C in Opiate Substitution Settings) project in New South Wales. Semi-structured interviews were conducted with 57 service users, 16 staff and three peer support workers. All the service users had chronic hepatitis C (HCV) and the staff were employed on the ETHOS project.

The findings found that service users largely welcomed HCV treatment as a practical, clinical intervention but that they also recognised it was part of a more holistic care approach. It disrupted some of the more negative and limited clinical exchanges and so opened up 'new relationships' between staff and service users. As Tracy said:
"*It was nice to know that somebody actually looked out for Tracy, not just 'Methadone Tracy'... they took the time out to realise that there was something more than me just coming to get methadone. I had other issues. And it [HCV] was something I didn't wanna address. And she [the ETHOS clinician] helped me address it*..."

Commentary: This is an exciting paper. It offers a glimpse of a future that moves far beyond a model of care where methadone dominates the proceedings. *Clinics where management of health is seen as the priority have the potential to transform how people view their own identity*. And before services with a heavy emphasis on 'recovery' start flag-waving I'd question whether the recent orientation toward 'recovery' comes close to delivering this kind of model. It's still too focused on the substances and often lurches into a paradoxical obsession with abstinence and reduction. Of course - and I would say this - primary care offers the easiest transition to a model that truly embraces health.

It wasn't an anticipated finding of this study and there are limitations as well - not least that the participants volunteered for the programme. Some of the changes in the individuals

weren't quite as explicit as they were from the staff. In retrospect, it is easy to see how HCV could engender some of these changes. Patients get more closely involved with their healthcare - side effects of treatment need to be explored and addressed, bloods get checked regularly, mental health is monitored, and there is a general appreciation for the physical and psychological welfare of the individuals.

General health of opioid substitution therapy clients. *Islam MM, Taylor A, Smyth C, Day CA. Intern Med J. 2013 Dec;43(12):1335-8*

This was a short report that assessed five common medical conditions in people on opioid substitution therapy at a health promotion event in Sydney. It was a hospital-based clinic. They had 58 participants and the areas looked at and their results were as follows: *Anthropometric data.* 42% had a normal BMI with 47% being overweight with a BMI of >25. The Australian general adult population has around 61% who have a BMI >25. Just six people (11%) were underweight with a BMI <20. *Spirometry.* COPD was detected in 30% of the people. *ECG.* An abnormal ECG was found in 17%. QTc prolongation was found in just two people. *Smear test.* Only 47% of the female participants reporting having had a smear in the previous two years. *Fibroscan.* Fibrosis was detected in 34% of participants. 60% had HCV antibodies and 40% were PCR positive - i.e. viraemic.

Commentary: There a number of bits from this paper I like and deserve a little bit of thought as they fit with a general health theme of some of the articles from the Update. It's not a huge sample but they have given these folk a thorough MOT. Most people won't be under any illusions about the scale of the HCV problem in this population. Over a third of this sample had clear evidence of liver fibrosis and a quarter of the overall sample were classified as severe fibrosis or cirrhosis. Clearly the health problems don't stop there and it's the spirometry one that stuck out for me. Three out of ten with COPD is high and this is further evidence of the poor respiratory health in this group. The authors also comment on the dismal success rate in smoking cessation programmes in this group.

Nearly one in five had some kind of abnormality on their ECG but only two were related to the QTc interval. We certainly experienced this when we started doing regular ECGs for folk on higher doses of methadone or risk factors - we started picking up a lot of medical problems such as missed MIs, left ventricular hypertrophy, signs of ischaemia etc. This

paper doesn't give further details on the other abnormalities they found but there might be a compelling case here for using ECGs more widely in the management of the health of users.

Pharmacological interventions for drug-using offenders (Review). *Perry AE, Neilson M, Martyn-St James M, et al. Cochrane Database of Systematic Reviews 2013, Issue 12, Art. No.: CD010862*

This review is one in a 'family of four' reviews looking at interventions for drug using offenders - though it seems that only three have been published by The Cochrane Collaboration thus far. The other two look at: interventions in female drug users and interventions in drug-using offenders with co-occurring mental illness. This review identified 17 trials containing 2,678 offenders and used the standard methodological procedures expected by The Cochrane Collaboration. The interventions considered were buprenorphine, methadone and naltrexone. Overall, the results do suggest that pharmacological interventions do significantly reduce subsequent drug use and criminal activity. There were a number of sub-group comments but there all need to be approached with extreme caution given the small numbers. There were no statistically significant differences between treatment settings.

