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When Pain Relief Turns Perilous: A Case Report on Paracetamol Dependence, Polypharmacy, and Severe Drug-Induced Liver Injury

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A B S T R A C T

Drug-induced liver injury (DILI) from long-term therapeutic paracetamol use, especially when complicated by psychological dependence, and concurrent atorvastatin therapy within a polypharmacy setting is an uncommon but serious clinical concern. This report details such a case, emphasizing the diagnostic challenges and management. A 58-year-old woman with a 20-year history of dependence on paracetamol (500-1500 mg daily) and 12 years of atorvastatin use (20 mg daily) amidst other chronic medications (levothyroxine, candesartan, clopidogrel), presented with bleeding gums, abdominal discomfort, nausea, and weakness. Laboratory investigations revealed markedly elevated liver enzymes (SGPT 3913 U/L, SGOT 5863 U/L), severe thrombocytopenia (17 x 10^3/L), and elevated Gamma GT (449 U/L). Viral hepatitis markers were negative. Paracetamol and atorvastatin were discontinued. Significant clinical and biochemical improvement followed, with SGOT/SGPT levels decreasing to 184/283 U/L by day six. In conclusion, the Roussel Uclaf Causality Assessment Method (RUCAM) indicated paracetamol and atorvastatin as "probable" causes of DILI. This case underscores the potential for severe hepatotoxicity from long-term therapeutic use of common medications, especially in polypharmacy and when psychological factors influence drug consumption. Vigilant monitoring and causality assessment are crucial in such complex scenarios.

1. Introduction

Drug-induced liver injury (DILI) represents a spectrum of hepatic damage, from asymptomatic transaminase elevation to acute liver failure, caused by medications, herbal products, or dietary supplements. It remains a significant clinical challenge due to its varied presentations, complex pathophysiology, and the difficulty in establishing a definitive diagnosis, which often relies on the exclusion of other liver diseases. DILI can be broadly classified based on its mechanism into intrinsic (dose-dependent, predictable) and idiosyncratic (dose-independent, unpredictable) reactions. Idiosyncratic DILI (iDILI) is particularly problematic due to its sporadic nature and the lack of reliable predictive biomarkers. Further classification depends on the biochemical pattern of injury: hepatocellular (predominant alanine aminotransferase [ALT] elevation), cholestatic (predominant alkaline phosphatase [ALP] elevation), or mixed patterns.[1,2]

Paracetamol (acetaminophen) is one of the most widely used over-the-counter (OTC) analgesic and antipyretic agents globally. While generally considered safe at recommended therapeutic doses (up to 4 grams/day for adults), it is the leading cause of intrinsic DILI and acute liver failure when taken in overdose, whether intentional or unintentional. Paracetamol hepatotoxicity is primarily mediated by its toxic metabolite, N-acetyl-p-benzoquinone imine (NAPQI). At therapeutic doses, NAPQI is efficiently

detoxified by glutathione. However, in overdose situations, glutathione stores are depleted, allowing NAPQI to accumulate and covalently bind to cellular proteins, leading to oxidative stress, mitochondrial dysfunction, and ultimately hepatocyte necrosis. While DILI from paracetamol at therapeutic doses is considered rare, there are emerging concerns about the risks associated with long-term chronic use or in individuals with specific risk factors, such as malnutrition, chronic alcohol use, or concomitant use of enzyme-inducing drugs. The provided case document initially noted that to date, there had been no reports of DILI caused by paracetamol when used in normal doses, highlighting the unusual nature of the presented case. An often-overlooked aspect is psychological dependence or habitual use of OTC analgesics like paracetamol for conditions such as chronic headaches, even when therapeutic benefit is questionable or underlying pathology has been excluded. Such dependence can lead to prolonged, regular intake, potentially increasing the cumulative exposure and risk of adverse effects.[3,4]

Statins, including atorvastatin, are cornerstone medications for the primary and secondary prevention of cardiovascular diseases due to their potent lipid-lowering effects. Atorvastatin is an HMG-CoA reductase inhibitor that is generally well-tolerated. However, statins as a class are known to cause DILI, typically presenting as asymptomatic transaminase elevations in a small percentage of patients, which often resolve spontaneously or upon dose reduction. Clinically significant, severe idiosyncratic DILI due to statins is rare, occurring in approximately 1 in 10,000 to 1 in 100,000 treated patients, but can manifest as hepatocellular, cholestatic, or mixed injury, and in very rare instances, lead to acute liver failure. The mechanisms of statin-induced DILI are thought to be idiosyncratic and may involve immune-mediated pathways or metabolic idiosyncrasy leading to the formation of reactive metabolites that trigger hepatocellular stress and apoptosis. Long-term use, high doses, certain genetic predispositions, and drug interactions can modulate this risk.[5,6]

