Pancreatitis associated with the use of GLP-1 analogs and DPP-4 inhibitors: a case/non-case study from the French Pharmacovigilance Database.

Jean-Luc Faillie, Samy Babai, Sabrina Crépin, Virginie Bres, Marie-Laure Laroche, Hervé Le Louet, Pierre Petit, Jean-Louis Montastruc, Dominique Hillaire-Buys

▶ **To cite this version:**

Jean-Luc Faillie, Samy Babai, Sabrina Crépin, Virginie Bres, Marie-Laure Laroche, et al.. Pancreatitis associated with the use of GLP-1 analogs and DPP-4 inhibitors: a case/non-case study from the French Pharmacovigilance Database.. Acta Diabetologica, 2013, 51 (3), pp.491-497. 10.1007/s00592-013-0544-0 . hal-00922480

HAL Id: hal-00922480
https://unilim.hal.science/hal-00922480

Submitted on 6 Apr 2022

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Pancreatitis associated with the use of GLP-1 analogs and DPP-4 inhibitors: a case/non-case study from the French Pharmacovigilance Database

Jean-Luc Faillie, Samy Babai, Sabrina Crépin, Virginie Bres, Marie-Laure Laroche, Hervé Le Louet, Pierre Petit, Jean-Louis Montastruc, Dominique Hillaire-Buys and the French Pharmacovigilance Centers Network

Affiliations

Jean-Luc Faillie, Virginie Bres, Pierre Petit and Dominique Hillaire-Buys
CHRU Montpellier, Pharmacovigilance Regional Center, Department of Medical Pharmacology and Toxicology, Montpellier, France.

Samy Babai and Hervé Le Louet
CHU Créteil, Pharmacovigilance Regional Center, Créteil, France.

Sabrina Crépin and Marie-Laure Laroche
CHU Limoges, Pharmacovigilance Regional Center, Department of Pharmacology and Toxicology, Limoges, France.

Jean-Louis Montastruc
CHU Toulouse, Pharmacovigilance Regional Center, Department of Medical and Clinical Pharmacology, Toulouse, France.

Jean-Luc Faillie and Jean-Louis Montastruc
INSERM U1027, Department of Pharmacoepidemiology, Faculty of Medicine, Toulouse, France.

Dominique Hillaire-Buys
INSERM U1058, Faculty of Medicine, Montpellier, France.

Correspondence to:

Jean-Luc Faillie
Department of Medical Pharmacology and Toxicology
371 Avenue du Doyen Gaston Giraud
34295 Montpellier, France
Phone : +33 4 67 33 67 52
Fax : +33 4 67 33 67 51
E-mail : jl-faillie@chu-montpellier.fr

Abstract

In the recent past, concerns have raised regarding the potential risk of acute pancreatitis among type 2 diabetic patients using incretin-based drugs such as glucagon-like peptide 1 (GLP-1) analogs and dipeptidyl peptidase 4 (DPP-4) inhibitors. The aim of this study is to investigate the association between exposure to incretin-based drugs and the occurrence of pancreatitis reported in the French Pharmacovigilance Database. The case/non-case method was performed from serious adverse drug reactions (ADRs) involving antihyperglycemic agents (except insulin alone) reported to the French Pharmacovigilance System between March 2008 (first marketing of an incretin-based drug in France) and March 2013. Cases were defined as reports of pancreatitis, all other serious ADRs were considered non-cases. Disproportionality was assessed by calculating reporting odds ratios (ROR) adjusted for age, gender, history of pancreatitis, other antihyperglycemic drugs and other drugs associated with a higher risk of pancreatitis.
Among 3,109 serious ADRs, 147 (4.7%) reports of pancreatitis were identified as cases and 2,962 reports (95.3%) of other ADRs as non cases. Among the cases, 122 (83.0%) involved incretin-based drugs. Disproportionality was found for all incretin-based drugs (adjusted ROR : 15.7 [95%CI: 9.8-24.9]), all GLP-1 analogs (29.4 [16.0-53.8]), exenatide (28.3 [12.8-62.3]), liraglutide (30.4 [15.4-60.0]), all DPP-4 inhibitors (12.1 [7.3-20.0]), sitagliptin (12.4 [7.3-21.0]), saxagliptin (15.1 [4.3-52.7]), vildagliptin (7.4 [3.1-17.6]). Temporal analysis found disproportionality for incretin-based drugs since their first year of marketing in France. Compared with other antihyperglycemic agents, use of incretin-based drugs is associated with an increased risk of reported pancreatitis in France.

