



## SMMGP CLINICAL UPDATE – DECEMBER 2009

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**Consequences of chronic ketamine self-administration upon neuro-cognitive function and psychological wellbeing: a 1-year study** Morgan C, Muetzelfeldt, Curran HV. *Addiction* 2009. doi:10.1111/j.1360-0443.2009.02761.x

This longitudinal study was designed to consider what effects, if any, ketamine has on neurocognitive function and psychological wellbeing in groups of frequent, infrequent and abstinent ketamine users over a 12 month period.

The study identified a cohort of 150 individuals and they used a 'snowballing' sampling technique before placing them into one of five groups: frequent ketamine users (more often than x4/week); infrequent users (less than x4/week but more than x1/month); abstinent (no ketamine for >1 month); matched polydrug users; and non-drug users.

The study participants went through a battery of neurocognitive and psychological tests at baseline which were then repeated 12 months later (when they still had 80% of their cohort).

They did not rely on self-reporting of ketamine use and they used hair analysis to confirm that participants were in appropriate groups for frequency of use. The results showed that most of the cognitive deficits were in those that used ketamine frequently – i.e. more than x4/week. The frequent users had significantly more errors in the spatial working memory task than all other groups. There were also deficits in pattern recognition memory and a trend toward poorer verbal recognition memory in this group.

There was also evidence of delusional symptomatology in *all* groups fitting with previous research that has suggested 'chronic ketamine use may model aspects of psychosis'.

There was also a 'dose-response' with frequent users being more affected. This adds weight to the suggestion of direction causation by ketamine itself. There was also an association with increased depression in frequent users but abstinent users were also depressed (as measured by Beck Depression Inventory).

The researchers had hypothesised that there might be increasing ketamine use amongst users as they developed tolerance. There was no self-reported evidence of this but the hair samples did show double the concentrations in recreational users at follow-up.

### **SMMGP comment:**

The problems with ketamine abuse are becoming increasingly evident and clinicians are becoming more aware of effects such as bladder problems. This robust study is timely and suggests that there are also adverse effects to cognitive function and psychological wellbeing. There is more on ketamine from the SMMGP at <http://tinyurl.com/SMMGPNetwork27>.

The findings of this study have direct clinical relevance and are well worth putting in context. Users may have short and long-term memory issues and these will worsen with increased frequency of use. There was also evidence of mild delusional ideation and this, again, increased with frequency of use. Soberingly, two of the frequent user groups (n=30) died in the 12 month follow-up period and these were in ketamine-related accidents. The dissociative state that ketamine induces places users at high risk of physical harm and while infrequent recreational use may not be associated with cognitive impairments (but still mild delusional symptoms) the risks associated with repeated heavy use are mounting.

**High potency cannabis and the risk of psychosis.** *Di Forti M, Morgan C, Dazzan P, et al. British Journal of Psychiatry 2009. 195, 488–491. doi:10.1192/bjp.bp.109.064220*

**Cannabis and suicide: longitudinal study.** *Price C, Hemmingsson T, Lewis G, et al. British Journal of Psychiatry 2009. 195, 492-497. doi: 10.1192/bjp.bp.109.065227*

This month the British Journal of Psychiatry published a pair of papers on cannabis.

The first study took 280 people who had a first episode of psychosis and assessed their cannabis use. This was a case-control study and the 280 people with psychosis were compared with 174 individuals who were recruited through advertisements and leaflets in the local PCT area. Those controls who agreed to participate were administered the Psychosis Screening Questionnaire and excluded if they met criteria for a psychotic disorder or reported a previous diagnosis of psychotic illness.

There were some interesting results. There was no difference between the cases and the controls in terms of lifetime cannabis use. Similar proportions had used cannabis and the age of first use was much the same. The big differences were in the frequency of use and type of cannabis use. The cases were around 6 times more likely to use daily than the controls (OR 6.4 95% CI 3.2-28.6) and they were nearly 7 times more likely to use sinsemilla or 'skunk' (OR 6.8 95% CI 2.6-25.4). Longer use of cannabis (for more than 5 years) was initially associated with psychosis but once confounders had been controlled for this was no longer statistically significant.

