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**OPINION REVIEW**

- 2889** Circulating exosomal miRNAs as potential biomarkers for Barrett's esophagus and esophageal adenocarcinoma  
*Lv J, Zhao HP, Dai K, Cheng Y, Zhang J, Guo L*

**REVIEW**

- 2902** Ever-increasing diversity of drug-induced pancreatitis  
*Weissman S, Aziz M, Perumpail RB, Mehta TI, Patel R, Tabibian JH*
- 2916** Nutrition in alcohol-related liver disease: Physiopathology and management  
*Kamran U, Towey J, Khanna A, Chauhan A, Rajoriya N, Holt A*
- 2931** Liver-related effects of chronic hepatitis C antiviral treatment  
*Laursen TL, Sandahl TD, Kazankov K, George J, Grønbaek H*
- 2948** Regenerative medicine of pancreatic islets  
*Arutyunyan IV, Fatkhudinov TK, Makarov AV, Elchaninov AV, Sukhikh GT*
- 2967** Benign gallbladder diseases: Imaging techniques and tips for differentiating with malignant gallbladder diseases  
*Yu MH, Kim YJ, Park HS, Jung SI*

**MINIREVIEWS**

- 2987** COVID-19 pandemic: Its impact on liver disease and liver transplantation  
*Sahin TT, Akbulut S, Yilmaz S*
- 3000** Diagnostic challenges in non-cirrhotic portal hypertension - porto sinusoidal vascular disease  
*Nicoară-Farcău O, Rusu I, Ștefănescu H, Tanțău M, Badea RI, Procopeț B*
- 3012** Extralevator abdominoperineal excision for advanced low rectal cancer: Where to go  
*Tao Y, Han JG, Wang ZJ*

**ORIGINAL ARTICLE****Basic Study**

- 3024** High plasma levels of COL10A1 are associated with advanced tumor stage in gastric cancer patients  
*Necula L, Matei L, Dragu D, Pitica I, Neagu AI, Bleotu C, Dima S, Popescu I, Diaconu CC, Chivu-Economescu M*

- 3034** Hsa\_circRNA\_102610 upregulation in Crohn's disease promotes transforming growth factor- $\beta$ 1-induced epithelial-mesenchymal transition *via* sponging of hsa-miR-130a-3p  
*Yin J, Ye YL, Hu T, Xu LJ, Zhang LP, Ji RN, Li P, Chen Q, Zhu JY, Pang Z*

- 3056** Optimal dosing time of Dachengqi decoction for protection of extrapancreatic organs in rats with experimental acute pancreatitis  
*Yao JQ, Zhu L, Miao YF, Zhu L, Chen H, Yuan L, Hu J, Yi XL, Wu QT, Yang XJ, Wan MH, Tang WF*

#### Case Control Study

- 3076** Single-nucleotide polymorphisms based genetic risk score in the prediction of pancreatic cancer risk  
*Wang XY, Chen HT, Na R, Jiang DK, Lin XL, Yang F, Jin C, Fu DL, Xu JF*

#### Retrospective Study

- 3087** Infection recurrence following minimally invasive treatment in patients with infectious pancreatic necrosis  
*Gao CC, Li J, Cao F, Wang XH, Li A, Wang Z, Li F*

#### Observational Study

- 3098** Intestinal dysbiosis in pediatric Crohn's disease patients with *IL10RA* mutations  
*Xue AJ, Miao SJ, Sun H, Qiu XX, Wang SN, Wang L, Ye ZQ, Zheng CF, Huang ZH, Wang YH, Huang Y*

#### CASE REPORT

- 3110** Giant splenic artery aneurysm presenting with massive upper gastrointestinal bleeding: A case report and review of literature  
*Panzer F, Inchingolo R, Rizzi M, Biscaglia A, Schievenin MG, Tallarico E, Pacifico G, Di Venere B*

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## Ever-increasing diversity of drug-induced pancreatitis

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### Abstract

With over 100000 hospital admissions per annum, acute pancreatitis remains the leading gastrointestinal cause of hospitalization in the United States and has far-reaching impact well beyond. It has become increasingly recognized that drug-induced pancreatitis (DIP), despite accounting for less than 3% of all cases, represents an important and growing though often inconspicuous cause of acute pancreatitis. Nevertheless, knowledge of DIP is often curtailed by the limited availability of evidence needed to implicate given agents, especially for non-prescription medications. Indeed, the majority of available data is derived from case reports, case series, or case control studies. Furthermore, the mechanism of injury and causality for many of these drugs remain elusive as a definitive correlation is generally not established (< 10% of cases). Several classification systems have been proposed, but no single system has been widely adopted, and periodic updates are required in light of ongoing pharmacologic expansion. Moreover, infrequently prescribed medications or those available over-the-counter (including herbal and other alternative remedies) are often overlooked as a potential culprit of acute pancreatitis. Herein, we review the ever-increasing diversity of DIP and the potential mechanisms of injury with the goal of raising awareness regarding the nature and magnitude of this entity. We believe this manuscript will aid in increasing both primary and secondary prevention of DIP, thus ultimately facilitating more expedient diagnosis and a decrease in DIP-related morbidity.

