SMMGP Clinical Update

SMMGP Clinical Update is compiled by Euan Lawson. This issue includes:

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Sustained-release dexamfetamine in the treatment of chronic cocaine-dependent patients on heroin-assisted treatment: a randomised, double-blind, placebo-controlled trial.
Nuijten M, Blanken P, van de Wetering B, Nuijen B, van den Brink W, Hendriks VM. The Lancet 2016, Mar. Published online 22 March 2016.

This study was based in the Netherlands and was a multicentre, randomised, double-blind, placebo-controlled trial. All the patients who were included had at least two previously failed attempts to reduce or give up cocaine use. They were still using crack cocaine for eight or more days per month and they were all currently enrolled at heroin-assisted treatment centres in the Netherlands. Patients were randomly assigned to either 12 weeks of daily supervised dexamfetamine (60 mg per day oral sustained release) or placebo in addition to co-prescribed methadone or diacetylmorphine. The primary outcome was the number of self-reported days of cocaine use during the study treatment and this was assessed every four weeks.

They enrolled 73 people into the study of whom 38 were assigned to the dexamfetamine group and 35 to the placebo group. The participants who received dexamfetamine had significantly fewer days of cocaine use than those who received placebo (mean 44.9 days vs 60.6 days, p=0.031). Just under three-quarters of patients in the dexamfetamine group reported one or more adverse events but just under half of patients in the placebo group did as well. These were mostly transient, such as sleeping problems and irritability, and did not cause significant problems.

Commentary: At present one of the difficulties with managing cocaine dependence is that the most effective interventions are psychotherapies of various hues. In resource scarce treatment services this is an often unfulfilled niche and, increasingly, as budgets get constrained further, it may be less likely to occur as treatment services, in response to unmanageably low budgets, are frequently moving towards group-based treatment rather than individual psychotherapeutic options. In terms of prescribing, the evidence for agonist replacement has always been limited with studies that have had various flaws: too few participants, inadequate dosing, or too many dropouts being typical problems. This study, as the accompanying Lancet commentary by Dürsteler and Vogel highlights, answers a lot of those questions.

However, before you go rushing for the prescription pad it is worth considering some of the limitations. Perhaps, the most important one is the context of this study. The dropout rate in previous dexamfetamine studies has been often an issue but this has been elegantly side-stepped in this study by tagging it on a heroin-assisted treatment centre. Clearly, people attending are seen on a regular basis, sometimes up to 3 times daily, to receive pharmaceutical heroin under medical supervision. That's a very different model of care to your average opioid substitution therapy treatment scenario in the UK.

It is also worth remembering that participants still continued to use cocaine on more than half of the days on average. Harm reduction it is; miracle cure it isn't. There were unquestionably significant reductions but, perhaps due to the long acting nature of the stimulant compared to desirable short-acting hit of cocaine, it is a step on the road to what Dürsteler and Vogel call "the quest for an effective pharmacotherapy".

Trends in drug misuse deaths, 1999 to 2015. Public Health England (2016).
Available at: http://www.nta.nhs.uk/uploads/trendsdrugmisusedeaths1999to2014.pdf

Public Health England summarise some of the facts around drug-related deaths in this report. Here are some key points:

- Almost one in nine deaths registered among people in their 20s and 30s in England and Wales in 2014 were related to drug misuse.
- In recent years the Office for National Statistics (ONS) has reported year-on-year increases with a 17% increase in 2014 (and this was after a 21% increase in 2013).
- Opiates are the substance most frequently mentioned and are consistently mentioned in over 80% of deaths, the most common being heroin, then methadone and tramadol.
- The ONS data also showed an increase of at least 21% in opiate deaths in 2013.
- Alcohol is mentioned in combination with illicit drugs in 36% of cases of drug misuse deaths in 2012 (similar to previous years).
- Benzodiazepines are the most commonly mentioned non-opiate drug with 16% in 2012 and it was noted there was an increase of at least 21% in benzodiazepine deaths in 2013.
- There has been an increase in mentions of stimulants such as cocaine and amphetamine since around 2010. And, unsurprisingly, drug misuse deaths in novel psychoactive substance continued to rise in 2012 but the provisional figures for 2013 suggest a fall (and they only constitute 4% of drug misuse deaths).
- Although three quarters of the deaths in 2012 were classified as accidental the remainder were classified as suicide. Older patients, women, and opiates other than heroin and methadone are more likely to be involved in these.
- There are clear markers that among the heroin deaths complex poly-substance deaths are more common. The median age at death increased from 30 to 1999 to 41 in 2012.

