Articles You Might Have Missed

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Article #1: Ahmadi J, Jahromi MS, Ghahremani D, London ED: Single high-dose buprenorphine for opioid craving withdrawal. *Trials*. 2018 19(1):675.

Background: Treatment for opioid use disorder (OUD) in the emergency department (ED) is often logistically difficult. In Iran, where this study was performed, buprenorphine diversion is common as no products are co-formulated with naloxone. Therefore, prescribers are reluctant to provide extended buprenorphine courses. In the USA, the barriers for ED prescribers include a lack of trained x-waivered physicians. A single dose of buprenorphine provided in the ED may work initially, but symptoms of opioid withdrawal quickly recur.

Research Question: Can a single high-dose buprenorphine treatment prevent craving for an extended time period in patients with OUD?

Methods: This was a double-blinded randomized control trial involving 90 patients divided into three groups who each received a single sublingual dose of buprenorphine: 32, 64, or 96 mg. All patients were men admitted to an inpatient psychiatric unit; there was no control group. Patients with other substance use disorders, organic mental disorders, or a major medical disease were excluded. Buprenorphine was administered once the patient manifested four or five opioid withdrawal symptoms. Vital signs, respiratory rate, and gastrointestinal effects were monitored and recorded every hour for the first day and then every 6 hours for the remainder of the 5-day trial. A visual analog scale was used to measure opioid craving. Over 5 days, cravings and adverse effects were evaluated. A thin-layer chromatography urine drug test was sent

before treatment, during the trial, and at the end of the 5-day period. ANOVA, post hoc *t* tests, and chi-square analyses were used to compare groups.

Results: All patients completed the study; no illicit opioid use was detected (via urine drug testing) during the study period. Lower cravings were reported in the 64 and 96 mg groups compared with the 32-mg group; there was no statistical difference between the two higher dose groups.

Nine patients developed an adverse effect: two (7%) of the 96-mg group had fluid-responsive hypotension; five (2 in 64-mg group, 3 in 96-mg group) developed nausea and vomiting; and 2 developed nausea alone (both in 32-mg group).

Conclusion: High-dose buprenorphine therapy was relatively safe, and few significant adverse effects occurred at higher doses. The 64- and 96-mg groups were equally effective at reducing cravings, but no relapse was noted in all 3 groups. However, more adverse events occurred with increased doses.

Critique: The small study size limited power calculations; some adverse events may have been missed. Additionally, the clinical significance was questionable as differences in subjective scores were small, and the study setting (inpatient psychiatric unit) limits generalizability.

Implication for Toxicologists: Single high-dose buprenorphine administration may be an option for ED physicians without an x-waiver who intend to discharge patients with close follow-up. This option may also work for other patients at risk for diversion. However, further study is required before this process can be generalized in the USA.

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Article #2: Kaya H, Polat B, Albayrak A, Mercantepe T, Buyuk B: Protective effect of an L-type calcium channel blocker, amlodipine, on paracetamol-induced hepatotoxicity in rats. *Human and Experimental Toxicology* 2018;37:1169.

Background: Acetaminophen (APAP)-induced hepatotoxicity is largely mediated by production of N-acetyl-para-benzoquinone imine (NAPQI) with subsequent depletion of

glutathione, mitochondrial oxidative stress, and hepatocellular necrosis. Excess calcium levels in hepatocytes can exacerbate cell death, and prior animal studies show the L-type calcium channel is involved in Kupffer cell activation which are implicated in liver fibrosis. Amlodipine has previously demonstrated protective effects against superoxide-induced damage in the hepatocytes of hypertensive rats.

Research Question: Does the administration of amlodipine to rats administered hepatotoxic APAP doses reduce the level of hepatocellular damage?

Methods: The study involved five groups (6 in each group) of male albino Wistar rats: (1) control group; (2) APAP 2 g/kg only; (3) APAP 2 g/kg and amlodipine 5 mg/kg; (4) APAP 2 g/kg and amlodipine 10 mg/kg; (5) amlodipine 10 mg/kg only. When given, amlodipine was administered an hour after APAP. Rats were killed using thiopental 24 hours after study initiation. Various biomarkers (AST/ALT), enzymes, and RNA/cDNA were analyzed; liver biopsies were also performed.