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**Core tip:** Despite living in an era of pharmacologic expansion, our knowledge of drug-induced pancreatitis (DIP) is often curtailed by evidence needed to implicate particular medications. Several causative agent classification systems (with medication lists) have been reported and their mechanisms proposed. Nonetheless, they require regular updates and a complete review of this topic is warranted. In addition, infrequently prescribed medications or those available over-the-counter are often omitted from those summarized lists. We review the ever-increasing diversity of DIP and their potential mechanisms of injury to aid in increasing both primary and secondary prevention of DIP.

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## INTRODUCTION

Acute pancreatitis is an acute, inflammatory, potentially life-threatening condition of the pancreas. With over 100000 hospital admissions per annum, acute pancreatitis is the leading gastrointestinal cause of hospitalization in the United States and the 10<sup>th</sup> most common non-malignant cause of death among all gastrointestinal, pancreatic, and liver diseases<sup>[1-3]</sup>. It is a major cause of morbidity and healthcare expenditure not only in the United States, but worldwide. There are numerous established etiologies of acute pancreatitis, among which gallstones and alcohol are the most common (40%-70% and 25%-35%, respectively)<sup>[4]</sup>. The remaining cases are primarily attributable to the following etiologic factors: Hypertriglyceridemia, autoimmune, infection, hyper/hypocalcemia, malignancy, genetics, endoscopic retrograde cholangiopancreatography, and trauma. Despite accounting for approximately only 1%-2% of cases overall, drug-induced pancreatitis (DIP) has become increasingly recognized as an additional and vitally important, albeit often inconspicuous, etiology of acute pancreatitis<sup>[5,6]</sup>.

The World Health Organization database lists 525 different medications associated with acute pancreatitis (*i.e.* DIP)<sup>[7]</sup>. Many of these medications are widely used to treat highly prevalent medical conditions. Unfortunately, few population-based studies on the true incidence of DIP exist, limiting knowledge of true incidence and prevalence. In this setting, we review the ever-increasing diversity of DIP, with emphasis on the wide range of drug classes reported and their respective pathophysiologic mechanisms - in an attempt to raise awareness of the true and underestimated prevalence of DIP. We hope this manuscript will aid in increasing secondary prevention of DIP ultimately leading to a decrease in overall acute pancreatitis-related hospitalizations and economic burden on the health care system.

## PUBLIC HEALTH IMPORTANCE OF DIP

As there is no standardized approach to stratifying patients to determine their risk of developing acute pancreatitis, primary prevention for the majority of etiologies cannot be fully implemented. Secondary prevention of acute pancreatitis, on the other hand, can more easily be executed. For example, abstinence from alcohol reduces the risk of alcoholic pancreatitis, cholecystectomy reduces the risk of gallstone pancreatitis, and tight control of triglycerides reduces the risk of recurrent episodes of pancreatitis secondary to hypertriglyceridemia. On this notion, unique to DIP, is the fact that it can be prevented in both the primary and secondary fashion. Unfortunately, however, most of the available data in reference to DIP is derived from case reports, case series, or case control studies. In this vein, the causality between specific medications and acute pancreatitis has been established in only a minority of



cases (< 10%)<sup>[7]</sup>. In addition, oftentimes, lack of a known etiology for acute pancreatitis directly increases length of hospitalization due to delayed diagnosis and subsequent treatment<sup>[8,9]</sup>. Moreover, patients unaware of an adverse drug reaction to a prior medication may continue taking that medication leading to repeat hospitalizations<sup>[8,9]</sup>. Finally, with the rapid expansion of pharmacologic agents, widespread legalization of cannabis, increase in recognized medications, supplements, and alternative medications reported to induce pancreatitis, the need to become familiar with this esoteric group remains imperative, and knowledge in the form of awareness regarding certain medications is warranted<sup>[10-12]</sup>.

## CHALLENGES IN ESTABLISHING A DIAGNOSIS OF DIP

Numerous factors limit the ability of clinicians to causally link acute pancreatitis with medications. First, the lack of mandatory adverse drug reporting systems allow many cases to go unreported<sup>[6]</sup>. Second, bias exists, in the sense that clinicians tend to forgo linking unusual medication suspects to a rare adverse event<sup>[6]</sup>. Third, it is often difficult to rule out other, more common, causes of drug-induced pancreatitis, especially in patients who have multiple comorbidities and underlying risk factors<sup>[6]</sup>. Fourth, many cases lack a re-challenge test or drug latency period to definitively link acute pancreatitis to a particular drug<sup>[13]</sup>. Finally, evidence is lacking to support the use of any serial monitoring technique - namely, imaging or pancreatic enzymes to help detect cases of drug-induced pancreatitis<sup>[14]</sup>. Despite these limitations, as illustrated in **Figure 1**, following a thorough algorithm can aid in detecting cases of drug-induced pancreatitis that would otherwise have been difficult to diagnose (**Figure 1**).