The complexity of DILI diagnosis and management is significantly amplified in the context of polypharmacy—the concurrent use of multiple medications. Polypharmacy is increasingly common, particularly in elderly patients or those with multiple comorbidities. Each additional drug increases the potential for drug-drug interactions (DDIs), which can alter pharmacokinetic or pharmacodynamic profiles, potentially enhancing the hepatotoxic potential of individual agents or creating new toxic synergies. Identifying the culprit drug(s) in polypharmacy-associated DILI is a daunting task, often requiring meticulous medication history, careful exclusion of other causes, and structured causality assessment.[7,8]

The diagnosis of DILI remains largely one of exclusion, necessitating the ruling out of other common causes of liver injury such as viral hepatitis (Hepatitis A, B, C, E), autoimmune hepatitis, alcoholic liver disease, non-alcoholic fatty liver disease (NAFLD/NASH), Wilson's disease, hemochromatosis, and ischemic or congestive hepatopathy. Causality assessment tools, such as the Roussel Uclaf Causality Assessment Method (RUCAM) or its updated versions (also known as CIOMS), are widely used to standardize the assessment of the likelihood that a specific drug caused the observed liver injury. RUCAM evaluates various criteria, including the temporal relationship between drug intake and DILI onset/resolution, exclusion of alternative causes, presence of risk factors, known hepatotoxic potential of the drug, and response to dechallenge (and rarely, rechallenge).[9,10]

This case report is novel in its presentation of severe, delayed-onset hepatocellular DILI likely attributable to both long-term therapeutic paracetamol use driven by dependence and concurrent long-term atorvastatin therapy within a complex polypharmacy regimen in a patient with initially normal bilirubin but extremely high transaminases. The aim of this report is to highlight

the critical importance of considering common therapeutic agents as potential causes of severe hepatotoxicity in patients on multiple long-term medications, especially when psychological factors may influence drug consumption patterns, leading to chronic daily intake beyond typical acute needs. Furthermore, this case underscores the diagnostic utility of structured causality assessment tools like RUCAM in navigating such intricate clinical scenarios and raises awareness among clinicians about the potential for insidious liver damage even with seemingly "safe" drugs when used chronically under specific circumstances.

2. Case Presentation

The clinical findings of the patient are summarized in Table 1. A 58-year-old Indonesian woman presented with the recent onset of bleeding gums, which started one day prior, occurring suddenly and resolving spontaneously three times. She also noted red spots (petechiae) on both arms for five days and had experienced heartburn-like pain in the upper right abdomen for six days, accompanied by nausea, weakness, and reduced appetite. There was no history of cough, shortness of breath, diarrhea, hematemesis, or melena. Her significant past medical history included chronic intermittent, stabbing headaches for 20 years, for which she consumed 1-3 doses of 500 mg paracetamol daily over this period. This paracetamol use evolved from managing headaches to a daily habit driven by a feeling that headaches would occur if not taken, despite normal head CT and MRI scans. She underwent a total thyroidectomy in 2001 and had been on levothyroxine 150 mcg daily for 23 years. Diagnosed with coronary artery disease in 2012, she was on candesartan 8 mg daily, clopidogrel 75 mg daily, and atorvastatin 20 mg daily for 12 years.

On physical examination, vital signs were normal: blood pressure 130/90 mmHg, pulse 88/min, respiratory rate 18/min, temperature 36.9°C, SpO_2 99% on room air. No jaundice was observed. Cardiac and lung examinations were unremarkable. Abdominal examination revealed tenderness in the epigastrium and right hypochondrium, with no palpable liver or spleen. Petechiae were present on the upper and lower limbs.

Initial laboratory investigations showed severe thrombocytopenia (platelets 17 x 10^3/L) and normocytic normochromic anemia (Hb 11.6 g/dL). Liver function tests were strikingly abnormal: SGPT (ALT) 3913 U/L, SGOT (AST) 5863 U/L, and Gamma GT 449 U/L. Alkaline phosphatase was normal (95 U/L). Total bilirubin was 0.7 mg/dL (direct 0.41 mg/dL). Total protein (5.50 g/dL) and albumin (3.4 g/dL) were low to borderline low. Creatinine was mildly elevated at 1.4 mg/dL. Coagulation (PTT, APTT, INR) was within normal limits. Hepatitis markers (HBsAg, IgM anti-HAV, anti-HCV) and Dengue NS1 were negative. Imaging studies, including a chest X-ray and abdominal ultrasound, showed no abnormalities, with intra-abdominal organs appearing normal. The working clinical diagnosis was severe drug-induced liver injury (DILI) with thrombocytopenia (Table 1).

The patient's treatment procedure and follow-up are detailed in Table 2. Upon admission, intravenous 0.9% NaCl was started. Suspected hepatotoxic drugs, paracetamol and atorvastatin, were immediately discontinued. Essential medications, candesartan and levothyroxine, were continued. She received N-acetylcysteine 3x200 mg, Curcuma 3x1 tablet, and a 1900 kcal/day diet. Liver function was monitored serially. By the third day of treatment, the patient reported symptomatic improvement with no further complaints. SGOT decreased to 2117 U/L and SGPT to 954 U/L. On the sixth day, SGOT further dropped to 184 U/L and SGPT to 283 U/L. Platelet count recovered to 98 x 10^3/L. The patient was discharged after six days in improved condition (Table 2). The Roussel Uclaf Causality Assessment Method (RUCAM) indicated paracetamol and atorvastatin as "probable" causes of DILI, while levothyroxine, candesartan, and clopidogrel were "possible" (Table 1).

