

# Acute Hepatocellular Drug-Induced Liver Injury From Bupropion and Doxycycline

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## Abstract

The management and diagnosis of drug-induced liver injury (DILI) is often challenging, particularly when patients are taking multiple medications. We present a 29-year-old African American man who presented with jaundice and malaise after starting bupropion and doxycycline 2 weeks prior. He was found to have acute hepatocellular drug-induced liver injury with autoimmune features, and made a complete recovery with prednisone. Although bupropion and doxycycline are both known to cause liver toxicity, a closer inspection of the signature of liver injury and a review of prior related DILI cases assigns causality more to bupropion than doxycycline.

## Introduction

Drug-induced liver injury (DILI) is an important cause of liver disease, affecting 1 in 10,000 to 100,000 patients, and is a primary reason for medication withdrawal.<sup>1</sup> Several hundred prescription and over-the-counter medications, in addition to herbal drugs and nutritional supplements, have been implicated. The clinical presentation of DILI can be widely variable and can mimic almost any form of liver disease, including acute and chronic infectious hepatitis. Diagnosis remains challenging, especially when patients are on several medications, making it difficult to identify the culprit. Management is mainly withdrawal of the offending agent, but early recognition is key to avoiding serious health consequences and mortality.

## Case Report

A 29-year-old African American man presented with jaundice and malaise that began 14 days after starting bupropion (150 mg sustained-release daily) for depression and doxycycline (100 mg twice daily) for acne. He did not have abdominal pain, edema, fever, itching, mental status changes, or rash. He did not have any recent history of hypotension, shock, or ischemia. His only other medication was as-needed acetaminophen-oxycodone (325 mg/5 mg orally) for back pain, which he was taking once a week. He denied additional herbal/nutritional drugs and alcohol consumption. He self-discontinued all medications on the day of admission.

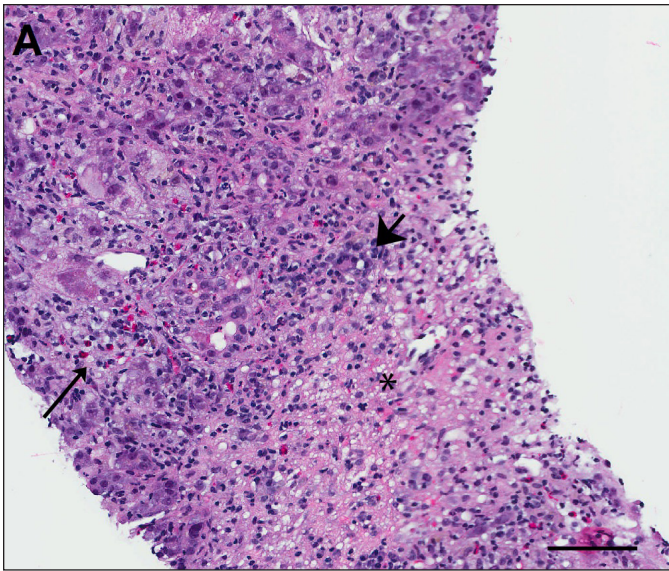
Physical exam was only remarkable for scleral icterus and there was no stigmata of chronic liver disease. Laboratory examination revealed an alanine aminotransferase (ALT) of 896 U/L, aspartate aminotransferase (AST)

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**Figure 1.** H&E stain histology from liver biopsy showing severe inflammation with interface hepatitis, prominent plasma cells (short arrow), eosinophil clusters (long arrow), and extensive parenchymal collapse (asterisk). Bar=100 microns.

of 1228 U/L, total bilirubin of 19.9 mg/dL, direct bilirubin of 16.2 mg/dL, alkaline phosphatase (ALP) of 234 U/L, international normalized ratio of 3.0, mild eosinophilia (5.2%), and an undetectable acetaminophen level. Anti-smooth muscle antibody was positive (1:40 titer) with an elevated IgG of 1864 mg/dL. Viral serologies (hepatitis A, B, and C, cytomegalovirus, Epstein-Barr virus) were negative, as were anti-nuclear and anti-mitochondrial antibodies. Right upper quadrant abdominal ultrasound and abdominal/pelvic contrast-enhanced computed tomography were unremarkable. Liver biochemistries from 1 year prior were normal.