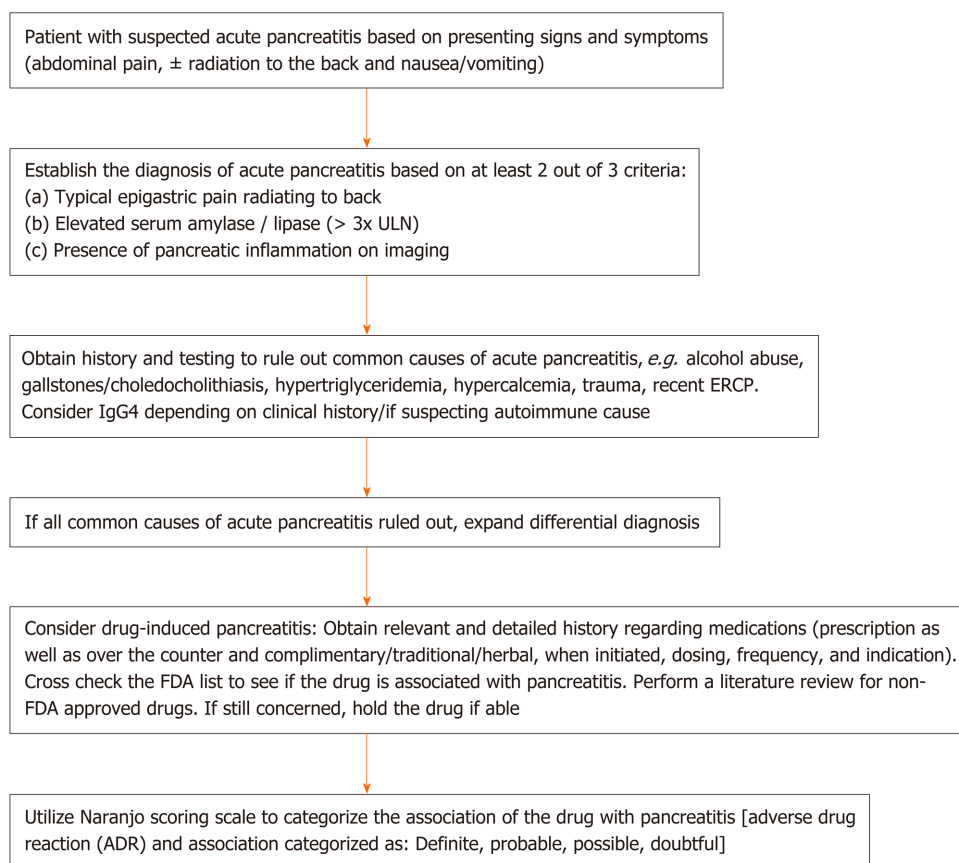
## APPROACH AND AVAILABLE METHODS TO ESTABLISH DIP

In accordance with the aforementioned limitations, evidence implicating numerous medications is inconsistent and, at times, even contradictory. Hence, although not uniform, nor universally accepted, official tier systems exist to help quantify the likelihood of a drug to be established as a culprit of acute pancreatitis. The earliest classification system was developed in 1980 and was designed to include three classes; Class I: Included drugs that were implicated to induce pancreatitis in a minimum of 20 cases of which at least one case documented drug re-exposure, Class II: Included drugs that were implicated to induce pancreatitis in 10-20 cases with or without documented drug re-exposure, and Class III: Included all drugs implicated in pancreatitis<sup>[15]</sup> (**Table 1**). Trivedi *et al*<sup>[16]</sup> reviewed the top 100 prescription medications in the United States for their association with acute pancreatitis using this three-tier classification system. They noted that, of the top 100 most frequently prescribed medications, 44 were Class III pancreatitis medications. Additionally, 14 of these medications were Class I or II<sup>[16]</sup>.

The most recent classification system was developed by Badalov *et al*<sup>[13]</sup>, in which the authors categorized implicated drugs into four classes (**Table 2**). Class I drugs are medications in which a re-challenge was established in at least one case report. This class is further divided into whether other causes of acute pancreatitis were ruled out (Ia) or not (Ib). Class II drugs are medications in which there is a latency period in 75% of at least four reported cases, all with no evidence of re-challenge. Class III drugs are medications that neither a re-challenge nor a consistent latency period was established but had two or more case reports published. Class IV drugs are medications that neither a re-challenge nor a consistent latency period was established, and only 1 case report had been published<sup>[13]</sup>.

Additionally, the Naranjo adverse drug reaction probability scale can be helpful in establishing the degree of association between a drug and an adverse reaction<sup>[17]</sup>. This tool determines the likelihood of an adverse drug reaction based on the cumulative score on 10 questions. A score of < 1 signifies a doubtful drug reaction, 1-4 a possible drug reaction, 5-8 a probable drug reaction, and > 9 a definitive drug reaction (**Figure 2**).

