



## Articles You Might Have Missed

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**Keywords** Synthetic cannabinoids · Acetaminophen · Vaping · Nitrogen dioxide

**Article #1:** Kourouni I, Mourad B, Khouli H, Shapiro JM, Mathew JP: Critical illness secondary to synthetic cannabinoid ingestion. *JAMA Network Open* 2020;3(7):e208516.

**Background:** Synthetic cannabinoids (SC; aka K2, spice, fake weed) became a public health concern around 2012 due to its availability, varying potency, and potential for clinical toxicity.

**Research Question:** What are the clinical manifestations of acute, severe SC intoxication?

**Methods:** A retrospective chart review of adult patients admitted to a single, urban academic medical center with acute life-threatening complications of “historically confirmed” SC use. These admissions occurred between 2014 and 2016. Patients were excluded if they denied SC use; had a high alcohol concentration or urine drug screening positive for phencyclidine, amphetamines, or cocaine; and reported use within the prior 3 days. Collected data included demographic information, medical history, physical examination findings, laboratory and imaging results, treatments (including intubation), intensive care unit (ICU), and hospital lengths of stay (LOS) and outcomes.

**Results:** A total of 42 patients were identified; of these 30 were included for analysis and had the following demographics: 80% male, mean age 41 (range 21–59) and 13 were homeless. Most ( $n=23$ ) were admitted to an ICU; 7 received critical care in the Emergency Department. All patients admitted to the ICU had neurological effects ( $n=26$ ) and/or acute respiratory failure ( $n=18$ ). Clinical findings included the following: acute respiratory failure ( $n=18$ , 60%; 12 had hypercarbia, 3 had hypoxia, and 3 had aspiration pneumonia), agitation ( $n=10$ , 33%), coma ( $n=10$ , 33%), seizure

( $n=6$ , 20%), QT prolongation ( $n=9$ , 30%), rhabdomyolysis or acute renal failure ( $n=8$ , 26%), and bradycardia ( $n=5$ , 16%). There was one death in an asthmatic woman who presented with acute respiratory distress syndrome. Almost half ( $n=14$ , 46%) had co-ingestions based on urine testing; 10 out of 14 (71%) patients with co-ingested opioids did not respond to naloxone. A majority ( $n=25$ ) had a history of polysubstance abuse or psychiatric illness (including personality disorders). Twenty patients reported smoking K2, and 10 others were witnessed to have used K2 prior to symptom onset.

**Conclusion:** SC toxicity can cause life threatening illnesses, particularly neurologic and/or respiratory compromise. Optimal care appears to be based on aggressive supportive care with focus on the airway. Routine (urine) toxicological testing can be negative (due to the assay’s inability to detect SC) or show other co-ingestions.

**Critique:** This was a small sample of suspected SC intoxication; confirmatory testing (including quantification) of the SC was not performed. It is also unknown if other illicit drugs or prescription medications were involved in patients’ presentations.

**Implication for Toxicologists:** Medical toxicologists and poison center staff must consider SC in the differential of patients presenting with acute, severe neurological, and/or respiratory dysfunction that cannot be explained by routine toxicologic testing. Significant morbidity and death are possible. Care should be focused on airway, cardiovascular, and renal support; ICU admission is often required. There is, however, not enough data at this point to suggest a specific toxidrome that can be causally attributed to SC.

**Article #2:** Martinez-De la Torre A, Weiler S, Bräm DS, et al.: National poison center calls before vs after availability of high-dose acetaminophen (paracetamol) tablets in Switzerland. *JAMA Network Open*. 2020;3(10):e2022897.

**Background:** Acetaminophen (APAP) is one of the most used analgesic/antipyretic medications and readily

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available over the counter (OTC) worldwide. Although it is considered safe in therapeutic dosage, overdose is a leading cause of liver failure. Increased APAP-related calls to poison centers have led several countries to regulate pack size. In 2003, 1000-mg APAP tablets by prescription became available in Switzerland, an increase from the previous maximum of 500 mg.

**Research Questions:** Was the introduction of the 1000-mg APAP tablets associated with an increased number of APAP-related calls to the National Poison Centre in Switzerland (Tox Info Suisse; TIS)? What were the characteristics of APAP total sales and poisonings?