Commentary: It is worth linking this PHE report to a talk given at a recent conference on this subject held in Manchester. One of the slides reported on data from a drug treatment service in the region. It's what they didn't find that is so interesting: no association with opioid substitution therapy; no apparent link with change in services (the 'churn' of tendering/retendering being worrisome); no other factors other than the high prevalence of

physical health issues. And, perhaps, this hits it exactly on the nose, a light bulb moment, that could explain why we are seeing an upward trend. We've got an ageing population, pulling in terrifying amounts of comorbidity and it is entirely logical that people who are physically less well, more likely to suffer adverse consequences from drug use, are more susceptible to drug-related deaths.

How do we manage that? If physical health concerns are the key factor then we need sophisticated, integrated services that can manage complex care needs and it will be a slow process. There's no magic bullet. To make long-term headway we need, preferably, to stop people overdosing in the first place and, as important as naloxone is, the discussion around naloxone can swamp the discourse around drug-related deaths. Primary care has an enormous role in managing ageing users with complex co-morbidity.

Two other important wrinkles to mention: Firstly, the second section of the report matches deaths to drug treatment data and in 57% of opiate misuse deaths in 2012 the person had no contact with community treatment services for many years highlighting the importance of being in treatment; secondly, a quarter of the deaths in 2012 were classified as suicide. That also needs a very different approach but is seldom emphasised.

Association between routes of drug administration and all-cause mortality among drug users. *Onyeka, Basnet S, Beynon CM, Tiihonen J, Jaana F, Kauhanen. Journal of Substance Use. Published online 26 January 2016.*

This study used regression models to calculate adjusted hazard ratios for all cause deaths. They used data from 2766 primary users of opiates and stimulants who were being treated in Helsinki, Finland. These people were then linked to the national cause of death register. The results showed that there were statistically significant differences in all-cause deaths by route of administration (ROA). These ran at 12.7% among the intravenous drug users, 11.5% among all users, 7.9% among smokers, 6.9% amongst snorters, and 16.5% among those with unspecified ROA.

Commentary: The point about this paper is not so much to highlight the risks of injecting drug use. That is pretty well known and is confirmed here. It's the findings around the edges that pique interest. There were some deficiencies in these data - in the subgroup where ROA wasn't documented there were the highest rates of all-cause and overdose deaths. This could, perhaps, represent the most chaotic group of people, those where engagement has been turbulent, fleeting, where even these basic data haven't been gathered. The use of stimulants as the primary drug compared to opiates also independently daily increased the risk. (Amphetamine is quite dominant in the Finnish drug scene and this will also be familiar to certain corners of the UK.)

Their results also showed that previous attempts of suicide independently increase the risk of all-cause deaths by 83%. This highlights, as done so by the authors, that people who attempt suicide are a subgroup of users with particularly poor psychological and social function. The result also confirmed that male gender was an independent risk factor for death. This suicide theme is worth considering in light of the PHE drug-related death data - it's not an insignificant problem and I wonder if we are doing enough to intervene.

Loperamide induced torsades de pointes: a case report and review of the literature.
Mukarram O, Hindi Y, Catalasan G, Ward J. Case Reports in Medicine 2016;2016:1-3.

Loperamide, the anti-diarrhoeal medication, is an opioid agonist that has high mu receptor specificity but is thought to have low abuse potential because it cannot cross the blood brain barrier. This is a case report about a 26-year-old male who had a history of heroin abuse and arrived in the emergency room after an episode of loss of consciousness. He had a couple of episodes of self-limiting torsades de pointes while being monitored and after a couple of days in the hospital he was able to give a history that he had been taking high doses of loperamide as he believed it could give him a similar high to heroin. On the day of his admission he actually managed to take 192 mg of loperamide - amounting to 96 tablets.

Commentary: There have been some internet reports that taking loperamide in combination with omeprazole can somehow cause loperamide to have a greater effect. Perhaps one of the main points of a paper like this is just to demonstrate, and remind us, that the determined person who wants to misuse substances will usually find a way somehow with, at first glance, the unlikeliest of medications. Sometimes we'll need to ask specific questions to get answers and while novel psychoactive substances have certainly helped broaden my history-taking this is another one to add to the list.

SMMGP Policy Update

Public Health England (PHE) Structured Brief Advice Tool (Alcohol). *PHE, May 2016.*
http://tinyurl.com/o8pmfrd
In the light of CMO guidance, PHE have recently updated the popular "IBA tool" on the Alcohol Learning Resources site. The tool is presented with "key components" of FRAMES based brief advice.

Having prompts and visual aids such as those available in his handy tool, assist the practitioners to remember various things that may be useful to discuss with a drinker, to help identify something that is relevant to the person. More information is available in this blog post https://alcoholiba.com/

For more information about FRAMES see link: http://tinyurl.com/zkmpln2