Finally, and most recently, our proposed specific drug-induced pancreatitis probability scale (modified from the Naranjo scale to be more pancreatitis-specific) can serve as a standardized tool for determining the likelihood of drug-induced pancreatitis based on the aggregate score from a series of 10 questions. A score of < 2 suggests doubtful DIP, 3-5 possible DIP, 6-8 probable DIP, and > 9 highly probable DIP (**Figure 3**). We believe this tool, in particular, enhances one's ability to accurately



**Figure 1** Flow diagram to help identify the potential cause of acute pancreatitis, including cases of drug-induced pancreatitis. ERCP: Endoscopic retrograde cholangiopancreatography; FDA: Food and Drug Administration.

identify and implicate potential acute pancreatitis-causing drugs.

## DRUGS AND MECHANISMS INVOLVED

While consensus has yet to be reached regarding the cause of drug-induced pancreatitis in many cases, numerous potential mechanisms have been speculated. These include, pancreatic/biliary duct constriction, cytotoxic effects, metabolic effects, accumulation of a toxic metabolite or intermediary, and idiosyncratic and/or hypersensitivity reaction, with idiosyncratic response or direct toxic effect likely accounting for the majority of cases<sup>[18,19]</sup> (Figure 4).

Studies concerning the incidence of drug-induced pancreatitis have established a range of 0.3% to 1.4% of all acute pancreatitis cases being due to drugs<sup>[5,20-22]</sup>. Certain medications such as azathioprine/mercaptopurine and didanosine are well-known culprits of drug-induced pancreatitis with incidences of 5% and 23% respectively<sup>[23]</sup>. As illustrated in Table 3, compiling a list of drug classes implicated in pancreatitis may yield clinical use owing to increased clinician awareness of other medications in these classes.

### **Statin-induced pancreatitis**

Among the many drugs that have been associated with pancreatitis, statins have been increasingly reported as a cause of acute pancreatitis<sup>[19,24]</sup>. In fact, as numerous members of this class (atorvastatin, fluvastatin, rosuvastatin, simvastatin, and pravastatin) have been implicated in acute pancreatitis, statin-induced pancreatitis may indeed be a class-effect<sup>[19,24]</sup>. Mechanisms of action of statin-induced acute pancreatitis are associated with rhabdomyolytic and cytochrome P-450 interactions leading to an immune-mediated inflammatory response, direct cellular toxicity, or perhaps a metabolic effect<sup>[25]</sup>. As with many other drugs, its true prevalence in acute pancreatitis remains unknown, as the onset of statin-induced pancreatitis has been observed from hours to years after treatment<sup>[25]</sup>. Interestingly, the degree of P-450 CYP4A inhibition correlates with individual statin safety profiles<sup>[26]</sup>.



**Table 1** The earliest classification system of drug-induced pancreatitis, as proposed by Trivedi *et al*<sup>[16]</sup>

Class I	Class II	Class III
≥ 1 case documenting a positive re-challenge ≥ 20 case reports	With or without drug re-challenge 10-20 case reports	All drugs associated with drug induced pancreatitis < 10 case reports

**5-aminosalicylic acid-induced pancreatitis**

Although rare, several 5-aminosalicylic acid (5-ASA)-induced acute pancreatitis cases have been published in the literature. Interestingly, both oral and enema mesalamine preparations have been implicated in causing pancreatitis within days<sup>[27,28]</sup>. In addition, sulfasalazine has been implicated in inducing pancreatitis perhaps through an immune-mediated mechanism<sup>[29]</sup>. In general, however, a hypersensitivity mechanism seems to be involved and pancreatitis can occur from days to years after starting mesalamine therapy<sup>[27,29]</sup>.

**Antibiotic-induced pancreatitis**

Metronidazole has been reported in association with acute pancreatitis, although the mechanism is not fully known<sup>[30,31]</sup>. Free-radical production, immune-mediated, direct toxic affect, and metabolic effects have been suggested as possible pathophysiological mechanisms<sup>[30,31]</sup>. Notably, a study showed that patients receiving metronidazole as part of *Helicobacter pylori* triple-therapy have an approximate eight-fold increased risk of acute pancreatitis<sup>[32]</sup>. The tetracycline class (tetracycline, minocycline, and oxytetracycline) has also been associated with acute pancreatitis, with the mechanism believed to be a direct toxic-effect, or hypersensitivity reaction<sup>[33-36]</sup>. In addition, numerous cases of erythromycin-induced pancreatitis have been reported to date<sup>[37,38]</sup>. Although less established, other antibiotics such as ampicillin, ceftriaxone, clarithromycin, trimethoprim-sulfamethoxazole, and nitrofurantoin have been implicated in pancreatitis as well<sup>[39-43]</sup>.

