Minimal data elements for proper DILI adjudication
Case study on a published DILI case

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Assessment of drug-induced liver injury: key rules and common pitfalls. How to make a clinical narrative

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PRO-EURO DILI NETWORK
Prospective European Drug-induced Liver Injury Network

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Reporting of an hepatic adverse reaction

FACTS	IMPACTS
Many prescription medications as well as herbal and dietary supplements can produce DILI	Data on hepatotoxicity is not always easily accessible
Develop a prospective body of reliable, interpretable literature for agents that cause DILI	Quality and clinical utility of published reports. A case report publication does NOT prove the drug is hepatotoxic.
Published DILI case reports can provide significant clinical insight (not detected in clinical trials)	Detection and awareness of DILI. Prompt further investigation
Accurate reporting of drug-induced liver disease is important in terms diagnosing and causality assessment	Case reports are often not well described and critical clinical information is frequently lacking, limiting the reviewer's ability to establish a causal relationship

HEPATOLOGY
Official Journal of the American Association for the Study of Liver Diseases
AASLD

Hepatology. 2016;63:590-603

Categorization of Drugs Implicated in Causing Liver Injury: Critical Assessment Based on Published Case Reports

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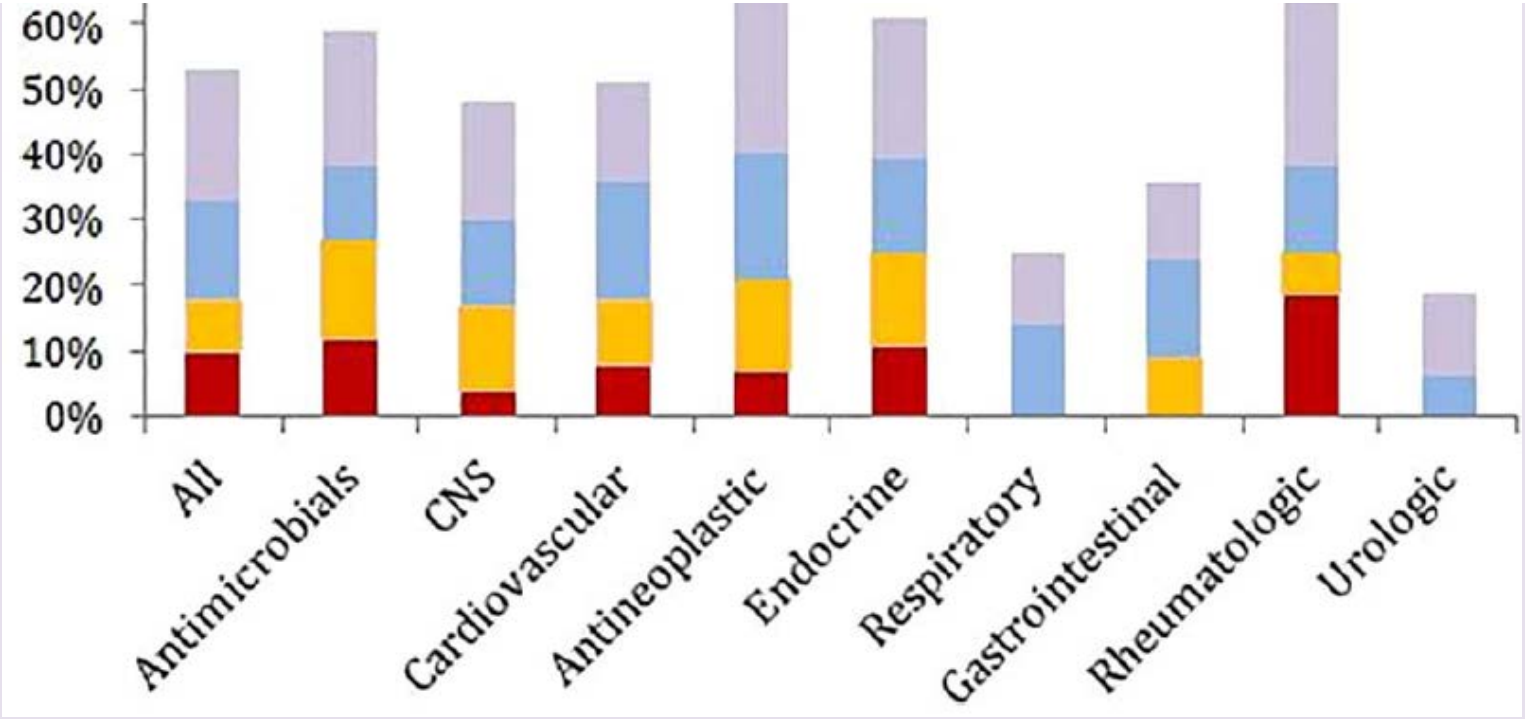

The Quality of Published Adverse Drug Event Reports

William N Kelly

Ann Pharmacotherapy 2003

BACKGROUND: Case reports of adverse drug events (ADEs) are an important source of information.

OBJECTIVE: To determine what variables are reported in ADE case reports, how causality was assessed for each report, and what criteria are specified for publishing ADE case reports.

