

# Was it really pancreatitis from GLP-1 receptor agonist therapy?

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We read with interest the recent publications alluding to the link between GLP-1 receptor agonist therapy (GLP-1RA) and the risk of acute pancreatitis.<sup>1–5</sup> We write to highlight that this seems at odds with our own experience in two nationwide audits of GLP-1RA use, with the reported cases of pancreatitis being very rare in both audits.

The Association of British Clinical Diabetologists (ABCD) conducted audits on the use of exenatide twice daily (2007–2009) and liraglutide (2009 – ongoing) to evaluate the safety and efficacy of these agents in real-life clinical practice. The structure and major findings of the exenatide audit, including the reported cases of acute pancreatitis, were published previously in this journal.<sup>6</sup> We have also recently reported on the frequency of acute pancreatitis among patients in the liraglutide audit.<sup>7</sup> The pertinent feature of both audits was the specific enquiry into the occurrence of pancreatitis in the audit query. To our knowledge, both audits are as yet still the largest reported audits of GLP-1RA use in clinical practice (6717 and 6010 patients, respectively). ABCD received grants from Eli Lilly and Novo Nordisk for these audits, but the audits were conducted independently of the pharmaceutical companies, as was the reporting of pancreatitis cases from the individual participating sites.

As published previously, there were four cases of acute pancreatitis reported in the ABCD nationwide exenatide audit. After scrutiny of each reported case, three cases had alternative causes for the episode of pancreatitis – gallstones, significant alcohol consumption and significant hypertriglyceridaemia. Only one case had no obvious alternative cause.<sup>6</sup> The audit monitored 3336 years of exposure to exenatide. With one case which might be related to exenatide therapy, this represents an incidence of 0.030 per 100 patient years of exposure to exenatide. The equivalent finding in the ABCD nationwide liraglutide audit was one possible related case among 3720 monitored years of exposure, representing an incidence of 0.027 per 100 patient years of exposure to liraglutide.<sup>7</sup>

## Key factors

A key lesson we learned from conducting the audits was that the correct adjudication of pancreatitis cases is extremely important, especially when the frequency of an adverse event is very low. There were three reported cases of abdominal pains in the exenatide audit with concerns for pancreatitis but with subsequent normal amylase levels. These were deemed not to be cases of pancreatitis. A particular strength of the audits, one that was not easily performed by an administrative claims database study as reported recently,<sup>4</sup> was our ability to clarify with the individual centre reporting pancreatitis cases to obtain the full details of the event. We also think that findings of gallstones, significant alcohol consumption or significant hypertriglyceridaemia are inherently not statistically-adjustable as attempted in

the administrative claims database study;<sup>4</sup> there was either a different cause of pancreatitis or there was not!

## Further issues

The audits do possess weaknesses with issues such as incomplete recall or under-reporting of cases. We also believe that further studies are required to clarify on the issue of ‘sub-clinical pancreatitis’ or pancreatic mass expansion, with the background concern of pancreatic cancer.<sup>3</sup> However, we are concerned that a flawed conclusion of pancreatitis risk in a self-selected obese study population that shares many risk factors for the occurrence of pancreatitis has unwittingly bolstered alarm concerning what is otherwise a useful class of drug treatment for diabetes.

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## Declaration of interests

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