**Steroid and non-steroidal anti-inflammatory drug-induced pancreatitis**

Numerous steroids (dexamethasone, prednisone, prednisolone, cortisone acetate, and adrenocorticotrophic hormone) have been associated with inducing acute pancreatitis nearly all with a short latency period<sup>[44-47]</sup>. As a large proportion of these cases resulted in death, it has been suggested that this drug class may be linked to a more severe disease course<sup>[13,46]</sup>. The most common non-steroidal anti-inflammatory drugs (NSAIDs) that have been reported to cause pancreatitis are sulindac and salicylates, with latency ranging from weeks to years, however others have been implicated as well<sup>[48-55]</sup>. A clear limitation that exists is the fact that NSAIDs may be initiated in response to early symptoms of unrecognized pancreatitis leading to erroneously attributing the pancreatitis to this class of medication<sup>[56,57]</sup>. Interestingly, naproxen has been recommended as the preferred analgesic in this scenario owing to its limited risk of inducing acute pancreatitis<sup>[58]</sup>. The mechanism being, a structural (compression or obstruction) effect on the sphincter of Oddi leading to acute pancreatitis. Of note, both diclofenac and indomethacin may significantly reduce the risk of acute pancreatitis post-endoscopic retrograde cholangiopancreatography<sup>[59,60]</sup>.

**Immunotherapy-induced pancreatitis**

Immunotherapy agents have long been associated with acute pancreatitis, however their increased use in recent decades has led to a concomitant increase in immunotherapy-associated pancreatitis. Interleukin-2 immunotherapy-associated pancreatitis in particular has been reported<sup>[61]</sup>. The mechanism of injury is believed to be either immune-mediated or a direct drug toxicity. Newer programmed cell death protein 1 blockers (*i.e.* nivolumab) and anti-cytotoxic T-lymphocyte-associated protein 4 agents (*i.e.* ipilimumab) have been associated with acute-pancreatitis as well<sup>[62,63]</sup>. The exact mechanism is currently unknown, but it is speculated to be associated with T-lymphocyte mediated inflammation<sup>[62,63]</sup>.

**Angiotensin-converting-enzyme inhibitor-induced pancreatitis**

There have been many well-documented case reports of acute pancreatitis due to Angiotensin-converting-enzyme inhibitors (ACE-Is)<sup>[64-70]</sup>. One case-control study suggested a dose-dependent correlation with an odds ratio of 1.5<sup>[71]</sup>. While enalapril has been the most extensively reported culprit in this class<sup>[64,69]</sup>, other agents (such as lisinopril, captopril, ramipril, benazepril, quinapril, and perindopril) have been described in the literature as well<sup>[65-68,70-72]</sup>. Similar to ACE-Is, angiotensin receptor blockers (such as telmisartan and losartan) has also been implicated in acute

**Table 2** The more recent classification system of drug-induced pancreatitis, proposed by Badalov *et al.*<sup>[13]</sup>

	Minimum No. of case reports	Re-challenge required	Latency established	Alternative causes of pancreatitis excluded
Class Ia	1	Yes	N/A	Yes
Class Ib	1	Yes	N/A	No
Class II	4	No	Yes <sup>1</sup>	N/A
Class III	2	No	No	N/A
Class IV	1	No	No	N/A

<sup>1</sup>In greater than 75% of cases. N/A: Not applicable.

pancreatitis<sup>[73,74]</sup>. Interestingly, the latency period between ACE-I initiation and an associated pancreatitis event may range from days to years and may be associated with severe disease<sup>[64-66,69]</sup>. The proposed mechanism involved is due to decreased bradykinin degradation, increasing pancreatic vascularity and edema, and pancreatic enzyme trapping causing local tissue damage secondary to pancreatic duct obstruction<sup>[75]</sup>.

### **Anti-glycemic medication-induced pancreatitis**

Although proven to be relatively safe for the management of type 2 diabetes mellitus, numerous classes of oral anti-glycemic agents including biguanides (metformin)<sup>[76]</sup>, dipeptidyl peptidase-4 inhibitors<sup>[77-79]</sup>, glucagon-like peptide-1 (GLP-1) analogues<sup>[80-86]</sup>, and sodium glucose co-transporter-2 inhibitors<sup>[87,88]</sup> have been associated with acute pancreatitis. The highest incidence is reported with GLP-1 analogues<sup>[81,83-85]</sup>, of which exenatide has the highest association with an up to 6-fold increase in the rate noted in post-marketing surveillance<sup>[80,82,86]</sup>. The proposed mechanism is pancreatic acinar cell hypertrophy, the subsequent release of proinflammatory cytokines, leading to increased vascular permeability, resulting in pancreatic inflammation<sup>[89]</sup>. Another hypothesis suggests an obstructive type phenomenon, as an increased incidence of gallstones with the use of GLP-1 analogues has been recorded<sup>[90]</sup>.