METHODS: A descriptive analysis of highly significant ADE case reports published in English over a 20-year period was performed. Main outcome measures included frequency distributions for the types of variables reported. The presence of causality assessment and the criteria for submitting an ADE report to practitioner journals were also examined.

RESULTS: A highly significant ADE was described in 1520 published case reports during the study period. Three patient variables were reported >90% of the time, while 12 others were reported <25% of the time. Only 1 drug variable was reported >90% of the time; 6 others were reported 14–74% of the time. Most of the relevant ADE variables were reported most often. Added information for drug interactions, medication errors, and allergic drug reactions were reported 61–99% of the time. Less than 1% of ADE reporters objectively assessed the probability of the ADE. All but one journal publishing the most ADE reports did not require such assessment.

CONCLUSIONS: Professional journals might consider stricter requirements for publishing ADE reports. As a minimum, requirements should include an objective assessment of ADE causality, with explicit recognition in the published text and abstract of the report.

KEY WORDS: adverse drug events, quality of reports.

Ann Pharmacother 2003;37:1774-8

Pul

***The Annals of Pharmacotherapy* requires the use of the Naranjo probability scale prior to publication of a potential adverse drug reaction**.

The Naranjo scale is not liver-especific. Its use for suspected dili should not be recommended

Garcia-Cortes M, Lucena MI, Pachkoria K et al. *Aliment Pharmacol Ther* 2008; 27, 780

Relevance of data collected in DILI diagnosis

CLINICAL GASTROENTEROLOGY AND HEPATOLOGY 2010;8:463–470

Important Elements for the Diagnosis of Drug-Induced Liver Injury

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Conclusions

Reports of drug-induced liver diseases often do not provide the data needed to determine the causes of the adverse effects.

Efforts **to promote** and include **a list of essential diagnostic elements** in research articles could increase the quality and clinical utility of published case reports of drug toxicity.

	Bilirubin	**12%**	**3%**
Medical history	**Type of liver damage**	**49%**	**29%**
	Prior drug adverse reaction	**86%**	**80%**

Minimal elements for reporting drug-induced liver injury

Agarwal et al, Clin Gastroneterol Hepatol, 2010

- Patient sex and age
- Drug and its dose
- Primary disease (for which the drug was prescribed)
- Concomitant diseases (special attention to heart failure, hypotension, sepsis and parenteral nutrition)
- Pertinent past medical history (including medications)
- History of alcohol use
- Drug therapy start and stop dates
- Symptoms: dates and descriptions
- Pertinent physical findings at the time of presentation (such as hypersensitivity features)

Minimal elements for reporting drug-induced liver injury

Agarwal et al, Clin Gastroneterol Hepatol, 2010

- Pharmacological history (at least up to 3 month prior to onset)
- Laboratory tests (baseline liver profile values, at onset and follow-up until resolution, including INR values)
- Laboratory tests to exclude alternative causes (such as HAV, HBV, HCV, autoantibodies)
- Imaging test results (abdominal ultrasound, CT or MRI)
- Liver histology results and biopsy date (if performed)
- Whether a rechallenge with the causative agent was performed and, if so, results

Case presentation 1

A 64 year-old male had been *taking glucosamine/chondroitin sulfate as food supplement during 4 weeks*, but was not on any prescription medication. The patient presented with a 3-week history of nausea and vomiting and two weeks of jaundice, dark urine and acholia. On examination the patient was jaundiced. An abdominal ultrasound showed normal results. Liver profile elevations were detected: ALT 1461 U/L, TBL 24.5 mg/dL, ALP 141 U/L together with a markedly elevated ferritin level (genotyping for hemochromatosis was negative). No history of alcohol excess, intravenous drug use, blood transfusion, hepatobiliary diseases. Alternative aetiologies excluded by testing for HAV, HBV, HCV, EBV, CMV, autoantibodies (ANA, ASMA, AMA), IgA, IgG and IgM. After treatment cessation ALT improved, while bilirubin continued to rise. Renal failure and coagulopathy occurred (followed by encephalopathy) and the patient was listed for an emergency liver transplantation. While on the waiting list the patient developed a peritoneal infection, sepsis and died. A postmortem examination of the liver showed massive necrosis.

No objective assessment of causality was made

BMJ Case Rep, 2009

Sufficient information?

Patient sex and age: **available 46-y male**

Drug and its dose: **dosage information missing**

Primary disease (for which the drug was prescribed) : **missing**

Concomitant diseases (special attention to heart failure, hypotension, sepsis and parenteral nutrition): **no information**

Pertinent past medical history (including medications): **no information**

History of alcohol use: **available**

Drug therapy start and stop dates — **Available, but could be more detailed**

Symptoms: dates and descriptions — **to provide a clearer picture**

Pertinent physical findings at the time of presentation (such as hypersensitivity features): **no information**

Sufficient information?