Results: Several beneficial effects were demonstrated, including decreased AST/ALT levels among amlodipine-treated rats. In the APAP-only group, ALT/AST were 106.91 ± 25.39 and 174.74 ± 37.01 respectively, whereas in the amlodipine 5 mg/kg and 10 mg/kg groups, ALT/AST were 67.29 ± 14.01 and 102.07 ± 25.60 , and 68.66 ± 20.79 and 95.13 ± 10.49 (respectively). The levels of superoxide dismutase and glutathione were reduced by APAP, but higher in amlodipine-treated rats. Amlodipine treatment also decreased mRNA expression of TGF- β and TNF- α near control levels. On liver biopsy, rats given amlodipine showed morphology similar to controls, without sinusoidal congestion or hemorrhage that typified APAP poisoning. TNF- α expression was absent in rats given 10 mg/kg of amlodipine and reduced in those given 5 mg/kg. Amlodipine-treated rats also demonstrated decreased histological activity index scores (indication of decreased inflammation).

Conclusion: In this animal model of APAP toxicity, amlodipine treatment demonstrated improvement in liver biopsy appearance, reduction in expression and level of inflammatory mediators, increased anti-inflammatory enzymes, and decreased levels of AST/ALT compared with rats given acetaminophen alone. Inhibition of calcium influx may provide benefit in APAP-induced hepatotoxicity, but further investigation is needed.

Critique: There were several obvious design characteristics that limited generalization to humans, including animal model, large dosing and schedule (1 hour after APAP) of amlodipine, limited study period (only 24 hours after poisoning), and no evaluation of N-acetylcysteine treatment. A model showing the utility of late administration of amlodipine would be insightful. Although statistically significant effects were identified in enzyme, biomarker expression, and

histopathologic changes, it was unclear if these would impact survival or liver fibrosis.

Implication for Toxicologists: This study is a precursor to future studies evaluating the potential benefits of calcium blockers in APAP-induced hepatotoxicity.

Article #3: Haight BR, Learner SM, Laffont CM, et al: Efficacy and safety of a monthly buprenorphine depot injection for opioid use disorder: a multicentre, randomized, double-blind, placebo-controlled, phase 3 trial. *Lancet* 2019;393:778.

Background: Extended-release buprenorphine (BUP-XR or RBP-6000) is a subcutaneously injected, monthly (28 days) buprenorphine treatment for opioid use disorder (OUD).

Research Question: What are the efficacies of different BUP-XR dosing regimens in the treatment of patients with OUD?

Methods: This was a two-phase randomized, double-blinded, placebo-controlled trial performed at 36 treatment centers in the USA. The first phase was an open-label 2-week treatment period with buprenorphine-naloxone sublingual film (daily dosing ranging from 8/2 to 24/6 mg). Phase two had three groups: (1) controls (receiving placebo injections); (2) BUP-XR 300/300 (300 mg/month for 6 months); and (3) BUP-XR 300/100 (300 mg/month for 2 months and then 100 mg/month for 4 months). All participants also received a 5-day buprenorphine-naloxone sublingual film dose taper following the first injection (to help preserve blinding) and were followed for 24 weeks (during which time they all received counseling treatment). Primary efficacy endpoint was participants' percentage abstinence from opioid use, by self-report and urine drug testing, from weeks 5 to 24. Missing urine drug screens or self-reports were considered positive for opioids. Secondary endpoints included treatment success ($\geq 80\%$ abstinence), treatment retention, Clinical Opiate Withdrawal Scale (COWS) scores, opioid craving visual analog scale (VAS) scores, and pharmacokinetic data concerning longitudinal plasma concentrations for the two dosing regimens with clinical endpoints.

