

# Why zolpidem increases the risk of falls and fractures in patients with cirrhosis



## To the Editor:

We thank Tapper and colleagues for their interesting and relevant article on deprescribing benzodiazepines in patients with cirrhosis.<sup>1</sup> The authors conclude that deprescribing zolpidem reduces the risk of falls and fractures in these patients. Yet, the article does not provide an explanation of why specifically zolpidem, and not traditional benzodiazepines, is associated with fractures and falls. We have reason to believe these findings can be explained by the largely altered pharmacokinetics of zolpidem in patients with cirrhosis. Moreover, pharmacokinetic considerations might favour benzodiazepines with a short half-life and glucuronidation as an elimination route above other benzodiazepines. In this letter, we would like to add these pharmacological aspects to the findings of Tapper *et al.* concerning the safety of benzodiazepines in patients with cirrhosis.

Benzodiazepines are all lipophilic drugs that target receptors in the brain. As with other lipophilic drugs, the liver clears benzodiazepines from the blood. Yet, the extent of clearance depends on the specific drug. In patients with cirrhosis, the ability of the liver to clear medicines from the systemic circulation is affected.<sup>2</sup> This results in increased exposure to drugs and consequently an increased risk of adverse drug reactions. Increased exposure is most prominent for zolpidem. A pharmacokinetic study on zolpidem showed that peak plasma levels were doubled in patients with cirrhosis.<sup>3</sup> More importantly, elimination half-life increased from about 2 h in individuals without cirrhosis to 10 h in those with cirrhosis, and total exposure was fivefold higher in the group of patients with cirrhosis. The impaired clearance and longer half-life increase the duration of action, the risk of drowsiness in the morning and consequently the risk of falls and fractures. As mentioned, other benzodiazepines are also cleared by the liver. Yet, such large increases in exposure were not seen with these other benzodiazepines.<sup>4</sup>

Benzodiazepines have also been linked to an increased risk of (worsening) hepatic encephalopathy.<sup>4,5</sup> In the current study, deprescribing benzodiazepines did not decrease the incidence of

hepatic encephalopathy. In patients with compensated cirrhosis, the impact of benzodiazepines is more likely to be seen in the early stages of hepatic encephalopathy (grade 1 or 2), and measurement was outside the remit of the study. Moreover, the risk of (worsening of) hepatic encephalopathy is highest in the first weeks of starting the benzodiazepine, as demonstrated by Gronbeak *et al.*<sup>5</sup> Several cases of hepatic encephalopathy associated with zolpidem have been described in the literature,<sup>6–8</sup> which suggest that the higher exposure to zolpidem in patients with cirrhosis impacts the risk of hepatic encephalopathy.

When looking at the safety of all benzodiazepines in patients with cirrhosis, we agree with the general conclusion of the authors that caution is needed, and that these drugs should be avoided and deprescribed if possible. While we can side with this notion, we favour a granular approach and suggest prescribing benzodiazepines least affected by impaired metabolism in cirrhosis. Most benzodiazepines are metabolized by CYP450-enzymes (mainly CYP3A4, CYP2C19) leading to one or more active metabolites, some benzodiazepines are only glucuronidated, *i.e.* lorazepam, oxazepam and temazepam.<sup>9</sup> Glucuronidation is considered to be less affected by cirrhosis than CYP450-mediated metabolism.<sup>10</sup> As a consequence, alterations in critical pharmacokinetic parameters (half-life and clearance) of these drugs are less prominent and occur mostly only in advanced cirrhosis. This possibly results in fewer side effects, although this hypothesis is not yet supported by clinical data.

In conclusion, we suggest the fivefold increase in half-life and exposure to zolpidem is the explanation for the higher risk of falls and fractures found in the study by Tapper and colleagues. All benzodiazepines are potentially inappropriate medicines in patients with cirrhosis; yet, based on pharmacokinetic alterations, zolpidem is certainly a benzodiazepine to avoid in patients with cirrhosis. If benzodiazepine use is necessary, we advise choosing a benzodiazepine without these large pharmacokinetic alterations, such as lorazepam, oxazepam or temazepam.

## Financial support

The authors received no financial support to produce this manuscript.

## Conflicts of interest

The authors declare no conflicts of interest that pertain to this work.

Please refer to the accompanying ICMJE disclosure forms for further details.

## Authors' contributions

Rianne Weersink: conceptualisation, writing – original article. Joost Drenth: writing – review and editing. Sander Borgsteede: writing – review and editing.

## Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jhepr.2022.100528>.

Keywords: Cirrhosis; Pharmacology; Benzodiazepines; Zolpidem.

Received 2 June 2022; accepted 15 June 2022; available online 27 June 2022



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