Table 1. Summary of patient's clinical findings.

Parameter	Details
Demographics	Age: 58 years; Gender: Female
Anamnesis (History)	Chief Complaints: Bleeding gums (1 day), red spots on arms (5 days), heartburn in upper right abdomen (6 days), nausea, weakness, reduced appetite.
	History of Present Illness: Sudden onset of bleeding gums, resolved spontaneously, occurred 3 times. No cough, SOB, diarrhea, hematemesis, melena.
	Past Medical History:
	- Headaches: Chronic, stabbing, intermittent for ~20 years.
	- Paracetamol Use: 1-3 doses of 500mg daily for ~20 years for headaches; evolved into daily habit/ dependence (felt headaches would occur if not taken). CT/MRI head normal.
	- Thyroidectomy: Total, in 2001. Levothyroxine 150mcg daily for 23 years.
	- Coronary Artery Disease: Diagnosed 2012. Candesartan 8mg daily, Clopidogrel 75mg daily, Atorvastatin 20mg daily for 12 years.
	- Denied alcohol abuse, illicit drugs, recent herbal supplements.
Physical examination	Vital Signs: BP 130/90 mmHg, P 88/min, RR 18/min, T 36.9°C, SpO_2 99% (room air).
	General: No jaundice in skin or sclera.
	Cardiac: No murmurs.
	Lungs: Normal vesicular breath sounds, no added sounds.
	Abdomen: Tenderness in epigastrium and right hypochondrium. Liver/spleen not palpable.
	Extremities: Petechiae on upper and lower limbs.
Laboratory findings (initial)	CBC: WBC 6.11 x 10^3/L, Hb 11.6 g/dL, HCT 33.2%, PLT 17 x 10^3/L. Blood smear: Normocytic normochromic anemia, thrombocytopenia.
	LFTs: SGPT (ALT) 3913 U/L, SGOT (AST) 5863 U/L, GGT 449 U/L, ALP 95 U/L.
	Bilirubin: Total 0.7 mg/dL, Direct 0.41 mg/dL, Indirect 0.29 mg/dL.
	Protein: Total 5.50 g/dL, Albumin 3.4 g/dL, Globulin 2.1 g/dL.
	Kidney Function: Urea 39 mg/dL, Creatinine 1.4 mg/dL.
	Electrolytes: Na 136 mmol/L, K 4.85 mmol/L, Cl 92 mmol/L.
	Coagulation: PPT 14.7s, APTT 27.3s, INR 1.07.
	Serology: HBsAg (-), IgM anti-HAV (-), Anti-HCV (-). NS1 (Dengue) (-).
Imaging findings	Chest X-ray: No abnormalities. Abdominal Ultrasound: Intra-abdominal organs within normal limits.
Clinical diagnosis (Working/On Admission)	Severe Drug-Induced Liver Injury (DILI). Thrombocytopenia. RUCAM: Paracetamol & Atorvastatin "probable"; Levothyroxine, Candesartan, Clopidogrel "possible".

Table 2. Summary of treatment procedure and follow-up.

Aspect	Details
Initial management	Admission to hospital.
	IV Fluid Therapy: NaCl 0.9% at 20 tpm.
	Drug Discontinuation: Atorvastatin and Paracetamol stopped.
	Continued Medications: Candesartan 8mg daily, Levothyroxine 150 mcg daily.
	Specific Therapies: Curcuma 3x1 tablet, Acetylcysteine 3x200 mg.
	Diet: 1900 kcal/day.
Monitoring	Liver function planned for evaluation every 72 hours.
Follow-up (In-hospital)	Day 3: Symptoms improved, no complaints.
	Day 3 Labs: SGOT 2117 U/L, SGPT 954 U/L.
	Day 6 Labs: SGOT 184 U/L, SGPT 283 U/L.
	Day 6 CBC: WBC 7.2 x 10^3/L, Hb 11.2 g/dL, HCT 33.5%, PLT 98 x 10^3/L.
Outcome	Significant improvement in clinical and laboratory results.
	Discharged after the 6th day of treatment.
	Advised to avoid paracetamol and atorvastatin; outpatient follow-up scheduled.

