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The Risk of Acute Pancreatitis and Selective Serotonin Reuptake Inhibitors Use: A Meta-Analysis of Case–Control Studies

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Abstract

Background/Objective: Some case series and case report have shown the association between the risk of acute pancreatitis and use of selective serotonin reuptake inhibitors. The results of systematic studies were not consistent.

Methods: A meta-analysis was performed to investigate the risk of acute pancreatitis associated with use of selective serotonin reuptake inhibitors.

Results: There was no statistical association between the risk of acute pancreatitis and selective serotonin reuptake inhibitors use (odds ratio: 1.19, 95% confidence interval: 0.93-1.51).

Conclusions: Despite reaching no statistical significance, the possibility of the association between the risk of acute pancreatitis and selective serotonin reuptake inhibitors use cannot be totally excluded.

Keywords
acute pancreatitis, selective serotonin reuptake inhibitors

Introduction

Acute pancreatitis is acute inflammation of the pancreas, and it is a multifactorial disease. The incidence rate of acute pancreatitis in Europe ranged from 4.6 to 100 per 100 000 population per year.[1] The crude incidence rate of acute pancreatitis in Taiwan was 56.9 per 100 000 persons in 2005.[2] Gallstones and long-term use of alcohol account for 60% to 80% of cases with acute pancreatitis.[3-5] Only 0.1% to 3.4% of cases are potentially caused by medications use.[6-8]

Selective serotonin reuptake inhibitors are used to treat depression, obsessive compulsive disorder, social anxiety disorder, and panic disorder.[9,10] No animal study investigated the association between the risk of acute pancreatitis and selective serotonin reuptake inhibitors use. Till now, case reports and case series have shown the potential association between the risk of acute pancreatitis and selective serotonin reuptake inhibitors use.[11-13] Several systematic studies have investigated such an association,[14-16] but the results were not consistent. Some studies showed a positive association,[14,16] but others showed no association.[15] In order to add updated evidence to this issue, a meta-analysis was performed to investigate the risk of acute pancreatitis associated with selective serotonin reuptake inhibitors use.

Methods

PubMed was used to find studies of interest, published up to July 2019. In order to avoid the time-window bias frequently found in cohort study, only case–control studies were included. The following key words were used: "acute pancreatitis," "selective serotonin reuptake inhibitors," and "case–control study." The odds ratio and 95% confidence interval were used

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Table 1. Characteristics of Eligible Studies.

Author	Country	Year	Study Design	Number of Acute Pancreatitis	Number of Nonacute Pancreatitis
Norgaard et al	Denmark	2007	Case–control study	3083	30 830
Ljung et al	Sweden	2012	Case–control study	6161	61 637
Lin et al	Taiwan	2017	Case–control study	4631	4631

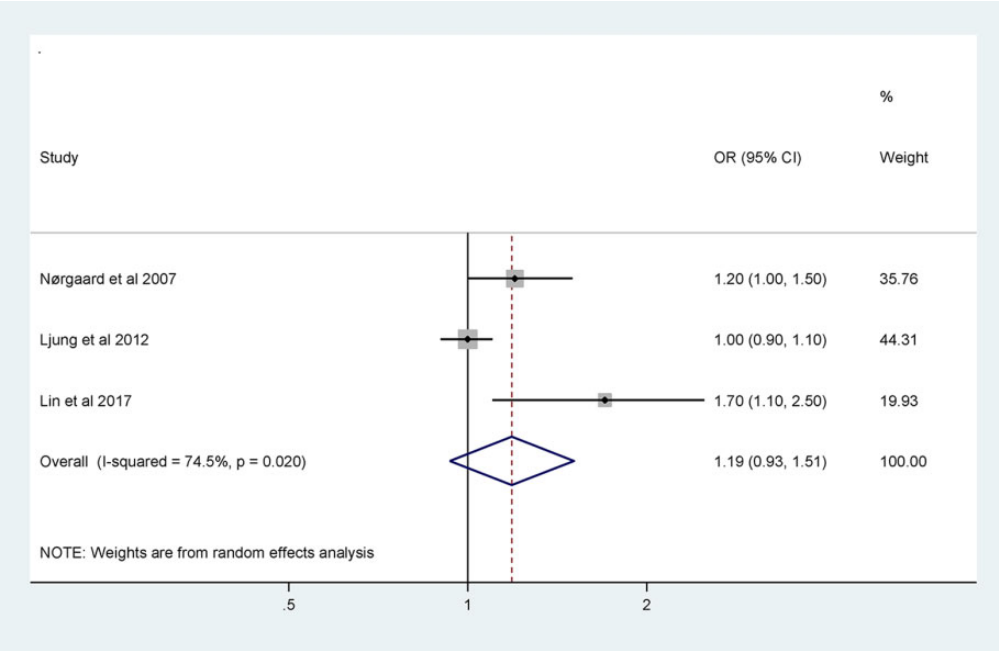

Figure 1. Odds ratio and 95% confidence interval of association between acute pancreatitis and selective serotonin reuptake inhibitors use.

to calculate the association between the risk of acute pancreatitis and selective serotonin reuptake inhibitors use.