**Methods:** A quasi-experimental interrupted time series analysis was performed using population based cross sectional data from TIS. The number of unique calls for APAP poisoning from Jan 1, 2000, to Dec 31, 2018, was extracted. A comparator analysis was done with the number of unique calls for ibuprofen over the same time period (ibuprofen did not undergo policy change in this time period). Cross-sectional data for APAP sales, stratified by strength, were reviewed; cases with follow-up underwent subgroup analysis. When available, clinical data were review including dose(s) of ingested substances, intentionality, clinical findings severity, causal assessment, treatments, and outcome.

**Results:** A total of 15,790 APAP-related calls were included in the analysis. There was a significant increase in the number of APAP calls to the TIS after the introduction of 1000-mg tablets as evidenced by the change in slope pre- and post-intervention ( $z$  score,  $-3.01$ ;  $P=0.002$ ). The increase of calls was seen primarily in the accidental (414 [19.9%] to 4185 [30.5%];  $P<0.001$ ) and APAP only ingestions (618 [29.7%] to 6233 [55.5%];  $P<0.001$ ). The accidental poisonings with the 1000-mg tablets was significantly higher compared with the 500-mg tablets (81 [43.8%] vs 19 [15.4%];  $P<0.001$ ). Post-intervention calls increased in the under 6 years (234 [11.3%] vs 1924 [14.0%];  $P<0.001$ ), 45 to 65 years (115 [5.5%] vs 1404 [10.2%];  $P<0.001$ ) and over 65 years age groups (19 [0.9%] vs 471 [3.4%];  $P<0.001$ ). The age group (16–24 years) with the greatest number of calls overall had no significant change. The majority of calls (97.4%) in children younger than 10 were accidental ingestions.

A total of 6657 patients had follow-up data regarding dose, use of antidote, severe symptoms, and death. An increase in the number of calls for ingestions  $>10,000$  mg was seen post intervention (120 [15.3%] vs 1140 [30.6%];  $P<0.001$ ). There was an increase in patients who received n-acetylcysteine (424 [44.1%] vs 3157 [55.4%];  $P<0.001$ ) and those with a severe outcome (55 [5.7%] vs 406 [7.1%];  $P<0.001$ ) after the introduction of 1000-mg tablets suggesting more clinically significant overdoses occurred with larger dose tablets available.

**Conclusion:** The number of APAP-related poisonings increased after the availability of a 1000-mg tablet; this increase was significant for accidental ingestions. A larger dose ( $>10,000$  mg) ingestion, associated with more severe toxicity, was more common among patients ingesting 1000 mg tablets.

**Critique:** Data was collected from one country thereby limiting external validity. A larger sample size, that includes specific data concerning clinical effects and treatment, would provide more conclusive data. A large percentage of the analyzed “follow-up” data involved unknown APAP formulation.

**Implication for Toxicologists:** Medical toxicologist should be aware of all available drug formulations and the potential implications for higher drug doses resulting in larger ingestions with worse outcomes.

**Article #3:** Lallai V, Manca L, Fowler, CD: E-cigarette vape and lung ACE2 expression: implications for coronavirus vulnerability. *Environ. Tox & Pharm.* 2021:86.

**Background:** E-cigarette smoking has increased in use and popularity in the USA and Europe with an estimated 2.5 million users in the USA alone. Nicotine actions at nicotinic acetylcholine receptors (nAChR) affect multiple pulmonary mechanisms, including the renin-angiotensin system (RAS). Angiotensin-converting enzyme 2 (ACE2) located on cellular membrane mediates cell fusion and entry for coronaviruses. ACE2 expression in lung tissues appears to be upregulated in cigarette smokers and those with COPD.

**Research Question:** Does E-cigarette vapor inhalation, with or without nicotine, affect ACE2 expression in lung tissue of mice?

**Methods:** Mice were exposed to vaporized nicotine (7.5 mg/mL, free base) or vehicle during 1-h daily sessions across five consecutive days in a sealed chamber with regulated airflow (1 L/min). For each session, animals were exposed to one puff every five min for a total of 12 puffs per hour session; each puff administration allowed for 40 s of vapor exposure. A control group of mice were handled each day for five consecutive days. Two hours after the last vapor exposure session, mice were placed under 4% isoflurane anesthesia for blood collection and sacrifice; lung tissue were obtained for analysis. Real-time quantitative polymerase chain reaction was performed for ACE2 subunits (alpha-5, implicated in lung cancer; and alpha-7, involved with immune/inflammatory responses), and the housekeeping gene, B-actin (ActB).

