Journal of Pharmacovigilance and Drug Research
October-December 2023
JPADR, 2023; 4(4):9-15
DOI: 10.53411/jpadr.2023.4.4.2



Journal home page: www.jpadr.com

RESEARCH ARTICLE

Analysis of drug–induced pancreatitis reports within the United States Food and Drug Administration and Veterans Health Administration Drug Event Reporting Systems

Kristen Wilhite [a, *], Jennifer Meyer Reid [b], Carrie Isaacs [b], Matthew Lane [b]

[a] Department of Pharmacy, Robley Rex Veterans Affairs Medical Center, Louisville, KY

[b] Department of Pharmacy, Veterans Affairs Health Care System, Lexington, KY

ARTICLE INFO

Received 06 September 2023;
Revised 26 October 2023;
Accepted 25 November 2023.

Keywords:
incretin, GLP-1 agonists, DPP-4 inhibitors, adverse drug events, antipsychotic

ABSTRACT

OPEN ACCESS

Introduction: A true case of drug-induced pancreatitis (DIP) can be difficult to define due to a lack of monitoring parameters and potential confounders to the diagnosis of pancreatitis. Adverse drug event (ADE) reporting systems may give insight into which medications and drug classes are most commonly associated with DIP.
Objectives: This study aimed to analyze two United States (US) ADE reporting systems to determine the most common drugs associated with a report of DIP and to compare what is reported to what is published about drugs that carry a high risk of DIP.
Methods: We conducted a retrospective, cross-sectional evaluation of ADE reports from the Food and Drug Administration (FDA) and the Veterans Health Administration (VHA) between 2007 – 2021.
Results: We identified 53,181 and 1,520 reports of suspected DIP from the FDA and VHA databases, respectively. Incretin-based therapies (GLP-1 RAs and DPP-4is) were the most common drugs with DIP reports in both databases.
Conclusions: Incretin-based therapies comprised approximately 1 in every 5 reports of suspected DIP submitted to two major US ADE databases from 2007 - 2021. These newer medication classes appear to be associated with pancreatitis more frequently than traditional culprit medications.

An official publication of the Global Pharmacovigilance Society.

Introduction

Each year in the United States (US) there are approximately 220,000 cases of acute pancreatitis and 80,000 new diagnoses of chronic pancreatitis (Hung & Lanfranco, 2014). While most cases of pancreatitis are due to obstructive gallstones, excessive alcohol consumption, or hypertriglyceridemia, medications are thought to cause up to 2% of all pancreatitis cases (Balani & Grendell, 2008).

According to the World Health Organization database, 525 different drugs have been associated with drug-induced pancreatitis (DIP) – with proposed mechanisms including pancreatic duct constriction, cytotoxic effects of a given drug, an accumulation of a toxic metabolite, hypersensitivity reactions, and/or drug-induced

* Corresponding Author
Kristen Wilhite
E-mail: Kristen.wihite@va.gov
Contact: +(502)-287-6481

© Copyright: 2582-7235 // © 2023 The Author(s).
Published by Global Pharmacovigilance Society.
This is an open-access article under the CC BY-NC-ND license.

Available online 1 December 2023

hypertriglyceridemia and chronic hypercalcemia (Weissman, Aziz, Perumpail, Mehta, Patel, & Tabibian, 2020; Jones, Hall, Kaye & Kaye, 2015).

Historically, DIP has been difficult to define due to a lack of monitoring parameters and potential confounders to the diagnosis of pancreatitis. If a drug is linked to a patient's pancreatitis diagnosis, it is unlikely that the drug will ever be re-trialed in that individual, leading to a lack of evidence of causation.

Multiple studies and reviews have been conducted to help define drugs associated with elevated risk of DIP. Mallory and Kern created classifications to establish the risk of pancreatitis associated with a given drug. They created one of the first classification scales with values of a definite, probable, or possible association with pancreatitis (Crockett et al., 2018). Trivedi and colleagues reviewed PubMed and the National Library of Medicine cases of DIP. They categorized the top 100 prescription medications, incorporating a modified version of the Mallory and Kern classification scale. Trivedi's classification system primarily assessed several reported cases of DIP along with cases with positive rechallenge to categorize drugs into classes I-III for risk of DIP (Trivedi & Pitchumoni, 2005).