Key words

Type 2 diabetes mellitus, glucagon-like peptide 1 analogs, dipeptidyl peptidase 4 inhibitors, pancreatitis, pharmacovigilance

Introduction

Since 2005, new pharmacological classes of drugs potentiating the activity of the incretin hormones have been marketed in the USA in second or third-line treatment of type 2 diabetes mellitus: analogs of glucagon-like peptide 1 (GLP-1) and dipeptidyl peptidase-4 (DPP-4) inhibitors. Safety concerns regarding a potential risk for pancreatitis rapidly raised as several cases were reported. In October 2007, the FDA issued a first alert regarding 30 cases of pancreatitis associated with exenatide, the first GLP-1 analog [1]. Postmarketing cases reported in the FDA Adverse Event Reporting System (AERS) database were analyzed by Elashoff *et al.* in 2011: incretin-based drugs were associated with a 10-fold increase of reported pancreatitis [2]. This study has been a large subject of debate regarding the methodology used and the author's conclusions [3, 4]. Another case/non-case study of pancreatitis using the same database for the period 2004-2009, found disproportionality with exenatide (ROR: 1.76 [95% CI: 1.61-1.92]) and with sitagliptin, the first DPP-4 inhibitor (ROR: 1.86 [95% CI: 1.54-2.24]) [5]. In France, the first incretin-based drugs were marketed in March 2008. The objective of this study is to investigate, five years after initial marketing, the association between exposure to incretin-based drugs (GLP-1 analogs and DPP-4 inhibitors) and reports of pancreatitis in the French Pharmacovigilance Database.

Methods

The French Pharmacovigilance Database registers all adverse drug reactions (ADR) spontaneously reported by health professionals to the 31 French Regional Pharmacovigilance Centers since 1985. ADRs are coded according to the MedDRA® (Medical Dictionary for Regulatory Activities) classification [6]. "Serious" ADRs include reactions resulting in death, life-threatening event, hospitalization, prolongation of existing hospitalization, significant disability, congenital anomaly, birth defect or other significant medical event. We selected serious ADRs reported in type 2 diabetic patients between 2003 and 2013. Analyses were conducted on serious ADRs reported between March 2008 (first marketing of an incretin-based drug in France) and March 2013. Type 2 diabetes was defined by the presence in the report of an antihyperglycemic agent, alone or in association, except when insulin was reported alone.

The case/non-case method was chosen to assess the disproportionality of reports for pancreatitis associated with incretin-based drugs compared to other type 2 diabetic drugs [7]. Cases were defined as reports of pancreatitis according to the MedDRA terms corresponding for acute or chronic pancreatitis or elevated pancreatic enzymes considered serious by the reporter. Other reports of serious ADRs were considered non-cases. Exposure was defined by the presence in the report of one or more incretin-based drugs currently marketed in France: GLP-1 analog (exenatide, liraglutide) or DPP-4 inhibitor (sitagliptin, vildagliptin, saxagliptin), whether or not the drug was suspected of causing the reaction. Disproportionality was assessed by calculating reporting odds ratios (ROR) and corresponding 95% confidence intervals for each antihyperglycemic drug and for the pharmacological classes of incretin-based drugs. The ROR is used to compare the rate of exposure to incretin-based drugs in cases of pancreatitis versus that in non cases [8, 9]. Logistic regression model was used to adjust for potential confounders including age, gender, history of pancreatitis, other antihyperglycemic drugs (metformin, sulfonylurea derivatives, glinides, thiazolidinediones, acarbose, and insulin) and other drugs associated with pancreatitis (angiotensin converting enzyme inhibitors, angiotensin receptor antagonists, statins, tetracycline, metronidazole, isoniazid, pentavalent antimony, azathioprine, mercaptopurine, 5-aminosalicylic acid drugs, valproic acid, estrogens, codeine, and sulindac) [10].