Results

Table 1 shows that 3 case–control studies were included. The case number of acute pancreatitis enrolled in these 3 studies ranged from 3083 to 6161, and the number of controls ranged from 4631 to 61 637.[14-16] Figure 1 shows that there was no statistical association between the risk of acute pancreatitis and selective serotonin reuptake inhibitors use (odds ratio: 1.19, 95% confidence interval: 0.93-1.51).

Discussion

In our meta-analysis, cases with acute pancreatitis were about 1.2 times more likely to be exposed to selective serotonin reuptake inhibitors than those without acute pancreatitis but without reaching statistical significance. Clinically, a rechallenge test is needed to confirm the key drug being able to induce acute pancreatitis.[17,18] Due to ethical concerns, it is difficult to perform a rechallenge test in a randomized controlled trial or in a cohort study. Similarly, the causal relationship cannot be established by this meta-analysis because all studies included were a case–control design. A causal relationship between selective serotonin reuptake inhibitors use and acute pancreatitis cannot be confirmed by a traditional statistical methodology. Therefore, spontaneous report of adverse drug reaction, case series, or case report remains to be the first choice to add evidence to the pharmacovigilance databases, as previous reports have shown.[11-13] There are not any obvious clinical features to definitely distinguish drug-related acute pancreatitis from other cause-related acute pancreatitis. Drug-related acute pancreatitis remains a diagnostic challenge. It only depends on a high index of clinical suspicion to make a diagnosis of drug-related acute pancreatitis.

The pathogenetic mechanisms of drug-related acute pancreatitis have not been completely elucidated. The relevant literature hypothesizes several plausible mechanisms as follows: a direct toxic effect of the key drug to the pancreas, a drug–drug interaction effect to the pancreas between the key drug and other drugs, key drug-induced spasm of the sphincter of Oddi, and an idiosyncratic reaction to the key drug.[19-23]

Among the 3 case–control studies included, Ljung et al's study showed no association between acute pancreatitis and selective serotonin reuptake inhibitors use after adjusting for confounding factors (adjusted odds ratio: 1.0, 95% confidence

interval: 0.9-1.1).[15] Norgaard et al's study showed a positive association between acute pancreatitis and selective serotonin reuptake inhibitors use (adjusted odds ratio: 1.2, 95% confidence interval: 1.0-1.5), but the authors explained that the result could be caused by confounding factors and they did not support that the current use of selective serotonin reuptake inhibitors is a risk factor for acute pancreatitis.[14] Lin et al's study showed a positive association between acute pancreatitis and selective serotonin reuptake inhibitors use (adjusted odds ratio: 1.7, 95% confidence interval: 1.1-2.5).[16] The authors explained that because the etiologies of acute pancreatitis were not recorded in the database used, whether acute pancreatitis found in their study was really caused by selective serotonin reuptake inhibitors use could not be confirmed.[16]

Some limitations need to be discussed. First, because no case report showed a positive rechallenge test, a causal relationship between selective serotonin reuptake inhibitors use and acute pancreatitis remains unsettled. More case reports with a positive rechallenge test are needed to confirm such a causal relationship. Second, to date, only 3 case–control studies have investigated the association between acute pancreatitis and selective serotonin reuptake inhibitors use. More real-world data and animal studies are needed to clarify this issue.

Finally, although not significant in our meta-analysis, the odds of selective serotonin reuptake inhibitors use was about 1.2 times higher in cases with acute pancreatitis versus those without acute pancreatitis. Therefore, our meta-analysis has not totally excluded the association between the risk of acute pancreatitis and selective serotonin reuptake inhibitors use. We suggest that clinicians who participate in taking care of patients with acute pancreatitis but unable to find the definite cause should take into consideration the possibility of drug-related acute pancreatitis, such as selective serotonin reuptake inhibitors.

Authors' Note

Shih-Wei Lai and Cheng-Chan Yu initiated the conception of the article, wrote the draft of the article, and contributed equally to the article. Cheng-Li Lin and Kuan-Fu Liao conducted data analysis.