Badalov and colleagues developed another novel categorization system for drugs associated with pancreatitis. Classes were based on number of DIP cases associated with a given drug, positive rechallenge, consistent latency, and/or presence of confounders (alcohol, hypertriglyceridemia, gallstones, etc.) (Badalov et al., 2007). Utilizing the same classification system and methods as Badalov, Simons-Linares developed a more contemporary list of drugs associated with pancreatitis (Simons-Linares, Elkhouly, & Salazar, 2019). These classification systems are useful to determine if a suspected drug may be related to a case of pancreatitis.

Previous studies classifying medications based on their association with pancreatitis found that immunotherapies along with agents such as renin-angiotensin-aldosterone-system (RAAS) inhibitors, HMG-CoA reductase inhibitors (statins), and certain over-the-counter products, namely the histamine H2 antagonists, carry the highest risk for DIP (Trivedi & Pitchumoni, 2005; Badalov et al., 2007; Simons-Linares et al., 2019).

One notably absent medication class from these previous studies is the incretin-based therapies. incretin-based therapies include the glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and dipeptidyl peptidase 4 (DPP-4) inhibitors and are relatively new hypoglycemic agents, with the first incretin-based therapy receiving FDA approval in 2005 (Ahrén, 2019). Incretin-based therapies either indirectly or directly stimulate beta and alpha cells in the pancreas to increase cellular glucose uptake and decrease hepatic glucose output (Singh, Yadav, Sharma, & Jin, 2021). It is theorized that continuous stimulation of GLP-1 receptors may cause an overgrowth of exocrine duct cells found in the pancreas, which may lead to hyperplasia and chronic or acute inflammation of the pancreas (Saisho, 2018). A meta-analysis conducted by Tkáč and Raz assessing DPP-4 inhibitors specifically found an increased risk of acute pancreatitis with treatment with these agents (Tkáč & Raz, 2017). A separate meta-analysis by Meier and Nauck indicated that there was no excess risk of acute pancreatitis with treatment with GLP-1 Ras (Meier & Nauck, 2014). As utilization of incretin-based therapies expands given their potential benefits in other disease states, it is important to appropriately assess the risk of DIP.

Suspected cases of DIP may be reported to Adverse Drug Event (ADE) reporting systems. Two US ADE reporting systems include the Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) and the Veterans Health Administration (VHA) Veterans Affairs Drug Event Reporting System (VA ADERS). FAERS, which is linked directly to MedWatch, is a voluntary ADE reporting system that both healthcare professionals and patients can report directly to. FAERS publishes publicly available reports on ADEs that are searchable by individual drug and symptom – this database is updated quarterly (Center for Drug Evaluation and Research, 2020).

The VA ADERS database, established in March 2007, is a web-based system utilized to spontaneously report ADEs to a centralized VA database. VA facilities report observed ADEs to VA ADERS. Data is available for analysis utilizing a standardized coding system (Veterans Affairs, 2014).

This study aims to analyze the FAERS and VA ADERS databases to describe commonly reported drugs in suspected cases of DIP and to compare findings to previously published lists of DIP-associated medications.

Methods

This was a retrospective, cross-sectional data analysis of deidentified reports of DIP from two separate databases – FAERS and VA ADERS.

A manual search of the FAERS database was conducted utilizing the keywords: "pancreatitis", "acute pancreatitis", and "chronic pancreatitis" to identify drugs associated with a report of DIP from January 1, 2007, to December 31, 2021. This period was chosen because FAERS is organized by calendar year.

VA ADERS was queried to return reports of acute and chronic pancreatitis with the corresponding suspect drug from October 1, 2007, to December 31, 2021. This period alters slightly from the FAERS period because VA

ADERS is organized by fiscal quarter – with extractable data only going back to Oct 1, 2007.

Data extracted from the FAERS and VA ADERS databases were organized into top 10 lists and descriptively analyzed for trends.

FAERs and VA ADERS's top 10 DIP report data was compared to the top DIP-associated drugs that were categorized in the trials conducted by Trivedi et al., Badalov et al., and Simons-Linares et al. to assess for similarities and differences.

Results

The FAERS database included 53,181 reports of suspected DIP and the VA ADERS database included 1,520 reports of suspected DIP. The complete Top 10 lists for each database can be seen in Table 1. The top 10 drugs from the FAERS database include the GLP-1 receptor agonists (14.7%), antipsychotic agents (8.3%), immunosuppressant drugs (6%), and DPP-4 inhibitors (5%). The top 10 drugs from the VA ADERS database also varied between drug classes, with the most commonly reported drugs being from the GLP-1 receptor agonists (10.7%), thiazide diuretics (10.6%), ACE-inhibitors (9.6%), and DPP-4 inhibitors (8.1%).

