Frequency of Acute Pancreatitis Associated with Glucagon-Like Peptide-1 Receptor Agonist Use: A Systematic Review

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Background

Glucagon-like Peptide-1 receptor agonists (GLP-1) are a class of incretin-based antidiabetic therapies that have typically been excluded from treatment consideration in patients presenting with an increased concern for pancreatitis. Patients with uncontrolled type 2 diabetes often present with a spectrum of comorbidities consistent with the metabolic syndromes such as obesity, cardiovascular disease, and renal dysfunction in addition to being at an inherently increased risk for pancreatitis. GLP-1 agonists have been shown to improve clinically relevant endpoints in these disease states in addition to exerting their antidiabetic effect in lowering HbA1c with an unclear effect on pancreatitis incidence due to conflicting literature. **Clinical uncertainty remains regarding the use of GLP-1 agonists in patients with perceived risk for developing pancreatitis.**

Design and Methods

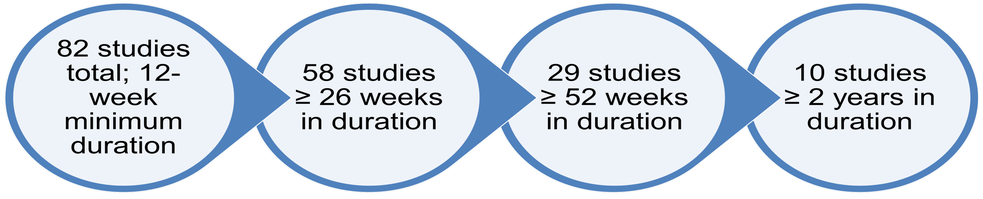
EMBASE© and PubMed Searches Conducted in Compliance with PRISMA protocol	•Search Terms: "pancreatitis", "GLP-1 RA", "albiglutide", "dulaglutide", "exendin 4", "liraglutide", "lixisenatide", "semaglutide"
210 Records Screened for Duplicates and Inclusion/Exclusion	•**Inclusion**: Clinical trials, patients with T2DM, GLP-1 therapy, placebo, active comparator, the same intervention at different dose, with at least 12-week study duration, with reported incidence of acute pancreatitis
82 Records Included in Review	•17 duplicate records removed before screening •193 records screened with 128 records being excluded •17 additional records identified through search of references of excluded MA/SA/PA

Incidence of Pancreatitis by GLP-1 Agent

GLP-1	Number of Studies	Number of Patients	Events of Acute Pancreatitis	Incidence (%)
Albiglutide	12	8059	17	0.21
Dulaglutide	16	11013	39	0.35
Exenatide	18	11594	37	0.32
Liraglutide	25	13256	26	0.20
PEG Loxenatide*	1	82	0	0.00
Semaglutide	5	4023	15	0.37
Taspoglutide*	2	468	0	0.00
Tirzepatide**	2	296	2	0.68
Total	**88**	**53448**	**142**	**0.27**
Comparator	**74**	**39679**	**93**	**0.23**

* Not FDA approved
**GIP/GLP-1, Not FDA approved

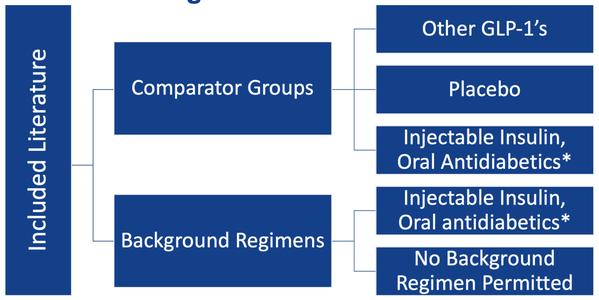
Summary of Study Durations:



Results

A total of 93,127 patients were included in the studies, 53,448 (57%) in the GLP-1 groups and 39,679 (43%) in the comparator groups. Overall, there was a low incidence of acute pancreatitis in the GLP-1 groups with 142 events (0.27%) and slightly lower incidence in the comparator groups with 93 events (0.23%). A broad spectrum of background antidiabetic agents were included within the assessed record's study designs. A robust and heterogenous composition of class, combination, and number of agents were represented.

Trial Designs of Reviewed Literature



*Metformin, DPP4i, SGLT-2i, sulfonylurea, TZD

Conclusion

The large sample size extracted from the literature with a large degree of heterogeneity provides near real-world evidence to begin resolving the unclear association between GLP-1 utilization and pancreatitis. **Increased incidence of pancreatitis associated with GLP-1 usage may not be as elevated as previously presumed.** Further clinical trial data mimicking real world conditions may be paramount for future type 2 diabetes GLP-1 therapy optimization.