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Over-The-Counter Cough Medication (Dextromethorphan) Abuse: A Case Report of Dexing or Robo-tripping

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Abstract Dextromethorphan (DXM) and DXM-containing cough preparations are available over-the-counter (OTC) and are commonly abused for their euphoriant and hallucinogenic properties. These effects occur when DXM is taken in high doses (10-20 times the amount recommended for cough suppression). Awareness of DXM abuse in the primary care setting is warranted due to its prevalent use and potential to result in drug-induced liver injury (DILI). Reaching a diagnosis of DILI involves an extensive workup to exclude other known causes. If a physician is to identify the use of a single drug as the cause of a patient's liver injury, a high level of suspicion must be held. We herein present a case of an 82-year-old male who was dependent on over-the-counter, DXM-containing products and who used them regularly for three years. This case report highlights DILI as one potential consequence of chronic OTC DXM use, as is evident from our diagnostic workup.

Keywords: *OTC Abuse dextromethorphan*

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1. Introduction

DXM is a readily-available OTC medication (attainable without a prescription) intended to ameliorate cough symptoms, usually in association with the common cold. It is an effective cough suppressant and has minimal side effects when used therapeutically and as directed. DXM was previously classified as a synthetic opioid due to having a chemical structure similar to codeine. Today, DXM is labeled as an antitussive medication with both sigma-1 agonist and N-methyl-D-aspartate (NMDA) receptor antagonist effects, exhibiting a psychoactive effect at high doses [1]. The recreational use of DXM for its dissociative effects is not uncommon and has been described colloquially and in literature as "dexing" or "robo-tripping." With continued and habitual use of DXM, tolerance is likely to develop, manifesting to the user as a diminishing desired effect over time. Inevitably, many DXM users will resort to escalating the dosage over time to achieve the same effect. The exact prevalence of DXM tolerance or dependence is not known, but probably higher than current estimates [2]. Chronic abuse of DXM can lead to DILI, manifesting as hepatic steatosis, pancreatitis [4], or elevated aminotransferase levels. The risk of DILI is only further increased by co-toxicity when a tolerant user of DXM attempts to increase the effect by combining it with another OTC formulation. The additional medication of choice is most commonly acetaminophen, an antihistamine, or a pseudoephedrine-containing decongestant.

We herein present a case of an 82-year-old male who used over-the-counter DXM-containing products regularly and had been dependent on them for three years. This case report highlights a potential consequence of OTC DXM use, namely, DILI, as was evident from this patient's diagnostic workup. It is imperative for internists, primary care providers, and the frontiers of healthcare to be aware of the association between DXM abuse and DILI, prompting early recognition and management.

2. Case Description

An 82-year-old Hispanic male with a past medical history of primary hypertension, gastroesophageal reflux disease (GERD), and benign prostatic hypertrophy presented with a complaint of abdominal discomfort beginning one day before arriving at the hospital. The patient reported that his discomfort was predominantly epigastric, intensity: 6/10, constant, and with no known

