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Drug-Induced Pancreatitis
Incidence, Management and Prevention

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Abstract

Drugs are a relatively rare cause of acute pancreatitis, with an estimated incidence of 0.1–2%. Many drugs have been suspected of causing pancreatitis, but the true incidence is not known as the evidence is derived mainly from random case reports. Case reports with the strongest evidence are those that clearly diagnose pancreatitis and exclude common aetiologies, provide the dose and time interval between the start of treatment with the suspected drug and the development of pancreatitis, document response to withdrawal of the drug, and demonstrate recurrent pancreatitis upon rechallenge with the drug. Few data exist on the mechanisms of drug-induced pancreatitis. Certain subpopulations such as children, women, the elderly and patients with advanced HIV infection or inflammatory bowel disease may be at higher risk. The diagnosis of drug-induced pancreatitis is often challenging because there are no unique clinical characteristics to distinguish drugs from other causes of pancreatitis. The majority of cases are mild, but severe and even fatal cases may occur, thus making identification of the offending agent critical. Management of drug-induced acute pancreatitis requires withdrawal of the offending agent and supportive care. Prevention of

drug-induced pancreatitis requires an up-to-date knowledge of drugs that have the strongest evidence linking their use to the development of pancreatitis as well as the proposed mechanisms through which they may cause the reaction. In this paper, the epidemiology, diagnosis, management and prevention of drug-induced pancreatitis is reviewed. Drugs and classes of drugs strongly implicated as causing acute pancreatitis, based on well documented case reports, are discussed in detail.

Acute pancreatitis is a severe disease with an overall mortality of approximately 5%, though in subpopulations with necrotizing pancreatitis and infected necrosis, mortality may be as high as 17% and 30%, respectively.[1] The most common aetiologies are excessive alcohol use and gallstone disease, comprising 70–80% of all cases. Other aetiologies include autoimmune disease, iatrogenic injury, inflammatory bowel disease, infections, inherited disorders, neoplasia, structural abnormalities, toxins, trauma, ischaemia and some drugs.[2] Drug-induced pancreatitis is remarkably rare, given the large number of drugs prescribed. Due to its rarity and the lack of unique clinical characteristics, the true epidemiology and risk factors for drug-induced pancreatitis remain unknown, and diagnosis of this adverse effect is challenging.

The first cases of drug-induced pancreatitis were reported with chlortalidone and cortisone in the 1950s.[3,4] Since then, over 500 medications have been associated with pancreatitis,[5] and the list continues to expand. Most of the evidence comes from random case reports. These reports are often incomplete, with inadequate data regarding drug dose, latency between initiating the drug to development of pancreatitis and exclusion of other common causes. Many case reports do not meet sufficient criteria to diagnose acute pancreatitis, and most do not provide evidence of rechallenge with the drug. Furthermore, random case reports are subject to selection and publication bias. Selection bias is influenced by the reporting and prescribing behaviours of clinicians. Publication bias may be present because the more severe adverse reactions are reported, whereas many cases of mild pancreatitis may not be reported or come to clinical attention.

In this paper, the epidemiology, diagnosis, management and prevention of drug-induced pancreatitis are reviewed. Drugs and classes of drugs strongly implicated as causing acute pancreatitis, based on well documented case reports, are discussed in detail.

1. Literature Search Methodology

A MEDLINE search (1950–2007) of the English language literature was conducted using the search terms 'drug-induced pancreatitis' and '*x* and pancreatitis', where '*x*' was the name of any drug that has been proposed to cause pancreatitis based on previous clinical reviews.[6-11] The references in these papers were used to obtain additional case reports. Case reports were considered well documented if they met the criteria established by Mallory and Kern.[6] These criteria stipulate that pancreatitis develops during treatment with the drug, resolves upon discontinuing the drug, recurs upon readministration of the drug, and other likely causes of pancreatitis are not present. Additionally, case reports were required to contain adequate criteria for the diagnosis of pancreatitis.[1] These case reports are considered to provide the best evidence for drug-induced pancreatitis and are further discussed in section 6. For a number of commonly used drugs, such as corticosteroids, furosemide and omeprazole, the available case reports fail to meet criteria established by Mallory and Kern and are therefore not discussed in this paper. Extensive reviews of drug-induced pancreatitis have been published recently, highlighting both common and uncommon drugs that may cause pancreatitis.[7-12] Drug classes and individual drugs frequently associated with pancreatitis are listed in table I.

2. Epidemiology

Determining the true incidence of drug-induced pancreatitis is difficult because of the lack of adequate and consistent reporting. Epidemiological studies suggest an overall incidence of 0.1–2%,[127-131] and that the risk may be increas-

Table I. Drugs commonly associated with acute pancreatitis

Class	Drug
Cardiovascular	
ACE inhibitors	Enalapril,[13,14] lisinopril,[15,16] ramipril[17]
Angiotensin receptor blockers	Losartan[18,19]
Centrally acting	Methyldopa[20,21]
Loop diuretics	Furosemide[22,23]
Thiazide diuretics	Chlorothiazide,[24] hydrochlorothiazide[25]
Antiarrhythmics	Amiodarone[26]
HMG-CoA reductase inhibitors	Simvastatin,[27,28] pravastatin,[29] fluvastatin[30]
Other cholesterol-lowering drugs	Bezafibrate[31]
Antimicrobials	
Antibacterials	Tetracycline,[32,33] metronidazole,[34,35] dapsone,[36] cotrimoxazole,[37,38] nitrofurantoin,[39,40] clarithromycin[a][41-43] erythromycin[a][44-49]
Antituberculars	Isoniazid[50-53]
Antivirals	Nelfinavir,[54] lamivudine,[55] didanosine,[56,57] interferon/ribavirin[a][58-63]
Others	Pentamidine,[64,65] sodium stibogluconate,[66] meglumine antimonate[67]
Gastrointestinal	
Acid suppressants	Omeprazole[68]
Inflammatory bowel disease drugs	Azathioprine,[69-71] mercaptopurine,[72] aminosalicylates (mesalamine,[73-76] olsalazine,[77] sulphasalazine[78])
Neuropsychiatric	
Anticonvulsants	Valproic acid[79-81]
Antipsychotics	Clozapine[a][82-90]
Hormone-related	
Estrogens	Conjugated estrogens,[91-93] clomifene,[94,95] premarin,[96] tamoxifen[a][97-102]
Anti-thyroid	Thiamazole,[103] carbimazole[104]
Oncological	
Alkylating agents	Ifosfamide[105]
Antimetabolites	Cytarabine[106-108]
Other	Asparaginase[a][109-116]
Analgesics	
Opioids	Codeine[117]
NSAIDs	Sulindac[118-120]
Other	Marijuana,[121,122] isotretinoin,[a][123-125] propofol[126]

a No case reports with rechallenge.

ing.[131] Certain patient populations may be at increased risk (table II). Extremes of age may be a risk factor for development of drug-induced pancreatitis. Drugs are often implicated in children as a cause of pancreatitis because this population is an otherwise low-risk group for developing pancreatitis. The elderly may be an at-risk group, though it is often difficult to diagnose in this population because of polypharmacy and multiple co-morbidities. Women may have a higher rate of drug-induced pancreatitis based on epidemiological studies,[130,131] though the reason is unclear. Patients with advanced HIV infection have a high incidence (14%) of pancreatitis.[132] This is believed to be multifactorial, with infection, neoplasm, gallstones, use of some drugs and other factors possibly contributing. Patients with in-

Table II. Risk factors for drug-induced pancreatitis

Paediatric population
Female sex
Elderly patients taking multiple medications
Advanced HIV disease with CD4 counts <200 cells/mm^3
Inflammatory bowel disease
Cancer chemotherapeutic agents

flammatory bowel disease may be at increased risk of drug-induced pancreatitis, but this subgroup of patients are also believed to have a higher risk of pancreatitis in general.[133] Patients do not seem to have a higher predisposition to allergic disorders or drug reactions.[12] Mortality rates of 9–15% have been reported in some series,[130,131] though this rate is likely inflated due to selection bias.

3. Diagnosis

The diagnosis of drug-induced pancreatitis is often difficult to make because there are no unique clinical, biochemical or radiological features to distinguish this aetiology of pancreatitis from other causes of pancreatitis. Furthermore, data regarding the mechanisms through which drugs cause pancreatitis are limited, with few animal studies. The first step is to confirm the diagnosis of pancreatitis. This requires two of the following three features: (i) abdominal pain characteristic of acute pancreatitis; (ii) serum amylase and/or lipase ≥3 times the upper limit of normal; and (iii) characteristic findings of acute pancreatitis on CT scan.[1] A careful clinical evaluation should be performed to exclude other common aetiologies of pancreatitis. Important information from the history should include alcohol use, biliary tract disease or gallstones, abdominal surgery, personal or family history of pancreatitis, recent abdominal trauma, and weight loss. A careful review of current medications and their duration of use should be obtained. Blood tests within the first 24 hours should include liver function tests, and calcium and triglyceride levels. An abdominal ultrasound should be obtained on admission to assess for gallstones. Contrast-enhanced CT scan, preferably a thin-section multidetector-row CT scan, can be helpful in determining the aetiology of pancreatitis if the clinical history is unrevealing.

