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(REVIEW ARTICLE)

# Drug-induced acute pancreatitis: Pathophysiology, imaging, clinical pharmacology, and causality assessment: An evidence-informed narrative review

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## Abstract

**Background**: Drug-induced acute pancreatitis (DIAP) is an uncommon but important adverse drug event. Diagnosis continues to be difficult due to the similarity of clinical, laboratory, and radiological findings to more common causes of acute pancreatitis such as gallstones, alcohol-induced pancreatitis, hypertriglyceridemia, hypercalcemia, pancreatic-biliary obstruction, cancer, infections, injuries and post-endoscopic retrograde cholangio-pancreatography (ERCP)-induced pancreatitis. Wrong diagnosis can result in repeated pancreatic injury on re-exposure or inappropriate termination of treatment.

**Objective**: This evidence-informed narrative review seeks to synthesize existing evidence about DIAP from pathophysiologic, radiologic, pharmacologic, and causality evaluation points of views, especially on clinical practice.

**Methods**: Structured literature search was carried out in PubMed/MEDLINE, Scopus, Web of Science, and Google Scholar. Priority was placed on acute pancreatitis guidelines, updated Atlanta classifications, systematic reviews, evidence-based DIAP classifications, pharmacoepidemiologic and pharmacovigilance studies, cohorts, case-control studies, and case series with sufficient diagnostic and etiologic evidence.

**Findings to note**: DIAP should be understood as a diagnosis made using a probabilistic approach rather than a temporal association. Proposed mechanisms include direct acinar cell injury, mitochondrial injury, oxidative stress, immune mediated damage, microvascular ischemia, duct or sphincter involvement, and metabolic injury indirectly caused by the medicine. Even though various medicines have been associated with DIAP, the quality of evidence is highly variable. Imaging has an important role in ruling out causes and excluding biliary, ductal, structural, or malignant conditions.

**Conclusion**: Diagnosis of DIAP demands demonstration of pancreatitis, elimination of common causes, drug chronology, analysis of latency and rechallenge, evaluation of drug literature, patient susceptibility and multi-disciplinary opinion.

**Keywords:** Drug Induced Acute Pancreatitis; Causality assessment; Pharmacovigilance; Computed Tomography; Magnetic Resonance Imaging; Ultrasonography; Clinical Pharmacology; Adverse Drug Reaction.

## 1. Introduction

Acute pancreatitis (AP) is a common condition in gastrointestinal emergencies that ranges from self-limiting disease with mild inflammatory signs to necrosis and organ dysfunction, ultimately ending in death(1, 2). According to

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international classification systems and treatment protocols, the definition of AP involves the demonstration of at least two of the following criteria: characteristic abdominal pain, three-fold higher serum amylase or lipase levels, and supporting radiological findings(3, 4). After confirming AP, identification of the cause of the disease is a key step since it impacts future recurrence prevention, prescribing medications, managing biliary issues, addressing metabolic abnormalities, patient monitoring, and counseling(2).

The most prevalent causes include gallstones and alcohol intake, but there are other possible causes such as hypertriglyceridemia, hypercalcemia, idiopathic autoimmune pancreatitis, neoplastic causes, anatomical anomalies, blunt injury, infectious causes, ERCP procedure, and drug-induced causes(5). Drug-induced acute pancreatitis (DIAP) is relatively rare, usually comprising less than 5% of all AP patients, but it matters because, when identified, the risk of recurrence can be prevented if the patient avoids taking the causative drug again(6-8). On the contrary, over-diagnosis can lead to unnecessary cessation of medications used to treat malignant conditions, epilepsy, inflammatory bowel diseases, transplantations, HIV, diabetes, cardiovascular and autoimmune diseases(2, 9, 10).The modern DIAP literature presents the paradox that although more drugs keep being associated with this condition based on reports and from pharmacovigilance databases, their evidence is generally poor. Earlier classification approaches depended on rechallenge, latency period, and number of cases reported, but current ones focus on more rigorous criteria involving better diagnostic approach, exclusion of other causes, and higher-level evidence such as randomized controlled trials, cohort studies, case-control studies, and pharmacoepidemiologic methods(7, 11, 12). This is significant since case reports in journals lack proper etiological exclusion, results of laboratory investigations, imaging findings, and causality assessment(6, 7, 13). Even though the interest in DIAP has grown over time, diagnostic uncertainties have still been quite high due to the fact that a lot of these drug-related cases rely heavily on spontaneous reporting data, incomplete case reports, or even just temporal relationship and lack of exclusion of the common causes of the condition. Additionally, the role of clinical pharmacy in causality evaluation should not be ignored. Thus, the need for an evidence-based approach is evident.(14, 15)

This review attempts to introduce an evidence-informed, radiologically informed, and pharmacologically informed approach to suspected DIAP. The discussion encompasses the mechanisms involved, evidence hierarchy, classification of drug types, diagnostic procedure, radiology role, management of DIAP, follow-up, prevention, and further investigation needed. The significance of the work is thus more about helping the physicians, radiologists, and clinical pharmacists together to assess the probability of DIAP, rule out unnecessary causality, and minimize recurrence.

### *Highlight*

- Acute pancreatitis caused by drugs must be classified as a probabilistic diagnosis and not one based solely on association with time.
- The strength of evidence differs widely among the offending medications, from very strong associations to weak pharmacovigilance alerts.
- Imaging is crucial for confirming pancreatitis, evaluating its severity, identifying complications, and ruling out other causes such as biliary or anatomical reasons, but it alone cannot confirm drug causality.
- Causality evaluation must take into account the confirmation of acute pancreatitis, exclusion of common causes, timing of medications, latent period, de-challenge/rechallenge data, drug-specific data, and individual patient predisposition.
- Symptomatic and risk-based surveillance is better than screening tests in asymptomatic low-risk individuals.

## 2. Methods: Literature Review and Evidence Synthesis

The aim of the current paper is to conduct an evidence-informed narrative review and provide synthesis of current knowledge on the drug-induced acute pancreatitis (DIAP) considering its gastroenterological, radiological, clinical pharmacological and pharmacovigilance aspects. As the purpose of this paper is to make a practical synthesis, rather than to carry out meta-analysis, no formal statistical meta-analysis was done.