aggravating or alleviating factors. He denied subjective fever, chills, malaise, weakness, chest pain, dyspnea, nausea, vomiting, diarrhea, constipation, and bloody or dark-colored stool. The patient reported that he was recently retired, a lifetime non-smoker, and a former drinker of alcohol (ceased ten years ago). He denied any significant personal or family history of autoimmune disease, cardiac disease, or gastrointestinal malignancy. Home medications included amlodipine 10 mg once daily and losartan 25 mg once daily. The patient reported chronic use of DXM products, including Robitussin®. He denied any concomitant acetaminophen use. On physical exam, the patient was alert, cooperative, and oriented to person, place, and time. Body mass index: 22.9 kg/m2, blood pressure: 127/83 mmHg, heart rate: 78 beats/min and regular, temperature: 98.6 Fº, peripheral oxygen saturation: 98% breathing ambient air; respiratory rate: 18/min. Mild jaundice was noted without palmar erythema, pallor, or tremor. Bowel sounds were positive with regular frequency in four quadrants. The abdomen was soft, was not tender to palpation, and no mass was appreciated. There were no physical exam findings suggestive of hepatic failure. Chest and heart examinations were unremarkable. Laboratory testing revealed: Rapid COVID-19 antigen test: negative. Serum chloride: 102 mmol/L (reference: 98-107 mmol/L). *Slight increase in anion gap* (AG): 14 mmol/L (reference: 4-13 mmol/L). Serum osmolarity: 277 mOsm/kg (reference: 285-305 mOsm/kg). Serum creatinine (Cr): 1.07 mg/dL (reference: 0.8-1.4 mg/dL). Blood urea nitrogen (BUN): 23 mg/dL (reference: 8-26 mg/dL). BUN/Cr ratio: 21 mg/dL (reference: 10-14 mg/dL). Liver function tests were consistent with hepatocellular injury as follows: *Elevated alkaline phosphatase* (ALKP): 173 U/L (reference: 38-126 U/L). *Predominantly elevated alanine aminotransferase* (ALT): 750 U/L (reference 0-35 U/L). *Elevated aspartate aminotransferase* (AST): 509 U/L (reference 15-46 U/L). Total bilirubin: 1.6 mg/dL (reference: 0.2-1.3 mg/dL), direct bilirubin: 0.8 mg/dL (reference: 00-0.3 mg/dL), albumin: 4.7 (reference: 3.5-5.0 g/dL). Total protein: 7.5 g/dL (reference: 6.3-8.2 g/dL). Globulin: 2.8 g/dL (reference: 2.3-3.5 g/dL). AG ratio: 1.7. *Increased serum lipase*: 382 U/L (reference: 23 - 300 U/L). Lactate dehydrogenase (LDH): 1000 U/L, (reference: 120-246 U/L). The *blood alcohol level and acetaminophen level were within normal limits (WNL)*. Iron studies, coagulation, and lipid profiles were unremarkable. *Inflammatory markers (including serum ferritin and transferrin saturation) were WNL*. An acute hepatitis panel (including hepatitis A IgM antibody (anti-HAV IgM), hepatitis B surface antigen (HbsAg), hepatitis B core antigen (anti-HB-c), hepatitis C virus antibodies (anti-HCV), and hepatitis C virus RNA (HCV-RNA)) were negative. *A full urine toxicology screen returned negative* for amphetamine, barbiturates, benzodiazepines, cocaine, opiates, methadone, phencyclidine (PCP), and tetrahydrocannabinol (THC). A negative stool antigen test ruled out Helicobacter pylori (H. pylori) infection. *Laboratory studies to evaluate for less common causes of liver disease returned negative*, including anti-nuclear antibody, alpha-fetoprotein (hepatocellular carcinoma), antimitochondrial antibody (primary biliary cholangitis), anti-smooth muscle antibody (autoimmune hepatitis), and A1ATD (alpha-1 antitrypsin deficiency). *PSA levels were* undetectable. *Routine urinalysis was unremarkable*.

A chest radiograph showed no focal pulmonary consolidations, pleural effusions, or pneumothorax. ECG showed a normal sinus rhythm with 90 beats/minute. An abdominal ultrasound (US) showed the liver was normal in size, had regular margins, a smooth surface contour, and no conspicuous focal lesions. There was evidence of diffusely increased hepatic echogenicity (a hyperechoic appearance caused by the scattering of the ultrasound beam by lipid droplets). Periportal and diaphragmatic echogenicities were noted, suggesting hepatic steatosis grade I-II (Figure 1). The portal and hepatic veins (right, left, and middle) were patent. No thickening or distension of the gallbladder was noted. There was no intra-hepatic or extra-hepatic biliary dilatation. The common bile duct was not dilated and the sonographic Murphy sign was absent. A CT of the abdomen showed no acute intra-abdominal or intra-pelvic abnormalities. There was no evidence of pancreatitis, radiopaque gallstones, wall thickening, pericholecystic fluid collections, or biliary duct dilations. The ***calculated FIB-4 Index*** was 11.93, correlating with a high risk of liver fibrosis and other liver-related pathologies (reference: 0-1.29 = low risk; 1.30-2.67 = intermediate risk; >2.67 = high risk [5]).

