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ORIGINAL RESEARCH ARTICLE

Antidepressant-Induced Acute Liver Injury: A Case–Control Study in an Italian Inpatient Population

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Abstract

Introduction Pre-marketing clinical trials show that antidepressant-induced liver injury seems to be a rare adverse event. Because of short follow-up trial duration, the incidence of liver injury due to antidepressant use could be underestimated.

Objectives We aimed to quantify the risk of acute liver injury associated with antidepressant use through a case–control analysis among an inpatient population.

Methods A multicenter study was carried out in nine Italian hospitals from October 2010 to January 2014, within the DILI-IT (Drug-Induced Liver Injury in Italy) study project. After exclusion of all patients with a clear competing cause of liver injury, cases were defined as adults admitted to the hospital with a diagnosis of acute liver injury, while controls had any other acute clinical condition not related to the liver. Antidepressant exposure was evaluated within 90 days prior to the date of the first sign/symptom of liver injury. Odds ratio (OR) with 95% confidence interval (95% CI) was calculated as a measure of risk estimates for liver injury.

Results We included 17 cases exposed to antidepressants matched to 99 controls. According to the features of liver injury, all cases showed symptomatic liver function test abnormalities at hospital admission, with the main signs/symptoms represented by fatigue, nausea, asthenia, or dark urine. Citalopram was the antidepressant mostly involved in the increase of liver enzymes, mainly alanine aminotransferase. Compared with non-use, current use of antidepressants was associated with a significantly increased risk of liver injury (adjusted OR, OR_{ADJ}, 1.84; 95% CI 1.02–3.32). Specifically, an increased, but not significant, risk of developing liver injury was observed for citalopram, a selective serotonin-reuptake inhibitor (OR_{ADJ} 1.82; 95% CI 0.60–5.53).

Conclusion The use of antidepressants is not as safe in terms of liver injury as expected; instead, the risk of antidepressant-induced liver injury is likely underestimated. The lack of significance does not reflect the absence of risk, but rather suggests the need to evaluate it in a wider setting of antidepressant users.

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Key Points

The pattern of liver injury due to antidepressants is predominantly hepatocellular, with high and symptomatic increases of alanine aminotransferase.

Since routinely monitoring liver function tests during antidepressant therapy is unlikely, clinicians should be at least aware of their potential increase and should educate patients to recognize and promptly report symptoms of liver toxicity.

The likelihood of developing acute liver injury among antidepressant users is 84% higher than among non-users, but this risk needs to be confirmed in a larger study population.

1 Introduction

Antidepressant-induced liver injury (AILI) is a rare, although severe, event [1]. Liver function tests have been evaluated in some pre-approval depression randomized controlled trials (RCTs), but the rate of hepatotoxicity usually did not differ among active and placebo groups [2]. Indeed, depression RCTs are generally 12 weeks or shorter, thus cases with delayed presentation can be missed. Therefore, estimation of the incidence of such a rare event in RCTs is a challenge because of limited inclusion of patients from real-life settings and short follow-up duration. Definitely, first cases of liver injury due to use of antidepressants (ADs) were reported after medicine commercialization, when a larger number of patients were exposed [3–5]. Moreover, abnormalities of liver enzymes, providing an indication of clinically significant drug-induced liver injury (DILI), are usually asymptomatic and, for this reason, are difficult to detect, especially during early stages of the disease. As a consequence, the incidence of AILI can be likely underestimated [6, 7]. Post-marketing observational studies from spontaneous reporting system of adverse drug reactions showed a heterogeneous reporting rate of liver injury requiring hospitalization among patients receiving antidepressants ranging from 1.28 cases every 100,000 patient-years for sertraline to 28.96 cases for nefazodone [2, 7]. Apart from case reports and data mining on databases from spontaneous reporting systems or from medical records for signal detection of liver injury [7–9], so far there is no evidence addressing the risk of liver injury due to AD use.

In 2010, the Drug-Induced Liver Injury in Italy (DILI-IT) project was established to quantify the risk of acute and serious liver injury associated with the use of nimesulide and other non-steroidal anti-inflammatory drugs (NSAIDs) among inpatients [10]. An additional goal was to assess the risk of acute liver injury induced by other hepatotoxic drugs, including antidepressants. This latter aim is reported in this study.

2 Methods

A multicenter case–control study was carried out from October 2010 to January 2014 in nine Italian hospitals, located in four regions representative of the Northern (Veneto and Emilia Romagna), Central (Tuscany) and Southern (Campania) Italian population.

2.1 Case and Control Selection

Cases and controls were selected from all hospitalized patients aged 18 or over by using a similar approach on definition, identification and validation. Details of the assessment process have been previously described [10].