Therefore, a comprehensive literature search was conducted in PubMed/MEDLINE, Scopus, Web of Science, and Google Scholar. The objective of this literature search was to find articles that discuss the epidemiology, pathophysiology, causality assessment, imaging characteristics, specific classes information, DIAP surveillance, treatment, prevention of DIAP recurrence and pharmacovigilance of DIAP. For that purpose, the following keywords and Medical Subject Headings (MeSH) terms were used: “drug-induced pancreatitis,” “drug-induced acute pancreatitis,” “medication-induced pancreatitis,” “adverse drug reaction,” “causality assessment,” “Naranjo,” “WHO-UMC,” “Badalov,” “Simons-Linares,” “Wolfe,” “Saini,” “pharmacovigilance,” “FAERS,” “VigiBase,” “computed tomography,” “magnetic resonance imaging,” “MRCP,” “ultrasonography,” “acute pancreatitis guidelines,” “valproate,” “thiopurines”.

Especially considered were guidelines for acute pancreatitis, the Revised Atlanta Classification articles, systematic reviews, evidence-based DIAP classification models, pharmacoepidemiology and pharmacovigilance research, cohort studies, case-control studies, and case series, which included detailed diagnostic and etiological information. Individual case reports were selected only if they provided valuable information on the pathogenesis of acute pancreatitis, causality assessments, proper de-challenge/rechallenge information, or issues in the reporting(5, 7, 10, 16).

Articles were considered as highly valuable when they followed well-defined diagnostic criteria for acute pancreatitis, thoroughly ruled out common confounders (e.g., gallstones, alcoholic pancreatitis, hypertriglyceridemia, hypercalcemia, ERCP-induced pancreatitis, biliary obstruction, infections, trauma, malignancies), and accurately described information about the medication use (initiation time, dosing changes, latency period, discontinuation, recurrence). Articles that lacked diagnostic criteria, did not properly conduct etiological evaluations, failed to provide medication information, or provided wrong causal associations were critically reviewed. The core components, priority of evidence, and clinical emphasis of the methodology used in this review are structured and summarized in Table 1

**Table 1** Methodological approach used for this evidence-informed narrative review.

| Component | Approach used in this narrative review |
|---|---|
| Review question | How should DIAP be recognized, investigated, imaged, managed, and prevented using current evidence? |
| Priority evidence | Guidelines, systematic reviews, evidence-based classifications, cohort/case-control studies, pharmacovigilance studies, high-quality case series. |
| Lower-priority evidence | Single case reports without complete etiologic exclusion, unclear latency, absent imaging, or no causality assessment. |
| Evidence interpretation | Causality was treated as probabilistic and drug-specific rather than assumed from temporal association alone. |
| Clinical emphasis | Integration of radiological assessment with clinical pharmacology and medication chronology. |

## 3. What Does This Review Contribute?

Whereas DIAP has already been reviewed before and was included in some classification systems, several clinically relevant knowledge gaps exist. Most of the published literature addresses lists of causative drugs(2, 7), but the diagnostic algorithm of the disease includes not only identification of clinical symptoms and confirmation with biochemical markers, exclusion of frequent causes by imaging and analysis of their timeline, but also pharmacological plausibility and causality of drug's involvement. This review provides a multidisciplinary approach that combines radiological examinations with clinical pharmacology and drug-causality considerations.

Main contribution of this review is the construction of an evidence-informed framework for assessing suspected cases of DIAP as a probable diagnosis. It provides information about the difference between signals from pharmacovigilance system and actual causality, the use of imaging for confirmation of pancreatitis and exclusion of other possible causes, and the participation of clinical pharmacy in reconstruction of drug exposure, interaction assessment, and safe withdrawal or substitution.

The review can help to prevent both under-diagnosis (that can cause recurrence after repeated exposure) and over-diagnosis (discontinuation of vital therapy).

## 4. Epidemiology and clinical relevance

The incidence of DIAP is highly variable due to the extent of investigation into alternative causes and definitions of causality. Old studies suggested that medications were implicated in 0.1-2% of AP cases, while most modern clinical discussions suggest rates closer to 5%. Hospital-based research suggests prevalence estimates of around 3-4%, though there might be bias involved with selection criteria, local practice patterns, and medication reconciliation efforts(17-19).

Underdiagnosis happens when there are new medication exposures that are missed, if pancreatitis occurs in complicated patients with cancer or transplants, or if milder DIAP episodes resolve before any causality assessments

take place. On the other hand, overdiagnosis occurs when the presence of medication is linked to the development of pancreatitis despite having gallstones, alcohol abuse, hypertriglyceridemia, biliary or pancreatic obstruction, infection, or systemic disease(5-7, 20). The epidemiology of DIAP is also evolving. With the advent of novel oncologic drugs, checkpoint inhibition therapy, biologics, antidiabetics, antiretrovirals, immunomodulating medications, and multiple-drug combinations, the panorama of suspectable pancreatotoxicities continues to grow(4, 21). Concurrently, spontaneous reporting databases are now capable of identifying drug-adverse event associations among many thousands of drug-adverse event combinations. Such data are helpful for formulating hypotheses but cannot establish causation since denominator exposure data, context, and exclusion of alternative explanations are lacking(22-24).

Clinical importance extends beyond severe cases. DIAP, even when mild, can lead to readmission due to drug reintroduction. In certain high-risk populations, such as patients with acute lymphoblastic leukemia, inflammatory bowel disease, or epilepsy, issues of causality will not only concern the health of the pancreas but also control of the underlying disease(8, 25, 26).

## 5. Pathophysiological mechanisms

DIAP is not a single mechanistic entity. It represents a heterogeneous group of adverse drug reactions in which the pancreatic injury phenotype may arise through direct toxicity, immune mechanisms, metabolic disturbance, vascular injury, ductal effects, or interaction between drug exposure and host susceptibility. The same clinical syndrome may therefore develop through different biological pathways, and the same drug may plausibly act through more than one mechanism(21, 27, 28). Figure 1 summarizes an integrated mechanism framework.

Direct acinar toxicity and toxic metabolite formation are proposed for several agents. Potential downstream events include intracellular calcium dysregulation, mitochondrial dysfunction, adenosine triphosphate depletion, impaired autophagy, lysosomal instability, premature zymogen activation, endoplasmic reticulum stress, and inflammatory amplification(29-34). Valproic acid and some older antiretroviral agents have been discussed in relation to mitochondrial injury or toxic metabolites(35, 36). However, the rarity of pancreatitis relative to widespread drug exposure indicates that host vulnerability and co-factors are usually necessary.(37-40)

Immune-mediated or idiosyncratic reactions are particularly relevant for thiopurines, 5-aminosalicylic acid derivatives, sulfonamides, and selected antimicrobials. These reactions may be dose-independent, occur early after exposure, and lack classical allergic features such as rash, eosinophilia, or fever. Thiopurine-induced pancreatitis is a useful model because genetic susceptibility has been linked to HLA-DQA1-HLA-DRB1 variation in inflammatory bowel disease populations(41-46).

