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Title:
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Date:
2022-07-01

Citation:
Yeomans, N. D. (2022). Editorial: risk of gastric and duodenal ulcers among new users of low-dose aspirin. Alimentary Pharmacology and Therapeutics, 56 (2), pp.334-335. https://doi.org/10.1111/apt.17062.

Persistent Link:
https://hdl.handle.net/11343/336520

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Editorial: risk of gastric and duodenal ulcers among new users of low-dose aspirin

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At first reading, the paper by Nguyen *et al* appears to present a conundrum.[1] Using two prospective databases, one in UK with about quarter of a million patients plus a smaller one in south-west Germany, the authors found about a three-fold increase in the risk of gastric ulcer and four-fold increase for duodenal ulcer in patients who were taking low dose aspirin (LDA). However, the association was only found in those who were new users—defined as participants who commenced LDA after they had been enrolled in the cohort for more than two years in the German study, and those starting LDA at any time after baseline in the UK study. The conundrum was their finding in both databases that those who were already using LDA at baseline ('prevalent users') were much less likely to develop an ulcer compared with non-users, over follow-up periods of more than ten years. The authors put forward two plausible explanations for the low risk of an LDA ulcer in the 'prevalent user' cohorts. One has been called the 'healthy user' effect or the 'sick stopper' bias.[2,3] In essence, this arises because individuals who have been on treatment for some time before entering a study are more likely to have demonstrated their tolerance to the treatment. Others who had an adverse effect would often have proven themselves ineligible for the study or refused to take the medication again. Another alternative, which the authors mention, is adaptation to the gastroduodenal toxic effects of aspirin during continuous dosing. There is good evidence for this with aspirin and other nonsteroidal anti-inflammatory drugs in rats, where tolerance develops rapidly.[4,5] However, whether such an adaptation occurs in humans has been controversial. The paper by Nguyen *et al* might provide a little support for the possibility that aspirin adaptation occurs in some patients.

It is of interest that in the 'new user' cohort, Nguyen *et al* found a numerically higher hazard ratio for the development of duodenal ulcer than gastric ulcer. Much of the aspirin literature has focussed on the gastric damage, and there is also evidence that erosions—the superficial precursors of ulcers—are more numerous in the stomach than the duodenum in patients who take LDA.[6] However, this present study reminds us that the duodenum is also at risk of ulceration in patients taking aspirin. As a side issue, one surprising finding from the study was that the use of acid suppressants, in the UK cohort only, increased the incidence of duodenal ulcer. This flies in the face of all the evidence that gastric acid is important in ulcer pathogenesis, as well as the randomised controlled trials that showed that proton pump inhibitors reduce the risk of LDA-induced duodenal ulcer.[7,8] The authors reasonably

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/apt.17062

conclude that some unidentified confounder was responsible for this finding. Confounders are always a hazard of epidemiological studies; the other side of the coin is the opportunity with such research to follow large populations – as occurred here.

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