4. Management

In addition to evaluating for the more common causes of acute pancreatitis, drugs should also be considered. It is crucial that suspected drugs be discontinued immediately to prevent any ongoing pancreatic injury. Further management should consist of aggressive intravenous fluid replacement, frequent checking of vital signs including monitoring of oxygen saturation, and relief of abdominal pain with a parenterally administered narcotic medication. Patients with signs of organ dysfunction, such as sustained hypoxaemia, hypotension refractory to intravenous fluids, renal insufficiency that does not respond to fluid boluses and mental status changes should be transferred to an intensive care unit for closer observation and management. Patients with significant abdominal pain, distention, nausea and vomiting should avoid oral intake until their symptoms and overall clinical course improves, which in most cases takes 3–7 days. In more severe cases of pancreatitis, nutritional support may be needed, particularly when it becomes clear that the patient will not be able to eat for more than 7 days. If feasible, enteral nutrition should be given in preference to parenteral nutrition.[1]

5. Prevention

It must be kept in mind that drug-induced pancreatitis is a rare phenomenon, despite the large number of drugs available today. In an asymptomatic individual, routine monitoring of serum pancreatic enzymes, particularly amylase, and discontinuing a medication because of transient hyperamylasaemia is not recommended. Serial abdominal imaging is also not advocated.[12] Prevention of drug-induced pancreatitis consists largely of recognition of which drugs have the strongest evidence for being causally associated with pancreatitis, the identification of high-risk groups, maintenance of a high index of suspicion, and withdrawal of the offending agent immediately when pancreatitis is suspected. A knowledge of the possible mechanisms of drug-induced pancreatitis may be helpful in the prevention of this adverse reaction. For example, for drugs known to induce hypertriglyceridaemia, monitoring serum triglyceride levels may be useful. Other proposed mechanisms include hypersensitivity reaction, pancreatic duct constriction, immunosuppression, osmotic or metabolic effects, vascular thrombosis, direct cellular toxicity, accumulation of toxic metabolites and hepatic involvement.[134] Cases believed to be due to an idiosyncratic drug reaction are difficult to prevent because they are not predictable, are not dose-dependent, occur in susceptible patients only, and cannot be explained by a known mechanism of action of the drugs. These types of reaction

are usually detected after the drug has been approved for general use.

The question of whether to re-institute a drug after a bout of suspected drug-induced pancreatitis requires a benefit-risk analysis of the drug and the patient's medical condition. Rechallenge can only be ethically justified if there are no alternative medications available, as is the case with many chemotherapeutic agents, and/or if the potential benefits outweigh the risks. In such cases, informed consent should be obtained prior to the rechallenge. If the risks outweigh the benefits, then the offending agent and drugs within the same class should not be reintroduced.

6. Drugs Strongly Implicated as Causing Acute Pancreatitis

6.1 ACE Inhibitors and Angiotensin Receptor Antagonists

ACE inhibitors are one of the most commonly prescribed classes of medication, as they are used for hypertension, heart failure and proteinuria. The first reported case of ACE inhibitor-induced pancreatitis was seen with enalapril.[135] In addition to enalapril,[13,14,136,137] there have been case reports of other ACE inhibitors associated with pancreatitis, including captopril,[138,139] lisinopril,[15,16,140-143] quinapril,[144] ramipril[17,145] and perindopril.[146] In one case-control study, the use of ACE inhibitors was associated with an increased risk of acute pancreatitis, with an odds ratio of 1.5. The risk increased with higher daily doses and was highest during the first 6 months of therapy.[147] At least two well documented cases of enalapril-induced acute pancreatitis recurring with rechallenge have been reported.[13,14] The dosage of enalapril was 10–20 mg/day. Latency between initiating enalapril and onset of pancreatitis ranged from 5 weeks to 1 year, with positive rechallenge occurring within 6 hours to 10 days. Cases of recurrent pancreatitis with lisinopril[16] and ramipril [17] have also been reported. In general, most cases of ACE inhibitor-induced pancreatitis occur early after initiating the medication. The majority of case reports had a mild outcome with rapid resolution upon discontinuing the ACE inhibitor. However, severe cases associated with use of enalapril,[13,137] ramipril[145] and lisinopril[141] have also been reported.

Angiotensin receptor antagonists, which have an improved adverse effect profile compared with ACE inhibitors, have also been associated with pancreatitis.[18,19,148] Two cases involving the use of losartan with rechallenges have been published.[18,19] In each case, the dosage was 50 mg daily, with a latency of 3 and 7 days before the onset of pancreatitis and subsequent withdrawal of the drug. Upon rechallenge, recurrent pancreatitis occurred within 1–3 days. Both cases of pancreatitis were mild. Interestingly, in one case report enalapril had been discontinued due to pancreatitis, before losartan was started. The patient subsequently developed pancreatitis twice with losartan,[19] which is suggestive of a class effect.

One proposed mechanism of action of ACE inhibitor-associated pancreatitis is angioedema of the pancreatic duct secondary to interference with the kallikrein-kinin system, causing decreased degradation of kinins. However, angiotensin receptor antagonists do not directly interact with the kallikrein-kinin system[149] and their mechanism of action in causing pancreatitis is not known. The pancreatic microcirculation and ductal anion secretion are influenced in a paracrine or autocrine way by the pancreatic renin-angiotensin system.[150] ACE inhibitors and angiotensin receptor blockers may disrupt the physiology of this system, causing pancreatitis.[14] There is no evidence that ACE inhibitor or angiotensin receptor blocker-induced pancreatitis is a class effect. However, once a patient develops pancreatitis secondary to one of these medications, rechallenge should not be attempted. Though pancreatitis is presently regarded as a rare adverse effect of these medications, the number of cases is likely to increase, given their increasing use in medicine.

6.2 HMG-CoA Reductase Inhibitors

HMG-CoA reductase inhibitors ('statins'), are the first-line medications prescribed for the treatment of dyslipidaemia. Acute pancreatitis has been reported with simvastatin,[27,28,151,152] fluvastatin,[30] atorvastatin,[153-155] rosuvastatin,[155] lovastatin[156,157] and pravastatin.[29,158] There have been over 53 case reports of pancreatitis following use of statins.[159] Based on a review of observational stud-

ies on statin use[5,160] and development of pancreatitis, an odds ratio of 1.41 was calculated for patients who had used statins in the past year.[159] Two case reports with well documented rechallenges have been published. [27,29] With pravastatin, the patient developed a mild case of pancreatitis after taking pravastatin 20 mg for 6 months. Within 3 days of a rechallenge with 40 mg daily, the patient developed a recurrent mild episode of pancreatitis.[29] Similarly, a patient developed pancreatitis after taking simvastatin 20 mg daily for 6 months. Symptoms improved promptly upon discontinuation, but recurred within 7 days of restarting simvastatin. The second episode was more severe than the first.[27] The large majority of cases reported in the literature have been mild.[155]

The strategy of using lower doses of statins to prevent or reduce the severity of adverse reactions is not likely to prevent pancreatitis, as this has been shown to occur at either low or high dosages. The duration of treatment is likely to be more important in the development of pancreatitis than the dose.[159] Pancreatitis rarely occurs early in the course of treatment, with the risk being the lowest during the first 3 months of therapy.[160] Statin-induced pancreatitis may be a class effect, as one study showed recurrent pancreatitis despite switching statins.[155] The mechanism of statin-induced pancreatitis is not known, though drug interactions are thought to play a role.[16] Clinicians should keep the possibility of statin-induced pancreatitis in mind when evaluating a patient on these medications who develops abdominal pain of unknown aetiology. As the use of statins continues to increase, the adverse effect of acute pancreatitis may be detected more frequently.

6.3 Tetracycline

Tetracycline was initially noted to be associated with pancreatitis in patients with acute fatty liver of pregnancy.[161] Similar reports of tetracycline-associated fatty liver disease with pancreatic dysfunction, particularly with large intravenous doses, have been described in both pregnant and non-pregnant women.[162-165] However, there have been no reports of intravenous tetracycline-induced pancreatitis in the absence of liver disease.

Cases of oral tetracycline-induced pancreatitis without liver disease have been reported in the setting of young patients being treated for non-gonococcal urethritis or facial acne.[32,33,166] Two of the cases had documented rechallenges.[32,33] The dosages ranged from 1 to 2 g daily. Latencies ranged from 5 days to 2 months, with recurrent pancreatitis upon rechallenge seen within 4 days to 3 months. All cases of pancreatitis were mild. One review of drug-induced pancreatitis suggested the mechanism of action involved the accumulation of a toxic metabolite,[167] though no metabolite has been identified to date. It is also unclear if the related antibiotics, minocycline and doxycycline, are associated with a similar adverse effect.