Table 1: Top 10 drug-induced pancreatitis-associated drugs 2007 to 2021 based on data from the Veterans Affairs Adverse Drug Event Reporting System (VA ADERS) and Food and Drug Administration Adverse Event Reporting System (FAERS) databases

VA ADERS Reports of Suspected DIP Total n=1,520	n (%)	FAERS Reports of Suspected DIP Total n=53,181	n (%)
1. Hydrochlorothiazide	161 (10.6)	1. Exenatide	3504 (6.6)
2. Lisinopril	146 (9.6)	2. Quetiapine fumarate	3311 (6.2)
3. Liraglutide	108 (7.1)	3. Liraglutide	3023 (5.7)
4. Divalproex	103 (6.8)	4. Sitagliptin phosphate	2653 (5.0)
5. Alogliptin	66 (4.3)	5. Adalimumab	1401 (2.6)
6. Saxagliptin	58 (3.8)	6. Dulaglutide	1287 (2.4)
7. Dulaglutide	54 (3.6)	7. Metformin hydrochloride	1280 (2.4)
8. Azathioprine	45 (3.0)	8. Olanzapine	1097 (2.1)
9. Simvastatin	36 (2.4)	9. Methotrexate	890 (1.7)
10. Hydrochlorothiazide/Lisinopril	37 (2.4)	10. Infliximab	880 (1.7)

Overall, incretin-based therapies are the most reported drugs in both databases. In FAERS there were the following counts: Exenatide (3,504 reports); Liraglutide (3,023 reports); Sitagliptin (2,653 reports); and Dulaglutide (1,287 reports) – which comprises 19.7% of all reports submitted during the study period. In VA ADERS there were the following counts: Liraglutide (108 reports); Alogliptin (66 reports); Saxagliptin (58 reports); and Dulaglutide (54 reports) – which comprises 18.8% of all reports submitted during the study period.

Reports of DIP associated with incretin-based therapies are currently increasing in the VA ADERS database (Figure 1), with a similar rise in FAERS reports approximately 8 years prior (Figure 2). When comparing the most reported drugs associated with DIP to the high-risk DIP drugs identified and classified by previous studies, there are several differences with only a small subset of the most commonly reported drugs being classified as the highest risks drugs (Class 1a or Class 1b) (Table 2).

Table 2: Simones-Linares class 1a and 1b drugs with bolded and asterisked drugs being those that were in either the Veterans Affairs Adverse Drug Event Reporting System (VA ADERS) and Food and Drug Administration Adverse Event Reporting System (FAERS top 10 drugs associated with drug-induced pancreatitis

Class 1a • At least 1 case report with positive rechallenge • Excluding all other causes such as alcohol, hypertriglyceridemia, gallstones, and other drugs		Class 1b • At least 1 case report with positive rechallenge • The case report failed to document the exclusion of other causes or • Other possible etiologies were available	
Acetaminophen	Methyldopa	**Azathioprine***	Nelfinavir
Acetaminophen-codeine	Metronidazole	Bortezomib	Nitrofurantoin
5-Aminosalicylate	Nadolol	Carbamazepine	Omeprazole
Amiodarone	Pravastatin	Clonidine	Paclitaxel
Androgenic Anabolic steroids	Perindopril	Clozapine	Pentamidine
	Procainamide	Cytosine arabinoside	Prednisone
Arsenic trioxide	Pyritinol	Dapsone	Propofol
Cannabis	Ranitidine	Dexamethasone	**Quetiapine***
Carbimazole	Rosuvastatin	Fenofibrate	Sodium stibogluconate
Cimetidine	**Saxagliptin***	Hydrocortisone	
Clomiphene	**Simvastatin***	6-Metcaptopurine	Sorafenib
Enalapril	Sulindac	Methimazole	Tigecycline
Estrogen and related products	Tamoxifen	Mirtazapine	**Valproic acid***
	Telaprevir		
Furosemide	Tetracycline		Valsartan
In vitro fertilization	Trimethoprim/ sulfamethoxazole		
Isoniazid			
Losartan			

Discussion

The top reported drugs associated with DIP differed between the FAERS and VA ADERS databases, as can be seen in Table 1. However, a notable similarity is that incretin-based therapies (GLP-1 RAs + DPP-4 inhibitors) were the most reported drugs in each database – accounting for approximately 1 out of every 5 reports over the almost 15-year study period.