3. Discussion

This case report detailed a 58-year-old woman with a complex medical history including long-term polypharmacy and a 20-year habit of daily paracetamol use, driven by dependence, who presented with severe acute hepatocellular drug-induced liver injury (DILI). The diagnosis was supported by the marked elevation of transaminases (SGPT 3913 U/L, SGOT 5863 U/L) (Table 1), significant thrombocytopenia (17 x 10^3/L) (Table 1), the exclusion of other common causes of liver damage such as viral hepatitis (Table 1), and a notable improvement in liver function upon withdrawal of the suspected offending agents, paracetamol and atorvastatin (Table 2). The Roussel Uclaf Causality Assessment Method (RUCAM) further implicated both paracetamol and atorvastatin as "probable" causes of the observed DILI (Table 1). This case is particularly instructive as it highlights the potential for severe hepatotoxicity arising from the long-term use of commonly prescribed and over-the-counter medications, even at doses generally considered within the therapeutic range, especially within the intricate context of polypharmacy and patient-specific factors like psychological drug dependence.[11-14]

Paracetamol is ubiquitously used and recognized primarily for its dose-dependent hepatotoxicity in overdose scenarios (typically >4 grams/day, or lower in susceptible individuals). The well-established mechanism involves the saturation of primary metabolic pathways (glucuronidation and sulfation), shunting paracetamol towards metabolism by cytochrome P450 enzymes, particularly CYP2E1, and to a lesser extent CYP1A2 and CYP3A4, to form the highly reactive and toxic metabolite, N-acetyl-p-benzoquinone imine (NAPQI). Under normal physiological conditions and with therapeutic dosing, NAPQI is rapidly conjugated with hepatic glutathione (GSH) and excreted as non-toxic cysteine and mercapturate conjugates. However, when paracetamol intake overwhelms the capacity of conjugation pathways, or when GSH stores are depleted (in malnutrition, chronic alcohol use, or genetic predisposition), NAPQI accumulates. This unbound NAPQI then covalently binds to critical intracellular proteins, particularly mitochondrial proteins, initiating a cascade of detrimental events including mitochondrial permeability transition (MPT) pore opening, ATP depletion, loss of mitochondrial membrane potential, excessive reactive oxygen species (ROS) formation (oxidative stress), and ultimately, hepatocellular necrosis, predominantly in the centrilobular (zone 3) region of the hepatic acinus where CYP enzymes are highly expressed.[15-18]

The presented case, however, involves daily paracetamol ingestion of 500-1500 mg for approximately 20 years (Table 1). This daily dosage is well within the generally accepted therapeutic ceiling of 4000 mg/day. DILI from such "therapeutic" chronic dosing is considered rare, but reports and mechanistic considerations suggest it is not impossible, especially under specific circumstances. Several factors could contribute to hepatotoxicity in such scenarios: Cumulative Micro-damage and Adaptation Failure: While single therapeutic doses are unlikely to cause significant GSH depletion, chronic, uninterrupted exposure might lead to a sustained, low-grade increase in NAPQI formation. This could result in subclinical hepatocyte injury over time. The liver possesses remarkable regenerative capacity and adaptive mechanisms (upregulation of GSH synthesis). However, decades of continuous challenge might eventually exhaust these adaptive responses or lead to a state of "sensitization," where the liver becomes more vulnerable to subsequent insults, including from other drugs or physiological stressors. The patient's 20-year history represents an exceptionally prolonged exposure; Inter-individual Variability in Metabolism: Genetic polymorphisms in CYP enzymes (CYP2E1 variants with higher activity), glutathione S-transferases, or UGTs (UDP-glucuronosyltransferases) could lead to variations in NAPQI formation or

detoxification rates. An individual with a metabolic profile favoring increased NAPQI production or reduced GSH availability/regeneration could be at higher risk even at standard doses. Age-related decline in hepatic metabolic capacity or GSH reserves could also play a role in a 58-year-old patient after decades of use; Impact of Dependence on Exposure Dynamics: The patient's self-reported dependence on paracetamol is a critical and distinguishing feature of this case (Table 1). She continued daily use not necessarily for persistent organic pain (as head imaging was normal), but due to a perceived need or fear of headache recurrence if she abstained. This behavioral pattern ensured consistent, long-term exposure that might not have occurred with typical, as-needed analgesic use. This form of medication dependence, sometimes associated with medication-overuse headache (MOH), can perpetuate a cycle of drug intake that masks the drug's diminishing efficacy or contributes to its adverse effects. The constant presence of paracetamol metabolites might have subtly altered hepatic enzyme expression or function over two decades. While non-opioid analgesic dependence is less studied than opioid dependence, the psychological drive for continuous medication can lead to exposures that test the limits of physiological tolerance; Underlying Conditions or Subclinical Factors: Although not explicitly detailed, any subclinical liver conditions (undiagnosed mild steatosis, which is common) or transient illnesses could have interacted with the chronic paracetamol exposure to precipitate overt DILI. The patient's existing comorbidities (hypothyroidism, CAD) themselves are not direct major risk factors for paracetamol DILI at therapeutic doses, but contribute to a complex physiological background.