### **Illicit drug-induced pancreatitis**

Marijuana (cannabis) is the most common illicit drug globally with over 4% of the population using it per annum<sup>[91,92]</sup>. As such, many case reports suggesting the association between cannabis and pancreatitis have been published in the literature, and may even suggest a dose-dependent phenomenon<sup>[91-95]</sup>. While cannabinoid receptors are found in the islet of Langerhans cells, the exact pathophysiology of cannabis-induced pancreatitis is currently not well-understood<sup>[93-95]</sup>. Cocaine-induced pancreatitis has also been reported, and is believed to be due to splanchnic vasoconstriction and thrombotic microangiopathy leading to ductal obstruction<sup>[96-98]</sup>. Similarly, codeine has also been described in the literature with regards to inducing acute pancreatitis with a mechanism believed to relate to dysfunctional sphincter of Oddi contraction as well<sup>[99-101]</sup>.

### **Highly active anti-retroviral therapy-induced pancreatitis**

The highly active anti-retroviral therapy drugs have long thought to be associated with the development of acute pancreatitis<sup>[102,103]</sup>. The most common offenders include nucleoside reverse transcriptase inhibitors (NRTIs), non-NRTIs (NNRTIs), and protease inhibitors (PIs)<sup>[104]</sup>. In a large retrospective cohort study including nearly 5000 patients who received antiretroviral therapy, 3.2% developed AP<sup>[103]</sup>. Furthermore, 5.2% of patients who received didanosine, 4.2% of patients who received a PI plus either an NRTI or a NNRTI, and 3.5% of patients who received NRTIs combined with NNRTIs—developed acute pancreatitis<sup>[25,103]</sup>. The exact mechanism by which NRTIs and NNRTIs cause pancreatitis is unidentified, but it is thought to be related to direct drug toxicity or ductal obstruction leading to mitochondrial damage resulting in cellular death and organ damage<sup>[18]</sup>. PIs are directly related to induction of hypertriglyceridemia which is a well-established cause of pancreatitis in the literature<sup>[105,106]</sup>.

### **Diuretic-induced pancreatitis**

Diuretics [e.g. furosemide, chlorothiazide, hydrochlorothiazide (HCTZ), and others] have long been implicated in the development of acute pancreatitis, with the majority of cases suggesting a short latency period and a more mild disease course<sup>[107-113]</sup>. Notably, HCTZ has well-established side effects of causing hypercalcemia and hyperlipidemia, both of which are well known to lead to acute pancreatitis<sup>[25,114]</sup>.

Naranjo adverse drug reaction probability scale				
Question	Yes	No	Do not know	Score
Are there previous conclusive reports on this reaction?	+1	0	0	
Did the adverse event reappear after the suspected drug was administered?	+2	-1	0	
Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	+2	-1	0	
Did the adverse event reappear when the drug was re-administered?	+2	-1	0	
Are there alternative causes (other than the drug) that could on their own have caused the reaction?	-1	+2	0	
Did the reaction reappear when a placebo was given?	-1	+1	0	
Was the drug detected in blood (or other fluids) in concentrations known to be toxic?	+1	0	0	
Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0	
Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0	
Was the adverse event confirmed by any objective evidence?	+1	0	0	
Total score:				

Figure 2 The Naranjo adverse drug reaction probability scale<sup>[17]</sup>.

HCTZ can further cause hyperparathyroidism, which can also lead to hypercalcemia-induced pancreatitis<sup>[25]</sup>. It has been postulated that furosemide affects the pancreas by causing a hyper-stimulation of secretions leading to a direct toxic injury and/or ischemia<sup>[25,114]</sup>.

### **Hormone replacement therapy and oral contraceptive-induced pancreatitis**

Numerous cases have been reported in which estrogen-containing products were thought to induce acute pancreatitis<sup>[115-119]</sup>. Hypercoagulability and hypertriglyceridemia have been speculated as the main cause of inducing pancreatitis in patients taking hormone replacement therapy and oral contraceptives<sup>[115-119]</sup>. Nonetheless, patients with existing hypertriglyceridemia and familial hyperlipoproteinemia can have an exacerbation of their underlying condition leading to pancreatitis<sup>[18,25,115,120,121]</sup>.

### **Anti-acid-induced pancreatitis**

Although both H<sub>2</sub>-blockers and proton-pump inhibitors have been reported in the literature to cause acute pancreatitis, the evidence regarding this relationship is controversial<sup>[122]</sup>. A retrospective study conducted by Eland *et al*<sup>[56]</sup> failed to identify any association of pancreatitis with the use of ranitidine (RR: 1.3; 95%CI: 0.4-4.1), cimetidine (RR: 2.1; 95%CI: 0.6-7.2), and/or omeprazole (RR: 1.1; 95%CI: 0.3-4.6). Case reports in the literature have generally linked pancreatitis in these cases to excessive consumption of antacids which likely was directly related to hypercalcemia<sup>[123,124]</sup>.