The differences between the two databases are likely related to multiple factors. According to recent Census Bureau data, 77% of the veteran population is white, and 91% male, with a median age of 65 years (Vespa, 2020). The homogeneity of the veteran population contrasts with the more diverse patient population that is reporting ADEs to the FDA. Additionally, FAERS collects ADE reports from healthcare providers and consumers, while VA ADERS reports are only supplied by VHA healthcare professionals. The VHA follows a closed formulary utilizing specific drugs or drug classes impacting the prescribing patterns within the VHA. While the VHA is a large national healthcare system that collects many ADE reports, when compared to the national FAERS database it is evident that the VA ADERS database is much smaller in terms of the number of reports (n=1,520 vs. n=53,181).

The incretin-based therapies were first introduced to VHA's formulary around 2014, with utility steadily increasing since then due not only to their hypoglycemic effects but also their weight loss and cardiorenal protective benefits. Since 2017 the number of DIP reports associated with the incretin-based therapies has surpassed all other drug classes in the top 10 within the VHA as shown in Figure 1.

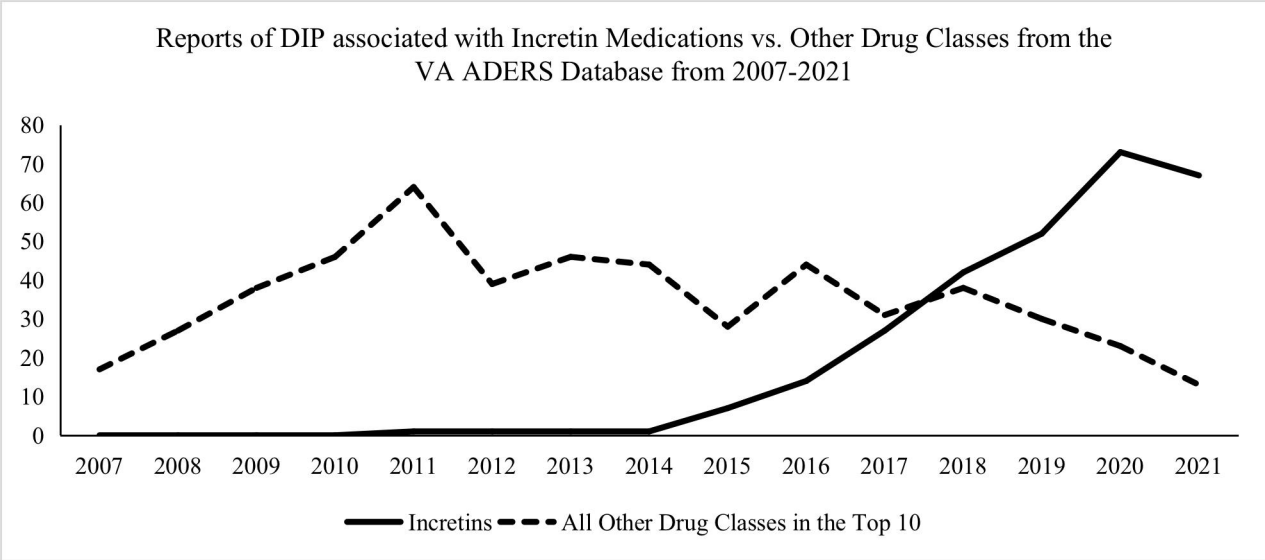


Figure 1: Reports of drug-induced pancreatitis (DIP) associated with incretin medications compared to all other drug classes within the top 10 drugs associated with DIP according to the Veterans Affairs Adverse Drug Event Reporting System (VA ADERS) database from 2007-2021

The FAERS data also shows that most DIP reports during the study period were associated with incretin-based therapies, with a steep increase seen approximately 8 years before the increase seen within the VHA (Figure 2). The 8-year delay seen in the VHA data is likely due to VHA formulary status compared to community use. Within FAERS, incretin-based therapy-associated reports of DIP have declined since their peak in 2012, potentially due to a decrease in pharmacovigilance as the time for the drug class being on the market increased.

