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A Case Report on Bupropion Induced Febrile Delirium & Reversible Liver Injury

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ABSTRACT

Bupropion, an atypical antidepressant and smoking cessation aid, is generally well-tolerated but has been linked to rare instances of hepatotoxicity. We report a case of a 81-year-old non alcoholic male who developed jaundice, fatigue, and right upper quadrant discomfort three months after starting bupropion. Laboratory tests showed elevated liver enzymes and hyperbilirubinemia, while extensive workup excluded other causes of liver dysfunction. The temporal association with bupropion and exclusion of other etiologies led to a diagnosis of bupropion-induced liver injury. Discontinuation of bupropion and supportive care resulted in gradual improvement and normalization of liver enzymes and resolution of fever and delirium state within three months. This case underscores the importance of considering bupropion-induced febrile delirium and reversible liver injury in patients with unexplained liver dysfunction and highlights the necessity for early recognition and drug cessation for recovery. Bupropion is also known to cause unexplained delirium. Conditions which can result in such a state can range from very diverse perspectives, such as infectious conditions like pneumonia or urinary tract infections, metabolic disorders like electrolyte imbalance, and disorders of the central nervous system like encephalitis. Keen medical evaluation is very essential for determining the root cause, as treatment mostly depends on prompt action for causative diseases to avoid further complications.

INTRODUCTION

Bupropion, an aminoketone derivative, is approved for treating mood disorders and aiding smoking cessation. It weakly inhibits the reuptake of norepinephrine, serotonin, and dopamine but is chemically different from other antidepressants. Its mechanism for aiding smoking cessation is unclear but may involve noradrenergic and dopaminergic pathways. Generally well-tolerated and safe, it is prescribed to 25% of individuals using smoking cessation aids, with 8.7 million prescriptions annually in the U.S. Approved in 1985 for depression and later for seasonal affective disorder and smoking cessation, it has about 4 million annual prescriptions. It is available in immediate and sustained release tablets (75-300 mg) under the names Wellbutrin, Zyban and Bupron. The recommended adult dosage is 75-300 mg daily. Common side effects include drowsiness, dizziness, agitation, headache, nausea, abdominal pain, and dry mouth.[1,2]

Bupropion can lead to liver injury through a mechanism known as idiosyncratic drug-induced liver injury (DILI). Idiosyncratic DILI is a rare but severe reaction that occurs unpredictably in response to a medication, even at therapeutic doses. The immune-mediated response of Bupropion can result in a range of liver injury manifestations, from mild transaminase elevations to severe hepatocellular injury or even fulminant liver failure. The exact mechanisms by which bupropion induces liver injury are not fully

understood, but it is believed to involve a complex interplay of immune responses, metabolic pathways, and genetic factors. Monitoring liver function tests during bupropion therapy is crucial to detect any signs of liver injury early and prevent severe complications[3]

In managing bupropion-induced liver injury, the primary approach is to discontinue bupropion immediately. This step aims to halt further liver damage and allow the liver to recover. Supportive care is essential, including close monitoring of liver function tests, hydration, and nutrition support. Depending on the severity of the liver injury, additional interventions may be required, such as administering medications to manage symptoms or complications. In severe cases, the patient might need specialized care in a hospital setting, potentially including liver transplant evaluation if liver failure occurs. Regular follow-up visits with healthcare providers are crucial to assess liver function recovery and ensure ongoing monitoring for any potential long-term effects[4]. This case report aims to provide a detailed account of a patient who developed significant liver injury after initiating bupropion therapy, highlighting clinical presentation, diagnostic evaluation, and management strategies. By examining this case, we hope to contribute to the growing body of literature on drug-induced liver injury and offer insights into the safe use of bupropion in clinical practice.

Delirium with fever can be a concerning medical symptom that requires prompt evaluation by a healthcare professional. Delirium is characterized by acute confusion and changes in cognition that can develop rapidly over a short period of time. When it occurs in conjunction with fever, several potential underlying causes need to be considered such as infection, metabolic disturbance, CNS disorders, ADR of medications used etc.. Bupropion is known to cause drug induced febrile therapy illness and delirium state.[10][11]

CASE REPORT

A 81 year old non alcoholic gentleman presented with low grade fever and altered sensorium for 3 days. He also had right knee pain on and off. He was on treatment for diabetes mellitus, hypertension, parkinsonism, and depressive illness. On examination his BP was 140/68 mmHg, PR 72, RR 26, febrile 100.5, no icterus. On CNS examination higher functions, the patient was disoriented to place and time and intermittent incoherent speech and agitation was observed, GCS E4V4M6 - 14/15. He was moving all limbs, with mild B/L rigidity of both upper limbs(cogwheel) and both plantar flexor. CVS S1 S2 heard normal, RS clear. On abdomen examination, soft non tender no hepatosplenomegaly.