Indirect metabolic mechanisms are clinically important because they are detectable and modifiable. Estrogens, retinoids, some antiretrovirals, atypical antipsychotics, and selected anticancer therapies may contribute to severe hypertriglyceridemia. Thiazides, lithium, vitamin D/Ca++ excess, and cancer treatments can cause hypercalcemia, leading to drug-induced AP in this manner. The importance of this mechanism is that not only will treatment need to address the metabolic cause and any possible toxicity to the pancreas but also will involve reassessment of the medication being used(5, 11, 47-56).

Ischemia, microvascular injury, vascular injury, endothelial injury, thrombosis, dehydration, hypotension, and vasoconstriction have all been considered for certain drugs, but only in special cases. Obstruction of the duct or sphincter of Oddi has been implicated for certain drugs as well(16-18, 42). In conclusion, drug-induced AP should be regarded as a multifactorial process resulting from the interaction between medication properties, exposure environment, individual vulnerability, and other injuries to the pancreas. Figure (1) Provides an overview of the proposed mechanisms associated with drug-induced acute pancreatitis and the possible relationship between drug injury and host susceptibility to clinical settings.

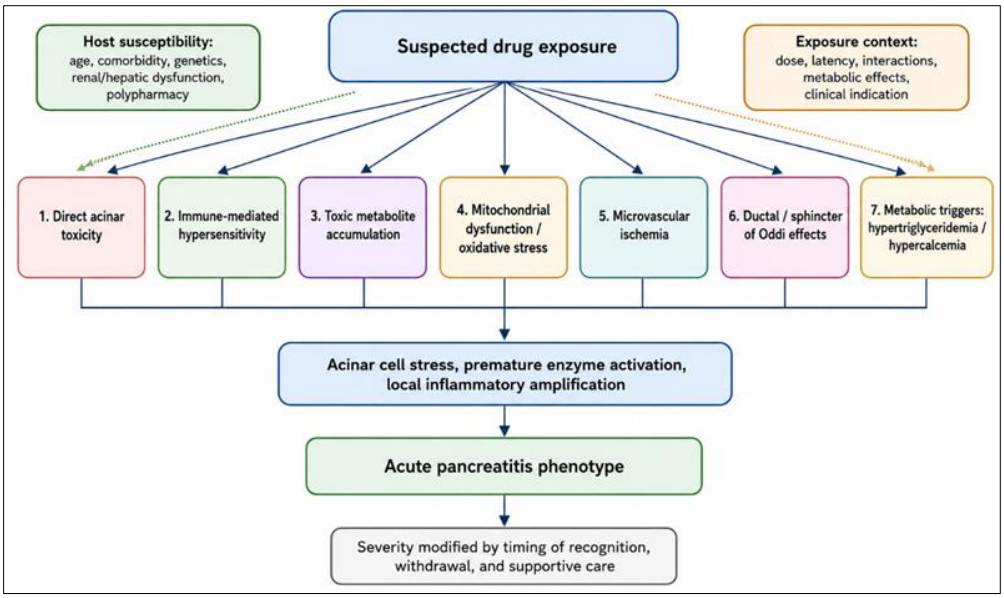


**Figure 1** Mechanistic perspective on drug-induced acute pancreatitis. Created by the authors based on previous mechanistic reviews and evidence-based discussions of drug-induced acute pancreatitis pathophysiology.

## 6. Drug Associations and Degree of Evidentiary Support

One difficulty in drug-induced acute pancreatitis is that drug exposure alone does not imply causality. Several drugs have been associated with acute pancreatitis, yet the degree of evidentiary support differs dramatically. There are drug associations for which there is rechallenge data, an identifiable clinical pattern, an observational study, or a system of evidence-based classification, whereas other associations are based predominantly on single case reports or pharmacovigilance data(2, 21, 43, 57).

The previous classifications like the Badalov system were useful in grouping the implicated drugs depending upon rechallenge, latency, and the number of published cases. Nonetheless, in subsequent systematic reviews and revisions of the evidence-based classification system, it was established that a great majority of associations had weak evidence due to lack of a thorough diagnostic evaluation, absence of exclusion of other causes, and an inadequate timeline for the drug intake(12, 51, 58).

There are some drug classes with stronger and more clinically relevant data. Thiopurines, specifically azathioprine and 6-mercaptopurine, are implicated in early onset idiosyncratic pancreatitis in patients with inflammatory bowel diseases. Valproate is also known to be an associated medication; however, latency periods might vary and be prolonged in some cases. Another example is L-asparaginase-induced pancreatitis in patients with acute lymphoblastic leukemia where risk-benefit considerations are very individual(25, 35, 51, 59, 60).

There are other drug classes which need a more careful approach. Anti-infectives, antivirals, antidiabetics, cardiovascular agents, lipid-regulating drugs, hormonal medications, and oncology/biologicals can be seen in the literature on DIAP; however, all these associations are complicated by infections, metabolic disorders, cholelithiasis, cancer, polypharmacy, or confounding due to indication(10, 17, 31, 34, 49).

Certain drugs can induce pancreatitis indirectly by virtue of their metabolic effect on the body, rather than due to a direct effect of the drug on the pancreas. Estrogen, retinoid, corticosteroids, atypical antipsychotics, certain antiretroviral drugs, and certain antineoplastics may act by inducing severe hypertriglyceridemia, whereas thiazide diuretics, lithium, calcium preparations, excessive intake of vitamin D, and certain treatments for cancer may act via hypercalcemia. It is clinically relevant to appreciate these mechanisms since they require that the metabolic disturbance be corrected and that the suspected drug be reevaluated(24, 31, 61, 62).

Overall, the crucial clinical question is not what medications have been shown in the literature to cause pancreatitis, but whether the relationship between the drug and the condition in question is plausible for a particular individual. A practical drug-class-specific interpretation of the evidence, major confounders, features supporting causality, and clinical implications is summarized in Table 2.

