Articles You May Have Missed

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Article #1: Richardson K, Fox C, Maidment I, et al.: Anticholinergic drugs and risk of dementia: case-control study. *BMJ* 2018;361:k1315. doi: <https://doi.org/10.1136/bmj.k1315>. PMID: 29695481.

Background: Dementia is a leading cause of death and disability worldwide. Anticholinergic drugs have been frequently associated with a negative effect on cognition and increased risk of dementia. Previous studies have been restrained by comorbid medical problems in associating the diagnosis of dementia with anticholinergic drugs.

Research Questions: What is the association between chronic anticholinergic drug use and future dementia? Are the effects specific to a particular drug class? Is there a dose response?

Methods: This was a nested case-control study using the United Kingdom's Clinical Practice Research Datalink (CPRD). The CPRD includes demographics, clinical data, life style information, and prescribing records for 11.3 million patients in 674 primary care practices in the UK. Eligible cases were patients aged 65–99 with a diagnosis of dementia made between April 2006 and July 2015. Incidence density sampling was used to select matched controls (typically seven) for each subject from the CPRD database. A drug exposure period (DEP) of at least 1 year was required and the DEPs were between 4 and 20 years prior to the diagnosis of dementia. The diagnosis of dementia was made using medical coding, symptoms, referral, or prescription of a 'cognitive enhancer.' Cases were excluded if the onset of dementia was unknown or the patient was diagnosed with motor neuron disease, HIV/AIDs, MS, Down's syndrome or pre-existing alcohol abuse. Anticholinergic potency was assigned using

the 2012 version of the Anticholinergic Cognitive Burden (ACB) scale. The ACB scale categorizes anticholinergic agents into one of three groups: 1 (possibly anticholinergic), 2 (definitely anticholinergic), or 3 (anticholinergic and associated with delirium). The authors assigned values to UK drugs (e.g., TCAs) not included in the ACB scale. Each drug was also categorized based on its World Health Organization (WHO) coded drug class (e.g., antidepressant, antipsychotic, cardiovascular). Estimations for total drug use were based on DEPs and WHO-defined daily doses and durations. Covariates for the development of dementia were also defined and controlled for. Adjusted odds ratios (aORs; reported with 95% CIs) were calculated using multiple conditional logistic regression.

Results: 40,770 cases with 283,993 controls were analyzed. During the DEP, 89% of cases and 87% of controls were prescribed at least one medication with an ACB score of 1, and 35% of cases and 30% of controls were prescribed at least one drug with a score of 3. A positive association between dementia and drugs with an ACB score of 1, 2, and 3 were found; aORs of 1.10 (1.06–1.15), 1.10 (1.03–1.16), and 1.11 (1.08–1.14), respectively. Dose response effects were seen for drugs with ACB score of 3, as well as increased total exposure (sum of all exposures) to anticholinergic drugs. Some classes of drugs with ACB score 3 were significantly associated with future diagnosis of dementia; these were antidepressant, antiparkinson, and urological medications. Some medications showed an apparent protective effect, including gastrointestinal (ACB score 1 or 3) and cardiovascular drugs (ACB score 1).

Conclusion: Increasing use of certain anticholinergic drugs was associated with the future diagnosis of dementia. Specifically, antidepressants, antiparkinsonian and urologic drugs were shown to increase risk.

Critique: The sample size was considerable and allowed for analysis of multiple classes of drugs and degrees of exposure. The definition of dementia for included cases was not very stringent. There is concern that the ACB scale might not

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adequately risk-stratify medications and differed when compared to other scoring systems (the anticholinergic drug scale). Estimations of DEPs used the number of prescriptions written, which cannot account for compliance or use of other medications. Since the study's granularity was limited by the details in primary care notes, social determinants of health and demographic information, the potential for other confounders exists.

Implication for Toxicologists: These data suggest that certain anticholinergic drugs share an association with the later diagnosis of dementia. This understanding should be taken into consideration when the decision is made to start (or continue) anticholinergic drugs chronically and may help advocate for reducing anticholinergic medications in elderly or at-risk patients.

Article #2: Akakpo JY, Ramachandran A, Kandel SE, et al.: 4-Methylpyrazole protects against acetaminophen hepatotoxicity in mice and in primary human hepatocytes. *Human & Exper Tox* 2018; doi: <https://doi.org/10.1177/0960327118774902>. PMID: 29739258.

Background: The hepatotoxicity caused by acetaminophen (APAP) toxicity involves NAPQI depletion of hepatic glutathione (GSH). This process is amplified by a protein kinase cascade resulting in the activation of cytosolic c-Jun N-terminal kinase (JNK). Fomepizole (4-methylpyrazole; 4MP) has been shown to inhibit CYP2E1 (the enzyme that converts APAP to NAPQI) and was reported in a single case report as assisting in the management of a massive APAP overdose.