### **Anti-depressant medication-induced pancreatitis**

Many cases have linked antidepressants (e.g. mirtazapine and sertraline) to acute pancreatitis<sup>[125-128]</sup>; nonetheless, a population-based study by Nørgaard *et al*<sup>[129]</sup> failed to demonstrate a significant association between selective serotonin reuptake inhibitors (SSRIs) and acute pancreatitis. Only a mild increase in the risk of pancreatitis was seen with first-time users of SSRI (aOR: 2.8, 95%CI: 1.1-7.0); however, the results are limited due to confounding variables<sup>[129]</sup>. A recent meta-analysis demonstrated a significant association between SSRIs and acute pancreatitis (aOR: 1.26, 95%CI: 1.13-1.40)<sup>[130]</sup>. The risk was much higher in the first 2 weeks of following initiation of SSRIs<sup>[130]</sup>. The exact mechanism by which SSRIs can lead to pancreatitis is unknown, though it is speculated that SSRIs can cause cellular apoptosis, insulin secretion

Question	Yes	No	Don't know	Score
1 Are there published reports of the drug causing acute pancreatitis?	1	0	0	
2 Was there short latency ( $\leq 7$ d) between initiation of the drug and the diagnosis of acute pancreatitis?	2	0	0	
3 Was there a temporal relationship ( $\leq 1$ mo) between initiation of the drug and onset of acute pancreatitis symptoms?	1	-1	0	
4 Did the acute pancreatitis resolve following discontinuation of the drug?	1	-1	0	
5 If a drug re-challenge was performed, did acute pancreatitis recur?	2	-1	0	
6 Were all commonly recognized causes of acute pancreatitis ruled out? (e.g. gallstones/choledocholithiasis, alcohol, hypertriglyceridemia, hypercalcemia, ERCP, trauma)	1	-1	0	
7 Was a serum IgG4 level checked? (to rule out autoimmune pancreatitis)	1	0	0	
8 Does the patient have or was the patient recently diagnosed with an infection (bacterial, fungal, or viral) which could cause pancreatitis?	-1	1	0	
9 Was an EUS and/or MRCP performed? (e.g. to rule out occult microlithiasis, pancreatic malignancy, and pancreatic divisum)	1	-1	0	
10 Was genetic testing (SPINK-1, CFTR, and PRSS-1) performed to rule out hereditary pancreatitis? (in patients age $< 30$ yr)	1	0	0	
Summative score				

**Figure 3 Proposed drug-induced pancreatitis probability assessment scale in which a total summative score of  $> 9$ : highly probable, 6-8: probable, 3-5: possible, and  $\leq 2$ : doubtful.** ERCP: Endoscopic retrograde cholangiopancreatography; EUS: Endoscopic ultrasound; MRCP: Magnetic resonance cholangiopancreatography.

inhibition, and further development of diabetes and chronic pancreatitis as well<sup>[130]</sup>. Roberge *et al.*<sup>[131]</sup> additionally reported a case of a patient who developed acute pancreatitis due to an acute overdose of clomipramine.

#### **Anti-seizure medication-induced pancreatitis**

Numerous anti-seizure medications (clozapine, olanzapine, and valproic acid) have been associated with inducing pancreatitis, especially in the pediatric population<sup>[132-142]</sup>. Interestingly, this class seems to be associated with a more severe disease course that may result in pancreatic necrosis and death<sup>[136,138,142]</sup>. The mechanism has been postulated to involve a direct toxic effect on pancreatic cells causing depletion of superoxide dismutase, catalase, and glutathione peroxidase on a biochemical level<sup>[25,136,142]</sup>.