A sensitivity analysis was performed using a stricter definition of pancreatitis when elevated pancreatic enzymes considered serious were excluded. Another model studied disproportionality of incretin-based drugs differentiating whether they were alone or in association with other antihyperglycemic agents. In order to study variation in reporting rate and the presence of a notoriety effect [11], we performed a year by year analysis and compared the RORs before and after March 2011 (when the first study suggesting a risk of pancreatitis in the FDA AERS database was published) [2].

Analyses were conducted using SAS software version 9.2 (SAS Institute, Cary, NC, USA).

Results

During the study period from March 2008 to March 2013, we identified 3,109 serious ADRs involving antihyperglycemic agents. In total, 147 were cases of pancreatitis and 2962 non cases. No alcoholic, lupic or auto-immune pancreatitis were observed. Among the cases, 122 (82.99%) involved incretin-based drugs: 55 (37.41%)

GLP-1 analogs, 64 (43.54%) DPP-4 inhibitors and 3 (2.04%) both of them. Since their marketing, reports of pancreatitis involving an incretin-based drug increased every year for both pharmacological classes (figure 1.)

Characteristics of pancreatitis cases are shown in table 1. Mean age was 60.4 ± 11.4 for incretin-based drugs (59.0 ± 10.2 for GLP-1 agonists and 61.5 ± 12.2 for DPP-4 inhibitors) and 65.2 ± 13.8 for other antihyperglycemic drugs. Males represented 58% of pancreatitis cases in association with incretin-based drugs. GLP-1 agonists and DPP-4 inhibitors were the only antihyperglycemic drugs reported in, respectively, 46.6% and 25.4% of the cases. Overall, hospitalization rate was high (89.8%) and fatal outcomes occurred in 2.1% of the reports. BMI or alcohol use were frequently unavailable in the analysed reports.

Table 1. Characteristics of pancreatitis cases associated with incretin-based drugs and other antihyperglycemic drugs (French Pharmacovigilance Database, March 2008-March 2013).

Characteristics	**GLP-1 agonists (N=58)**		**DPP-4 inhibitors (N=67)**		**Other antihyperglycemic drugs (N=25)**	
	no.	%	no.	%	no.	%
Age						
<60	32	55.2	29	43.3	9	36.0
60-69	19	32.8	20	29.9	6	24.0
70-79	4	6.9	11	16.4	4	16.0
≥80	2	3.4	5	7.5	6	24.0
Missing	*1*	*1.7*	*2*	*3.0*	*0*	*0.0*
BMI						
<20	0	0.0	1	1.5	0	0.0
20-24	4	6.9	2	3.0	6	24.0
25-29	6	10.3	11	16.4	3	12.0
30-34	9	15.5	10	14.9	1	4.0
≥35	14	24.1	4	6.0	0	0.0
Missing	*25*	*43.1*	*39*	*58.2*	*15*	*60.0*
Gender						
Females	24	41.4	28	41.8	13	52.0
Males	34	58.6	38	56.7	12	48.0
Missing	*0*	*0.0*	*1*	*1.5*	*0*	*0.0*
History of pancreatitis	3	5.2	4	6.0	2	8.0
Alcohol use						
Yes	1	1.7	3	4.5	4	16.0
No	2	3.4	2	3.0	4	16.0
Missing	*55*	*94.8*	*62*	*92.5*	*21*	*84.0*
Regimen						
Monotherapy	27	46.6	17	25.4	17	68.0
Dual therapy	12	20.7	26	38.8	7	28.0
Triple therapy	14	24.1	21	31.3	1	4.0
Quadruple therapy	5	8.6	3	4.5	0	0.0
Outcome						
Hospitalization	51	87.9	60	89.6	24	96.0
Death	0	0.0	2	3.0	1	4.0