6.4 Metronidazole

Metronidazole was first introduced in 1959. It has been used for various gynaecological and parasitic infections, amoebiasis, pseudomembranous colitis, *Helicobacter pylori* infections, anaerobic bacterial infections, and Crohn's disease. There have been nine case reports of metronidazole-induced pancreatitis.[34,35,130,168-173] One study estimated the statistical occurrence rate of metronidazole-induced pancreatitis requiring hospitalization was 3.9/10 000 prescriptions, or 4.6/10 000 recipients.[174] The diagnosis of mild cases not requiring hospitalization is difficult to make, as nausea, vomiting and abdominal cramping are known adverse effects of metronidazole. There have been two well documented cases of metronidazole-induced pancreatitis with positive rechallenge.[34,35] In one case the patient was inadvertently prescribed metronidazole three times, and subsequently developed mild pancreatitis each time, within 12–24 hours of ingestion.[35] In the second case, a patient developed mild pancreatitis four times, within 3–7 days of ingesting metronidazole. The dosage in both of these studies was 250 mg three times daily. All cases in the literature have shown a mild and self-limiting course. Interestingly, all except one of the cases reported have involved females.[173] None of the reported cases in the literature have been associated with eosinophilia or drug rash. The mechanism of action of metronidazole-induced pancreatitis is unknown, though metronidazole is known to diffuse into the pancreas,[175] suggesting a possible direct toxic effect of free radicals on pancreatic secretory cells.[34,170] The clinician should be well aware of this potential adverse reac-

tion to metronidazole, given its increasing use in treating *Clostridium difficile* colitis.

6.5 Isoniazid

Isoniazid is the treatment of choice for chemoprophylaxis and part of the first-line treatment for tuberculosis. Isoniazid-induced pancreatitis was first reported in 1975,[176] and there have been seven additional case reports in the literature,[50-53,177-179] some with well documented rechallenge.[50-53] The dosage most commonly associated with pancreatitis is 300 mg/day, though pancreatitis with 200 mg/day has also been seen. In these case reports, latency from initiation of isoniazid to development of pancreatitis ranged from 11 to 21 days. After rechallenge, pancreatitis recurred from 6 hours to 21 days. Pancreatitis secondary to isoniazid is likely to be a hypersensitivity reaction.[51] Most cases of isoniazid-induced pancreatitis have a mild outcome. It should be noted that pancreatitis occurring during the treatment of tuberculosis is often attributed to rifampicin[180,181] or antiretroviral drugs,[181] leading to discontinuation of these drugs instead of isoniazid. Therefore, it is important to recognize isoniazid as a potential cause of pancreatitis.

6.6 Pentavalent Antimony (Sodium Stibogluconate and Meglumine Antimonate)

Pentavalent antimonial drugs, sodium stibogluconate and meglumine antimonate are commonly used to treat leishmaniasis. The first reports of sodium stibogluconate- and meglumine antimonate-associated pancreatitis were in 1979[182] and 1993,[67] respectively. Pancreatitis associated with use of pentavalent antimonial drugs is the fourth most reported example of drug-induced pancreatitis in the literature.[10] Many reports have involved renal transplant patients or patients with HIV infection, though a large percentage of cases have also occurred in otherwise healthy patients with leishmaniasis.[66,183-186] Two well documented cases with rechallenge have been reported.[66,67] The dosage of each antimonial was 20 mg/kg/day. Latency between initiation of drug and onset of clinical pancreatitis ranged from 3 to 7 days in each of these cases. Recurrence upon rechallenge occurred in 4 days in both cases. The majority of cases reported in the literature were mild, although reports of severe forms have been published.[182,187,188]

In one study, 98% of patients developed elevated amylase and lipase during treatment with stibogluconate, with almost 50% developing clinical symptoms of pancreatitis. However, the majority of patients were able to continue the medication to completion of therapy,[66] a phenomenon that was noted in other reported cases as well.[183,184] This suggests that in otherwise healthy patients who are asymptomatic, sodium stibogluconate may be continued, while monitoring amylase and lipase levels and noting any clinical signs or symptoms of pancreatitis. If amylase or lipase levels increase rapidly, or if patients develop abdominal pain typical of pancreatitis, the medication should be stopped. Once symptoms improve and serum amylase and lipase levels decrease, a rechallenge has been proposed.[66] One study suggested a shorter course of therapy may be as effective and less toxic in treating cutaneous leishmaniasis.[186] However, given the availability of alternative drugs to treat leishmaniasis – such as amphotericin B, allopurinol in combination with ketoconazole, paramomycin and miltefosine – selection of one of these agents would be a more appropriate choice, especially given the high rates of resistance to antimonials in certain regions of the world, including North West India, Bangladesh, Brazil and Sudan.[189]

6.7 Azathioprine and Mercaptopurine

The first reports of azathioprine-induced pancreatitis were seen in renal transplant patients.[190] Since then, both azathioprine and its metabolite mercaptopurine have been frequently associated with pancreatitis. Over 86 cases of azathioprine-induced pancreatitis and 59 cases of mercaptopurine-induced pancreatitis have been reported in the literature.[10] The majority of cases have been reported in patients with inflammatory bowel disease.[69-72,191-196] Azathioprine-induced pancreatitis was first seen in patients with Crohn's disease in 1972.[191] In the National Cooperative Crohn's Disease Study, 5% of patients treated with azathioprine developed pancreatitis, all within 21 days of initiating the medication.[192] In a study of mercaptopurine for the treatment of inflammatory bowel disease, 3%

of patients developed pancreatitis. All but one of the cases occurred within 2 weeks of initiating the drug. Seven patients were rechallenged, including some patients with one-eighth the usual dose, or 6 mg, and all developed recurrent pancreatitis within hours to 2 weeks.[194]

The strongest case reports for a link between these related immunomodulator medications and pancreatitis were seen in those with a documented rechallenge.[69-72] The doses varied from 50 to 150 mg daily. Latency from ingestion of medication to development of pancreatitis ranged from 3 to 4 weeks, with recurrence of pancreatitis after rechallenge occurring within hours to 2 days. All cases were mild, with recovery times of 1–11 days. The rapidity of recurrent pancreatitis suggests that the mechanism of toxicity is likely an idiosyncratic reaction. It may be immunological, or possibly metabolic, such as by inhibiting the intracellular mechanisms involved in acinar cell secretion. Azathioprine and mercaptopurine should not be reintroduced once the patient develops pancreatitis as an adverse effect, assuming that all other likely causes have been ruled out. Desensitization has been unsuccessful.[194]

6.8 5-Aminosalicylic Acid Drugs

5-Aminosalicylic acid (5-ASA) drugs are commonly used in the treatment of inflammatory bowel disease. All formulations of 5-ASA drugs have been implicated in pancreatitis, including sulfasalazine,[78,197-199] olsalazine,[77,200] mesalazine[73-76] and mesalazine enema.[201] There have been at least 59 reported cases in the literature,[10] and a few well documented case reports with rechallenge.[73,74,76,77] The dosages of 5-ASA have ranged from mesalazine 1.2–2.4 g/day to olsalazine 1.5 g/day. The latency period between initiating the medication and development of pancreatitis has ranged from 2 days to 1 month, though in one report the patient had been taking mesalazine for 1 year.[76] After rechallenge, pancreatitis recurred in 12–48 hours, suggesting a hypersensitivity reaction. However, there have been reports of pancreatitis following long-term treatment with 5-ASA drugs.[76,202]

Mesalazine seems more likely than sulfasalazine to cause acute pancreatitis.[8,203] A proposed mechanism is that there is a small amount of systemic absorption of 5-ASA, which may have a direct effect of increasing pancreatic duct permeability.[204] Switching between sulfasalazine and other 5-ASA formulations does not prevent recurrent pancreatitis from developing.[77,205]

6.9 Valproic Acid

Valproic acid is used for various types of epilepsy, bipolar disorder, neuropathic pain, and migraine prophylaxis. The first reported case of valproic acid-induced pancreatitis was in 1979,[206] and over 80 cases have been reported since then in the literature.[10] The paediatric population accounts for 75% of reported cases,[11] a population in which pancreatitis is otherwise rare. Three well documented case reports with rechallenge data have been published.[79-81] Dosages were 1.5–2 g daily. Latency ranged from 3 months to 17 months, with recurrent pancreatitis upon rechallenge in 6–12 weeks. There have been some reported cases of pancreatitis occurring after many years of valproic acid therapy.[207,208] Pancreatitis is usually mild, but severe cases have been reported.[79,80,131,209-214] In one study of valproic acid-induced pancreatitis in children aged 4–16 years, children who had a history of drug allergies with skin rash were at increased risk, whereas duration of treatment, serum valproic acid levels, and presence of concomitant antiepileptic drugs were not considered risk factors.[215] The serum lipase level may be more sensitive than the serum amylase level, and should be obtained when pancreatitis is suspected secondary to valproic acid.[216] The long latency for recurrence in most studies suggests the accumulation of a toxic metabolite.