Pharmacological history (at least up to 3 month prior to onset): **missing**

Laboratory tests (base line liver profile values, at onset and follow-up until resolution, including INR values): **base line values missing, limited follow-up data**

Laboratory tests to exclude alternative causes (such as HAV, HBV, HCV, autoantibodies): **available, but lack detailed information and test dates**

Imaging test results (adominal ultrasound, CT or IMR): **available**

Liver histology results and biopsy date (if performed): **postmortem liver examination data available**

Whether a rechallenge with the causative agent was performed and, if so, results: **not applicable**

DILI expert comments

- A delayed presentation (4-26 weeks) of fulminant hepatic failure manifestations (encephalopathy) with regard to initiation of jaundice is characteristic for idiosyncratic hepatotoxicity. The delayed onset of encephalopathy in this case was 9 days, which is typical of paracetamol-induced acute liver failure. Likewise, renal failure is commonly seen with paracetamol overdoses.
- In this case there is no information on the use of paracetamol and/ or NSAID which is critical in this case because the suspected drug is supposed to be used for osteoarthritis.

Case 1 → Scottish Fatal Accident Inquiry

Committee on TOXICITY

Committee on toxicity of chemicals in food, consumer products and the environment (COT) was asked to consider whether a causal association was plausible

Conclusions:

Current **evidence does not suggest that glucosamine is likely to be a cause of hepatitis** although a causal link cannot be completely excluded. It should be noted, however, that the likelihood of an individual user of glucosamine experiencing adverse effects is, at most, very low.

At present, it is unlikely that further research will resolve the uncertainty since if hepatitis is caused by glucosamine then it appears to occur by an idiosyncratic mechanism. Thus **any human study would need to be extremely large to demonstrate the hazard due to the rarity of the outcome and the many potential confounding factors such as the use of other medication**.

COT statement 2009/01, April 2009

Case presentation 2

A 77-year old woman presented with one week of increasing fatigue, vomiting and loss of appetite. She had been treated with low-dose quetiapine (12.5 mg twice a day) for 9 days as prescribed for symptoms of agitation and severe insomnia. She had no history of liver disease or abnormal liver biochemistry. A liver profile analysis three weeks prior to the episode revealed aminotransferase values within the normal range. She gave no history of alcohol use, substance abuse or smoking and was not receiving any medication other than quetiapine. On examination, she was afebrile, not alert and disorientated. She had a blood pressure measurement of 94/62 mm Hg, a heart rate of 112 beats/minute, a respiratory rate of 28 breaths/minute, and an oxygen saturation rate of 96% on a 2-liter nasal cannula. She presented elevations in the liver profile: ALT 1565 U/L (ULN=35), AST 1415 (ULN=35), ALP 178 (ULN=155), GGT 95 (ULN=32), TBL 4.77 mg/dL, dBL 3.38 mg/dL, albumin 3.32, prothrombin time 56.5 s, INR 4.12, ammonia 104 g/dL. Diagnostic evaluation for viral, autoimmune and metabolic diseases was negative. An abdominal ultrasound showed nothing abnormal. Quetiapine was discontinued and her liver profile improved over the next seven days (AST 942 U/L, ALT 1020 U/L), however her condition deteriorated significantly and she died on day 8 of her hospitalization in the intensive care unit due to overwhelming multiorgan system failure. The causal relationship between quetiapine and hepatotoxicity was evaluated using Naranjo criteria

Am J Psychiatry, 2011

Sufficient information?

Patient sex and age: **available**

Drug and its dose: **available**

Primary disease (for which the drug was prescribed) : **available**

Concomitant diseases (special attention to heart failure, hypotension, sepsis and parenteral nutrition): **missing**

Pertinent past medical history (including medications): **missing**

History of alcohol use: **available**

Drug therapy start and stop dates } **available**

Symptoms: dates and descriptions }

Pertinent physical findings at the time of presentation (such as hypersensitivity features): **some information available, but not complete**

Sufficient information?

Pharmacological history (at least up to 3 month prior to onset): **missing**

Laboratory tests (base line liver profile values, at onset and follow-up until resolution, including INR values): **available, but not complete**

Laboratory tests to exclude alternative causes (such as HAV, HBV, HCV, autoantibodies): **available, but lack detailed information and test dates**

Imaging test results (adominal ultrasound, CT or IMR): **available**

Liver histology results and biopsy date (if performed): **missing**

Whether a rechallenge with the causative agent was performed and, if so, results: **not applicable**

DILI expert comments

- This case refers to a 77-year-old, fragile woman started on a low dose of quetiapine for agitation and severe insomnia 9 days before attending a geriatric clinic with symptoms of increasing fatigue, vomiting, and loss of appetite for 1 week.

- A variety of acute disorders may present in geriatric patients with agitation. It might be possible that quetiapine were started in this patient once the underlying disorder that caused the liver damage was present.

- This particular case include competing factors suggestive of alternative etiologies, such as ischemic hepatitis, that has not been sufficiently discarded.

Consequences

- A published case report with insufficient information that could have led to an incorrect DILI diagnosis is a collective failure of the authors, reviewers and editors involved
- This may lead to that a specific drug is incorrectly ‘marked’ as having a high hepatotoxicity potential or even be considered as a hepatotoxic compound
- Additionally, authors may reference the misleading case report without considering later documents that question the same publication


Thank you for your attention!