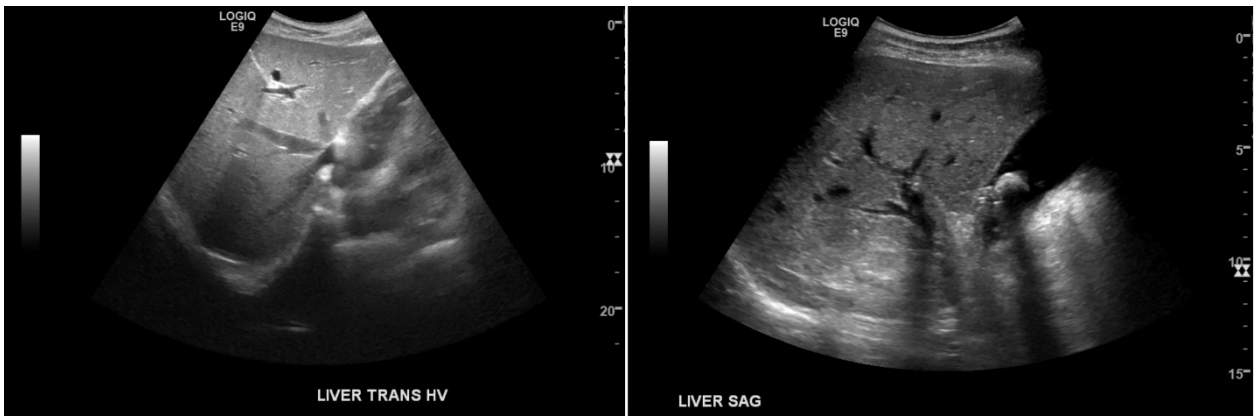

Figure 1. Ultrasound scan showing increased echogenicity of the liver in comparison to echotexture of the renal cortex (not shown here): grade I -II fatty liver

Based on this patient's history, physical exam, imaging, and laboratory studies, the differential diagnosis includes: 1.) Hepatocellular injury secondary to ischemia (supported by elevation of LDH). This is a nonspecific finding, however, and no precipitating factor was identified. 2.) Non-alcoholic hepatic steatosis (supported by a history of alcohol use). This is unlikely in a patient that has remained abstinent from alcohol for ten years to date. 3.) Another rare disease resulting in liver injury. This too is unlikely given that all studies for rare liver diseases returned negative). 4.) Drug-induced liver injury or pancreatic injury (supported by increased lipase) secondary to chronic and habitual DXM use.

The patient was admitted to the inpatient unit and was kept NPO. Intravenous fluids and a proton pump inhibitor (PPI) were initiated for his GERD symptoms. On hospital day three, the patient's liver enzyme studies showed improvement but not to WNL (ALKP: 146 U/L, ALT: 484 U/L, and AST: 151 U/L). Intravenous fluids were discontinued. The patient was managed conservatively, continuing his home medications and PPI. The patient was clinically and hemodynamically stable throughout the remainder of the hospital course. His abdominal pain resolved. In-hospital patient counseling included instructions to avoid OTC non-steroidal anti-inflammatory drugs (NSAIDs) and acetaminophen-containing medications. For improvement of his liver steatosis, the patient underwent lifestyle-modification counseling with a goal of a 5-10% reduction in weight. We advised the patient to discontinue the use of DXM altogether and educated him about the drug-induced liver injury it may incur.

Two weeks after discharge, the patient was seen and reported continued abstinence from the use of DXM. His liver enzymes were measured to be WNL. For continued support, the patient received instructions for regular follow-ups with his primary care provider, as well as Addiction and Rehabilitation Medicine consults.