Declaration of Conflicting Interests

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References

1. Roberts SE, Morrison-Rees S, John A, Williams JG, Brown TH, Samuel DG. The incidence and aetiology of acute pancreatitis across Europe. *Pancreatology*. 2017;17(2):155-165.
2. Shen HN, Lu CL. Incidence, resource use, and outcome of acute pancreatitis with/without intensive care: a nationwide population-based study in Taiwan. *Pancreas*. 2011;40(1):10-15.
3. Forsmark CE, Vege SS, Wilcox CM. Acute pancreatitis. *N Engl J Med*. 2016;375(20):1972-1981.
4. Del Vecchio Blanco G, Gesuale C, Varanese M, Monteleone G, Paoluzi OA. Idiopathic acute pancreatitis: a review on etiology and diagnostic work-up. *Clin J Gastroenterol*. 2019;12(6):511-524.
5. Chang MC, Su CH, Sun MS, et al. Etiology of acute pancreatitis—a multi-center study in Taiwan. *Hepatogastroenterology*. 2003;50(53):1655-1657.
6. Balani AR, Grendell JH. Drug-induced pancreatitis: incidence, management and prevention. *Drug Saf*. 2008;31(10):823-837.
7. Jones MR, Hall OM, Kaye AM, Kaye AD. Drug-induced acute pancreatitis: a review. *Ochsner J*. 2015;15(1):45-51.
8. Barreto SG, Tiong L, Williams R. Drug-induced acute pancreatitis in a cohort of 328 patients. A single-centre experience from Australia. *JOP*. 2011;12(6):581-585.
9. Vaswani M, Linda FK, Ramesh S. Role of selective serotonin reuptake inhibitors in psychiatric disorders: a comprehensive review. *Prog Neuropsychopharmacol Biol Psychiatry*. 2003;27(1):85-102.
10. Kasper S, Resinger E. Panic disorder: the place of benzodiazepines and selective serotonin reuptake inhibitors. *Eur Neuropsychopharmacol*. 2001;11(4):307-321.
11. Kvande KT, Madsen S. Selective serotonin uptake inhibitors and pancreatitis [in Norwegian]. *Tidsskr Nor Laegeforen*. 2001;121(2):177-178.
12. Malbergier A, de Oliveira Junior HP. Sertraline and acute pancreatitis: a case-report [in Portuguese]. *Braz J Psychiatry*. 2004;26(1):39-40.
13. Gülpamukcua A, Demircana A, Bildika F, Gülbinaygencelb S. Paroxetine-induced acute pancreatitis: Case Report/Paroksetine Bagli Akut Pankreatit. *Turkiye Klinikleri J Gastroenterohepatol*. 2009;16(2):84-87.
14. Norgaard M, Jacobsen J, Gasse C, Pedersen L, Mortensen PB, Sorensen HT. Selective serotonin reuptake inhibitors and risk of acute pancreatitis: a population-based case-control study. *J Clin Psychopharmacol*. 2007;27(3):259-262.
15. Ljung R, Ruck C, Mattsson F, Bexelius TS, Lagergren J, Lindblad M. Selective serotonin reuptake inhibitors and the risk of acute pancreatitis: a Swedish population-based case-control study. *J Clin Psychopharmacol*. 2012;32(3):336-340.
16. Lin HF, Liao KF, Chang CM, Lin CL, Lai SW. Association of use of selective serotonin reuptake inhibitors with risk of acute pancreatitis: a case-control study in Taiwan. *Eur J Clin Pharmacol*. 2017;73(12):1615-1621.
17. Badalov N, Baradarian R, Iswara K, Li J, Steinberg W, Tenner S. Drug-induced acute pancreatitis: an evidence-based review. *Clin Gastroenterol Hepatol*. 2007;5(6):648-661.

18. Simons-Linares CR, Elkhouly MA, Salazar MJ. Drug-induced acute pancreatitis in adults: an update. *Pancreas*. 2019;48(10): 1263-1273.
19. Lai SW, Lin CL, Liao KF. Digoxin use may increase the relative risk of acute pancreatitis: a population-based case-control study in Taiwan. *Int J Cardiol*. 2015;181:235-238.
20. Lai SW, Lin CL, Liao KF, Lin CY. Amiodarone use and risk of acute pancreatitis: a population-based case-control study. *Heart Rhythm*. 2015;12(1):163-166.
21. Hastier P, Buckley MJ, Peten EP, et al. A new source of drug-induced acute pancreatitis: codeine. *Am J Gastroenterol*. 2000; 95(11):3295-3298.
22. Harinstein L, Wu E, Brinker A. Postmarketing cases of eluxadoline-associated pancreatitis in patients with or without a gallbladder. *Aliment Pharmacol Ther*. 2018;47(6):809-815.
23. Wurm S, Schreiber F, Spindelboeck W. Mefenamic acid: a possible cause of drug-induced acute pancreatitis. *Pancreatology*. 2015;15(5):570-572.