**Results:** In male mice exposed to nicotine vapor, lung tissue revealed significant increase in ACE2 mRNA and protein ( $p=0.0005$  compared to controls); no significant difference were seen in female mice ( $p=0.4434$ ). Lung nAChRs containing the alpha-5 subunit were downregulation in both mice genders under both study conditions: nicotine and vehicle (control) inhalation. No significant differences were

found in alpha-7 subunit. There were no increased ACE2 concentrations in blood following vapor inhalation.

**Conclusion:** E-cigarette vaping (with or without nicotine) induces an increased density of ACE2-positive cells in the lungs of male but not female mice. This suggests a gender-based biological link between vaping, ACE2 upregulation, and increased susceptibility to coronavirus infection.

**Critique:** This was an animal (mice) model using a short-term (5 days) proxy for vaping exposure, thereby limiting extrapolation to humans. The exposure to vaping is variable among humans with different patterns of use throughout each day; it is possible that females can have their ACE2 altered and become significant in their expression. The affinity for coronavirus to human ACE2 is higher than that for mice, and there is conflicting data concerning nicotine exposure and COVID-19 infections. The gender-specific difference in nicotine effects is difficult to explain.

**Implication for Toxicologists:** Although preliminary, these data can be used to better educate patients about the health risks associated with vaping.

**Article #4:** Meng X, Liu C, Chen R, et al.: Short term associations of ambient nitrogen dioxide with daily total, cardiovascular, and respiratory mortality: multilocation analysis in 398 cities. *BMJ* 2021;372:n534.

**Background:** Nitrogen dioxide (NO<sub>2</sub>) is a common pollutant from fuel combustion and has been associated with adverse effects on population health and mortality. Epidemiological studies on this issue have, however, included important limitations.

**Research Question:** Is there an association between short-term NO<sub>2</sub> exposure and population mortality?

**Methods:** Daily ground level concentrations for NO<sub>2</sub>, other pollutants (including particulate matter, ozone, sulfur dioxide, and carbon monoxide) and weather variables were collected from 398 cities in 22 countries/regions. Daily all-cause mortality data were obtained from the same cities; deaths from cardiovascular and respiratory diseases were obtained from 16 countries. Statistical analysis was used to adjust for multiple different factors including weather, co-pollutants, geographical location, and time of year. Two stages of analyses were conducted for city specific data: a time series quasi-Poisson generalized linear regression and a “new multilevel meta-analytic approach [that] defines more complex random effects [in hopes of providing] the best linear unbiased predictors for the associations between

NO<sub>2</sub> and mortality.” An a priori defined lag (NO<sub>2</sub> effect) of 0–3 days was used; several sensitivity analyses were conducted to test estimates.

**Results:** A total of 62.8 million deaths were recorded in the database from 1973 to 2018; of these, 19.7 million (31.4%) were attributable to cardiovascular and 5.5 million (19.9%) to respiratory disease. On average, the median annual mean NO<sub>2</sub> concentration was 26.9 ug/m<sup>3</sup> (25th–75th% = 19.5–36.2) and negatively correlated with mean temperature and relative humidity. For every 10 ug/m<sup>3</sup> increase in NO<sub>2</sub> concentration, there was an associated 0.46% (95% CI 0.36–0.57%) increase in total mortality, 0.37% (95% CI 0.22–0.51%) increase in cardiovascular mortality, and 0.47% (95% CI 0.21–0.72%) increase in respiratory mortality. Sensitivity analyses found similar associations between NO<sub>2</sub> and mortality.

**Conclusion:** This study provides evidence of an association between short term NO<sub>2</sub> exposure and increased total, cardiovascular and respiratory mortality.

**Critique:** Most data came from developed nations, and all data were could not be confirmed which introduced possible bias and limited generalizability. Lastly, the profile of NO<sub>2</sub> pollution changed drastically over time; collected health data might have been subject to reporting and/or coding changes over time.

**Implication for Toxicologists:** This study provides further evidence that there is an independent negative impact of nitrogen dioxide on public health that has previously been in question. The association between nitrogen dioxide concentrations and mortality could impact future discussions on air quality and public health.

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## Declarations

**Conflict of Interest** None.

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