**Table 2** Drug-class-specific interpretation in suspected drug-induced acute pancreatitis. Authors' synthesis is based on evidence-based DIAP classifications, systematic reviews, pharmacovigilance studies, and drug-specific clinical literature.

| Drug setting | Evidence problem | Key confounders | Findings that strengthen causality | Practical implication |
|---|---|---|---|---|
| Thiopurines | Relatively strong and clinically coherent association | IBD activity, gallstones, corticosteroids, infection | Early latency, exclusion of biliary/metabolic causes, recurrence after re-exposure, compatible host susceptibility | Usually discontinue permanently and avoid class rechallenge after probable DIAP |
| Valproic acid | Recognized association with variable latency | Epilepsy-related admissions, trauma, polytherapy, metabolic illness | Objective AP, no alternative cause, compatible chronology, improvement after withdrawal | Avoid rechallenge and substitute antiepileptic therapy when feasible |
| L-asparaginase | Well-recognized in ALL protocols, but decisions affect cancer therapy | Chemotherapy combinations, infection, corticosteroids, tumour burden | Temporal relation to asparaginase exposure, protocol timing, compatible severity pattern | Haematology-led risk-benefit decision regarding discontinuation or re-exposure |
| Antimicrobials / antivirals | Many reports, variable causality by agent | Infection, sepsis, dehydration, renal/hepatic impairment, concomitant drugs | Strong latency, negative biliary/metabolic work-up, previous high-quality evidence for same agent | Stop or substitute when feasible; document uncertainty if evidence is incomplete |
| Antidiabetic drugs | Safety signals complicated by baseline metabolic risk | Diabetes, obesity, gallstones, hypertriglyceridemia, rapid weight change | Recent initiation or dose escalation, no common aetiology, compatible chronology | Individualize; avoid over-labellingg without strong evidence |
| Cardiovascular / lipid agents | Common exposure may inflate apparent associations | Age, diabetes, dyslipidemia, chronic kidney disease, gallstone risk, polypharmacy | Clear latency, absence of competing pancreatitis risks, supportive de-challenge | Review indication carefully; avoid unnecessary discontinuation of essential therapy |
| Hormonal / metabolic agents | Often indirect through triglycerides or calcium | Obesity, diabetes, baseline dyslipidemia, endocrine disease, supplements | Severe hypertriglyceridemia or hypercalcemia temporally related to therapy | Correct metabolic trigger and reassess medication necessity |
| Oncology / biologic therapies | Rapidly evolving evidence in complex patients | Cancer, obstruction, infection, hypercalcemia, thrombosis, multi-agent therapy | Multidisciplinary adjudication, compatible immune or metabolic phenotype, exclusion of structural causes | Balance pancreatic risk with oncologic benefit |

## 7. Diagnostic Strategy and Etiological Evaluation

In order to diagnose acute drug-induced pancreatitis, it is necessary to confirm first that the patient indeed suffers from acute pancreatitis. The requirements include meeting of at least two recognized criteria: characteristic abdominal pain, increase in serum amylase and/or lipase above 3 times upper limit of normal and/or imaging compatible with acute pancreatitis. An enzyme elevation on its own cannot be regarded as sufficient evidence for pancreatitis, since hyperamylasemia or hyperlipasemia can result from renal insufficiency, critical illness, gastrointestinal disease, macroamylasemia, and even certain drugs without an actual presence of pancreatitis(4, 13, 17, 63).

After confirmation of acute pancreatitis, it is crucial to exclude other commonly recognized causes prior to attributing pancreatitis to the use of medication. The causes to consider are gallstone disease, biliary sludge, alcoholic disease, hypertriglyceridemia, hypercalcemia, post-ERCP pancreatitis, pancreaticobiliary obstruction, neoplasia, infection, trauma, autoimmune pancreatitis, and structural pancreatic disease(4, 26, 64, 65). Biliary disease is usually evaluated first by abdominal ultrasound; however, in case of continued suspicions for biliary/ductal pathology despite negative ultrasound, MRCP or EUS should be done. Levels of triglycerides and calcium need to be determined early on, since otherwise the contribution of these factors may be underestimated(4, 66, 67).

Drug history is essential to DIAP diagnosis. The medication history must include details about any prescriptions, recent use of any short-term medications, over-the-counter medications, supplements, hormones, antidiabetic medications, cycles of chemotherapy, dosing, duration, latency from exposure to development of symptoms, past exposures, de-challenge, and any rechallenges due to an accident. Any clinical improvement in the condition following cessation of the drug suggests causality, although such improvement alone does not confirm causality, since in many cases of acute pancreatitis the patient shows improvement with supportive treatment irrespective of causality(2, 8, 44, 68).

Some general causality instruments such as the Naranjo instrument and the WHO-UMC criteria can enhance clarity in causality assessment although these are not specific for DIAP. Some shortcomings of these general causality instruments are the ethical dilemma of performing rechallenges, absence of dose response relation, latency, and failure to deal with competing etiologies, such as gallstones or metabolic causes(69-71).It may be advisable to dissociate between two issues: whether the patient suffers from acute pancreatitis and whether there was a specific drug that caused the problem. In doing so, one can avoid under-diagnosing the condition, leading to its relapse upon re-exposure, and over-diagnosis, resulting in the discontinuation of important treatment(42, 60, 72). A practical multidisciplinary diagnostic and management pathway for suspected DIAP is illustrated in Figure 2 and the key domains that should be documented when evaluating suspected DIAP are summarized in Table 3