A liver biopsy revealed severe inflammation with interface hepatitis, prominent plasma cells, eosinophil clusters, and extensive parenchymal collapse without significant steatosis (Figure 1). Fibrosis and hepatocellular hemosiderin were absent on trichrome and iron stains. Based on these findings and the timing of medications, the diagnosis of acute DILI with autoimmune features was made. Because of the autoimmune features, centrilobular necrosis, and worsening liver function, a prednisone taper (starting dose 40 mg daily) was initiated on day 4 of hospitalization. The patient's status gradually improved clinically as well as biochemically, with a >50% decrease in liver function tests at discharge on day 9. Continued improvement in liver biochemistries was observed at an outpatient follow-up visit on day 19, with complete normalization on day 67. We will continue to follow the patient to exclude autoimmune hepatitis, in case of a misdiagnosis that coincided with starting bupropion and doxycycline. A re-challenge with either of the 2 medications was not performed due to patient

safety considerations and the availability of other therapies to treat his depression and acne.

## Discussion

Both bupropion and doxycycline are commonly prescribed and have a relatively safe profile, but have been shown mainly through case reports to be responsible for acute liver injury and failure.<sup>2-12</sup> Although either agent could be responsible, establishing a better definition of the signature or pattern of the liver injury associated with these agents can tilt causality toward one or the other. We advocate that clinicians utilize a 2-step systematic approach comprising a validated causality assessment model, such as the validated Roussel Uclaf Causality Assessment Method (RUCAM), and a review of prior anecdotal cases.<sup>12</sup> Since the RUCAM score for each bupropion and doxycycline is similar (score of 6, or probable association), the signature of liver injury should be approached with 6 components in mind: 1) latency to onset, 2) calculation of the initial R-value (ALT/upper limit of normal [ULN] divided by AP/ULN), 3) peak bilirubin, 4) presence or absence of autoimmune features, 5) presence or absence of immunoallergic features, and 6) time to recovery.<sup>12,13</sup> The R-value identifies the type of hepatic injury: cholestatic ( $\leq 2$ ), hepatocellular ( $\geq 5$ ), or mixed (2-5).<sup>12</sup>

Furthermore, a review of convincing bupropion- and doxycycline-induced DILI cases from LiverTox and PubMed were compared and proved useful in our case.<sup>13</sup> The latency to onset, peak bilirubin, and time to recovery varied widely, and thus were not helpful in assigning causality. However, upon closer inspection of the R-value and presence of immunoallergic and autoimmune features, our case suggested that bupropion was the more contributive agent. Our patient had a calculated R-value of 6.7, suggesting a hepatocellular pattern. While bupropion-induced DILI cases can present with all 3 types of injury, doxycycline-induced DILI only presents with either a mixed or cholestatic pattern. Further, patients with bupropion-induced DILI often exhibit autoimmune features, similar to those seen on our patient's liver biopsy. In contrast, doxycycline-induced DILI tends to present with immunoallergic features reminiscent of drug reaction/rash with eosinophilia and systemic symptoms (DRESS). Although our patient had mild eosinophilia, he did not have immunoallergic features to meet the diagnostic criteria for DRESS. Given the findings from our comparative analysis, causality was assigned more to bupropion than doxycycline.

In the era of polypharmacy, causative assignment of DILI can be a diagnostic dilemma. We advocate for a better definition of the signature of the liver injury with the assistance of a validated causality assessment scale, along with a careful comparison of prior documented reports, in solving com-

plicated DILI cases. This is particularly useful when more than one culprit medication may be involved or when a re-challenge is not possible or ethical.

## Disclosures

Author contributions: DM Tang authored all sections of the manuscript and is the article guarantor. C. Koh, EC von Roseninge, and H. Han edited the manuscript. WS Twaddell provided the histology image.

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