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Letter to the Editor

Late onset of serious agomelatine-induced liver injury

To the Editor,

Agomelatine is a melatonergic antidepressant that helps to promote sleep. The mechanisms of melatonin receptors (MT_1, MT_2) agonist and serotonin receptor ($5HT_{2C}$) antagonist facilitate the resynchronization of altered circadian rhythms [1]. Significant elevation in liver enzymes [transaminase titers of >3X upper limit of normal (ULN)] has been reported in 4.6% of patients, but serious hepatic reactions (transaminase titers of >10X ULN) were rare [2]. Blood liver enzymes are required before drug initiation and after 6, 12, and 24 weeks of treatment [3]. Here we present a case of late-onset, agomelatine-induced serious hepatic reaction.

A 32-year-old female with insomnia disorder was treated with agomelatine (Table 1). At the seventh month after initiation of treatment, alanine aminotransferase (ALT) was slightly increased. Transaminitis and increased direct bilirubin were evident at the ninth month after treatment. The patient had no other underlying disease and denied using alcohol, herbs, hormones, or over-the-counter drugs. She had no clinical abnormality, and the physical examination was normal. We stopped agomelatine treatment because serum transaminases exceeded >3X ULN as recommendation. One month later, the liver function tests returned to normal. Naranjo's algorithm score was seven (probable adverse drug reaction) [4].

To our knowledge, agomelatine-induced liver injury typically occurs within the first few weeks of treatment, and the incidence increases with higher doses. No data are available for agomelatine-induced liver injury after the sixth month of treatment [2]. We observed that agomelatine-induced serious hepatic reaction could present nine months after the initiation of treatment. Moreover, the reaction occurred eight months after the dose was increased to 50 mg per day. We recommend physicians carefully monitor liver enzymes during the first year of agomelatine treatment.

Table 1
Duration after starting agomelatine, agomelatine dose, and liver function test.

Month after starting agomelatine	Agomelatine dose (mg/day)	AST, ALT (U/L)	Total bilirubin, Direct bilirubin (mg/dl)
Day 0 (Apr/2020)	25	N/A	N/A
1st month (May/2020)	50	N/A	N/A
3rd month (Jul/2020)	50	14, 14	0.30, 0.14
7th month (Nov/2020)	50	26, **53**	N/A
9th month (Jan/2021)	50	**181, 392**	0.75, **0.42**
Agomelatine discontinuation			
1st month after drug discontinuation	–	26, 29	0.53, 0.20

Abbreviations: AST, aspartate aminotransferase; ALT, alanine aminotransferase; N/A, not applicable.
Normal range: AST 0–32 U/L.
ALT 0–33 U/L.
Total bilirubin 0.0–1.2 mg/dl.
Direct bilirubin 0.0–0.3 mg/dl.

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Conflict of interest

None.

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