The second study took a cohort of Swedish military conscripts and followed them up over 33 years. It started with a large cohort of 50,087 and only 2-3% of men in Sweden would have been exempt from the conscription.

There are some difficulties with the study – use of cannabis may not have been reliably reported on entry (and rates of 10.7% in the 'ever-used' group are considerably lower than modern experience) but the authors have thoughtfully considered the limitations. The confounding factors they adjusted for included problematic behaviour in childhood, other drug use, psychological adjustment, alcohol

consumption, tobacco use and psychiatric diagnosis at conscription.

The authors point out that the initial crude analysis shows a significant association with cannabis and suicide. However, once the confounders were then controlled for there was no evidence of an association. There was some evidence that use of drugs other than cannabis was associated with an increased risk of suicide.

#### **SMMGP comment:**

The cannabis and psychosis paper presents further evidence that cannabis could have a causal relationship with psychotic disorders (approximately doubling the risk of schizophrenia), with use commencing under the age of 16 years being a significant moderator of such risk. A major issue in case-control studies is the sampling and any differences between groups needs to be carefully considered. Although the authors have claimed that the groups were comparable with no significant differences there is, fairly obviously, a significant difference with controls being more likely to be in employment compared with cases ( $p=0.001$ ). It is alarming that a significant difference has not been commented on in the discussion; indeed, the authors state that there were no differences. Overall, even allowing for this flaw, this paper probably adds weight to the evidence that cannabis can cause psychosis. The increased use of skunk or sinsemilla is also noteworthy and fits with experimental studies where  $\Delta 9$ -tetrahydrocannabinol has induced psychosis. THC content in marijuana 1.0-3.0% whereas in skunk (the flowering heads of the plant it is 5.0-20.0%

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**Randomized controlled trial comparing the effectiveness and safety of intranasal and intramuscular naloxone for the treatment of suspected heroin overdose.** *Kerr D, Kelly A, Dietze P, et al. Addiction, 104: 2067-74. doi:10.1111/j.1360-0443.2009.02724.x*

The study was based in Australia and looked at the pre-hospital delivery by paramedics of naloxone. Ambulance crews in Melbourne attended around 178 cases of suspected opiate

overdose and randomly selected to give intranasal or intramuscular naloxone. They used a concentrated preparation of naloxone (2mg/ml) and gave 0.5ml into each nostril using a mucosal atomisation device. They measured response rates at 10 minutes and if necessary a further intramuscular dose could then be administered.

The overall results showed that intranasal naloxone could successfully reverse heroin overdose in 82% of patients. This is comparable to intramuscular naloxone and the reversal occurred in the same time. Despite this similar response rate there was a higher number in the intranasal naloxone group given a further 'rescue' dose of intramuscular naloxone at 10 minutes. However, this may well have been a result of the lack of blinding in the paramedics. A low adverse event rate was found for both routes.

#### **SMMGP comment:**

We reported on a small trial in the last Clinical Update (<http://tinyurl.com/updateOct2009>) which was concerned with peer-to-peer administration of naloxone. One significant barrier to its successful implementation is the issue of carrying around an injectable preparation. The intranasal option offers rescuers an effective needleless option as first-line treatment and may unlock further opportunities for wider distribution of naloxone for peer and non-health care administration.

The pre-hospital aspect of this impressively structured study makes it particularly pertinent to those in primary care. Intranasal naloxone would reduce clinical risk to staff using needles in a population with high levels of BBV infection. There may also be a role of intranasal naloxone where care is delivered in partnership with third sector organisations in less traditionally clinical settings.

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#### **Anabolic-androgenic steroid dependence: an emerging disorder.**

*Kanayama G, Brower KJ, Wood RI, et al. Addiction 104. 1966-1978. doi: 10.1111/j.1360-0443.2009.02734.x*

This paper explores the issue of anabolic-androgenic steroid (AAS) dependence and it

also considers the association between AAS and opiate dependence. The literature suggests that around 30% of steroid users will develop AAS dependence. The paper presents a case example and uses it as opportunity to raise some of the concerns around this problem.