Results: A total of 1187 patients were screened, 665 entered the first phase, and a total of 504 entered randomization in the second phase ($n = 100$ controls, $n = 201$ for BUP-XR 300 mg/300 mg, and $n = 203$ for 300 mg/100 mg); 489 were included in the final analyses. Study completion rates were as follows: 129 (64%) of the BUP-XR 300/300; 125 (62%) of the BUP-XR 300/100; and 34 (34%) of controls. All primary and secondary endpoints significantly favored BUP-XR arms. Abstinence rates were 41.3% (SD 38.7), 42.7% (SD 38.5), and 5% (SD 17) in the BUP-XR 300/300, BUP-XR 300/100, and controls, respectively. Treatment success ($\geq 80\%$ abstinence) was 29% (57 of 196), 28% (55 of 194), and 2% (2 of 100) respectively. COWS and opioid craving VAS were lower for both BUP-XR groups compared with controls. At

the end of the six monthly injections, mean average buprenorphine plasma concentration was 6.54 ng/mL in the BUP-XR 300/300 group and 3.2 ng/mL in the BUP-XR 300/100 group. The most common adverse events were headache, constipation, nausea, and injection-site pruritis, and these occurred at a higher frequency in BUP-XR groups compared with controls. Treatment adverse events lead to discontinuation of therapy in 5%, 3%, and 2% of participants, respectively.

Conclusion: BUP-XR via monthly subcutaneous injections appears to be an efficacious and safe treatment for OUD and is generally well tolerated.

Critique: A major limitation was the higher than expected attrition rate resulting in an underpowered study. Blinding was also likely imperfect given clear differences in withdrawal symptoms and cravings between BUP-XR and placebo groups. The study was also limited in generalizability, as patients with other co-occurring substance use disorders (specifically alcohol, cocaine, cannabis) were excluded.

Implication for Toxicologists: BUP-XR presents another treatment option for patients with severe OUD, particularly those with limited follow-up capacity.

Article #4: Spindle TR, Cone EJ, Schlienz NJ, et al: Acute effects of smoked and vaporized cannabis in healthy adults who infrequently use cannabis, a crossover trial. *JAMA Network Open* 2018;1(7):e184841.

Background: Cannabis vaping is an increasingly popular method for cannabis use, and regulation reforms have made cannabis more accessible.

Research Question: How do different methods of cannabis use affect subjective drug effects, cognitive and psychomotor performance, and cardiovascular measures in adults?

Methods: This was a within-participant, double-blinded study performed at a behavioral research unit. The study consisted of six sessions of either smoking or vaporizing cannabis doses of 0 mg, 10 mg, and 25 mg. There was a 1-week washout period between sessions which were completed in randomized clusters. Outcome measures included whole blood Δ^9 -tetrahydrocannabinol (THC) levels, heart rate, blood pressure, and cognitive performance tasks taken at multiple time points after cannabis use. These tasks included Digit Symbol Substitution

Task (DSST), Divided Attention Task (DAT), and the Paced Auditory Serial Addition Task (PASAT).

Results: A total of 17 healthy adults were studied; mean age was 27.3 years, and they had an average of 398 days since (self-reported) last cannabis use. Subjective drug effect measures included categories such as unpleasant, pleasant, sick, heart racing, anxious/nervous, paranoid, alert, restless, hungry, and dry mouth. The magnitude of drug effect was higher for vaporized THC compared with smoked. All three cognitive performance tasks were negatively impacted by inhalation of cannabis, by both methods, particularly at the higher doses. Cognitive deficits peaked 30–60 minutes after cannabis administration. THC levels were higher following vaporization vs smoked cannabis administration. Both methods of administration were associated with increased heart rate.

Conclusion: Different methods of cannabis administration were associated with a dose-response increases in drug effects, tachycardia, and cognitive impairment. Vaping administration had increased whole blood THC levels as well as increased drug effects.

Critique: The small number of habitual cannabis users limited the external validity for other users. Generally, cannabis effects are more difficult to predict in habitual users and only one form of THC containing substance was used: raw plant material with high THC/low CBD ratio.

Implications for Toxicologists: As cannabis and other THC containing products become more widely and legally available, understanding the difference in physiologic effects between different methods of use becomes increasingly important. This study demonstrates substantial pharmacokinetic and pharmacodynamic differences between vaping and smoking methods of administration.

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