Research Questions: What are the protective mechanisms of 4MP in an in vivo mouse model of APAP toxicity? What is the efficacy of 4MP in preventing APAP-induced hepatotoxicity in human hepatocytes?

Methods: An in vivo (mouse) and in vitro (primary human hepatocyte) models were used. In vivo mouse model: C57BL/6J mice received intra peritoneal co-injections of 300 mg/kg of APAP and either 50 mg/kg of 4MP or saline. Blood and liver tissues were collected at 30 min or 6 h post-injection for evaluation of liver function markers, APAP metabolites, and histologic tissue necrosis. In vitro hepatocyte model: human hepatocytes were treated for 24 h in 10 mM of APAP, 2 mM of fomepizole, or both, in a medium containing insulin, penicillin, and dexamethasone. Markers of cell death and release of cellular ALT were then assessed. Routine statistics (Student's *t* test and ANOVA) were used to compare results.

Results: In vivo mouse model: mice treated with APAP and saline developed severe hepatotoxicity at 6 h evidenced by ALT elevation, histologic hepatic necrosis, and DNA fragmentation. The mice treated concurrently with 4MP had almost no plasma ALT elevation, microscopic evidence of

necrosis, or DNA fragmentation. Additionally, in mice treated with only APAP, the activation of cytosolic JNK and translocation of phospho-JNK to the mitochondria was evident; these findings were absent in animals receiving 4MP. Depletion of GSH was > 90% in mice treated with APAP and saline, and extensive protein adjunct formation was noted. In mice co-treated with 4MP, GSH was depleted ~33% with almost no formation of protein adjuncts. 4MP was also shown to inhibit the activity of CYP2E1 and CYP1A2 in a dose-dependent fashion.

In vitro human hepatocyte model: hepatocytes treated with APAP alone for 24 h released ~40% of ALT into the medium and underwent cell death, whereas hepatocytes co-treated with 4MP had cellular ALT release of only ~10%, which was nearly identical to control and 4MP-only hepatocytes.

Conclusion: 4MP administration in mouse and human hepatocyte models of APAP toxicity resulted in the prevention of severe liver injury and resultant cell death. 4MP appeared to prevent the formation of APAP protein adducts and mitigate the depletion of hepatic glutathione. The mechanism of action appears to involve inhibition of APAP metabolism to NAPQI as well as inhibition of mitochondrial dysfunction.

Critique: While it is difficult to extract clinically relevant (human) information from animal and cellular data, this study is promising for a proposed mechanism and effect of 4MP in APAP toxicity. The group size (*n* = 5) for each experimental condition was small.

Implication for Toxicologists: While preliminary, this study suggests mechanisms for the utility of fomepizole in massive APAP poisoning. Fomepizole may have a role in treating APAP toxicity after more studies delineate its utility.

Article #3: Rose JJ, Nouraie M, Gauthier MC, et al.: Clinical outcomes and mortality impact of hyperbaric oxygen therapy in patients with carbon monoxide poisoning. *Crit Care Med*. 2018;46(7):e649-e655. doi: <https://doi.org/10.1097/CCM.000000000000135>. PMID 29629990.

Background: Survivors of carbon monoxide (CO) poisoning often suffer permanent neurocognitive deficits and may have increased mortality. Treatment is supportive, with supplemental oxygen, and at times hyperbaric oxygen therapy (HBOT). The efficacy of HBOT for CO toxicity is debated.

Research Questions: What are the acute and long-term mortality of patients with CO poisoning? Is HBOT associated with improved outcomes?

Methods: Retrospective chart review of adult patients cared for at a single academic medical system (15 hospitals) for CO poisoning between January 2000 and April 2014. Subjects were identified through electronic medical records (EMR) and relevant ICD-9-CM codes. Two authors reviewed the charts and collected information about

demographics, mechanism of poisoning, symptoms, laboratory values, clinical course, treatment, and in hospital mortality. Two variables containing combined risk stratification data were created: “cardiac complication” (cardiac arrest, shock, arrhythmia, MI, elevated troponin, need for vasopressors) and “high risk” (COHbg > 25%, LOC, pH < 7.20, fire exposure, or any cardiac complication). Univariate analysis of variables was performed between groups with and without HBOT or inpatient hospital admission. One-year mortality was determined by reviewing the EMR for repeat encounters beyond 1 year and the US Social Security Death Index.

