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# A Change in Blood Carbamazepine Levels Associated With Cannabis Use: Implications for Clinical Practice

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With state legalization, cannabis use is rising in the United States.<sup>1</sup> Cannabis use is common by individuals with psychiatric disorders and can be associated with alterations in mood and energy and other psychiatrically related symptoms.<sup>2</sup> Despite this rise in cannabis use, much is unknown about its pharmacokinetics as related to psychiatric medications. The cannabinoids  $\Delta$ -tetrahydrocannabinol (THC), cannabidiol (CBD), and cannabinol (CBN) are prominent cannabis components. These cannabinoids are metabolized by cytochrome P450 (CYP)3A4 (THC, CBD, and CBN), CYP2C9 (THC and CBN), and CYP2C19 (CBD)<sup>3</sup> and can inhibit CYP2C9, CYP1A1/2, CYP1B1 (THC, CBD, and CBN), CYP2D6, CYP2C19, CYP2B6, CYP2J2 (THC and CBD), and CYP3A4/5 (CBD).<sup>4,5</sup>

While many psychiatric medications are metabolized by these same enzymes, there is a paucity of data regarding interactions between psychiatric drugs and cannabis. Carbamazepine is an anticonvulsant medication commonly used for psychiatric disorders and approved by the US Food and Drug Administration for bipolar disorder treatment.<sup>6</sup> Carbamazepine is highly metabolized by CYP3A4 with minor metabolism by CYP2C8, 3A5, and 2B6.<sup>7</sup> Recently, carbamazepine was highlighted as a medication with a narrow therapeutic index, suggesting close monitoring when coadministered with cannabinoids.<sup>8</sup> Here, we describe a case of concurrent use and likely interaction between cannabis and carbamazepine in a patient with bipolar disorder diagnosed using *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition, criteria.

## Case Report

A 37-year-old male with a history of bipolar disorder and long-standing cannabis use presented with elevated mood, grandiosity, increased goal-directed activity, decreased need

for sleep, talkativeness, flight of ideas, distractibility, and risk-taking after stopping olanzapine for approximately 2 months. Carbamazepine 200 mg twice daily and olanzapine 5 mg at bedtime were started. Temazepam 15 mg was added to help with sleep after 1 week. After 2 weeks, carbamazepine was increased to 400 mg twice daily, and blood levels were therapeutic at 6.7  $\mu\text{g}/\text{mL}$  (Table 1). During treatment, olanzapine was titrated up to 20 mg and carbamazepine to 400 mg in the morning and 600 mg at bedtime until symptoms of mania improved, then temazepam was stopped and olanzapine tapered to 5 mg over the next few months. During this time, the patient reported smoking cannabis 1–2 joints daily, and his carbamazepine levels were 6.7–7.0  $\mu\text{g}/\text{mL}$ .

The patient stopped cannabis use, which was confirmed by urine toxicology screen 6 weeks after cessation. At this time, carbamazepine levels were 4.8  $\mu\text{g}/\text{mL}$ . The patient denied other medication, diet, or supplement changes. Carbamazepine was increased to 400 mg in the morning and 800 mg at bedtime. The patient restarted cannabis 1 joint daily, confirmed by urine toxicology screening 2 weeks after restarting. At this time, the carbamazepine level was noted to be 9.1  $\mu\text{g}/\text{mL}$ . With a decrease in the carbamazepine dose by 200 mg, the patient's carbamazepine level returned to 6.8  $\mu\text{g}/\text{mL}$ .

## Discussion

This case illustrates a likely interaction between cannabis and carbamazepine. The patient's carbamazepine level dropped with self-reported and laboratory confirmed cannabis cessation. CBD inhibits CYP3A4/5, and both THC and CBD inhibit CYP2B6<sup>3,5</sup>; CYP3A4 is the major metabolic pathway for carbamazepine, and CYP3A5 and CYP2B6 are 2 of the 3 minor metabolic pathways.<sup>7</sup> As such, stopping cannabis use may have led to the carbamazepine level reduction by increasing CYP activity. This is highlighted by the clinical observation that the patient's blood carbamazepine level was 4.8  $\mu\text{g}/\text{mL}$  when not smoking cannabis and 6.8  $\mu\text{g}/\text{mL}$  when smoking cannabis on the same carbamazepine dose. These results suggest the need for increased screening regarding cannabis use with carbamazepine and other medications and further research regarding potential drug-cannabis interactions. Other factors impacting cannabinoids and metabolism, including CYP polymorphisms<sup>9</sup> and routes of cannabis administration,<sup>3</sup> warrant further investigation.

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Table 1. Relation of Cannabis Use and Circulating Levels of Carbamazepine

Days Since Starting Carbamazepine	Cannabis Use?	Carbamazepine Dose	Carbamazepine Level, µg/mL
20	Yes <sup>a</sup>	200 mg twice daily	6.2
62	Yes	400 mg twice daily	6.7
97	Yes	400 mg in the morning, 600 mg at bedtime	7.0
190	No <sup>a</sup>	400 mg in the morning, 600 mg at bedtime	4.8
211	Yes <sup>a</sup>	400 mg in the morning, 800 mg at bedtime	9.1
227	Yes	400 mg in the morning, 600 mg at bedtime	6.8

<sup>a</sup>Indicates cannabis use was confirmed by urine toxicology at the same time. Others use data from patient report.

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