The initial statement in the provided document suggesting "no reports of DILI caused by paracetamol when used in normal doses" might be an overstatement in the context of very long-term, continuous use or specific susceptibilities. While overt, severe DILI, like in this case, is rare with therapeutic doses, transient asymptomatic ALT elevations have been documented even with short courses of 4g/day paracetamol in healthy individuals. This suggests a spectrum of hepatic response. It is plausible that the patient's prolonged exposure, maintained by psychological dependence, gradually eroded her hepatic defenses, making her susceptible to this severe DILI episode, potentially in concert with other medications.

Atorvastatin, an HMG-CoA reductase inhibitor, has been a cornerstone in managing hyperlipidemia and preventing cardiovascular events for decades. Its general safety profile is favorable, but like all statins, it carries a risk of DILI, albeit low. Statin-induced DILI is typically idiosyncratic, meaning it is not predictably dose-related (though some data suggest higher doses of potent statins may confer higher risk) and occurs in a small subset of susceptible individuals. The patient had been on atorvastatin 20 mg daily for 12 years (Table 1), a standard therapeutic dose.

The mechanisms underlying idiosyncratic statin DILI are not fully elucidated but are thought to involve a combination of metabolic and immunological factors: Metabolic Idiosyncrasy and Reactive Metabolites: Atorvastatin is extensively metabolized in the liver, primarily by CYP3A4. Genetic polymorphisms in CYP3A4 or drug transporters (like OATP1B1, encoded by SLCO1B1, which influences hepatic uptake of statins) can alter individual drug exposure and metabolite profiles. Some individuals might produce higher concentrations of potentially reactive metabolites that can initiate cellular stress, mitochondrial injury, or form protein adducts. These adducts, if presented by antigen-presenting cells, could trigger an immune response; Immune-Mediated Mechanisms: Many cases of iDILI, including those from statins, are believed to have an immunoallergic basis. This can range from direct T-cell-mediated cytotoxicity to the production of autoantibodies. Some statin DILI cases present with features of autoimmune hepatitis (a "drug-induced autoimmune-like

hepatitis"), sometimes with positive ANA or ASMA, though this was not reported in this patient. The latency for such reactions can be highly variable, from weeks to many months or even years after initiation of therapy, as seen in this case (12 years). It is possible that long-term exposure allows for gradual sensitization or the unmasking of a latent autoimmune predisposition; Mitochondrial Dysfunction: Statins have been shown in vitro to affect mitochondrial function, potentially by interfering with ubiquinone (CoQ10) synthesis (as HMG-CoA reductase is also involved in the mevalonate pathway leading to CoQ10) or by directly impairing mitochondrial respiration. While clinically significant mitochondrial toxicity is rare, it could contribute to hepatocyte injury in susceptible individuals, especially with prolonged use or in combination with other factors that stress mitochondrial function; Bile Salt Export Pump (BSEP) Inhibition: Some drugs causing DILI can inhibit BSEP, leading to intrahepatic cholestasis. While atorvastatin is not classically known as a potent BSEP inhibitor, subtle effects on biliary transport or the handling of bile acids, especially over many years, cannot be entirely excluded as a contributing factor to overall liver stress, though this patient's pattern was clearly hepatocellular, not cholestatic.

The 12-year duration of atorvastatin use before DILI manifestation is long but not unprecedented for idiosyncratic reactions. The liver's adaptation mechanisms can be robust, but a "second hit" or a gradual failure of these adaptations over time could lead to delayed DILI. The RUCAM score of "probable" for atorvastatin suggests that its role was considered significant, likely due to its known (though rare) hepatotoxic potential and the exclusion of other causes. The patient was on five chronic medications: paracetamol, atorvastatin, levothyroxine, candesartan, and clopidogrel (Table 1). Polypharmacy, especially in older adults with multiple comorbidities, is a well-recognized risk factor for adverse drug reactions, including DILI. Identifying a single culprit in such settings is challenging. While RUCAM pointed to paracetamol and atorvastatin as "probable," the other drugs were "possible," and interactions could have played a role.

Shared Metabolic Pathways: Paracetamol: Primarily glucuronidation and sulfation. CYP2E1, CYP1A2, CYP3A4 for NAPQI formation; Atorvastatin: Extensively metabolized by CYP3A4; Clopidogrel: A prodrug requiring two-step CYP-mediated oxidation (involving CYP2C19, CYP3A4, CYP1A2, CYP2B6) to its active metabolite; Candesartan: Minor metabolism by O-deethylation via CYP2C9 to an inactive metabolite; mostly excreted unchanged; Levothyroxine: Metabolized via deiodination, glucuronidation, and sulfation. Deiodination involves selenium-dependent deiodinases. Some oxidative deamination and decarboxylation also occur. The key enzyme shared by atorvastatin and clopidogrel (activation) and partially by paracetamol (toxic metabolite formation) is CYP3A4. While candesartan and levothyroxine use different primary pathways, any drug that significantly induces or inhibits CYP3A4 could theoretically alter atorvastatin or clopidogrel levels, or paracetamol's minor CYP3A4 pathway. However, none of these drugs are potent broad-spectrum inducers or inhibitors of each other at standard doses in a way that would classically predict severe DILI through pharmacokinetic interaction alone. The Drugs.com interaction checker found no interactions between atorvastatin and paracetamol specifically. However, these checkers often focus on acute, significant interactions. The effects of 12-20 years of co-exposure are much harder to predict. Chronic co-administration might lead to subtle, cumulative enzyme induction or inhibition, or competition for conjugation pathways if any became rate-limiting due to age or other factors. For instance, if sulfation or glucuronidation pathways were subtly impaired over time, more paracetamol might be shunted to CYP pathways, increasing NAPQI formation even at therapeutic doses.