In brief, adult patients admitted to the hospital with a primary diagnosis of liver injury were defined as cases of acute liver injury. Each hospitalized patient with abnormal liver enzymes, with or without symptoms, was identified through hospital medical records as a potential case of interest. Then, based on the definition of drug-induced liver injury [6, 11–15], the case was defined using the following criteria: (1) increase of two times the upper limit of normal (ULN) range for alanine aminotransferase (ALT) or aspartate aminotransferase (AST) serum activity in patients with or without symptoms; (2) increase of 1.5 $\times$ ULN of alkaline phosphatase (ALP) associated with an increase of ALT or AST and/or total bilirubin in patients with or without symptoms. Subsequently, according to international criteria [2, 16], type of liver injury was defined as (a) hepatocellular, when there was an increase above 2 $\times$ ULN in ALT alone or when the ratio (R) of serum activity of ALT/ALP was $\geq$5; (b) cholestatic, when an increase above 2 $\times$ ULN in ALP was found or when R $\leq$ 2; (c) mixed, in case of an increase above 2 $\times$ ULN in ALT together with any increase in ALP or 2 $<$ R $<$ 5.

The index date of the event was defined as the earliest date of the liver symptom/sign (i.e., fatigue, asthenia, lack of appetite, nausea/vomiting/epigastric pain, abdominal bloating/pain, dark urine, pale stools, jaundice, fever, rash, itching, dyspnea) or, in absence of these, the date of abnormal liver tests immediately preceding the diagnosis.

Within the same underlying population, we selected ten controls for each case, matched on gender, age ($\pm$5 years), participant hospital, and index date of the corresponding case. Controls were adult patients admitted to the hospital for any other acute clinical disorder, not involving liver

function (i.e., with normal value of liver enzymes), and with any contraindication for AD use. Selected admission diagnoses included non-alcohol-related trauma or fracture, acute appendicitis, bowel obstruction, intestinal perforation, acute pancreatitis, pneumonia in patients without risk factors, pneumothorax without previous chronic obstructive bronchitis or chronic obstructive pulmonary disease, renal colic, euthyroid nodule, bite, accidental injuries or burns, foreign bodies, abdominal gestation/fallopian tube rupture or miscarriage, testicular torsion and umbilical hernia.

Among the study population (both cases and controls), patients with clear and confirmed competing cause of liver injury were excluded according to the following primary exclusion criteria: viral hepatitis, biliary abnormality, history of alcohol abuse, autoimmune disease, genetic and metabolic disorders which may determine liver injury, a low α-1-antitrypsin level and an abnormal phenotype (that may suggest disease associated with a deficiency of this protein), Wilson's disease, HIV/AIDS, hepatic neoplasia or liver metastasis, systemic lupus erythematosus, mushroom poisoning, and drug addiction or detoxification treatment in the last 3 months. Finally, patients who were not resident in the study areas, who were discharged or died before interview, or those refusing the interview or unable to answer were also excluded (secondary exclusion criteria).

All selected cases and controls were finally validated by a panel of hepatology experts (External Advisory Board) who also served as support in case of debate about patient recruitment concerns.

2.2 Exposure Definition

Antidepressant exposure in the 90 days before the index date was evaluated in case and control patients by trained monitors in face-to-face interviews, using a standardized questionnaire (Case Report Form [CRF], see Electronic Supplementary Material 1). Patients were asked if using any of the following medicine: amitriptyline, clomipramine (among non-selective monoamine reuptake inhibitors); citalopram, escitalopram, sertraline, fluoxetine, paroxetine (among selective serotonin reuptake inhibitors); and trazodone, mirtazapine, duloxetine, ademetionine, venlafaxine, mianserin (among other ADs).

In an attempt to get a patient drug history as complete as possible and to reduce recall bias, after the administration of CRF, common symptoms usually occurring immediately after the use of the medicine of interest were listed to the patient, together with a picture collection reproducing the packaging of the ADs and other hepatotoxic drugs (i.e., NSAIDs, amoxicillin and amoxicillin clavulanate, macrolides, statins).

2.3 Patients' Comorbidities

Demographic data, medical history, coexisting illnesses (e.g., diabetes mellitus, dyslipidemia, hypertension), concomitant therapies, lifestyle and dietary habits, alcohol, tobacco, and coffee intake or use of herbal products were retrieved through the CRF, in addition to the information from clinical records collected at the time of hospital admission.

2.4 Statistical Analysis

Odds ratio (OR) with 95% confidence interval (CI) was calculated as measure of risk estimates for liver injury and was adjusted for potential confounders such as body mass index (BMI), alcohol intake, smoking, preexisting liver or heart comorbidities, and concomitant therapies. These variables were also tested as effect modifiers.