Results: 1099 unique patient encounters were identified, of which 80% had elevated COHbg recorded. The most common presenting symptom was headache in 55%; 25% had syncope, 11% had “cardiac complication,” 39% had at least one “high-risk” feature, 27% were admitted, and 26% received HBOT. The variable most predictive of receiving HBOT was COHbg > 19% which was present in 39% of patients. Of those receiving HBOT, 91% had at least one “high-risk” feature compared to 21% not receiving HBOT. Transferred patients were more likely to meet high-risk criteria (44.9%) and received HBOT (75%). More patients receiving HBOT were admitted (53 vs 18%). The factors most associated with death ($n = 14$, 1.3%) during initial hospitalization were cardiac arrest and COHbg > 29%. Of the 1073 survivors, 2.9% ($n = 32$) died within 1 year and 4.4% ($n = 47$) died within 2 years of CO poisoning. Factors most associated with 1-year mortality were older age, male sex, respiratory distress, renal dysfunction, and elevated troponin. A propensity score for inpatient mortality was calculated utilizing variables most predictive of HBOT. Compared to normobaric oxygen treatment, HBOT showed a 2.1% absolute risk reduction in both inpatient mortality (3.7–0.9%, $p = 0.001$) and 1-year mortality (3.8–0.4%, $p = 0.013$).

Conclusion: CO poisoned patients with high-risk features (cardiac arrest, shock, arrhythmia, MI, elevated troponin, need for vasopressors, COHbg > 25%, LOC, pH < 7.20, or fire exposure) were more likely to receive HBOT. Patients who received HBOT showed a small decrease in mortality during admission and at 1 year.

Critique: This study is limited by the retrospective design and use of EMR review. Etiology of exposure and clinical decision-making regarding treatment could not be examined. For example, perhaps some patients were not transferred for, HBOT due to critical illness? The overall mortality was low, and a very small number of those receiving HBOT died (2 of the 14 inpatient deaths, and 6 of the 32 1-year deaths) which makes meaningful mortality analysis difficult.

Implication for Toxicologists: This retrospective analysis with low numbers shows a small mortality benefit for HBOT in CO poisoning.

Article #4: Pizon AF, Lynch MJ, Benedict NJ, et al.: Adjunct ketamine use in the management of severe ethanol withdrawal. *Crit Car Med* 2018; 46(8):e768–e771. doi: <https://doi.org/10.1097/CCM.0000000000003204>. PMID: 29742583.

Background: Ethanol withdrawal complicates many hospital admissions and a subset of these patients requires large doses of GABA agonists, prolonged hospitalization, and sometimes mechanical ventilation. Ketamine, like ethanol, is an NMDA antagonist and may serve as adjunct therapy via a different mechanism of action, and shorter half-life, compared to long-acting GABA agonists.

Research Question: In patients admitted to the ICU with delirium tremens, does adjunctive use of ketamine result in shorter length of stay and less need for mechanical ventilation?

Methods: This was a retrospective observational cohort study at a single academic tertiary care hospital which added ketamine to its treatment guideline for severe alcohol withdrawal. Patients given the diagnosis of delirium tremens who were admitted to the ICU were identified using the center’s toxicology patient database and divided into two groups: pre-guideline (January 2008 to March 2011, $n = 29$) and post-guideline (April 2011 to January 2015, $n = 34$). All patients were given GABA agonists in a symptom-triggered fashion using a withdrawal assessment scale or physician bedside clinical evaluation. Decision to intubate was determined by the treating clinicians. For post-guideline patients, once a diagnosis of delirium tremens was made, GABA agonist therapy was supplemented with IV ketamine infusion at 0.15–0.3 mg/kg/h, with or without a bolus, until symptoms resolved. Patient-specific factors were analyzed using descriptive statistics and correlation coefficients were determined for the outcomes of interest.

Results: A total of 63 patients were analyzed. The post-guideline group showed a significant decrease in ICU length of stay by 2.83 days (96% CI, -5.58 to -0.089 days, $p = 0.043$) and decreased likelihood of intubation (odds ratio of 0.14 (95% CI 0.04–0.49, $p < 0.01$)). Additionally, decreased length of hospital stay for ketamine patients was noted but not statistically significant. Patients receiving ketamine received less benzodiazepines, mean benzodiazepine dose (in diazepam equivalents) 2525.1 mg (no ketamine) compared to 1508.5 mg (with ketamine).

Conclusion: The adjunctive use of ketamine for severe ethanol withdrawal was associated with decreased ICU length of stay and rate of mechanical ventilation. Further standardized investigations are needed to fully understand the potential of this treatment.

Critique: A small patient population, non-standardized treatment protocols, and non-randomization and retrospective designs limited this study. Most patients receiving ketamine infusion also received a bolus, or other medications including

dexmedetomidine, at the discretion of clinicians. Unidentified differences in treatment of delirium tremens over time may also have affected outcomes. This study showed a statistically significant decrease in mean GABA agonist use, unlike a previous related study by Wong A et al. [Evaluation of adjunctive ketamine to benzodiazepines for management of alcohol withdrawal syndrome. *Ann Pharm* 2015; 49(1): 14–19].

Implication for Toxicologists: Toxicologists should be aware of the potential benefits of using ketamine as adjunctive

therapy to standard GABA agonists for treatment of severe ethanol withdrawal.

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Compliance with Ethical Standards

Conflicts of Interest None.