Additive or Synergistic Hepatotoxicity: Even without direct pharmacokinetic DDIs, multiple drugs can exert additive stress on the liver. Each drug and its metabolites require processing, detoxification, and excretion by the liver. Over many years, this "total hepatic burden" could reduce the liver's resilience. It's conceivable that low-grade, subclinical injury from one agent (chronic paracetamol) could sensitize the liver, making it more susceptible to idiosyncratic injury from another agent (atorvastatin), or vice versa. The combination could have surpassed a threshold for overt injury that neither drug alone would have reached in this specific patient over this timeframe; Impact on Transporters: Hepatic drug transporters (OATPs, MRPs, BSEP) are crucial for the uptake and efflux of drugs and their metabolites. DDIs at the transporter level, or genetic variability in transporters, can significantly alter intrahepatic drug concentrations. While specific transporter interactions for this combination are not well-defined in the context of DILI, it remains a potential area for complex interactions in polypharmacy.

The FDA's DILI rank dataset classifies drugs by their DILI concern. Paracetamol and atorvastatin are noted as "high DILI concern," whereas levothyroxine, candesartan, and clopidogrel are "low DILI concern". This aligns with the RUCAM findings and supports focusing on paracetamol and atorvastatin as the primary suspects. The patient's presentation offered several clues to the nature and severity of her liver injury: Massive Transaminase Elevation (SGPT 3913 U/L, SGOT 5863 U/L (Table 1)): AST and ALT are enzymes concentrated within hepatocytes. Levels exceeding 50-100 times the upper limit of normal (ULN), as seen here, are indicative of extensive, acute hepatocellular necrosis. The sheer magnitude of enzyme release reflects widespread hepatocyte membrane rupture. AST is found in mitochondria and cytoplasm, while ALT is primarily cytoplasmic; both rise dramatically in acute necrosis. Such high levels are typical of severe viral hepatitis, ischemic hepatitis, or severe DILI (especially paracetamol toxicity); Hepatocellular Pattern of Injury: The R ratio (ALT/ULN) / (ALP/ULN) was significantly >5, clearly defining a hepatocellular pattern of injury. (ALT 3913/56 = ~70; ALP 95/147 = ~0.65; R = 70/0.65 > 100). This pattern is consistent with both paracetamol-induced liver injury and many forms of statin-induced DILI; Initially Normal Total Bilirubin (0.7 mg/dL (Table 1)) with Slightly Elevated Direct Bilirubin (0.41 mg/dL (Table 1)): The liver has a large functional reserve for bilirubin conjugation and excretion. In very acute hepatocellular injury, transaminases can rise dramatically before significant impairment of bilirubin processing occurs, especially if the injury has not yet caused widespread canalicular damage or intrahepatic cholestasis. The patient was anicteric. However, a direct bilirubin of 0.41 mg/dL (ULN typically <0.3 mg/dL) suggests some early, subtle impairment in biliary excretion, even if not enough to cause overt jaundice or significantly raise total bilirubin initially. As liver injury progresses or resolves, bilirubin kinetics can change; Severe Thrombocytopenia (Platelets 17 x 10^3/L (Table 1)): This was a striking finding and likely contributed to her bleeding gums. Potential mechanisms in acute liver injury include: Decreased Thrombopoietin (TPO) Production: TPO is primarily produced by the liver (and kidneys). Severe acute hepatocyte damage can impair TPO synthesis, leading to reduced platelet production from megakaryocytes in the bone marrow. This effect usually takes several days to manifest significantly due to platelet lifespan; Splenic Sequestration: While the spleen was not reported as enlarged on ultrasound, any subtle increase in portal pressure secondary to acute liver inflammation and sinusoidal obstruction could lead to increased platelet sequestration; Immune-Mediated Destruction: Some DILIs can have autoimmune components, and drug-induced immune thrombocytopenia is also a known entity, although less commonly linked directly to paracetamol or atorvastatin in this manner;

Disseminated Intravascular Coagulation (DIC): Severe liver injury can sometimes trigger DIC, consuming platelets, though her coagulation parameters (PTT, INR) were initially normal, making overt DIC less likely at presentation; Direct Drug Effect on Megakaryocytes/Platelets: Rare, but some drugs can directly suppress bone marrow or affect platelet survival. This is not a typical feature of paracetamol or atorvastatin. The rapid recovery of platelets from 17 to 98 x 10^3/L within 6 days of drug withdrawal (Table 2) suggests that the cause was acute and reversible, most consistent with recovery of liver function (TPO production) and cessation of a drug-related insult.