Dependent AAS users are more likely to be older and more muscular. They are more likely to have a first-degree relative with a substance use issue and they are generally less well-educated. There also seems to be some kind of a cross-over with opiate dependence – there is basic science supporting this which suggests that AAS dependence may arise through an opioidergic mechanism. Animal studies point toward the possibility that one of the effects of testosterone is to act as a partial opioid agonist. AAS users seem to be at particularly high risk of opioid abuse or dependence. One study quoted in this paper highlighted that 50% of dependent AAS users met the criteria for DSM-IV criteria for a life-time history of opioid abuse or dependence compared with 19% of the non-dependent AAS users.

#### **SMMGP comment:**

The issue of association with opiates is intriguing. This works both ways – we should also be wary of known opioid users developing AAS dependence. This may be particularly pertinent in prisons where a strong gym culture exists. The paper highlights that we may face a rising incidence of AAS dependence as users who started in the 1980s get older.

This paper is a good primer on the use of steroids. The one word that sums up anabolic steroid use is 'underground' and this group remains very much outwith the reaches of medical intervention and standard drug services. The evidence suggests that AAS users distrust health professionals and we may need to become more familiar with AAS in response to this. The article in SMMGP Network 25 in March 2009 (<http://tinyurl.com/SMMGPsteroids>) is well worth a read and sets out the problem and some simple strategies to tackle the issue.

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## **Smoking cessation interventions among individuals in methadone maintenance:**

**A brief review.** Chizimuzo TC Okoli, Khara M, Procyshyn RM, et al. *J Subs Abuse Treat.* October 2009. doi:10.1016/j.jsat.2009.10.001

## **Debunking the claim that abstinence is usually healthier for smokers than switching to a low-risk alternative, and other observations about anti-tobacco-harm-reduction arguments.**

Phillips CV. *Harm Reduction Journal* 2009, 6:29. doi: 10.1186/1477-7517-6-29

This first study systematically reviewed the literature to find papers that looked at the efficacy of smoking cessation treatments for those on methadone maintenance.

In the end, they found 8 papers that met their criteria. However, after an extensive review of these papers the conclusion was startlingly simple: to date, interventions among individuals in methadone treatment have been largely unsuccessful in achieving sustained smoking abstinence. One important finding is that smoking cessation treatment was not associated with increased substance use. Indeed, one study noted that individuals receiving a relapse prevention intervention for smoking cessation also had lower opiate use.

The second paper presents the case in favour of smokeless tobacco as a harm reduction measure. The author works through a rough calculation that suggests that any smoker who will take more than a month to stop smoking would have less overall health risk if they switched to smokeless tobacco – even if they continued with the smokeless tobacco for the rest of their life. The crux of the argument is that the risks associated with smokeless tobacco are trivial compared with the risks associated with even a further short period of smoking.

### **SMMGP comment:**

This is an important area and if we are serious about improving the health outcomes for substance users then this urgently needs addressing. The introduction in the systematic review reports that around 90% of users in treatment smoke tobacco. This won't come as a surprise to anyone working in this field.

How can we approach this? Perhaps we need interventions with far more intensity or perhaps we need to adjust the substance of the interventions. The authors in the review of smoking cessation in methadone briefly discuss the role of 'maintenance as opposed to abstinence' in methadone and then rather enigmatically suggest in their discussion that '*it may be that a similar conceptual shift will need to occur for tobacco use intervention among methadone maintained individuals desiring smoking cessation.*'

The issue of harm-reduction in smoking, through such options as smokeless cigarettes or nicotine replacement, is deeply controversial. The paper in the *Harm Reduction Journal* makes fascinating reading if one can suspend one's knee-jerk reaction to listen to the author's rather impassioned argument. The population of substance users who simply can't stop, who are facing devastating health consequences from smoking, may have the most to gain from a harm reduction approach.