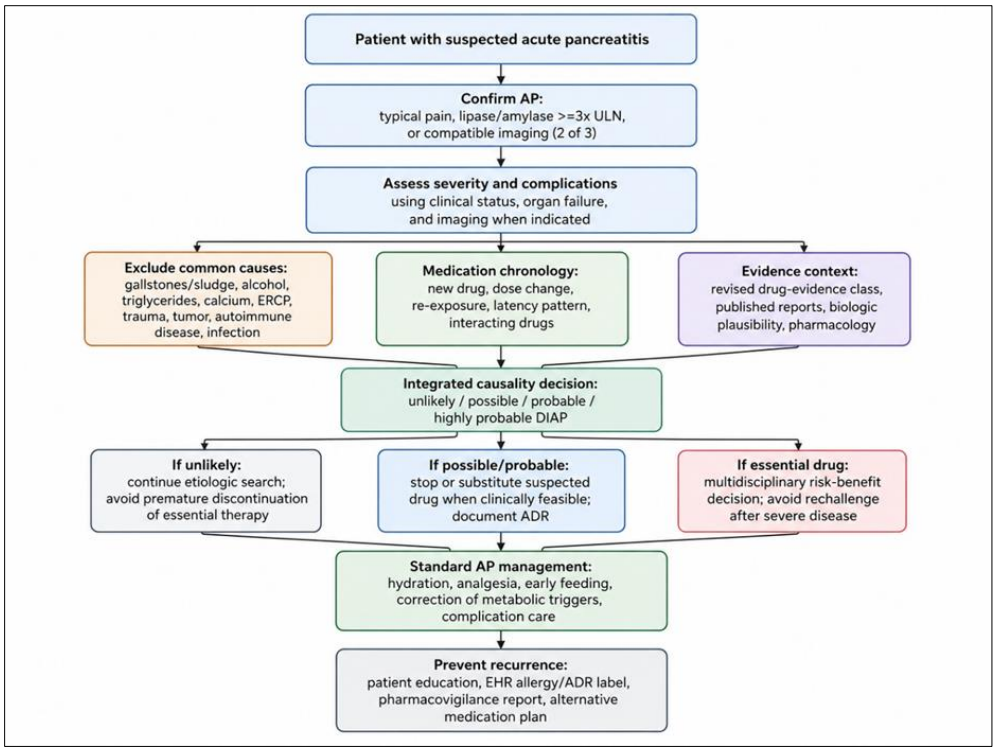


**Figure 2** Practical diagnostic and management algorithm for suspected drug-induced acute pancreatitis. Proposed by the authors based on AP guidelines and DIAP causality literature(42, 73, 74).

**Table 3** Checklist for causality assessment of suspected drug-induced acute pancreatitis. Proposed by the authors based on acute pancreatitis diagnostic criteria, general adverse drug reaction causality tools, and DIAP-specific causality literature.

| Assessment domain | Key questions | Common pitfall | Suggested documentation |
|---|---|---|---|
| AP confirmation | Are at least two diagnostic criteria present? | Treating asymptomatic enzyme elevation as AP. | Symptoms, enzyme values, imaging findings, date/time. |
| Etiologic exclusion | Were gallstones, alcohol, triglycerides, calcium, ERCP, obstruction, tumour, autoimmune disease, trauma, and infection considered? | Calling DIAP before excluding common causes. | Negative and positive findings with dates. |
| Medication chronology | Was there a plausible latency after initiation, dose change, or re-exposure? | Listing current medications without timeline. | Start/stop dates, dose, route, adherence, interaction history. |
| Dechallenge/rechallenge | Did symptoms/labs improve after withdrawal? Was re-exposure accidental? | Using clinical recovery alone as proof. | Time to improvement; rechallenge avoided or documented if accidental. |
| Evidence context | Is the drug supported by high-quality evidence or only case reports/signals? | Treating all published associations equally. | Evidence class or supporting literature. |
| Clinical decision | Is the drug essential? Are alternatives available? | Stopping essential therapy without specialist input. | Risk-benefit discussion and alternative plan. |

## 8. Imaging Assessment and Radiology Report

Imaging is crucial to the diagnosis of drug-induced acute pancreatitis, although it is not a causative test. There are no specific imaging features that can differentiate DIAP from biliary, alcoholic, metabolic, obstruction, or idiopathic acute pancreatitis. Therefore, the responsibility of the radiologist is to diagnose the acute pancreatitis if imaging is required, assess the type and severity, identify complications, rule out any other underlying conditions, and manage the patient accordingly(75-79).

The initial imaging modality that would be considered is the ultrasonogram because of its availability, safety, and effectiveness in the detection of gallstones, biliary sludge, abnormality in the gallbladder, bile duct distention, presence of ascites, and other hepatobiliary disorders. However, the ultrasound can have limitations in cases where there are bowel gas, obesity, severe pain, and early stages of pancreatitis, and therefore, normal or limited ultrasonogram cannot rule out the condition and microlithiasis, or small common bile duct stones(10, 66, 80).

CT with contrast is the primary modality for severity and complication assessment in severe, atypical, decompensating or worsening acute pancreatitis. This can include evaluation of pancreatic or peripancreatic necrosis, inflammation, collections, vascular complications, bleeding, bowel disease, bowel obstruction, or other abdominal pathology. CT is not generally necessary in early mild pancreatitis and can be less helpful in assessment of severity or complications if performed prematurely within the first 48-72 hours(67, 76, 81).

MRI and MRCP are useful when ductal/biliary disease is not clear, when iodinated contrast is not desirable, when soft tissue definition is important, or when follow-up of collections is necessary. MRCP can assist in identifying choledocholithiasis, disruption of the pancreatic duct, pancreas divisum, strictures, masses, or other anatomy. Endoscopic ultrasound is sensitive to microlithiasis, stones, pancreatic/biliary lesions, or chronic pancreatitis(79, 82, 83).

The radiology report should include revised Atlanta nomenclature as applicable, differentiating between interstitial edematous and necrotizing pancreatitis and describing the acute peripancreatic fluid collection, acute necrotic collection, pseudocyst or walled-off necrosis based on their temporal relationship and composition. Reports should include information regarding biliary disease, bile duct abnormalities, structural abnormality, vascular complications, and limitations of the study performed(66, 80, 84).

Of note, the report should not make a definitive diagnosis of "drug-induced pancreatitis," as causation has yet to be proven in this regard. Rather, a proper radiological impression should read: "Radiological findings suggestive of acute pancreatitis. No gallstones, bile duct dilation or obstructing pancreatico-biliary pathology seen in the present imaging study. No definitive drug-induced cause for this finding can be determined via imaging alone."(67, 85) The strengths and weaknesses of each imaging technique have been provided in Table 4, while the recommended components for radiological report writing that could enhance diagnostic accuracy and decrease misattribution of medication-induced pancreatitis have been detailed in Table 5.