6.10 Estrogens

Estrogen-induced pancreatitis was first reported in 1970.[91] Many case reports with a variety of estrogen preparations have been reported since, including both estrogens alone and in combination oral contraceptives.[92,93,96,217-225] Pancreatitis has been seen when estrogen has been used for birth control, postmenopausal symptoms, hormone replacement therapy, menstrual irregularities, and after prostatectomy for carcinoma.[6] Estrogen-induced pancreatitis is an important adverse reaction to identify, as estrogens are among the most commonly prescribed medications.[10] There have been

at least four case reports with documented rechallenges.[91-93,96] The particular doses of the estrogen-containing drugs causing pancreatitis vary, depending on the formulation. Latencies range from 2 months to 5 years after initiating the drug, with most cases seen within 3 months.[219] Recurrent pancreatitis after rechallenge typically occurs within 2–4 months. Most cases reported in the literature have been mild, with recovery within 2 weeks,[93] though severe cases have also been reported.[92,221,225]

The mechanism of estrogen-induced pancreatitis is thought to be linked with the hypertriglyceridaemic effect of estrogen. Hypertriglyceridaemia is known to occur with estrogen use, especially in patients with underlying hyperlipoproteinemia type I, IV or V,[91,92,217,218,226] with more significant elevations in women aged over 40 years[227] and with higher doses of estrogen.[228] Pancreatitis typically occurs when triglyceride levels exceed 1000 mg/dL.[11] It should be kept in mind that serum amylase levels may be normal in the setting of high levels of triglycerides. One author suggested that serum triglyceride levels should be checked before starting therapy and the administration of estrogen avoided if the levels are >200 mg/dL, especially in women over the age of 40 years. Once therapy has begun, serum lipids should be checked routinely.[93] If a patient receiving estrogen therapy develops pancreatitis, a serum lipoprotein electrophoresis may help to establish estrogen as the causative factor. Estrogen therapy should be discontinued immediately. This should lead to decreased serum triglycerides and promote recovery from pancreatitis.[92,218] In addition to discontinuing the estrogen compound, other measures should be instituted to lower triglyceride levels, including a low fat diet, gemfibrozil (1.2–1.5 g/day) and use of omega-3 fatty acids (4–15 g/day).[223] Interestingly, estrogen-induced pancreatitis has also been reported to occur in the absence of hypertriglyceridaemia.[96] A proposed mechanism is the development of intravascular thrombosis secondary to a hypercoagulable state induced by estrogen.[221]

6.11 Codeine

Codeine is widely used in prescription and over-the-counter preparations as an analgesic and as a cough suppressant. There have been a small number of reports of opiate-induced pancreatitis in the literature,[117,131,229-231] with two cases reporting well documented rechallenge with codeine.[117] The dosage of codeine ranged from 40 to 60 mg daily, and onset of mild pancreatitis was seen within 1.5–3 hours after ingestion. Codeine was discontinued, with rapid recovery in each case. Upon rechallenge, pancreatitis recurred within 1–2 hours. Interestingly, all patients had a prior cholecystectomy. The mechanism of action is likely to be sphincter of Oddi constriction. Opiates are known to cause a rapid but transient spasm of the sphincter, which can last for 2 hours.[232,233] Furthermore, laboratory studies have demonstrated a mild, transient hyperamylasemia following opiate administration.[234] It has been suggested that in post-cholecystectomy patients, an exacerbated spasm in the sphincter of Oddi and reduced bile storage capacity in the biliary tract can initiate an episode of acute pancreatitis.[117]

6.12 Sulindac

Sulindac, introduced in 1978, is an NSAID used in rheumatic diseases. It has been associated with various gastrointestinal adverse effects including abdominal pain, dyspepsia, nausea and constipation. Pancreatitis as an adverse effect has also been reported.[1,118-120,131,235-239] Three cases with well documented rechallenge have been reported[118-120] In these cases, the dosage of sulindac ranged from 300 to 800 mg daily and the latency between ingestion of sulindac and time to onset of pancreatitis ranged from 3 weeks to 5 years. Pancreatitis following rechallenge with sulindac occurred within 1–2 months. The mechanism of action of sulindac-induced pancreatitis is unclear. One proposed mechanism is an immunological idiosyncratic reaction to the active metabolite of sulindac, which is absorbed by the bile duct epithelium and leads to cholangitis.[238] In contrast to sulindac, other NSAIDs have not been consistently demonstrated to be associated with pancreatitis.

7. Conclusion

There are a number of drugs that have been reported in the literature to be causally associated with acute pancreatitis. Though most cases of possible drug-induced pancreatitis are mild, some have

been severe or even fatal. The true magnitude of drug-induced pancreatitis is not known and will require an active assessment for this adverse effect in future drug trials. Confounding factors such as alcohol use or gallstone disease, multiple medications, and underlying medical illnesses associated with pancreatitis, such as advanced HIV infection and inflammatory bowel disease, also make it difficult to determine the true epidemiology. Future studies on drug-induced pancreatitis should aim to identify which subsets of patients are susceptible to pancreatitis as an adverse effect associated with particular drugs, and the mechanisms that lead to pancreatitis.

A more formal system of reporting potential cases of drug-induced pancreatitis is needed. Ideally, case reports should: (i) provide the age and sex of the patient, along with the indication for treatment with a drug; (ii) provide the dose and frequency of the medication; (iii) document a definite case of pancreatitis based on current diagnostic guidelines; (iv) provide information on the time course between initiation of drug and onset of pancreatitis; (v) exclude the most common causes of pancreatitis; (vi) document a positive response to withdrawal of medication; and (vii) if available, provide the response to a rechallenge. In addition, such cases should be consistently reported to the appropriate drug regulatory agencies and published in the medical literature. Continued reporting will serve to increase awareness of the risks of pancreatitis with various drugs so that immediate recognition and management can be instituted.

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References

1. Banks PA, Freeman ML. Practice guidelines in acute pancreatitis. Am J Gastroenterol 2006; 101: 2379-400
2. Pandol SJ, Saluja AK, Imrie CW. Acute pancreatitis: bench to the bedside. Gastroenterology 2007; 132: 1127-51
3. Johnston DH, Cornish A. Acute pancreatitis in patients receiving chlorothiazide. JAMA 1959; 170: 2054-6
4. Zion MM, Goldberg B, Suzman MM. Corticotrophin and cortisone in the treatment of scleroderma [letter]. Q J Med 1955; 24: 215
5. Lancashire RJ, Cheng K, Langman MJ. Discrepancies between population-based data and adverse reaction reports in assessing drugs as causes of acute pancreatitis. Aliment Pharmacol Ther 2003; 17: 887-93
6. Mallory A, Kern F. Drug induced pancreatitis: a critical review. Gastroenterology 1980; 78: 813-20
7. Underwood TW, Frye CB. Drug-induced pancreatitis. Clin Pharm 1993; 12: 440-8
8. McArthur KE. Drug-induced pancreatitis. Aliment Pharmacol Ther 1996; 10: 23-38
9. Wilmink T, Frick TW. Drug-induced pancreatitis. Drug Saf 1996; 14: 406-23
10. Trivedi CD, Pitchumoni CS. Drug-induced pancreatitis: an update. J Clin Gastroenterol 2005; 39: 709-16
11. Badalov N, Baradarian R, Iswara K, et al. Drug-induced acute pancreatitis: an evidence-based review. Clin Gastroenterol Hepatol 2007; 5: 648-61
12. Dhir R, Brown DK, Olden KW. Drug-induced pancreatitis: a practical review. Drugs Today 2007; 43: 499-07
13. Maringhini A, Termini A, Patti R, et al. Enalapril-associated pancreatitis: recurrence after rechallenge. Am J Gastroenterol 1997; 92: 166-7
14. Carnovale A, Esposito P, Bassano P, et al. Enalapril-induced acute recurrent pancreatitis. Dig Liver Dis 2003; 35: 55-7
15. Gershon T, Olshaker JS. Acute pancreatitis following lisinopril rechallenge. Am J Emerg Med 1998; 16: 523-4
16. Kanbay M, Selcuk H, Yilmaz U. Recurrent acute pancreatitis secondary to lisinopril. South Med J 2006; 99: 1388-9
17. Kanbay M, Korkmaz M, Yilmaz U, et al. Acute pancreatitis due to ramipril therapy. Postgrad Med J 2004; 80: 617-8
18. Bosch X. Losartan-induced acute pancreatitis. Ann Intern Med 1997; 127: 1043-4
19. Birck R, Keim V, Fiedler F, et al. Pancreatitis after losartan [letter]. Lancet 1998; 351: 1178
20. Van der Heide H, Ten Haaft MA, Stricker BH. Pancreatitis caused by methyldopa. BMJ (Clin Res Ed) 1981; 282: 1930-1
21. Rominger JM. Gutierrez JG. Curtis D, et al. Methyldopa-induced pancreatitis. Am J Dig Dis 1978; 23: 756-8
22. Jones PE. Oelbaum MH. Furosemide induced pancreatitis. BMJ 1975; 1: 133-4
23. Juang P, Page RL, Zolty R. Probable loop diuretic-induced pancreatitis in a sulfonamide-allergic patient. Ann Pharmacother 2006; 40: 128-34
24. Cornish AL, McClellan JT, Johnston DH. Effects of chlorothiazide on the pancreas. N Engl J Med 1961; 265: 673-5
25. Rion RJ. Recurrent pancreatitis after treatment with hydrochlorothiazide. J Am Board Fam Pract 1994; 7: 74-6
26. Bosch X, Bernadich O. Acute pancreatitis during treatment with amiodarone [letter]. Lancet 1997; 350: 1300
27. Ceciliato R, Pezzilli R, Corinaldesi R, et al. Acute pancreatitis due to simvastatin therapy: increased severity after rechallenge. Dig Liver Dis 2004; 36: 639-40
28. Johnson JL, Loomis IB. A case of simvastatin-associated pancreatitis and review of statin-associated pancreatitis. Pharmacotherapy 2006; 26: 414-22
29. Anagnostopoulos GK, Tsiakos S, Margantinis G, et al. Acute pancreatitis due to pravastatin therapy. JOP 2003; 4: 129-32
30. Tysk C, Al-Eryani AY, Shawabkeh AA. Acute pancreatitis induced by fluvastatin therapy. J Clin Gastroenterol 2002; 35: 406-8
31. Gang N, Langevitz P, Livneh A. Relapsing acute pancreatitis induced by re-exposure to the cholesterol lowering agent bezafibrate. Am J Gastroenterol 1999; 94: 3626-8
32. Elmore MF, Rogge JD. Tetracycline-induced pancreatitis. Gastroenterology 1981; 81: 1134-6
33. Torosis J, Vender R. Tetracycline-induced acute pancreatitis. J Clin Gastroenterol 1987; 9: 580-1
34. Sanford KA, Mayle JE, Dean HA, et al. Metronidazole-associated pancreatitis. Ann Intern Med 1988; 109: 756-7