According to univariate analysis, use of all incretin-based drugs, younger age and pancreatitis history were associated with a higher reporting rate of pancreatitis. Among other antihyperglycemic drugs, thiazolidinediones and sulfonylureas/glinides showed a lower reporting rate (crude RORs: 0.16 [95%CI: 0.04-0.65] and 0.65 [95%CI: 0.46-0.91] respectively), other drugs did not reached statistical significance. After adjustment for age, gender, history of pancreatitis, other antihyperglycemic agents and other drugs associated with pancreatitis, disproportionality was found for all incretin-based drugs (overall adjusted ROR: 15.62 [95%CI: 9.81-24.87]), with a stronger signal for GLP-1

analogs (adjusted ROR: 29.36 [95%CI: 16.02-53.81]) than for DPP-4 inhibitors (adjusted ROR: 12.08 [95%CI: 7.30-20.00]) (table 2). Increased reporting rate was found for any individual drugs of these pharmacological classes. No other antihyperglycemic or concomitant drug showed significant disproportionality. In the model assessing all incretin-based drugs, older age was significantly associated with lower reporting rate: compared to less than 60, adjusted ROR for age 60 to 69, age 70 to 79 and age ≥80 were 0.70 [95%CI: 0.46-1.08], 0.30 [95%CI: 0.17-0.51] and 0.34 [95%CI: 0.18-0.66] respectively. Pancreatitis history and male gender were also associated with a higher reporting rate (adjusted ROR: 4.32 [95%CI: 1.75-10.69] and 1.44 [95%CI: 0.99-2.08] respectively).

Table 2. Adjusted Reporting Odds Ratio of pancreatitis for antihyperglycemic drugs (French Pharmacovigilance Database, March 2008-March 2013)

Drug or pharmacological class	Cases of pancreatitis (N=147)	Non-cases (N=2962)	Adjusted ROR[a]	95% CI		p value
All incretin-based drugs	122	568	15.62	9.81	24.87	<.0001
All GLP-1 agonists	58	150	29.36	16.02	53.81	<.0001
Exenatide	19	52	28.29	12.84	62.34	<.0001
Liraglutide	39	99	30.36	15.36	60.01	<.0001
All DPP-4 inhibitors	67	421	12.08	7.30	20.00	<.0001
Sitagliptin	53	315	12.36	7.29	20.97	<.0001
Vildagliptin	9	87	7.43	3.14	17.58	<.0001
Saxagliptin	5	23	15.09	4.32	52.72	<.0001
Metformin	84	1841	0.86	0.59	1.26	0.438
Sulfonylureas/Glinides	53	1381	1.24	0.83	1.85	0.295
Acarbose	2	137	0.41	0.09	1.89	0.255
Thiazolidinediones	2	235	0.31	0.07	1.32	0.114
Insulin	14	356	0.84	0.45	1.57	0.587

[a] ROR adjusted for age, gender, history of pancreatitis, use of angiotensin converting enzyme inhibitors, angiotensin receptor antagonists, statins, codeine, morphine and related opioid agonists (other drugs associated with pancreatitis were not included in the model because of lack of events).

Sensitivity analysis using a stricter definition of pancreatitis excluded 12 cases of elevated pancreatic enzymes considered serious among the 147 pancreatitis cases. Results were similar to those with the broader definition (adjusted ROR for all incretin-based drugs: 14.86 [95%CI: 9.24-23.92]). The model differentiating whether incretin-based drugs were alone or in association with other antihyperglycemic drugs showed a stronger disproportionality for incretin-based drugs alone (adjusted ROR: 30.30 [95%CI: 13.75-66.80]) than in association (adjusted ROR: 13.56 [95%CI: 8.35-22.02]).

Temporal analysis of cumulative ROR showed that disproportionality was present since the first year of marketing (figure 2). During marketing in France, no evidence for notoriety effect was found according to March 2011 when the first study using the FDA AERS database suggested a risk of pancreatitis [2].