3. Discussion

We present a case of chronic DXM use in an elderly patient, highlighting the need for increased awareness of OTC cough suppressant abuse and the potential harm it may inflict. Sporadic case reports have described the effects of DXM abuse [3,4,6,7], yet there is limited literature available on how the chronic use of OTC DXM-containing cough suppressants may lead to DILI in the elderly.

Various prescription medications are known to have the potential to cause DILI, however, the diagnosis is one of exclusion, thus, other known causes of liver injury must be eliminated. A suspected case of DILI should begin with a careful history focusing on risk factors of viral hepatitis, alcohol use, weight gain, autoimmune disease, cardiac failure, shock, and septicemia. In addition, a history of the patient’s prescription and non-prescription drug intake is imperative, including OTC and herbal supplements (listing the exact duration and dosage). In this case, the patient denied any pertinent history as listed above, apart from a remote history of alcohol use and current use of OTC DXM beginning three years prior. DILI usually has an insidious onset (months to years) after the medication is started (as reflected in our patient) and often presents as a picture of chronic liver disease rather than acute. Furthermore, serum AST and ALT elevation are generally mild but can be persistent [8]. In this case, the latency from when the patient began using DXM to the onset of jaundice, bilirubinemia, and elevation of transaminase levels was approximately three years. Moreover, DILI may also occur without any sign or symptom indicating liver disease, identified only by laboratory testing abnormalities.

The extensive evaluation of this patient showed no evidence of gallbladder or biliary system disease. The characterization of the liver was noted as Grade I-II steatosis suggestive of non-alcoholic fatty liver disease (NAFLD). Furthermore, the calculated blood-based diagnostic FIB-4 score (determined from the values of patient age, platelet count, AST, and ALT) was significantly elevated, reflecting the severity of the underlying and advanced fibrosis [5]. NAFLD includes a spectrum of diseases that range from simple steatosis to non-alcoholic steatohepatitis (NASH), liver cirrhosis, and hepatocellular carcinoma (HCC) [9]. Several mechanisms are potentially at play, including preexisting steatosis (rendering hepatocytes vulnerable to drug-induced toxicity), medication use (disrupting preexisting liver fats), and NASH, which can further alter the hepatic drug transporters and change drug pharmacodynamics and pharmacokinetics, affecting safety thresholds [8]. In this case, *the patient had no risk factors for a metabolic cause of steatosis* (including obesity, diabetes, hyperlipidemia, or metabolic syndrome) and the only risk was the chronic use of DXM for the preceding three years. The extensive workup illustrated in this case included a complete hepatitis panel and panels to evaluate for other rare causes of liver disease, including autoimmune hepatitis, HCC, primary biliary cholangitis, and other IgG-4-related fibroinflammatory diseases. For our patient, all of the aforementioned studies returned negative. Hence, we developed a differential diagnosis for hepatocellular injury. Based on a diagnosis of exclusion, it was concluded that DILI secondary to excessive and chronic DXM use is a plausible diagnosis.

In the United States, DXM is marketed as a cough suppressant that is neither a controlled substance or regulated chemical under the Controlled Substances Act. The antitussive effects of DXM usually persist for 5 to 6 hours after oral administration [1]. Long-term abuse of DXM is associated with severe psychological dependence that is dose-dependent, including mild stimulation at a dose of 100-200 mg, euphoria and hallucinations at a dose of 200-400 mg, and distorted visual perceptions, loss of motor coordination, and out of body sensations at a dose of 300-1500 mg results [2]. In a systematic review by Miller et al., 2005, the authors reported on DXM withdrawals and its dissociative effects, likely from DXM active metabolite Dextrorphan (DOR) [2]. In 2010, the Federal Drug Administration Advisory Committee issued a warning and reported on the concern for DXM abuse, especially among adolescents and young adults [10].

In summary, this case demonstrates OTC DXM abuse in an elderly patient. It highlights the implications of chronic use of OTC DXM as a cause of DILI, as evident from the diagnostic workup resulting in this diagnosis of exclusion.

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