35. Celifarco A, Warschauer C, Burakoff R. Metronidazole induced pancreatitis. Am J Gastroenterol 1989; 84: 958-63
36. Jha SH, Reddy JA, Dave JK. Dapsone-induced acute pancreatitis. Ann Pharmacother 2003; 37: 1438-40
37. Antonow DR. Acute pancreatitis associated with trimethoprim-sulfamethoxazole. Ann Intern Med 1986; 104: 363-5
38. Versleijen MW, Naber AH, Riksen NP, et al. Recurrent pancreatitis after trimethoprim-sulfamethoxazole rechallenge. Neth J Med 2005; 63: 275-7
39. Nelis GF. Nitrofurantoin-induced pancreatitis: report of a case. Gastroenterology 1983; 84: 1032-4
40. Christophe JL. Pancreatitis induced by nitrofurantoin. Gut 1994; 35: 712-3
41. Liviu L, Yair L, Yehuda S. Pancreatitis induced by clarithromycin. Ann Intern Med 1996; 125: 701
42. Schouwenberg BJ, Deinum J. Acute pancreatitis after a course of clarithromycin. Neth J Med 2003; 61: 266-7
43. Gonzalez Carro P, Perez Roldan F, Legaz Huidobro ML, et al. Acute pancreatitis and modified-release clarithromycin. Ann Pharmacother 2004; 38: 508-9
44. Trimble GX. Acute pancreatitis induced by erythromycin. Am J Med 1989; 87: 701
45. Hawksworth CR. Acute pancreatitis associated with infusion of erythromycin lactobionate [letter]. BMJ 1989; 298: 190
46. Gumaste VV. Erythromycin-induced pancreatitis [letter]. Am J Med 1989; 86: 725
47. Berger TM, Cook WJ, O'Marcaigh AS, et al. Acute pancreatitis in a 12-year-old girl after an erythromycin overdose. Pediatrics 1992; 90: 624-6
48. Fang CC, Wang HP, Lin JT. Erythromycin-induced acute pancreatitis. J Toxicol Clin Toxicol 1996; 34: 93-5
49. Tenenbein MS, Tenenbein M. Acute pancreatitis due to erythromycin overdose. Pediatr Emerg Care 2005; 21: 675-6
50. Chan KL, Chan HS, Lui SF, et al. Recurrent acute pancreatitis induced by isoniazid. Tuber Lung Dis 1994; 75: 383-5
51. Rabassa A, Trey G, Shukla U, et al. Isoniazid-induced pancreatitis. Ann Intern Med 1994; 121: 433-4
52. Stephenson I, Wiselka MJ, Qualie MJ. Acute pancreatitis induced by isoniazid in the treatment of tuberculosis. Am J Gastroenterol 2001; 96: 2271-2
53. Chow KM, Szeto CC, Leung CB, et al. Recurrent acute pancreatitis after isoniazid. Neth J Med 2004; 62: 172-4
54. Di Martino V, Ezenfis J, Benhamou Y, et al. Severe acute pancreatitis related to the use of nelfinavir in HIV infection: report of a case with positive rechallenge. AIDS 1999; 13: 1421-3
55. Soylu AR, Dokmeci G, Tezel A, et al. Lamivudine-induced acute pancreatitis in a patient with decompensated Hbv-related chronic liver disease [letter]. J Clin Gastroenterol 2004; 38: 134
56. Seidlin M, Lambert JS, Dolin R, et al. Pancreatitis and pancreatic dysfunction in patients taking dideoxyinosine. AIDS 1992; 6: 831-5
57. Maxson CJ, Greenfield SM, Turner JL. Acute pancreatitis as a common complication of 2′,3′-dideoxyinosine therapy in the acquired immunodeficiency syndrome. Am J Gastroenterol 1992; 87: 708-13
58. Eland IA, Rasch MC, Sturkenboom MJ, et al. Acute pancreatitis attributed to the use of interferon alfa-2b. Gastroenterology 2000; 119: 230-3
59. Tannir NM, Talpaz M, Ghazal H, et al. Acute pancreatitis associated with interferon alpha therapy for chronic myelogenous leukemia. Leuk Lymphoma 2000; 39: 647-50
60. Cecchi E, Forte P, Cini E, et al. Pancreatitis induced by pegylated interferon alfa 2b in a patient affected by chronic hepatitis C. Emerg Med Aust 2004; 16: 473-5
61. Chaudhari S, Park J, Anand BS, et al. Acute pancreatitis associated with interferon and ribavirin therapy in patients with chronic hepatitis C. Dig Dis Sci 2004; 49: 1000-6
62. Tahan V, Tahan G, Dane F, et al. Acute pancreatitis attributed to the use of pegylated interferon in a patient with chronic hepatitis C. J Gastrointestin Liver Dis 2007; 16: 224-5
63. Ozdogan O, Tahan V, Cincin A, et al. Acute pancreatitis associated with the use of peginterferon. Pancreas 2007; 34: 485-7
64. Murphey SA. Josephs AS. Acute pancreatitis associated with pentamidine therapy. Arch Intern Med 1981; 141: 56-8
65. Murphy RL, Noskin GA, Ehrenpreis ED. Acute pancreatitis associated with aerosolized pentamidine. Am J Med 1990; 88 (Suppl. 5N): 53N-6N
66. Gasser RA, Magill AJ, Oster CN, et al. Pancreatitis induced by pentavalent antimonials agents during treatment of Leishmaniasis. Clin Infec Dis 1993; 16: 83-90
67. de Lalla F, Pellizzer G, Gradoni L, et al. Acute pancreatitis associated with the administration of meglumine antimoniate for the treatment of visceral leishmaniasis. Clin Infect Dis 1993; 16: 730-1
68. Youssef SS, Iskandar SB, Scruggs J, et al. Acute pancreatitis associated with omeprazole. Int J Clin Pharmacol Ther 2005; 43: 558-61
69. Kawanishi H, Rudolph E, Bull FE. Azathioprine-induced acute pancreatitis [letter]. N Engl J Med 1973; 289: 357
70. Paloyan D, Levin B, Simonowitz D. Azathioprine associated acute pancreatitis. Dig Dis 1977; 22: 839-46
71. Guillaume P, Grandjean E, Male RJ. Azathioprine associated acute pancreatitis in the course of chronic active hepatitis. Dig Dis Sci 1984; 29: 78-80
72. Cappell MS, Das KM. Rapid development of pancreatitis following reuse of 6-mercaptopurine. J Clin Gastroenterol 1989; 11: 679-81
73. Sachedina B, Saibil F, Choen LB, et al. Acute pancreatitis due to 5-aminosaliscylate. Ann Intern Med 1989; 110: 490-2
74. Deprez P. Descamps C. Fiasse R. Pancreatitis induced by 5-aminosalicylic acid. Lancet 1989; 2 (8660): 445-6
75. Erdkamp F, Houben M, Ackerman E, et al. Pancreatitis induced by mesalazine. Neth J Med 1992; 41: 71-2
76. Toubanakis C, Batziou E, Galanopoulos G, et al. Acute pancreatitis after long term therapy with mesalazine, and hyperamylasemia associated with azathioprine in a patient with ulcerative colitis. Eur J Gastroenterol Hepatol 2003; 15: 933-4
77. Poldermans D, van Blankenstein M. Pancreatitis induced by disodium azodisalicylate. Am J Gastroenterol 1998; 83: 578-80
78. Suryapranata H, deVries H. Pancreatitis associated with sulfasalazine [letter]. BMJ 1986; 292: 732
79. Camfield PR. Pancreatitis due to valproic acid. Lancet 1979; i: 1198-9
80. Coulter DL, Allen RJ. Pancreatitis associated with valproic acid therapy for epilepsy [letter]. Ann Neurol 1980; 7: 92
81. Fecik SE, Stoner SC, Raphael J, et al. Recurrent acute pancreatitis associated with valproic acid use for mood stabilization. J Clin Psychopharmacol 1999; 19: 483-4
82. Koller EA, Cross JT, Doraiswamy PM, et al. Pancreatitis associated with atypical antipsychotics: from the Food and Drug Administration's MedWatch surveillance system and published reports. Pharmacotherapy 2003; 23: 1123-30
83. Bayard JM, Descamps OS, Evrard S, et al. Case report: acute pancreatitis induced by clozapine. Acta Gastroenterol Belg 2005; 68: 92-4
84. Wehmeier PM, Heiser P, Remschmidt H. Pancreatitis followed by pericardial effusion in an adolescent treated with clozapine. J Clin Psychopharmacol 2003; 23: 102-3
85. Garlipp P, Rosenthal O, Haltenhof H, et al. The development of a clinical syndrome of asymptomatic pancreatitis and eosi-