Commentary: This adds further evidence to the need for good pharmacological interventions - in this case related to mainly male offenders. There are a number of limitations with this review. Many of the studies were judged to be at considerable risk of bias in combination with the number of studies being small. It is worth highlighting that naltrexone was also swept up into the review - which makes me wonder if the review team have experience of these clinical interventions as it rather dampens down the utility of the overall conclusions.

It's worth pausing for a moment to consider the context for this review and its application in England. Are there prisons in England where people are being reduced off their opiate substitution therapy against their wishes? If this is occurring then this is largely attributable to the highly politicised IDTS policy guidance amendment in 2010. Doctors involved in prescribing opiate substitution therapy should take great care given they represent the final authority in matters of prescribing.

Strang's report *Medications in recovery: re-orientating drug dependence treatment* states that for sentences beyond six months "opioid reduction (detoxification) where indicated" and it references the Orange Book. We all need to be guided by the evidence and that word 'indicated' places considerable emphasis on the judgement of the prescriber. I'm not aware of any evidence that supports compelling reduction and a considerable body of evidence that supports pharmacological interventions such as methadone and buprenorphine. This Cochrane review adds to that evidence. Half-baked political policy that was set out to appease the anti-methadone lobby won't appease the GMC when doctors ride roughshod over the evidence and reduce methadone against the wishes of individuals.

The diversion and injection of a buprenorphine-naloxone soluble film formulation.
Larance B, Lintzeris N, Ali R. Drug and Alcohol Dependence. Available online ahead of print (doi 10.1016/j.drugalcdep.2013.12.005)
This paper looks at buprenorphine-naloxone (BNX) film - a newer preparation that is not actually available in the UK at this point. In Australia, since April 2012, BNX film has accounted for a larger market share than BNX tablets. This study compared the diversion and injection of BNX film with BNX tablets, buprenorphine on its own (BPN), and methadone in Australia.

They conducted interviews with two groups - 541 out-of-treatment people who inject drugs and 544 people in opiate substitution therapy (OST). Their primary outcomes measures were the prevalence and frequency of OST medication injections and they covered the period from 2004 to 2012. Among the OST clients BPN had higher levels of injecting - 'weekly or more frequent injecting' was at 11% compared with BNX film clients at 3%. There was no difference between BNX film when compared with BNX tablets and methadone. The results showed that in the out-of-treatment PWIDs levels of injection of BNX film were comparable to those for methadone and BNX tablets. The illicit market price was the same across the board for all the buprenorphine-based preparations.

Commentary: As clinicians it is important we don't get drawn into ever decreasing circles of discussion about preparations and diversion. As this paper shows, diversion will occur to some degree in any system, and with any medication. Sometimes our patients take advantage of it but if we lived in a world where no one ever experimented or diverted any medication it would probably be a world where there was no such thing as addiction. And it

is worth bearing in mind that, as this study also showed, the most common motivation for using diverted medication is frequently self-treatment of withdrawal symptoms. No one advocates diversion but when it influences key prescribing decisions, potentially at the expense of other benefits, then we need to stop and take stock.
The diversion of any buprenorphine-based medication for injection seems less of an issue in the UK than some countries - and if it influenced diversion for snorting then that might have great impact. This study showed higher levels of diversion of BPN but there was little to choose between the various BNX preparations and methadone. The authors of this study state: "At this time, there is no evidence that the BNX film is superior to the BNX tablet in reducing non-adherence and diversion".

The oral health of heroin drug users: case study in Bosnia and Herzegovina. *Terzic Supic Z, Petrovic R, Santric Milicevic M, et al. BMC Public Health 2013, 13:1202*
This was a cross-sectional study carried out as part of a UNICEF research project among injecting drug users (IDU). A total of 519 IDUs took part in the survey. They underwent face-to-face interviews using a structured questionnaire.

The questions around oral health asked about missing teeth, difficulty with chewing or swallowing, and dry mouth. These were scored out of 13 with anyone getting 7 or less being classified as having 'bad oral health'. Multiple logistic regression then showed that predictors of bad oral health included older participants, part-time employment and unemployment compared with full-time employment, and longer duration of drug injection.

Commentary: In 1999 I visited Banja Luka, one of the centres for this study, as part of NATO's SFOR, and the country of Bosnia and Herzegovina still has significant problems that we should bear in mind with this study. The main reason to highlight this paper is to encourage thoughts of dental health to bubble up into the consciousness. The parlous state of dental health in heroin drug users isn't unique to the post-war Balkans. How many services in the UK bake decent dental care into their package? We know that there is an association with dental health and wider health effects - the risk of cardiovascular disease for instance. Less well explored is the devastating effect on self-esteem - people *know* their teeth are bad. It would be good to hear about innovative approaches to dental care and perhaps these can be shared through the SMMGP blog or forum.
http://www.smmgp.org.uk/blog/