#### **Vitamin-induced pancreatitis**

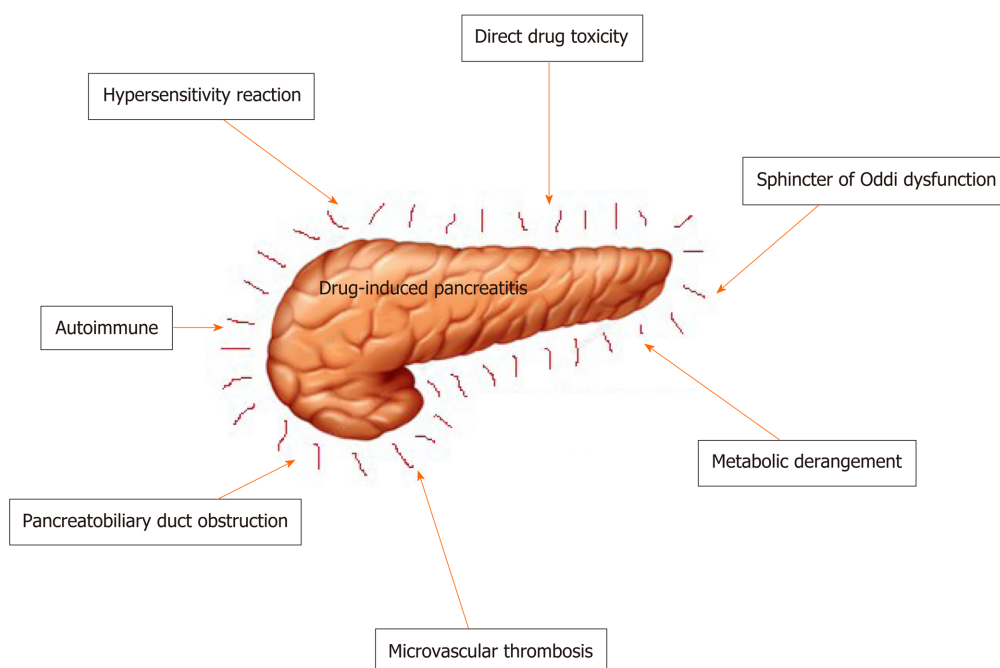
To our knowledge, two cases of vitamin-induced acute pancreatitis have been reported, both involving vitamin D. One involved oral vitamin D, wherein the injury was seemingly related to the hypercalcemic effect of vitamin D<sup>[143]</sup>. The other case involved tacalcitol (a vitamin D-analog) ointment as the inciting agent<sup>[144]</sup>. In addition, we recently encountered a second (suspected) case of oral vitamin D-induced acute pancreatitis (unpublished data), which we are currently examining.

#### **Herbal, supplement, and homeopathic medication-induced pancreatitis**

Although seldom in nature, several herbal medications have been reported in the literature as being associated with DIP. These including: Sambucol (black elderberry extract), "Immune factors" [combination of *Echinacea*, Goldenseal (*Hydrastis Canadensis*), and Shiitake, Maitake, and Reishi mushrooms], saw palmetto (*Serenoa repens*), and mangosteen (*Garcinia cambogia*)<sup>[145-148]</sup>. The mechanism of injury underlying these rare cases is unclear<sup>[145,147,148]</sup>. Some reports, however, believe these cases to be due to an induced hypercoagulable state *via* estrogen receptor activation<sup>[6]</sup>.

## **CONCLUSION**

In the setting of an ever-increasing armamentarium of pharmacological agents, drug-induced adverse effects including acute pancreatitis are increasingly encountered. DIP is a difficult diagnosis to establish and is thus likely underreported, owing in part to its often unsuspected nature as well as the technical difficulty in causally linking a drug to acute pancreatitis. Criteria for definite DIP are many and generally include requiring that the drug cause acute pancreatitis during or predictably after initiating treatment with the drug, resolution of pancreatitis upon discontinuation of the drug,



**Figure 4** The proposed mechanisms leading to pancreatic insult in drug-induced pancreatitis.

and reoccurrence of pancreatitis upon re-administration of the drug, granted that other likely causes of acute pancreatitis have been ruled out. With these caveats in mind, the current list of drugs associated with DIP is by no means complete nor fully understood, and further research is needed.

As cases of DIP are associated with higher morbidity, extended hospital stays, and increased healthcare costs, in large part due to delays in diagnosis, patients presenting with pancreatitis of unknown etiology should be carefully questioned regarding drugs that could be linked to DIP<sup>[8,9]</sup>. Notably, as new medications with known severe side effects are usually more closely monitored, drugs which are infrequently prescribed, or considered relatively harmless, such as over-the-counter medications and herbal supplements, may remain illusory and inadequately considered in this context. Hence, following a streamlined diagnostic approach for cases of possible DIP (Figure 1-3) and expeditiously identifying early-on the responsible agent are critical.



**Table 3** Classes of medications implicated in drug-induced pancreatitis grouped according to the three-class system of classification

Class I	Class II	Class III
Aminosaliculates	Alkylating antineoplastics	Aminosaliculates
Anticonvulsants	Angiotensin-converting enzyme inhibitors	Antacids
Antimetabolite antineoplastics	Anticonvulsants	Antiarrhythmics
Antimicrobials	Antimicrobials	Antibacterials
Hormone replacement therapies	Antitubercular agents	Anticholinesterases
Loop diuretics	Interferons	Anticonvulsants
Non-biologic immunosuppressives	Nonopioid analgesics	Antidepressants
Nonsteroidal anti-inflammatories	Reverse transcriptase inhibitors	Antifungals
Opiates	Somatostatin analogs	Antihypertensives
Reverse transcriptase inhibitors	Thiazides	Antimetabolite antineoplastics
Steroids		Antineoplastics
		Antiplatelets
		Antivirals
		Atypical antipsychotics
		Cholesterol lowering agents
		Cyclooxygenase II inhibitors
		Estrogens
		Immunomodulators
		Nonsteroidal anti-inflammatories
		Parasympathetic agents
		Proton pump inhibitors
		Selective serotonin agonists
		Somatostatin analogs
		Steroids
		TNF-alpha inhibitors
		Vitamins

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