nophilia after treatment with clozapine in schizophrenia: implications for clinical care, recognition and management. J Clin Psychopharmacol 2002; 16: 399-400
86. Cerulli TR. Clozapine-associated pancreatitis. Harv Rev Psychiatr 1999; 7: 61-3
87. Bergemann N, Ehrig C, Diebold K. Asymptomatic pancreatitis associated with clozapine. Pharmacopsychiatry 1999; 32: 78-80
88. Gatto EM, Castronuovo AP, Uribe Roca MC. Clozapine and pancreatitis [letter]. Clin Neuropharmacol 1998; 21: 203
89. Jubert P, Fernandez R, Ruiz A. Clozapine-related pancreatitis. Ann Int Med 1994; 121: 722-3
90. Martin A. Acute pancreatitis associated with clozapine use [letter]. Am J Psychiatry 1992; 149: 714
91. Banks S, Marks IN. Hyperlipemic pancreatitis and the pill. Postgrad Med J 1970; 46: 576-88
92. Davidoff F, Tishler S, Rosoff C. Marked hyperlipidemia and pancreatitis associated with oral contraceptive therapy. N Engl J Med 1973; 289: 552-5
93. Parker W. Estrogen-induced pancreatitis. Clin Pharm 1983; 2: 75-9
94. Castro MR, Nguyen TT, O'Brien T. Clomiphene-induced severe hypertriglyceridemia and pancreatitis. Mayo Clin Proc 1999; 74: 1125-8
95. Keskin M, Songur Y, Isler M. Clomiphene-induced acute pancreatitis without hypertriglyceridemia. Am J Med Sci 2007; 333: 194-6
96. Blake WE, Pitcher ME. Estrogen-related pancreatitis in the setting of normal plasma lipids [case report]. Menopause 2003; 10: 99-101
97. Alagozlu H, Cindoruk M, Unal S. Tamoxifen-induced severe hypertriglyceridemia and acute pancreatitis. Clin Drug Investig 2006; 26: 297-302
98. Lin HH, Hsu CH, Chao YC. Tamoxifen-induced severe acute pancreatitis [a case report]. Dig Dis Sci 2004; 49: 997-9
99. Artac M, Sari R, Altunbas H, et al. Asymptomatic acute pancreatitis due to tamoxifen-induced severe hypertriglyceridemia in a patient with diabetes mellitus and breast cancer. J Chemother 2002; 14: 309-11
100. Noguchi M, Taniya T, Tajiri K, et al. Fatal hyperlipaemia in a case of metastatic breast cancer treated by tamoxifen. Br J Surg 1987; 74: 586-7
101. Collis BM, George PM. Severe hypertriglyceridemia and hypercholesterolemia associated with tamoxifen use. Clin Oncol 1998; 10: 270-1
102. Elisaf MS, Nakou K, Liamis G, et al. Tamoxifen-induced severe hypertriglyceridemia and pancreatitis. Ann Oncol 2000; 11: 1067-9
103. Taguchi M, Yokota M, Koyano H, et al. Acute pancreatitis and parotitis induced by methimazole in a patient with Graves' disease. Clin Endocrinol 1999; 51: 667-70
104. Marazuela M, Sanchez de Paco G, Jimenez I, et al. Acute pancreatitis, hepatic cholestasis, and erythema nodosum induced by carbimazole treatment for Graves' disease. Endocr J 2002; 49: 315-8
105. Izraeli S, Adamson PC, Blaney SM, et al. Acute pancreatitis after ifosfamide therapy. Cancer 1994; 74: 1627-8
106. Altman AJ, Dinndorf P, Quinn JJ. Acute pancreatitis in association with cytosine arabinoside therapy. Cancer 1982; 49: 1384-6
107. McBride CE, Yavorski RT, Moses FM, et al. Acute pancreatitis associated with continuous infusion cytarabine therapy: a case report. Cancer 1996; 77: 2588-91
108. McGrail LH, Sehn LH, Weiss RB, et al. Pancreatitis during therapy of acute myeloid leukemia: cytarabine related? Ann Oncol 1999; 10: 1373-6
109. Shaw MT, Barnes CC, Madden FJ, et al. L-asparaginase and pancreatitis [letter]. Lancet 1970; 2: 721
110. Weetman R, Baehner R. Latent onset of clinical pancreatitis in children receiving L-asparaginase therapy. Cancer 1974; 34: 780-5
111. Jain R, Ramanan SV. Iatrogenic pancreatitis: a fatal complication in the induction therapy for acute lymphocytic leukemia [letter]. Arch Intern Med 1978; 138: 1726
112. McLean R, Martin S, Lam-Po-Tang PR. Fatal case of L-asparaginase induced pancreatitis. Lancet 1982; 2 (8312): 1401-2
113. Nguyen DL, Wilson DA, Engelman ED, et al. Serial sonograms to detect pancreatitis in children receiving L-asparaginase. South Med J 1987; 80: 1133-6
114. Alvarez OA, Zimmerman G. Pegasparaginase-induced pancreatitis. Med Pediatr Oncol 2000; 34: 200-5
115. Top PC, Tissing WJ, Kuiper JW, et al. L-asparaginase-induced severe necrotizing pancreatitis successfully treated with percutaneous drainage. Pediatr Blood Cancer 2005; 44: 95-7
116. Knoderer HM, Robarge J. Flockhart DA. Predicting asparaginase-associated pancreatitis. Pediatr Blood Cancer 2007; 49: 634-9
117. Hastier P, Buckley MJM, Peten EP, et al. A new source of drug-induced acute pancreatitis: codeine. Am J Gastroenterol 2000; 95: 3295-8
118. Memon A. Pancreatitis and sulindac. Ann Intern Med 1982; 97: 139
119. Klein SM, Khan MA. Hepatitis, toxic epidermal necrolysis and pancreatitis in association with sulindac. J Rheumatol 1983; 10: 512-3
120. Zygmunt D. Acute pancreatitis with long term sulindac. West J Med 1986; 44: 461-2
121. Wargo KA, Geveden BN, McConnell VJ. Cannabinoid-induced pancreatitis: a case series. JOP 2007; 8: 579-83
122. Grant P, Gandhi P. A case of cannabis-induced pancreatitis. JOP 2004; 5: 41-3
123. Flynn WJ, Freeman PG, Wickholdt LG. Pancreatitis associated with isotretinoin induced hypertriglyceridemia [letter]. Ann Intern Med 1987; 107: 63
124. McCarter TL, Chen YK. Marked hyperlipidemia and pancreatitis associated with isotretinoin therapy. Am J Gastroenterol 1992; 12: 1855-7
125. Jamshidi M, Obermeyer RJ, Govindaraj S, et al. Acute pancreatitis secondary to isotretinoin-induced hyperlipidemia. J Okla State Med Assoc 2002; 95: 79-80
126. Kumar AN, Schwartz DE, Lim KG. Propofol-induced pancreatitis: recurrence of pancreatitis after rechallenge. Chest 1999; 115: 1198-9
127. Thomson S, Hendry W, McFarlane G, et al. Epidemiology and outcome of acute pancreatitis. Br J Surg 1987; 74: 398-401
128. Lankisch PG, Dröge M, Gottesleben F. Drug-induced acute pancreatitis: incidence and severity. Gut 1995; 37: 565-7
129. Werth B, Kuhn M, Hartmann K, et al. Drug-induced pancreatitis: experience of the Swiss Drug Adverse Effects Centre. Schweiz Med Wochenschr 1995; 125: 731-4
130. Eland IA, van Puijenbroek EP, Sturkenboom MJ, et al. Drug-associated acute pancreatitis: twenty-one years of spontaneous reporting in the Netherlands. Am J Gastroenterol 1999; 94: 2417-22
131. Andersen V, Sonne J, Andersen M. Spontaneous reports on drug-induced pancreatitis in Denmark from 1968 to 1999. Eur J Clin Pharmacol 2001; 57: 517-21
132. Dutta SK, Ting CD, Lai LL. Study of prevalence, severity, and etiological factors associated with acute pancreatitis in patients infected with human immunodeficiency virus. Am J Gastroenterol 1997; 92: 2044-8