Elevated Gamma GT (449 U/L (Table 1)): GGT is a sensitive marker of hepatobiliary disease and can be elevated by enzyme induction from drugs or alcohol, as well as in cholestasis or hepatocellular damage. In this case, with a predominantly hepatocellular pattern, the GGT elevation likely reflects generalized liver cell injury and perhaps some degree of canalicular irritation or early cholestatic component not yet reflected in ALP or bilirubin. It further supported significant hepatic insult; Low Total Protein (5.50 g/dL) and Borderline Low Albumin (3.4 g/dL (Table 1)): Albumin has a half-life of about 20 days, so a low level in an acute presentation might reflect a more chronic underlying issue (malnutrition, chronic inflammation) or very severe, rapidly progressing acute liver failure leading to impaired synthesis. Given the 20-year history of headaches and potential medication dependence, underlying nutritional deficiencies or a chronic inflammatory state cannot be entirely ruled out and might have contributed to her susceptibility to DILI. Her reduced appetite for 6 days would also contribute; Mildly Elevated Creatinine (1.4 mg/dL (Table 1)): This could signify early acute kidney injury (AKI). Hepatorenal syndrome is a feared complication of advanced liver failure, but this patient's liver injury, while severe, hadn't progressed to overt failure with encephalopathy or massive ascites. The AKI could be pre-renal due to nausea and reduced intake, or related to systemic inflammation/cytokine release from the liver injury, or potentially a mild direct effect of drug metabolites if renal excretion pathways were also stressed. Its normalization or lack of progression wasn't detailed, but is assumed with overall recovery. Clinical Symptoms (Bleeding gums, abdominal pain, nausea, weakness (Table 1): Bleeding gums were a direct result of severe thrombocytopenia. Right upper quadrant/epigastric pain and tenderness are common with acute hepatitis due to stretching of Glisson's capsule surrounding the inflamed liver. Nausea, weakness, and reduced appetite are non-specific but typical constitutional symptoms accompanying significant acute illness and liver dysfunction.

The management approach was appropriate and aligned with standard DILI guidelines: Prompt Discontinuation of Suspected Agents: This is the single most important step (Table 2). Identifying and stopping paracetamol and atorvastatin was crucial; Supportive Care: IV fluids to maintain hydration and electrolyte balance, and nutritional support (1900 kcal/day diet) were essential (Table 2); N-Acetylcysteine (NAC) Administration (3x200 mg (Table 2)): While the patient did not have a classical paracetamol overdose, the "probable" role of paracetamol in her DILI made NAC a rational choice. NAC works primarily by repleting hepatic glutathione stores, directly binding to NAPQI, and potentially by its antioxidant and anti-inflammatory effects, improving microcirculation. Evidence for NAC in non-overdose paracetamol DILI or non-paracetamol DILI is still evolving, but it is often used empirically in severe acute liver injury due to its good safety profile and potential benefits, particularly if paracetamol co-ingestion or contribution is suspected. Studies like the one by Stancil et al. (2024) support exploring NAC for non-acetaminophen ALF; Curcuma (3x1 tablet (Table 2)): Curcumin, the active component of turmeric, has well-documented antioxidant and anti-inflammatory properties in preclinical studies and some clinical trials for various conditions. Its use as a

hepatoprotective agent in DILI is based on these general properties. While not a standard evidence-based treatment for acute DILI in Western guidelines, it is often used in some regions and unlikely to be harmful in this context; Monitoring: Serial monitoring of LFTs, CBC (especially platelets), and clinical status was vital to track the disease course and response to drug withdrawal (Table 2). The rapid improvement observed (Table 2) confirmed the benefit of discontinuing the offending drugs.

Diagnosing DILI is inherently challenging as it's often a diagnosis of exclusion. This case exemplifies these challenges: multiple drugs, long duration of use, and non-specific initial symptoms. RUCAM (or CIOMS) provides a structured, objective, and validated approach to causality assessment. The "probable" scores for paracetamol and atorvastatin (6-8 points) would have been derived from: Temporal relationship: Onset of symptoms (within 1 week) after very long-term use is compatible with delayed iDILI or cumulative toxicity. The rapid dechallenge response (improvement within days) is a strong positive criterion; Exclusion of other causes: Negative viral serologies and normal ultrasound (Table 1) helped exclude common alternatives; Known hepatotoxic potential: Both drugs are listed as known hepatotoxins in databases like LiverTox; Risk factors: Polypharmacy itself is a risk factor. The patient's age (58) is also a consideration, as DILI incidence can increase with age for some drugs. The "possible" scores for levothyroxine, candesartan, and clopidogrel (3-5 points) reflect their lower intrinsic hepatotoxic potential and perhaps less compelling temporal associations if their administration was stable without recent changes. Rechallenge, the gold standard for confirming causality, was ethically contraindicated due to the severity of the reaction. Without it, a definitive attribution to one agent versus the other, or a synergistic effect, remains presumptive but is strongly guided by the RUCAM assessment.