**Table 4** Role of imaging modalities in suspected drug-induced acute pancreatitis. Prepared by the authors based on acute pancreatitis imaging guidelines, revised Atlanta terminology, and radiology literature relevant to pancreatitis evaluation

| **Modality** | **Main role** | **Strengths** | **Limitations** | **Best use in suspected DIAP** |
|---|---|---|---|---|
| Ultrasound | Initial biliary assessment and alternative hepatobiliary diagnoses. | No radiation, widely available, identifies gallstones/sludge/dilatation. | Limited pancreatic visualization; may miss microlithiasis or small CBD stones. | First-line exclusion of common biliary causes. |
| CECT | Severity staging and complication detection. | Excellent for necrosis, collections, vascular complications, haemorrhage, bowel involvement. | Radiation, iodinated contrast, early CT may underestimate necrosis. | Severe, atypical, complicated, deteriorating, or non-improving cases. |
| MRI | Soft-tissue characterization and follow-up. | No radiation, good tissue contrast, useful when CT contrast is undesirable. | Time, availability, motion, unstable patients. | Equivocal CT, radiation-sensitive patients, follow-up of collections. |
| MRCP | Non-invasive biliary and ductal evaluation. | Defines ductal anatomy and obstruction. | May miss tiny stones; limited availability. | Persistent biliary suspicion after ultrasound or suspected ductal abnormality. |
| EUS | Occult biliary disease and subtle pancreaticobiliary lesions. | High sensitivity for microlithiasis and small lesions. | Invasive, operator-dependent, sedation. | Recurrent, idiopathic, or unexplained AP after non-invasive imaging. |
| Interventional radiology/endoscopy | Drainage or step-up management of complications. | Minimally invasive treatment of infected/symptomatic collections. | Procedural risks; not a causality tool. | Infected necrosis, symptomatic |

| | | | | |
|---|---|---|---|---|
| | | | | collections, obstruction, or selected complications. |

**Table 5** Suggested radiology reporting checklist for suspected drug-induced acute pancreatitis. Proposed by the authors based on clinical pharmacology principles, medication reconciliation practice, adverse drug reaction assessment, and pharmacovigilance reporting requirements.

| Report element | What should be stated | Why it matters for DIAP assessment |
|---|---|---|
| Diagnosis confirmation | Presence or absence of imaging features of acute pancreatitis; note if imaging is normal, limited, or equivocal. | Prevents labelling isolated enzyme elevation as pancreatitis. |
| Atlanta type | Interstitial oedematous pancreatitis versus necrotizing pancreatitis. | Defines the imaging phenotype and supports severity assessment. |
| Necrosis | Location and extent of pancreatic and/or peripancreatic necrosis, when present. | Affects prognosis, follow-up timing, and need for intervention. |
| Collections | Acute peripancreatic fluid collection, acute necrotic collection, pseudocyst, or walled-off necrosis according to timing and content. | Prevents incorrect terminology and inappropriate early drainage. |
| Biliary findings | Gallstones, sludge, common bile duct dilatation, visible duct stones, gallbladder wall changes, or biliary obstruction. | Biliary disease is one of the most important alternative aetiologies to exclude before diagnosing DIAP. |
| Ductal or structural causes | Pancreatic duct dilatation, pancreas divisum, stricture, mass, obstructive lesion, or features suggesting malignancy or autoimmune pancreatitis. | Avoids missing structural or malignant causes of acute pancreatitis. |
| Vascular and other complications | Venous thrombosis, pseudoaneurysm, haemorrhage, bowel involvement, ascites, or other local complications. | Determines severity, urgency, and need for multidisciplinary management. |
| Causality statement | Avoid definitive attribution to a drug; recommend clinical, biochemical, and pharmacological correlation. | Maintains radiological accuracy and reduces over-attribution of pancreatitis to medication exposure. |

## 9. Clinical Pharmacology, Medication Reconciliation and Pharmacist's Role:

Clinical pharmacology and medication reconciliation are indispensable parts of suspected drug-induced acute pancreatitis work-up since causality assessment is not possible without proper medication history reconstruction(18, 58, 86). Simple medication lists of admissions are not enough. Review should include prescription drugs, recently finished courses of drugs, OTC medications, herbs, supplements, vitamins, drugs containing calcium, hormonal drugs, antidiabetics, antiretrovirals, immunosuppressive drugs and chemotherapy treatment(22, 87).

Medication history should be presented chronologically including indication for the drug, dates of drug initiation and discontinuation, dose, route of administration, recent dose changes and modifications, adherence, dose adjustments based on renal or liver function, prior drug exposure, latency between exposure and symptoms, de-challenge and rechallenge(2, 7, 88).

Pharmacists will also find indirect or interaction-based mechanisms of medication association with pancreatitis. Some drugs can increase the risk of developing pancreatitis by their effects on triglycerides, hypercalcemia, dehydration, renal function, or metabolic interaction despite of lack of pancreatic toxicity. For patients who take many drugs, the best conclusion can be made about medication-associated pancreatitis(6, 89).

Withdrawal of suspected drugs should be based on both the degree of causality and necessity of the drug to the patient. Non-essential drugs with appropriate timing and alternative medications can be withdrawn early. Essential drugs such as anticonvulsants, chemotherapeutic agents, immunomodulating agents, antiretrovirals, and biologicals need consultation by different specialists before withdrawing, substituting, or readministering them(6, 11, 58).

Pharmacy intervention is also valuable for improving documentation and pharmacovigilance reporting. High-quality report consists of a suspect drug, medication time course, latency period, changes in dose, information about de-challenge/rechallenge, possible causes excluded from etiology, imaging findings, severity of the disease, other medications used, concomitant diseases, and overall causality assessment. Good documentation will reduce the risk of inappropriate rechallenge and unnecessary avoidance of a drug with unknown causality(6, 8, 11, 23, 90).Key clinical pharmacy responsibilities during DIAP assessment, medication change, recurrence prevention, and pharmacovigilance reporting are described in Table 6.

**Table 6** Clinical pharmacy checklist for suspected drug-induced acute pancreatitis.

| Pharmacy task | Minimum documentation | Reviewer value |
|---|---|---|
| Full exposure list | Prescription drugs, recent short courses, OTC drugs, supplements, hormones, antidiabetic injections, oncology cycles. | Prevents missed culprit exposure and improves reproducibility. |
| Chronology map | Start/stop dates, dose changes, latency to symptoms, prior exposure, adherence. | Differentiates plausible drug timing from incidental background therapy. |
| Interaction review | Renal/hepatic function, CYP/P-gp interactions, dehydration, lipid/calcium effects, polypharmacy. | Identifies multi-drug or indirect metabolic mechanisms. |
| Essentiality assessment | Is the drug replaceable, temporarily interruptible, or essential for survival/disease control? | Guides safe withdrawal without harming primary disease management. |
| Alternative plan | Substitute drug, dose adjustment, monitoring, specialist follow-up. | Prevents recurrence while preserving necessary therapy. |
| ADR documentation | Probability level, evidence basis, excluded causes, recommendation regarding rechallenge. | Improves future care and pharmacovigilance quality. |

## 10. Early Detection, Monitoring, and Prevention of Recurrence

The early detection of drug-induced acute pancreatitis is clinically significant because further drug administration could exacerbate or cause recurrence of the pancreatitis. There is no existing biomarker of preclinical DIAP. The routine serial testing of amylase and lipase in asymptomatic and low-risk patients is unjustified since unnecessary tests will lead to false positives, anxiety, unnecessary imaging studies, and unnecessary medication withdrawal.(7, 40, 57, 91).