Discussion

Our study demonstrates that reported pancreatitis in France were more than 15-fold increased with incretin-based drugs compared to other antihyperglycemic agents. Significant disproportionality was only found for incretin-based drugs, since their first year of marketing and among these pharmacological classes, a stronger association was found for GLP-1 analogs. Considering that the rate of pancreatitis associated with incretin-based drugs which are effectively reported to pharmacovigilance system could range from 5% to 20% [12], the 122 cases reported between 2008 and 2013 in France could hypothetically represent 610 to 2,440 actual cases.

The results presented here are consistent with previous disproportionality studies conducted by Elashoff *et al.* [2] and Raschi *et al.* [5] using data from the FDA AERS. However, we found higher ROR estimates for the association between incretin-based drugs and reported pancreatitis. This difference may be explained by the fact that we only selected "serious" ADRs which occurred in diabetic patients. Another recent analysis of the FDA AERS monitored reports of "serious" adverse events from July 2011 to July 2012 and found that reports of pancreatitis were 28.5 and 20.8 times more likely with respectively GLP-1 analogs and DPP-4 inhibitors than with control antihyperglycemic drugs (sulfonylureas and metformin) [13, 14]. These results are similar to those we found in the present study.

Case/non case analyses are subject to the inherent limitations of data-mining approaches from spontaneous reporting databases. Under-reporting is the main drawback of this type of data [15]. Indeed, under-reporting may vary depending on the antihyperglycemic drug involved in the ADR and may be less important for new drugs such as incretin-based drugs. Furthermore, since relationship between pancreatitis and incretin-based drugs was highlighted in previous alerts by the US FDA (before marketing in France) [1] and was mentioned in the corresponding products

information [16-20], clinicians could have been more aware of this particular ADR and could have more frequently detected and reported pancreatitis in their patients using incretin-based drugs. Hence, the notoriety effect inherent of studies using pharmacovigilance database cannot be excluded although it is difficult to assess in which extent this could have affected our results.

Incomplete data in spontaneous reports is also a limiting point since it may concern important information such as risk factors, medical or exposure history. Although we performed adjustment for age, gender, pancreatitis history and use of other drugs, confounding bias may still exist since we could not take into account risk factors such as smocking, BMI and alcohol consumption because of too numerous missing data for these variables in the reports. Precisely, adjustment for BMI should have been particularly relevant because obesity is often associated with a higher prescription of GLP-1 analogs which are known to reduce weight. Since obesity is a risk factor for pancreatitis, lack of adjustment for this confounder could have over-estimated corresponding ROR and might be an explanation for the higher ROR observed for GLP-1 analogs compared to DPP-4 inhibitors in this study. Lack of adjustment for alcohol consumption, a major risk factor for pancreatitis, is also an issue. However, since alcohol consumption is unlikely related to drug exposure, it is not believed to have played an important role in this analysis. Moreover, incompleteness of data on exposure history and time delays, which is frequent in pharmacovigilance databases, did not allow us to study the time period from first administration to onset of pancreatitis, or the impact of a newly increase in dosage of incretin-based drugs.

Several studies showed an increased risk of pancreatitis in patients with type 2 diabetes suggesting a role of diabetes itself [21-23]. In order to control confounding by this condition, we decided to perform this study only in reports which involved antihyperglycemic agents. However, our study could not take into account the potential effect played by the duration or the severity of diabetes. Thus, given the fact that incretin-based drugs are defined as second or third-line drugs, confounding by indication cannot be excluded. Nevertheless, considering that more severe diabetic patients are often receiving association of antihyperglycemic agents, the stronger disproportionality found for incretin-based drugs when they were reported alone does not support this potential bias.

Using antihyperglycemic drugs (excluding insulin alone) as a proxy for type 2 diabetes could have led to selection bias. For instance, it was not possible to exclude patients treated by metformin for polycystic ovary syndrome. Nonetheless, this indication is rare and probably negligeable. Likewise, exclusion of patients only treated by insulin alone in order to avoid selecting type 1 diabetes patients could have eliminated patients with advanced stage of type 2 diabetes. This could have led to under-estimate ROR for incretin-based drugs since type 2 diabetes patients treated by insulin are suspected to show a lower incidence of pancreatitis [21]. However, this selection error might have a minimal impact on our results as it likely concerns a small sample of patients. Another important point regarding population selection is the fact that, in this analysis, we have chosen to focus only on serious ADRs. This approach allowed us to compare pancreatitis reports to other serious events reports and to avoid a masking effect by numerous and irrelevant non-serious ADRs.