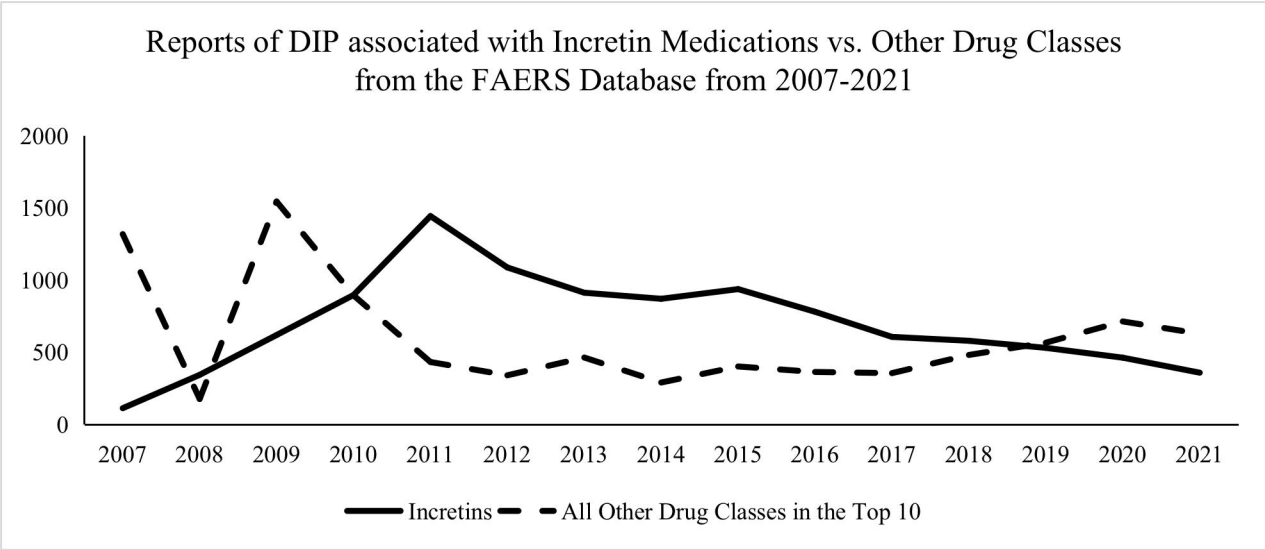


Figure 2: Reports of drug-induced pancreatitis (DIP) associated with incretin medications compared to all other drug classes within the top 10 drugs associated with DIP according to the Food and Drug Administration Adverse Event Reporting System (FAERS) database.

Previous studies categorizing the risk of DIP vary significantly when compared to the medications reported in FAERS and VA ADERS. In one of the more recent studies assessing the risk of DIP, Simons-Linares et al.

categorized drugs into different classes based on case reports and a given drug's likelihood to be related to a true case of DIP. According to Simons-Linares, et al., Class 1a and Class 1b drugs carry the highest risk of DIP. Interestingly, only one drug from the incretin-based therapy class (saxagliptin) is listed in the Class 1a or Class 1b category. Out of both Top 10 lists, only 5 of the most reported drugs are listed out of the more than 60 drugs categorized as Class 1a or 1b. Table 2 summarizes the class 1a and 1b drugs according to Simons-Linares et al., with the highlighted drugs being those that were also found to be in the top 10 drugs associated with DIP according to either the FAERS or VA ADERS databases. This comparison indicates that published reports of DIP differ from what is reported in the FDA and VHA databases.

This cross-sectional study has several important limitations. Adverse Drug Event reporting systems are underutilized and likely underrepresent true incidence rates. Additionally, ADE databases are generally de-identified and unvalidated (Heavner & Siner, 2015).

As prescribing rates increase so does the likelihood of ADEs. It is important to note that while the top 10 drugs associated with DIP according to the FAERS and VA ADERS databases have the most reported cases of suspected DIP, it may be directly related to their overall usage compared to other drugs. A review of VHA prescribing data revealed the number of prescriptions for incretin-based therapies has increased each year since 2017, which correlates with an increase in reports of suspected DIP. However, the prescribing rates of incretin-based therapies lag behind other highly utilized medication classes such as statins or non-steroidal anti-inflammatory drugs, so the number of suspected DIP reports associated with the incretin-based therapies is still notable.

This study could not analyze the causation of a reported case of pancreatitis. Some important confounders that future studies could address include the patient's risk factors for pancreatitis, past medical histories, concomitant medications, and any re-challenge of the medication.