133. Munk EM, Pedersen L, Floyd A, et al. Inflammatory bowel diseases, 5-aminosalicylic acid and sulfasalazine treatment and risk of acute pancreatitis: a population-based case-control study. Am J Gastroenterol 2004; 99: 884-8
134. Banerjee AK, Patel KJ, Grainger SL. Drug-induced pancreatitis: a critical review. Med Toxicol Adverse Drug Exp 1989; 4: 186-98
135. Tilkemeier P, Thompson P. Acute pancreatitis possibly related to enalapril. N Engl J Med 1988; 318: 275-6
136. Martin T, Taupignon A, Graf E, et al. Pancreatitis and hepatitis in a patient treated with enalapril maleate: a case report. Therapie 1989; 44: 449-50
137. Gonzalez Ramallo VJ, Muino Miguez A, Torres Segovia FJ. Necrotizing pancreatitis and enalapril [letter]. Eur J Med 1992; 1: 123
138. Jeandidier N, Klewansky M, Pinget M. Captopril-induced acute pancreatitis. Diabetes Care 1995; 18: 410-1
139. Iliopoulou A, Giannakopoulous G, Pagoy H, et al. Acute pancreatitis due to captopril treatment. Dig Dis Sci 2001; 46: 1882-3
140. Maliekal J, Drake CF. Acute pancreatitis associated with the use of lisinopril. Ann Pharmacother 1993; 27: 1465-6
141. Standridge JB. Fulminant pancreatitis associated with lisinopril therapy. South Med J 1994; 87: 179-81
142. Marinella MA, Billi JE. Lisinopril therapy associated with acute pancreatitis. West J Med 1995; 163: 77-8
143. Kanbay M, Sekuk H, Yilmaz U, et al. Acute pancreatitis associated with combined lisinopril and atorvastatin therapy. Dig Dis 2005; 23: 92-4
144. Arjomand H, Kemp DG. Quinapril and pancreatitis. Am J Gastroenterol 1999; 94: 290-1
145. Anagnostopoulos GK, Kostopoulos P, Tsiakos S, et al. Fulminant pancreatitis associated with ramipril therapy. Pancreas 2003; 27: 278-9
146. Gallego-Rojo FJ, Gonzalez-Calvin JL, Guilarte J, et al. Perindopril-induced acute pancreatitis. Dig Dis Sci 1997; 42: 1789-91
147. Eland IA, Sundstrom A, Velo GP, et al. Antihypertensive medication and the risk of acute pancreatitis: the European case-control study on drug-induced acute pancreatitis. Scand J Gastroenterol 2006; 41: 1484-90
148. Baffoni L, Durante V, Grossi M. Acute pancreatitis induced by telmisartan overdose [letter]. Ann Pharmacother 2004; 38: 1088
149. Cjaka C, Buclin T, Brunner HR, et al. Pharmacokinetic-pharmacodynamic profile of angiotensin II receptor antagonist. Clin Pharmacokinet 1997; 1: 1-29
150. Leung PS. Local rennin-angiotensin system in the pancreas. JOP J Pancreas (Online) 2001; 2: 3-8 [online]. Available from URL: www.joplink.net [Accessed 2008 Aug 25]
151. McDonald KB, Garber BG, Perreault MM. Pancreatitis associated with simvastatin plus fenofibrate. Ann Pharmacother 2002; 36: 275-9
152. Antonopoulos S, Mikros S, Kokkoris S, et al. A case of acute pancreatitis possibly associated with combined salicylate and simvastatin treatment. JOP 2005; 6: 264-8
153. Miltiadous G, Anthopoulou A, Elisaf M. Acute pancreatitis possibly associated with combined salicylate and atorvastatin. therapy. JOP 2003; 4: 20-1
154. Kanbay M, Sekuk H, Yilmaz U, et al. Acute pancreatitis associated with combined lisinopril and atorvastatin therapy. Dig Dis 2005; 23: 92-4
155. Singh S, Nautiyal A, Dolan JG. Recurrent acute pancreatitis possibly induced by atorvastatin and rosuvastatin: is statin induced pancreatitis a class effect? JOP 2004; 5: 502-4
156. Wong PW, Dillard TA, Kroenke K. Multiple organ toxicity from addition of erythromycin to long-term lovastatin therapy. South Med J 1998; 91: 202-5
157. Abdul-Ghaffar NU, el-Sonbaty MR. Pancreatitis and rhabdomyolysis associated with lovastatin-gemfibrozil therapy. J Clin Gastroenterol 1995; 21: 340-1
158. Tsigrelis C, Pitchumoni CS. Pravastatin: a potential cause for acute pancreatitis. World J Gastroenterol 2006; 12: 7055-7
159. Singh S, Loke YK. Statins and pancreatitis: a systematic review of observational studies and spontaneous case reports. Drug Saf 2006; 29: 1123-32
160. Thisted H, Jacobsen J, Munk EM, et al. Statins and the risk of acute pancreatitis: a population-based case-control study. Aliment Pharmacol Ther 2006; 23: 185-90
161. Ober WB, LeCompte PM. Acute fatty metamorphosis of the liver associated with pregnancy. Am J Med 1955; 19: 743-58
162. Schultz J, Adamson J, Workman W, et al. Fatal liver disease after intravenous administration of tetracycline in high dosage. N Engl J Med 1963; 269: 999-1004
163. Whalley PJ, Adams RH, Combes B. Tetracycline toxicity in pregnancy: liver and pancreatic dysfunction. JAMA 1964; 189: 103-8
164. Kunelis CT, Peters JL, Edmondson HA. Fatty liver of pregnancy and its relationship to tetracycline therapy. Am J Med 1965; 38: 359-77
165. Peters R, Edmondson H, Mikkelsen WP, et al. Tetracycline induced fatty liver in non-pregnant patients: a report of six cases. Am J Surg 1967; 113: 622-32
166. Nicolau DP, Mengedoht DE, Kline JJ. Tetracycline induced pancreatitis. Am J Gastroenterol 1991; 86: 1669-71
167. Steinberg WM. Acute drug and toxin induced pancreatitis. Hosp Pract 1985; 20: 95-102
168. Plotnick BH, Cohen I, Tsang T, et al. Metronidazole-induced pancreatitis. Ann Intern Med 1985; 103: 891-2
169. Corey WA, Doebbeling BN, DeJong KJ, et al. Metronidazole-induced acute pancreatitis. Rev Infect Dis 1991; 13: 1213-5
170. Sura ME, Heinrich KA, Suseno M. Metronidazole-associated pancreatitis. Ann Pharmacother 2000; 34: 1152-5
171. Feola DJ, Thornton AC. Metronidazole-induced pancreatitis in a patient with recurrent vaginal trichomoniasis. Pharmacotherapy 2002; 22: 1508-10
172. Nigwekar SU, Casey KJ. Metronidazole induced pancreatitis: a case report and review of the literature. JOP 2004; 5: 516-9
173. Tsesmeli NE. Giannoulis KE. Savopoulos CG, et al. Acute pancreatitis as a possible consequence of metronidazole during a relapse of ulcerative colitis. Eur J Gastroenterol Hepatol 2007; 19: 805-6
174. Friedman GD, Selby JV. How often does metronidazole induce pancreatitis? Gastroenterology 1990; 98: 1702-3
175. Wallace JR, Cushing RD, Bawdon RE, et al. Assessment of antimicrobial penetrance into the pancreatic juice in humans. Surg Gynecol Obstet 1986; 162: 313-6
176. Kvale PA, Parks RD. Acute abdomen: an usual reaction to isoniazid. Chest 1975; 68: 271-2
177. Mendoza JL, Lana R, Espinos D, et al. Acute pancreatitis induced by isoniazid, a causal association. Ann Med Interne (Paris) 1998; 15: 588-90
178. Izzedine H, Launay-Vachar V, Stomme T, et al. Acute pancreatitis induced by isoniazid. Am J Gastroenterol 2001; 96: 3208-9
179. Jin CF, Sabie R. Isoniazid-induced acute hepatitis and acute pancreatitis in a patient during chemoprophylaxis. J Clin Gastroenterol 2002; 35: 100-1
180. Chan TY. Isoniazid and rifampicin rarely cause acute pancreatitis in patients with tuberculosis [letter]. Int J Clin Pharmacol Ther 1999; 37: 109