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**Diversion and injection of methadone and buprenorphine among clients in public opioid treatment clinics in New South Wales, Australia.** Winstock AR, Lea T. 2010. *Substance use & misuse* 45 (1-2) 240-52. doi: 10.3109/10826080903080664

**Preference for buprenorphine/naloxone and buprenorphine among patients receiving buprenorphine maintenance therapy in France: A prospective multicenter study.** Daulouede J, Caer Y, Galland P, et al. *J Subs Abuse Treatment* 38 (2010) 83-89. doi: 10.1016/j.jsat.2009.07.2002

The first paper by Winstock and Lea looked at the interesting area of diversion of prescribed maintenance therapies in Australia. They surveyed 448 users who were in treatment at public opioid substitution treatment clinics in 2005. They used an interviewer-administered questionnaire and they used independent interviewers to reduce concerns when reporting diversion to actual clinic staff.

The results showed that, in the preceding 12 months, there was three times as much reported diversion in those getting supervised

buprenorphine (15.3%) versus those getting methadone (4.3%). Just over a quarter (26.5%) had ever injected buprenorphine while nearly two-thirds (65.9%) admitted to having ever injected methadone.

There was some further analysis of the sub-population that had admitted injecting their medications in the past. In both these groups the majority (just under two-thirds) said they now preferred to take it as directed. Nearly three-quarters (73.9%) of the buprenorphine group and two-thirds (66.2%) of the methadone group stated they wouldn't inject it again.

The second paper is a French study of buprenorphine/naloxone (Suboxone®) where they selected people who had been receiving 2-16mg of buprenorphine for at least 6 months. They excluded anyone who had 'misused' their buprenorphine and anyone who tested positive for illicit opioids. They also excluded users with a history of alcohol abuse or anyone who had had a recent dose increase in benzos. They recruited 53 patients in total. It was an open-label study – there was no attempt at blinding at all.

It was a 'within-subjects' study so they gave the patients buprenorphine for 2 days then switched them on to Suboxone® for 3 days. The primary endpoint was a 10cm visual analogue scale for global satisfaction (VAS). They also recorded adverse events.

There was no difference in the primary endpoint. There was a difference in the number of adverse events with 18 events in the Suboxone® group and just 5 in the buprenorphine group. Participants preferred the taste, size and dissolution speed of Suboxone®.

#### **SMMGP comment:**

The topic of diversion is a great one for vigorous debate but sadly anecdote, rather than evidence, prevails and it is good to get a grip of some harder evidence in this area to guide practice. The Winstock and Lea paper is a useful addition to a definite gap in the literature but the French Suboxone® study perhaps less so.

In the buprenorphine vs Suboxone® study it is worth emphasising that the primary endpoint,

which measured global satisfaction between buprenorphine and Suboxone®, showed no difference. There are some serious concerns in the study's methodology and also in the interpretation and even presentation of these data. At a paltry 5 days the treatment phase is ludicrously short and it difficult to translate this into real practice. It was open label and with such small patient numbers the risks of bias are high.

It does tell us that Suboxone® is a smaller tablet, tastes different and dissolves quicker. This did not really need a study to prove. The entire methodology is slightly curious, the presentation has a positive spin on thin results, and given the study's sponsors (Schering-Plough) it is difficult to see how much further can be drawn from the paper.

In contrast, in their discussion Winstock and Lea give a useful summary of the state of the literature in this area and is highly recommended. They also highlight that there was less diversion of buprenorphine (but methadone was much the same) in the public clinics compared with a previous study they have done in community pharmacies. Sadly, this study wasn't sufficiently large to scrutinise the factors that may have contributed to this and, in terms of UK practice, this might be critical. They also note that whether Suboxone® "will have a significant long-term impact upon the diversion and injecting misuse of buprenorphine is unclear". In addition, the diversion for their potential abuse when snorted isn't addressed in these papers and remains a concern to many clinicians.

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