Both databases queried rely on voluntary reporting and likely underrepresent the true incidence of all adverse events including DIP. Likewise, causality cannot be assessed from this type of research.

Conclusion

This study analyzed two prominent US ADE databases (FDA FAERS and VA ADERS) for reports of suspected DIP over an approximate 15-year time period. Incretin-based therapies (including drugs from the GLP-1 RA and the DPP-4 inhibitor classes) comprised approximately 1 in every 5 reports of suspected DIP submitted. When comparing the most frequently reported drugs associated with suspected DIP to what is currently published regarding drugs classified as high-risk for DIP, there are significant differences. Further research is needed to assess the true risk of DIP with certain medications, particularly the incretin-based medications.

Conflict of Interest

The authors have no actual or potential financial conflicts of interest about this manuscript

References

Ahrén, B. (2019). DPP-4 inhibition and the path to clinical proof. *Frontiers in endocrinology, 10*, 376.

Badalov, N., Baradarian, R., Iswara, K., Li, J., Steinberg, W., & Tenner, S. (2007). Drug-induced acute pancreatitis: an evidence-based review. *Clinical gastroenterology and hepatology, 5*(6), 648-661.

Balani, A. R., & Grendell, J. H. (2008). Drug-induced pancreatitis: incidence, management and prevention. *Drug safety, 31*(10), 823-837.

Crockett, S. D., Wani, S., Gardner, T. B., Falck-Ytter, Y., Barkun, A. N., Crockett, S., ... & Weinberg, D. (2018). American Gastroenterological Association Institute guideline on initial management of acute pancreatitis. *Gastroenterology, 154*(4), 1096-1101.

Heavner, J. J., & Siner, J. M. (2015). Adverse event reporting and quality improvement in the intensive care unit. *Clinics in Chest Medicine, 36*(3), 461-467.

Hung, W. Y., & Lanfranco, O. A. (2014). Contemporary review of drug-induced pancreatitis: a different perspective. *World journal of gastrointestinal pathophysiology, 5*(4), 405.

Jones, M. R., Hall, O. M., Kaye, A. M., & Kaye, A. D. (2015). Drug-induced acute pancreatitis: a review. *Ochsner Journal, 15*(1), 45-51.

Meier, J. J., & Nauck, M. A. (2014). Risk of pancreatitis in patients treated with incretin-based therapies. *Diabetologia, 57*, 1320-1324.

Research, C. for D. E. and. (2020). FDA Adverse Event Reporting System (FAERS) Public Dashboard. FDA. https://www.fda.gov/drugs/questions-and-answers-fdas-adverse-event-reporting-system-faers/fda-adverse-event-reporting-system-faers-public-dashboard

Saisho, Y. (2018). Incretin-based therapy and pancreatitis: accumulating evidence and unresolved questions. *Annals of translational medicine, 6*(7).

Simons-Linares, C. R., Elkhouly, M. A., & Salazar, M. J. (2019). Drug-induced acute pancreatitis in adults: an update. *Pancreas, 48*(10), 1263-1273.

Singh, A. K., Yadav, D., Sharma, N., & Jin, J. O. (2021). Dipeptidyl peptidase (DPP)-IV inhibitors with antioxidant potential isolated from natural sources: A novel approach for the management of diabetes. *Pharmaceuticals, 14*(6), 586.

Tkáč, I., & Raz, I. (2017). Combined analysis of three large interventional trials with gliptins indicates increased incidence of acute pancreatitis in patients with type 2 diabetes. *Diabetes Care, 40*(2), 284-286.

Trivedi, C. D., & Pitchumoni, C. S. (2005). Drug-induced pancreatitis: an update. *Journal of clinical gastroenterology, 39*(8), 709-716.

VA.gov | Veterans Affairs. (2014). Va.gov. https://www.va.gov/MS/Professionals/medications/VHA_Adverse_Drug_Event_Reporting_Program.asp

Vespa, J. E. (2020). Those who served: America's veterans from World War II to the War on Terror. *World War II (December 1941 to December 1946), 485*(463), 22.

Weissman, S., Aziz, M., Perumpail, R. B., Mehta, T. I., Patel, R., & Tabibian, J. H. (2020). Ever-increasing diversity of drug-induced pancreatitis. *World journal of gastroenterology, 26*(22), 2902.