Symptom-directed and risk-based monitoring is hence the better approach. Those who will initiate medication that has high risks of causing acute pancreatitis should be encouraged to report to their health practitioners in case they exhibit symptoms such as persistent abdominal pain, back pain, nausea, vomiting, fever, or any other unexpected clinical decline in condition. Triglyceride and calcium levels can also be measured at baseline or specifically targeted in those on medications that will affect their lipid and calcium metabolism.(6, 7).

Monitoring must be personalized in high-risk situations, including oncology, hematology, transplant medicine, inflammatory bowel diseases, epilepsy, and complicated antiretroviral therapy. Patients in such conditions can experience death or lack of control over their conditions due to stopping, changing, or restarting a suspect drug, and hence, decisions on monitoring must be part of multidisciplinary treatment.(15, 21, 59).

Prevention of recurrence requires proper documentation and communication. In case when the probability of DIAP is high, the suspected causative agent, its latency, the degree of reaction, the ruled out causes of reaction, reaction to dechallenge, and the decision about possible rechallenges should be written down in the patient's discharge note and adverse drug reaction list(2, 87, 92).

## 11. Management of Suspected Drug-Associated Acute Pancreatitis

Management of drug-induced acute pancreatitis starts with management of acute pancreatitis using the basic principles with the added advantage of ensuring no further injury from the drug. Management will involve assessment of severity, provision of pain relief, individual fluid resuscitation, correction of metabolic derangements, and use of oral or enteral nutrition early as well as monitoring for failure of organs or complications arising from the pancreatitis(18, 93, 94).

The medication suspected to cause the condition will usually be withdrawn where there is a moderate or high degree of certainty of causation, where the medication is not essential, where there is an option for use of a safe medication, or where the pancreatitis is moderate, severe, necrotizing, recurrent, or where there is temporality of the condition and the drug. Such drugs will include the thiopurines, valproic acid, didanosine, and L-asparaginase(5, 7, 32, 91, 95).

Rechallenge is best avoided in cases where the patient experienced moderate, severe, necrotizing, or recurrent pancreatitis. Even though recurrence upon rechallenge can provide good evidence that the drug caused the disease, rechallenge is rarely ethical. Accidental re-challenge should be well-documented, since it might provide strong evidence and prevent future accidents(4, 32, 90).

In the case of an essential drug, an individualized approach is recommended, which implies multidisciplinary discussion. This step is important when treating epilepsy with antiepileptics, using chemotherapy to treat cancer, using immunosuppressive therapy in transplant patients, antiretroviral therapy, biologics, and immune checkpoint inhibitors. When deciding what to do, it is important to take into account the risk of pancreatitis recurrence compared to the risks associated with stopping the treatment of the underlying disease(73, 80, 90).

Antibiotics should not be used for uncomplicated acute pancreatitis or sterile necrosis. Interventional radiology, endoscopy, or surgery should only be considered in case of clear indications like infected necrosis, symptomatic or complicated collections, obstruction, bleeding, or other complications using general principles of acute pancreatitis management(2, 96).

In summary, the treatment strategy must take into consideration the severity of pancreatitis as well as the likelihood of causality. The ultimate decision-making process must be clear to all members of the treatment team including the radiologist, clinical pharmacist, and the patient to avoid rechallenge or discontinuation of necessary therapy.

## 12. Special populations and high-risk clinical settings

Valproic acid, L-asparaginase, corticosteroids, combination of antiepileptic drugs, and metabolic and genetic considerations should all be closely considered. In children and adolescents, symptoms may be nonspecific, and imaging should be selected carefully to minimize unnecessary ionizing radiation.(17, 97). In older patients, potential risks include polypharmacy, weakness, renal and hepatic impairment, dehydration, biliary conditions, cardiovascular disease, and an atypical presentation. Medication review should include OTC drugs, supplements, any recent antibiotic exposure, and medication dose adjustments. Deprescribing assessment is equally significant as acute management(23, 98, 99).

In pregnant patients, ruling out cholelithiasis and hypertriglyceridemia is key. Ultrasonography and MRIs should always be used when possible while considering the risks associated with CT scanning for both mother and fetus. Medication history needs to consider the effect of pregnancy on lipids, bile secretion, and drug metabolism(2, 100, 101).

Oncology/hematology patients are among the hardest to deal with. The causes of AP can include chemotherapy, L-asparaginase, immune checkpoint inhibitors, tyrosine kinase inhibitors, infections, tumor obstruction, cholangiopathies, metabolic disorders caused by tumors, supporting drugs, and combinations of these factors. Any questions regarding discontinuation or reintroduction of agents require consultation with oncology/hematology specialists(13, 63, 102).

Inflammatory bowel diseases should also be considered individually. Pancreatitis from thiopurine agents is known as an early idiosyncratic phenomenon, but inflammatory bowel disease, duodenitis, gallstones, corticosteroids, mesalamine, and infections can interfere with proper diagnosis. Differentiation avoids both risky reintroductions and unnecessary withholding of therapeutic drugs(61, 72, 103, 104).

## 13. Pharmacovigilance, Reporting Standards, and Research Needs

Pharmacovigilance is important for drug-induced acute pancreatitis since adverse drug reactions are rare and cannot be detected during pre-marketing trials. Spontaneous reporting systems like FAERS, VigiBase, and national pharmacovigilance databases can detect possible signals and formulate hypotheses. Nevertheless, these reports alone cannot prove the association due to inherent weaknesses such as under-reporting, stimulated reporting, duplicates, lack of clinical information, reporting bias, and non-availability of valid denominator of exposure(18, 105-107).