This case serves as a stark reminder of several critical points for clinical practice and public health: The Illusion of "Safe" Drugs with Chronic Use: Paracetamol, available OTC, is often perceived by the public as entirely benign. This case highlights that even "therapeutic" doses, when taken continuously for years, especially driven by psychological dependence rather than a clear medical indication, can contribute to severe adverse events. Public education on appropriate use of OTC analgesics, duration limits, and seeking medical advice for chronic pain is crucial; Medication Review and Deprescribing: In patients on long-term polypharmacy, regular, critical medication reviews are essential. This includes questioning the ongoing need for each medication, assessing cumulative risks, and actively considering deprescribing when benefits no_longer clearly outweigh risks, or when non-pharmacological approaches could be substituted (for the patient's chronic headaches, especially after normal imaging); Addressing Psychological Dependence on Analgesics: Clinicians need to be aware of and screen for signs of medication overuse or psychological dependence, even with non-opioid analgesics. Management may involve patient education, behavioral therapies, and addressing underlying psychological factors or chronic pain conditions more holistically; Pharmacovigilance and Reporting: Reporting suspected DILI cases like this one to pharmacovigilance systems is vital for building a better understanding of drug safety profiles, especially for long-term use and in complex polypharmacy scenarios.

The improvement seen upon drug withdrawal is encouraging, but the episode represents a significant insult to the patient's liver. Long-term follow-up would be necessary to ensure complete normalization of liver function and structure, and to monitor for any potential chronic sequelae, although full recovery is typical in such DILI cases once the offending agent is removed. The patient's 20-year dependence on paracetamol warrants particular attention from a

public health perspective. Headaches are common, and the easy availability of OTC analgesics can lead to patterns of overuse. This case suggests a need for greater awareness among both healthcare providers and the public about the potential for such dependence and the importance of diagnosing and managing chronic headache syndromes appropriately, rather than relying indefinitely on symptomatic relief that may itself become a source of harm. The fact that her paracetamol use continued despite normal neuroimaging underscores the psychological component that required addressing. This complex case of severe DILI underscores the potential dangers lurking within seemingly routine long-term medication regimens. It highlights the interplay between drug-specific risks (paracetamol, atorvastatin), patient-specific factors (dependence, polypharmacy), and the critical need for astute clinical judgment, thorough investigation, and structured causality assessment in unraveling such intricate presentations. The successful outcome following drug withdrawal reaffirms the importance of identifying and removing the offending agents as the cornerstone of DILI management.[19,20]

4. Conclusion

This case report delineates a compelling instance of severe, delayed-onset hepatocellular drug-induced liver injury (DILI) in a 58-year-old woman subjected to long-term polypharmacy. Critically, her medication regimen included two decades of daily paracetamol use at therapeutic doses, a habit driven by dependence, alongside twelve years of atorvastatin therapy. The confluence of these factors culminated in a significant hepatic insult, characterized by massively elevated transaminases and severe thrombocytopenia, which resolved upon withdrawal of both paracetamol and atorvastatin. Application of the Roussel Uclaf Causality Assessment Method (RUCAM) identified both agents as "probable" causes of this DILI episode, underscoring the complexity of assigning causality in polypharmacy. This case offers profound insights into the insidious risks of chronic medication exposure. It highlights that paracetamol, despite its perceived safety and widespread over-the-counter availability, can be implicated in severe hepatotoxicity even within therapeutic dosage ranges when consumed persistently over extended periods, particularly if such use is perpetuated by psychological dependence rather than clear therapeutic indications. Furthermore, it reaffirms that atorvastatin, while a crucial cardiovascular therapeutic, carries a potential for delayed-onset, idiosyncratic liver injury that clinicians must remain vigilant for, even after years of uneventful use. The diagnostic journey underscores the necessity of a high index of suspicion for DILI in patients presenting with unexplained liver dysfunction amidst polypharmacy. Meticulous medication history, including patterns of non-prescription drug use, and the systematic exclusion of other liver pathologies are paramount. Structured causality assessment tools like RUCAM are indispensable in navigating these complex clinical scenarios, providing a standardized framework to evaluate potential drug culpability. Ultimately, this report serves as a crucial reminder for healthcare professionals to diligently review long-term medication regimens, actively address medication dependence issues, and educate patients on the potential cumulative risks associated with chronic drug therapies. The imperative for pharmacovigilance is clear: fostering a deeper understanding of DILI mechanisms, especially in the context of prolonged exposures and multiple drug use, is essential for enhancing patient safety and optimizing therapeutic outcomes. This case champions cautious prescribing, regular medication review, and heightened awareness of the subtle yet significant dangers that can accompany even the most common medications when their use extends over vast timelines.

5. References

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