Table 1

Values	
OT/PT	42/58 U/L
GGT	115.40 U/L
CRP	54.6/59.6
ESR	26
PT INR	1.4

His lab reports revealed derangements which are shown in Table 1. His blood cultures and urine cultures were normal. His covid and screening test for influenza panel was negative. His HBsAg, HCV-Ag were also negative.

He was on Bupropion 300 mg daily, which was maintained for an extended period of 2 years for his depressive illness along with his antiparkinsonism medication such as T. Syndopa Plus 125 mg 4 times a day and T. Pramipex 0.37mg BD, and antihypertensives - T.Cilnidipine 5 mg AM OD, as indicated by records. His USG abdomen and pelvis were normal other than Grade 1 fatty liver. After discontinuing the atypical antidepressant T. Bupropion 300mg for two weeks, his fever subsided and clinical condition improved, GCS returned to normal. His abnormal OT/PT, CRP, GGT, and ESR levels also showed improvement. (Table 2). Subsequently, his general condition improved. The patient was discharged on the note to hold T. Bupropion 300 mg daily.

Table 2

Improved Values	
ESR	11.6
OT/PT	24/26
CRP	10.7
GGT	55

On post discharge review after 2 weeks, the patient was asymptomatic and was given an alternative for Bupropion tablet. Therefore, Bupropion induced febrile delirium and reversible liver injury was suspected.

DISCUSSION

The liver activates enzymes according to the metabolic and biochemical demands. The liver has various enzymes which help for drug metabolism, primary mechanism for metabolizing drugs is via a specific group of cytochrome P-450 enzymes.

The liver's cytochrome P450 family of enzymes performs phase 1 reactions, including oxidation, reduction and hydrolysis reactions to enhance the water solubility of drugs and aid in their excretion. These reactions, mediated by iron, result in the production of water-soluble compounds that can be excreted in the bile [8]. Bupropion, an antidepressant also used for smoking cessation, works by inhibiting the reuptake of dopamine and norepinephrine. Animal studies have shown it can cause reversible liver toxicity, liver cell enlargement, and localized liver overgrowth due to enzyme induction. Hepatotoxicity from bupropion affects 0.1% to 1% of patients, with liver damage typically showing a hepatocellular or cholestatic pattern. The damage mechanism is mainly immune-mediated, often presenting with hypersensitivity symptoms like fever, rash, eosinophilia, and autoantibodies, usually occurring within 1-6 weeks [5].

Acute hepatitis and significant transaminase deviation was reported following bupropion therapy[6]. In our case, in addition to liver enzyme elevation, patient had febrile episodes and delirium which responded to discontinuation of bupropion and also substantiated immune mediated liver injury. Another case report by **Anandabaskaran and Ho** *et.al* explained about a patient who developed elevated liver enzymes after the intake of bupropion and which gradually reduces after its cessation[5]. Bupropion has the potential to elevate liver enzymes via many pathways. It may set off an immune-mediated response that results in a hypersensitivity syndrome, which can harm liver cells and induce inflammation. This condition is characterized by fever, rash, eosinophilia, and autoantibodies. Liver enzymes may be released into the circulation as a consequence of this immunological reaction. Furthermore, bupropion causes localized hepatic hyperplasia and hepatocellular enlargement via inducing hepatic enzymes. Liver enzyme levels in

blood tests may rise as a result of this increased enzyme synthesis and activity. Another pathway is direct hepatotoxicity, in which Bupropion and its metabolites may be harmful to liver cells, inflicting cellular stress, damage, and necrosis, all of which result in the production of liver enzymes. Reactive oxygen species (ROS) can be produced during metabolic stress caused by bupropion metabolism. These ROS can cause oxidative stress, mitochondrial malfunction, additional damage to liver cells, and the release of liver enzymes[7]. These interrelated processes demonstrate how Bupropion may be involved in increased liver enzyme levels, which may be a sign of underlying liver damage or malfunction.

CONCLUSION

In conclusion, bupropion-induced febrile delirium and reversible liver injury, though relatively rare, is a significant clinical condition. The mechanisms behind this hepatotoxicity include immune-mediated reactions, direct hepatocellular toxicity, and hepatic enzyme induction. Patients may present with elevated liver enzymes, hepatocellular or cholestatic liver damage, and symptoms of hypersensitivity. Awareness and monitoring of liver function are crucial in patients taking Bupropion, especially when taking for long term therapy and also in the initial period of therapy. Prompt recognition and discontinuation of Bupropion, along with supportive care, are essential to manage and mitigate liver injury.

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