It is known that chronic pancreatitis can give rise to diabetes (which can potentially be treated by antihyperglycemic drugs) and can cause several occurrences of acute pancreatitis. Thereby, errors in chronology of events may occur in pharmacovigilance reports, and reverse causation cannot be excluded in the association between antihyperglycemic drugs and pancreatitis. However, this phenomenon is unlileky to happen since all pancreatitis cases analyzed in the present study have been initially validated by physicians.

Despite the fact that the disproportionality approach cannot give quantitative risk assessment for a specific ADR (ROR cannot be interpreted as risk ratio), case/non case studies analyzing "real life" pharmacovigilance data have shown in the past to be useful to detect drug safety signals [24, 25]. As soon as 2009, animal studies have suggested a link between incretin-based drugs and pancreatic abnormalities including pancreatitis [26]. A recent review of the preclinical and postmaketing studies summarised by Butler *et al.* suggested a plausible pharmacological mechanism which involves pancreatic duct occlusion enhanced by duct proliferation secondary to activation of GLP-1 receptors in the pancreas [27]. Postmortem study in organ donors exposed to incretin-based drugs also showed pancreatic enlargement and precancerous changes [28]. These studies have raised a large debate [29-31]. In addition, evidence brought by clinical trials were insufficent to support a risk of pancreatitits in meta-analyses of GLP-1 analogs [32] or sitagliptin [33]. Rencently, two large randomised controlled trials did not found any increased pancreatitis risk with saxagliptin and alogliptin [34, 35]. Pharmacoepidemiological studies using large medical database are contradictory. The first studies which focused on this ADR failed to demonstrated significant association [36-40]. Recently, a case control study using a large US administrative database between February 2005 and December 2008 suggested that current use of GLP-1–based drugs was associated with increased risk of hospitalization for acute

pancreatitis (OR 2.24 [95% CI, 1.36-3.68]) [41]. Soon after, a retrospective population based cohort study in a large US claims database did not confirm this relationship [42]. Nonetheless, theses observational studies are still subject to substantial methodological drawacks (confounding, information and selection bias, statistical power) which cannot allow to draw firm conclusions.

Conclusions

Despite some limitations, the present study showed that incretin-based drugs were associated with an almost 16-fold increase in reported pancreatitis in France. These results strengthen and extend the pharmacovigilance signal undercovered by post-marketing spontaneous reports. It is all the more urgent to investigate the potential risk of pancreatitis associated with the use of incretin-based drugs as their benefits in terms of cardiovascular morbi-mortality have not been clearly demonstrated.

Acknowledgements

The authors thank the French Network of Pharmacovigilance Centres and Pascal Auriche (ANSM) for access and extraction of data from the French Pharmacovigilance Database. The authors assume responsibility for the content and conclusions of this article.

Funding

This study was not founded.

Conflict of interest

None

Contribution statement

Pascal Auriche extracted the data from the French Pharmacovigilance Database; Jean-Luc Faillie designed the study, analyzed and interpreted the data and drafted the manuscript; Samy Babai, Sabrina Crépin, Virginie Bres, Marie-Laure Laroche, Hervé Le Louet, Pierre Petit, Jean-Louis Montastruc and Dominique Hillaire-Buys reviewed and revised the manuscript; all authors approved the version to be published.