Quality reporting is hence imperative. For suspected case of DIAP, there should be established criteria for acute pancreatitis, history of medication, dosage and period of exposure, latency period, presence or absence of de-challenge and rechallenge, history of alcohol intake, status of gallstones, triglyceride and calcium level, imaging results, any co-morbid conditions, other drugs used, severity, treatment, and outcome. Reports which say only that pancreatitis developed during use of the drug have little scientific value(61, 108-110).

Several areas of ongoing knowledge deficiency persist as major limitations of this field. First, there is currently no validated causality score for DIAP. The existing general causality scores for adverse drug reactions have not adequately considered issues that are specific to DIAP, including latency, ethics of rechallenge, biliary risks, metabolic considerations, and imaging assessment of completeness. A future causality score specific for DIAP should take into account confirmation of acute pancreatitis, exclusion of biliary or structural cause of pancreatitis by imaging, triglyceride and calcium levels, timing of drugs, evidence for drug, host susceptibilities, and alternative causes(6, 17, 21, 72).

Second, a prospective multi-center registry would be required. Such a registry should collect data in a standard manner on demographics, co-morbidities, alcohol consumption, gallstone disease, triglyceride and calcium levels, starting and stopping dates of drug use, dosing changes, other medications, kidney and liver function, imaging phenotypes, severity and complications of pancreatitis, drug withdrawal, rechallenge, recurrence, and outcomes. Standardized case ascertainment is needed for any future systematic review to avoid reliance on uncertain case reports and limited pharmacovigilance data(7, 21, 40).

Third, pharmacogenomic and metabolomic factors should be considered in the study of high-risk medications. The link between thiopurine-induced pancreatitis shows that host susceptibility can be clinically important, although there are still many other categories of drugs whose mechanism remains unknown. Markers of pancreatic stress, mitochondrial dysfunction, dyslipidemia, calcium metabolism, and inflammatory activation could be potentially useful in separating susceptible individuals from tolerant ones who are exposed to a certain medication(41, 44, 111).

Fourth, pharmaco-epidemiologic analyses of real-world data should employ active comparators and control confounding by indication in the analysis of antidiabetics, lipids, cardiometabolic, antimicrobial, and oncological agents. Combining information on electronic health records, medication exposure history, lab results, radiological reports, and independent adjudication may provide a higher quality of future research(18, 105-107).

The use of artificial intelligence technologies may aid future DIAP research through identification of relevant electronic records, acute pancreatitis cases documented by imaging, creation of medication timelines, and detection of recurring patterns in big datasets. At the same time, proper validation is necessary to prevent over-attribution, overlooking other causes of pancreatitis, and alert fatigue (77, 112, 113). Required minimum reporting elements for suspected DIAP cases are presented in Table 7.

**Table 7** Minimum reporting checklist for suspected drug-induced acute pancreatitis cases proposed by authors based on reporting standards and DIAP literature.

| Reporting item | Minimum information required |
|---|---|
| AP confirmation | Pain description, serum lipase or amylase values, imaging findings when available, and diagnostic criteria fulfilled. |
| Aetiology exclusion | Gallstone assessment by ultrasound/MRCP/EUS when relevant, alcohol history, triglyceride level, calcium level, ERCP or trauma history, autoimmune markers when indicated, and tumour or obstruction assessment. |

| | |
|---|---|
| Medication timeline | Complete list of drugs, start and stop dates, dose and route, dose changes, latency from exposure to symptoms, interactions, previous exposure, and recent short courses or over-the-counter medications. |
| Causality reasoning | Naranjo or WHO-UMC assessment if used, drug-specific evidence class, biological plausibility, de-challenge response, rechallenge information if accidental, and competing aetiologies. |
| Severity and imaging | Atlanta severity category, interstitial versus necrotizing pancreatitis, fluid collections, vascular complications, organ failure, and interventions if performed. |
| Outcome and prevention | Drug withdrawal or substitution, clinical outcome, recurrence, discharge documentation, patient counselling, pharmacovigilance reporting, and recommendation regarding rechallenge. |

### *Limitations of the review*

There are various limitations with regard to this review. One, this is a narrative review without any pooled risk estimates or meta-analyses included. While the literature search process has been structured, the inclusion of the studies for evidence synthesis is driven by clinical significance, quality of methodology, and contributions to evidence synthesis without following systematic review methods.

Two, the conclusions with regards to DIAP would be limited by the quality of literature available. The association between many medications and DIAP has been reported based on case reports or case series and spontaneous pharmacovigilance, without the exclusion of common etiologies for acute pancreatitis, lack of imaging evidence, medication timing, and without causality evaluation.

Three, evidence for newer medications is very dynamic. There could be changes in associations for antidiabetics, oncology medications, biologics, immune checkpoint inhibitors, and multiple medication regimens in the near future with pharmacoepidemiologic studies and more robust pharmacovigilance data.

## 14. Conclusion

DIAP is a rare but significant cause of AP. It must not be diagnosed purely based on temporal association, since many patients with AP receive drugs that are coincidental rather than causative. An accurate diagnosis necessitates the demonstration of AP, exclusion of common causes, chronology of drug exposure, assessment of latency period and dechallange, analysis of drug-specific literature, host susceptibility and clinical reasoning.

Imaging contributes significantly by confirming AP where necessary, quantifying the severity, identifying complications, and ruling out biliary, ductal, structural or neoplastic etiologies. However, imaging findings do not have any drug-specificity and cannot prove causality on its own. Likewise, contribution of clinical pharmacy services in the form of reconstruction of the drug exposure history, identification of drug interactions or indirect metabolic pathways, evaluation of drug necessity and safe withdrawal/substitution is equally critical.

A pragmatic evidence-informed strategy will help avoid underdiagnosis, which might lead to recurrence after re-exposure and overdiagnosis, which might lead to unnecessary discontinuation of the required therapy. Further improvements in the future will demand a standardized case reporting format, registry of DIAP cases, DIAP-specific causality assessment scales, and application of pharmacogenomics, metabolomics, imaging and pharmacovigilance data.

## Compliance with ethical standards

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The authors have no acknowledgments to declare.

### *Disclosure of conflict of interest*

The authors declare that they have no conflicts of interest related to this manuscript.

*Statement of ethical approval*

Ethical approval was not required for this study because it is a narrative review based exclusively on previously published literature and does not involve human participants, animal subjects, patient records, clinical intervention, or identifiable personal data.

*Statement of informed consent*

Informed consent was not required because this article is a narrative review and does not include individual patient data, images, or identifiable clinical information.

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