181. Mattson K. Side effects of rifampicin: a clinical study. Scand J Respir Dis 1973; 82 Suppl.: 8-52
182. Broeckaert van Orshoven A, Michielsen P, Vandepitte J. Fatal leishmaniasis in a renal transplant recipient. Lancet 1979; ii: 740-1
183. McCarthy A, Keystone J, Kain K. Pancreatitis occurring during therapy with stibogluconate: two case reports. Clin Infect Dis 1993; 17: 952-3
184. Laguna F, Soriano V, Gonzalez-Labor J. Misdiagnosis in patients receiving treatment with pentavalent antimonial patients. Clin Infect Dis 1994; 19: 978-9
185. Aronson NE, Wortmann GW, Johnson SC, et al. Safety and efficacy of intravenous sodium stibogluconate in the treatment of leishmaniasis: recent US military experience. Clin Infect Dis 1998; 27: 1457-64
186. Wortmann G, Miller SR, Oster C. a randomized, double-blind study of the efficacy of a 10- or 20-day course of sodium stibogluconate for treatment of cutaneous leishmaniasis in United States military personnel. Clin Infect Dis 2002; 35: 261-7
187. McBride MO, Linney M, Davidson RN, et al. Pancreatic necrosis following treatment of leishmaniasis with sodium stibogluconate [letter]. Clin Infect Dis 1995; 21: 710
188. Delgado J, Macias J, Pineda JA, et al. High frequency of serious side effects from meglumine antimoniate given without an upper limit dose for the treatment of visceral leishmaniasis in human immunodificiency virus type-1 infected patients. Am J Trop Med Hyg 1999; 61: 766-9
189. Brundtland GH. World Health Organization Report on Infectious Diseases 2000. Overcoming antimicrobial resistance [online]. Available from URL: http://www.who.int/infectious-disease-report/2000/ [Accessed 2008 Aug 25]
190. Johnson WC, Nasbeth DC. Pancreatitis in renal transplantation. Ann Surg 1970; 171: 309-14
191. Nogueira JR, Freedman MA. Acute pancreatitis as a complication of imuran therapy in regional enteritis. Gastroenterology 1972; 62: 1040-1
192. Sturdevant RAL, Singleton JW, Deren JJ, et al. Azathioprine-related pancreatitis in patients with Crohn's disease. Gastroenterology 1979; 77: 883-6
193. Bank L, Wright JP. 6-Mercaptopurine-related pancreatitis in 2 patients with inflammatory bowel disease. Dig Dis Sci 1984; 29: 357-9
194. Haber CJ, Meltzer SJ, Present DH, et al. Nature and course of pancreatitis caused by 6-mercaptopurine in the treatment of inflammatory bowel disease. Gastroenterology 1986; 91: 982-6
195. Present DH, Meltzer SJ, Krumholz MP, et al. 6-Mercaptopurine in the management of inflammatory bowel disease: short and long-term toxicity. Ann Intern Med 1989; 111: 641-9
196. Floyd A, Pedersen L, Nielsen GL, et al. Risk of acute pancreatitis in users of azathioprine: a population-based case-control study. Am J Gastroenterol 2003; 98: 1305-8
197. Block MB, Genant HK, Kirsner JB. Pancreatitis as an adverse reaction to salicylazosulfapuridine. N Engl J Med 1970; 282: 380-2
198. Faintuch J, Mott C, Machado M. Pancreatitis and pancreatic necrosis during sulfasalazine therapy. Int Surg 1985; 70: 271-2
199. Rubin R. Sulfasalazine-induced fulminant hepatic failure and necrotizing pancreatitis. Am J Gastroenterol 1994; 89: 789-91
200. Garau P, Orenstein S, Neigut D, et al. Pancreatitis associated with olsalazine and sulfasalazine in children with ulcerative colitis. J Pediatr Gastroenterol Nutr 1994; 18: 481-5
201. Isaacs KL, Murphy D. Pancreatitis after rectal administration of 5-aminosalicylic acid. J Clin Gastroenterol 1990; 12: 198-9
202. Fernandez J, Sala M, Panes J, et al. Acute pancreatitis after long term 5-aminosalicylic acid therapy. Am J Gastroenterol 1997; 92: 2302-3
203. Ransford RA, Langman MJ. Sulphasalazine and mesalazine: serious adverse reactions re-evaluated on the basis of suspected adverse reaction reports to the Committee on Safety of Medicines. Gut 2002; 51: 536-9
204. Fiorentini MT, Fracchia M, Galatola G, et al. Acute pancreatitis during oral 5-aminosalicylic acid therapy. Dig Dis Sci 1990; 35 (9): 1180-2
205. Debongnie J, Dekoninck X. Sulfasalazine, 5-ASA, and acute pancreatitis in Crohn's disease. J Clin Gastroenterol 1994; 19: 348-9
206. Butalden PB, Van Dyne BJ, Cloyd J. Pancreatitis associated with valproic acid therapy. Pediatrics 1979; 64: 520-2
207. Buzan RD, Firestone D, Thomas M, et al. Valproate-associated pancreatitis and cholecystitis in six mentally retarded adults. J Clin Psychiatry 1995; 56: 529-32
208. Parker PH, Helinek GL, Ghishan FK, et al. Recurrent pancreatitis induced by valproic acid. Gastroenterology 1981; 80: 826-8
209. Williams LH, Reynolds RP, Emery JL. Pancreatitis during sodium valproate treatment. Arch Dis Child 1983; 58: 543-4
210. Wyllie E, Wyllie R, Cruse RP, et al. Pancreatitis associated with valproic acid therapy. Am J Dis Child 1984; 138: 912-4
211. Baskies AM. Pancreatic pseudocyst associated with valproic acid therapy. J Med Soc N J 1984; 81: 399-400
212. Ford DM, Portman RJ, Lum GM. Pancreatitis in children on chronic dialysis treated with valproic acid. Pediatr Nephrol 1990; 4: 259-61
213. Evans RJ, Miranda RN, Jordan J. Fatal acute pancreatitis caused by valproic acid. Am J Forensic Med Pathol 1995; 16: 62-5
214. Lott JA, Bond LW, Bobo RC, et al. Valproic acid-associated pancreatitis: report of three cases and a brief review. Clin Chem 1990; 36: 395-7
215. Sinclair DB, Berg M, Breault R. Valproic acid-induced pancreatitis in childhood epilepsy: case series and review. J Child Neurol 2004; 19: 498-02
216. Werlin SL, Kugathasa S, Frautschy BC. Pancreatitis in children. J Pediatr Gastroenterol Nutr 2003; 37: 591-5
217. Zorilla E, Hulse M, Hernandez A, et al. Severe endogenous hypertriglyceridemia during treatment with estrogen and oral contraceptives. J Clin Endocrinol Metab 1968; 28: 1793-6
218. Glueck CJ, Scheel D, Fishback J, et al. Estrogen-induced pancreatitis in patients with previously covert familial type 5 hyperlipoproteinemia. Metabolism 1972; 21: 657-66
219. Anon. Pancreatitis from oral contraceptives [editorial]. BMJ 1973; 4: 688-9
220. Molitich ME, Oill P, Odell WD. Massive hyperlipemia during estrogen therapy. JAMA 1974; 227: 522-5
221. Foster ME, Powell DEB. Pancreatitis, multiple infarcts, and oral contraception. Postgrad Med J 1975; 51: 667-9
222. Mungall IP, Hague RV. Pancreatitis and the pill. Postgrad Med J 1975; 51: 855-7
223. Glueck CJ, Scheel D, Fishback J, et al. Severe hypertriglyceridemia and pancreatitis when estrogen replacement therapy is given to hypertriglyceridemic women. J Lab Clin Med 1994; 123: 59-64
224. Ruman J, Brenner S, Sauer MV. Severe hypertriglyceridemia and pancreatitis following hormone replacement prior to cryothaw transfer. J Assist Reprod Genet 2002; 19: 94-7
225. Perego E, Scaini A, Romano F, et al. Estrogen-induced severe acute pancreatitis in a male. JOP J Pancreas (Online) 2004; 5 (5): 353-6 [online]. Available from URL: www.joplink.net [Accessed 2008 Aug 25]

226. Stuyt PM, Demacker PN, Stalenhoef AF. Pancreatitis induced by oestrogen in a patient with type I hyperlipoproteinemia [letter]. BMJ (Clin Res Ed) 1986; 293: 734
227. Wallace RB, Hoover J, Sandler D, et al. Altered plasma lipids associated with oral contraceptive or estrogen consumption. Lancet 1977; 2: 11-4
228. Stokes T, Wynn V. Serum lipids in women on oral contraceptives. Lancet 1971; 2: 677-80
229. Lankisch PG, Niederstadt H, Redlin-Kress E, et al. Acute pancreatitis: induced by heroin intoxication? Pancreas 1993; 8: 123-6
230. Beamish N, Schwarer P, Watson AM. Acute pancreatitis complicating a bone marrow harvest. Bone Marrow Transplant 1997; 19: 525-6
231. Moreno Escobosa MC, Amat Lopez J, Cruz Granados S, et al. Pancreatitis due to codeine. Allergol Immunopathol 2005; 33: 175-7
232. Steinberg WM, Toskes PP, Salvato RF. Non-specificity of the morphine-prostigmine test [abstract]. Gastroenterology 1979; 76: A1255
233. Roberts-Thompson IC, Toouli J. Abnormal responses to morphine-neostigmine in patients with undefined biliary-type pain. Gut 1985; 26: 1367-72
234. Gross JB, Comfort MW, Mathieson DR, et al. Elevated values for serum enzymes and lipase following the administration of opiates: a preliminary report. Proc Mayo Clinic 1951; 26: 81-7
235. Goldstein J, Laskin DA, Ginsberg GH. Sulindac associated pancreatitis. Ann Intern Med 1980; 93: 151
236. Siefkin AD. Sulindac and pancreatitis. Ann Intern Med 1980; 93: 932-3
237. Lilly EL. Pancreatitis after administration of sulindac [letter]. JAMA 1981; 246: 2680
238. Lerche A. Vyberg, M. Kirkegaard, E. Acute cholangitis and pancreatitis associated with sulindac (clinoril). Histopathology 1987; 11: 647-53
239. Sugarman HJ. Sulindac-induced acute pancreatitis mimicking gallstone pancreatitis. Am Surg 1989; 55: 536-8

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