References

[1] Information for Healthcare Professionals: Exenatide (marketed as Byetta) - 8/2008 Update. Available from http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm124713.htm, accessed 11 May 2012

[2] Elashoff M, Matveyenko AV, Gier B, Elashoff R, Butler PC (2011) Pancreatitis, pancreatic, and thyroid cancer with glucagon-like peptide-1-based therapies. Gastroenterology 141: 150-156

[3] Hawkes N (2011) Journal withdraws article after complaints from drug manufacturers. BMJ 342: d2335

[4] Hauben M, Patadia V, Gerrits C, Walsh L, Reich L (2005) Data mining in pharmacovigilance: the need for a balanced perspective. Drug Saf 28: 835-842

[5] Raschi E, Piccinni C, Poluzzi E, Marchesini G, De Ponti F (2013) The association of pancreatitis with antidiabetic drug use: gaining insight through the FDA pharmacovigilance database. Acta Diabetol 50: 569-577

[6] Hauben M, Madigan D, Gerrits CM, Walsh L, Van Puijenbroek EP (2005) The role of data mining in pharmacovigilance. Expert Opin Drug Saf 4: 929-948

[7] Wilson AM, Thabane L, Holbrook A (2004) Application of data mining techniques in pharmacovigilance. Br J Clin Pharmacol 57: 127-134

[8] Bate A, Evans SJ (2009) Quantitative signal detection using spontaneous ADR reporting. Pharmacoepidemiol Drug Saf 18: 427-436

[9] Moore N, Kreft-Jais C, Haramburu F, et al. (1997) Reports of hypoglycaemia associated with the use of ACE inhibitors and other drugs: a case/non-case study in the French pharmacovigilance system database. Br J Clin Pharmacol 44: 513-518

[10] Balani AR, Grendell JH (2008) Drug-induced pancreatitis : incidence, management and prevention. Drug Saf 31: 823-837

[11] Pariente A, Gregoire F, Fourrier-Reglat A, Haramburu F, Moore N (2007) Impact of safety alerts on measures of disproportionality in spontaneous reporting databases: the notoriety bias. Drug Saf 30: 891-898

[12] Hazell L, Shakir SA (2006) Under-reporting of adverse drug reactions : a systematic review. Drug Saf 29: 385-396

[13] Cohen D (2013) Reports of pancreatitis are 20-30 times more likely with GLP-1 drugs, analysis finds. BMJ 346: f2607

[14] Institute for Safe Medication Practices. Perspectives on GLP-1 agents for diabetes. 2013. Available from http://www.ismp.org/QuarterWatch/pdfs/2012Q3.pdf

[15] van der Heijden PG, van Puijenbroek EP, van Buuren S, van der Hofstede JW (2002) On the assessment of adverse drug reactions from spontaneous reporting systems: the influence of under-reporting on odds ratios. Stat Med 21: 2027-2044
[16] Galvus (vildagliptin). Summaries of Product Characteristics. EMA 2012. Available from http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000771/WC500020327.pdf
[17] Onglyza (liraglutide). Summaries of Product Characteristics. EMA 2012. Available from http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/001026/WC500050017.pdf
[18] Byetta (exenatide). Summaries of Product Characteristics. EMA 2012. Available from http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000698/WC500051845.pdf
[19] Januvia (sitagliptin). Summaries of Product Characteristics. EMA 2012. Available from http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000722/WC500039054.pdf
[20] Onglyza (saxagliptin). Summaries of Product Characteristics. EMA 2012. Available from http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/001039/WC500044316.pdf
[21] Gonzalez-Perez A, Schlienger RG, Rodriguez LA (2010) Acute pancreatitis in association with type 2 diabetes and antidiabetic drugs: a population-based cohort study. Diabetes Care 33: 2580-2585
[22] Noel RA, Braun DK, Patterson RE, Bloomgren GL (2009) Increased risk of acute pancreatitis and biliary disease observed in patients with type 2 diabetes: a retrospective cohort study. Diabetes Care 32: 834-838
[23] Girman CJ, Kou TD, Cai B, et al. (2010) Patients with type 2 diabetes mellitus have higher risk for acute pancreatitis compared with those without diabetes. Diabetes Obes Metab 12: 766-771
[24] Montastruc JL, Sommet A, Bagheri H, Lapeyre-Mestre M (2011) Benefits and strengths of the disproportionality analysis for identification of adverse drug reactions in a pharmacovigilance database. Br J Clin Pharmacol 72: 905-908
[25] Sommet A, Grolleau S, Bagheri H, Lapeyre-Mestre M, Montastruc JL (2008) Was the thrombotic risk of rofecoxib predictable from the French Pharmacovigilance Database before 30 September 2004? Eur J Clin Pharmacol 64: 829-834
[26] Matveyenko AV, Dry S, Cox HI, et al. (2009) Beneficial endocrine but adverse exocrine effects of sitagliptin in the human islet amyloid polypeptide transgenic rat model of type 2 diabetes: interactions with metformin. Diabetes 58: 1604-1615
[27] Butler PC, Elashoff M, Elashoff R, Gale EA (2013) A Critical Analysis of the Clinical Use of Incretin-Based Therapies: Are the GLP-1 therapies safe? Diabetes Care 36: 2118-2125
[28] Butler AE, Campbell-Thompson M, Gurlo T, Dawson DW, Atkinson M, Butler PC (2013) Marked Expansion of Exocrine and Endocrine Pancreas with Incretin Therapy in Humans with increased Exocrine Pancreas Dysplasia and the potential for Glucagon-producing Neuroendocrine Tumors. Diabetes 62: 2595-2604
[29] Nauck MA (2013) A critical analysis of the clinical use of incretin-based therapies: The benefits by far outweigh the potential risks. Diabetes Care 36: 2126-2132
[30] Kahn SE (2013) Incretin therapy and islet pathology: a time for caution. Diabetes 62: 2178-2180
[31] Drucker DJ (2013) Incretin action in the pancreas: Potential promise, possible perils, and pathological pitfalls. Diabetes 62:3316-3323
[32] Alves C, Batel-Marques F, Macedo AF (2012) A meta-analysis of serious adverse events reported with exenatide and liraglutide: acute pancreatitis and cancer. Diabetes Res Clin Pract 98: 271-284
[33] Engel SS, Round E, Golm GT, Kaufman KD, Goldstein BJ (2013) Safety and tolerability of sitagliptin in type 2 diabetes: pooled analysis of 25 clinical studies. Diabetes Ther 4: 119-145
[34] Scirica BM, Bhatt DL, Braunwald E, et al. (2013) Saxagliptin and Cardiovascular Outcomes in Patients with Type 2 Diabetes Mellitus. N Engl J Med 369: 1317-1326
[35] White WB, Cannon CP, Heller SR, et al. (2013) Alogliptin after Acute Coronary Syndrome in Patients with Type 2 Diabetes. N Engl J Med 369: 1327-1335

[36] Dore DD, Bloomgren GL, Wenten M, et al. (2011) A cohort study of acute pancreatitis in relation to exenatide use. Diabetes Obes Metab 13: 559-566
[37] Dore DD, Seeger JD, Arnold Chan K (2009) Use of a claims-based active drug safety surveillance system to assess the risk of acute pancreatitis with exenatide or sitagliptin compared to metformin or glyburide. Curr Med Res Opin 25: 1019-1027
[38] Garg R, Chen W, Pendergrass M (2010) Acute pancreatitis in type 2 diabetes treated with exenatide or sitagliptin: a retrospective observational pharmacy claims analysis. Diabetes Care 33: 2349-2354
[39] Romley JA, Goldman DP, Solomon M, McFadden D, Peters AL (2012) Exenatide therapy and the risk of pancreatitis and pancreatic cancer in a privately insured population. Diabetes Technol Ther 14: 904-911
[40] Wenten M, Gaebler JA, Hussein M, et al. (2012) Relative risk of acute pancreatitis in initiators of exenatide twice daily compared with other anti-diabetic medication: a follow-up study. Diabet Med 29:1412-1418
[41] Singh S, Chang HY, Richards TM, Weiner JP, Clark JM, Segal JB (2013) Glucagonlike peptide 1-based therapies and risk of hospitalization for acute pancreatitis in type 2 diabetes mellitus: a population-based matched case-control study. JAMA Intern Med 173: 534-539
[42] Eurich DT, Simpson S, Senthilselvan A, Asche CV, Sandhu-Minhas JK, McAlister FA (2013) Comparative safety and effectiveness of sitagliptin in patients with type 2 diabetes: retrospective population based cohort study. BMJ 346: f2267