3 Results

Among 179 overall cases of acute liver injury, 17 (9%) were exposed to ADs, and were matched to 99 (6% of 1770) controls. Among AD-exposed cases, women were the most represented group ($n = 14$, 82%) with mean age at index date of 64.3 years (SD ±14.4). Five patients had history of preexisting liver disease (cholelithiasis or cholecystectomy), while hypertension was a concomitant condition in eight patients, dyslipidemia in six patients, and diabetes in one patient. All cases presented with symptomatic liver function test abnormalities at time of hospital admission. Common signs/symptoms included fatigue, nausea (in 12 cases), asthenia or dark urine (in 10 cases), vomiting or lack of appetite (in 8 cases), fever or abdominal bloating (in 7 cases), headache or dyspnea (in 6 cases), joint aches, pale stools or itching (in 5 cases), jaundice or abdominal pain (in 4 cases) and rash (in 2 cases).

Overall, one case had triple AD therapy including citalopram, paroxetine, and trazodone, one case double AD therapy (mirtazapine and trazodone), while the remaining cases were exclusively exposed to one of the following ADs: citalopram (4 cases), sertraline or amitriptyline (3 cases per drug), paroxetine (2 cases), and clomipramine, fluoxetine, trazodone, mirtazapine or duloxetine (1 case per drug). As listed in Table 1, all cases were concurrently exposed to multiple therapies including other potential hepatotoxic drugs (e.g., acetaminophen, NSAIDs, antibiotics, or statins). The duration of treatment with ADs when DILI occurred was similar among patients; except patients 8 and 9 (for whom this information was not available), all of them were chronically treated with ADs (>3 months).

Table 1 Characteristics of the cases of antidepressant-induced liver injury

Patient (sex/age [y]/N. antidepressants)	Type of antidepressants	Dose; duration	Concomitant medications	Signs/symptoms of liver injury	ALT	AST	γ-GT	ALP	Indir. bilirubin	Dir. bilirubin	Type of liver injury[a]
P1 (F/60/1)	Amitriptyline	12 mL/d; >2 years	Moxifloxacin, alprazolam, atenolol, hydrochlorothiazide and potassium-sparing agents, piroxicam, cholecalciferol	Asthenia, fatigue, fever, lack of appetite, nausea and vomiting, abdominal pain	115	169	62	252	0.47	0.2	Mixed
P2 (F/60/1)	Citalopram	20 mg/d; 2 years	Bromazepam, paracetamol and combinations, aspirin 75 mg, rosuvastatin	Asthenia, fatigue, lack of appetite, fever, headache, nausea, abdominal pain, jaundice	2938	2971			0.9	0.2	Hepatocellular
P3 (F/86/2)	Mirtazapine, trazodone	15 mg, 75 mg/d; >2 years	Ceftazidime, norfloxacin, paracetamol and combinations, ramipril, allopurinol, acetylsalicylic acid, furosemide, rabeprazole, nimesulide, olanzapine	Nausea and vomiting, bloating and abdominal pain, joint aches, fever, headache, rash, jaundice, dark urine and pale stools	130	145			1.4		Hepatocellular
P4 (F/66/1)	Clomipramine	2 × 20 mg/d; 3 months	Delorazepam, olanzapine	Fatigue, lack of appetite, nausea, jaundice, itching, abdominal pain and bloating, dark urine and pale stools	389	140			4.5		Hepatocellular
P5 (F/57/1)	Citalopram	40 mg/d; >2 years	Levothyroxine, paracetamol and combinations, oxcarbazepine, levetiracetam	Fatigue, epigastric pain	369	744			0.8		Hepatocellular
P6 (F/72/1)	Citalopram	20 mg/d; 7 months	Hydrochlorothiazide, tramadol, paracetamol and combinations, alendronate/cholecalciferol, esomeprazole, ramipril, mesalazine	Asthenia, fatigue, epigastric pain, fever, headache, nausea and vomiting, itching, bloating, dark urine	438	359	314	188	0.75		Mixed
P7 (F/54/3)	Paroxetine, citalopram, trazodone	20 mg, 20 mg, 100 mg/d; >5 years	Clonazepam, simvastatin	Asthenia, fatigue, nausea and vomiting, itching, abdominal bloating	198	102	59				Hepatocellular
P8 (F/57/1)	Paroxetine	NA	Levothyroxine, rifaximin, lansoprazole, loperamide, nimesulide, estradiol, amoxicillin/clavulanate	Asthenia, fatigue, nausea, epigastric pain, abdominal bloating, headache, dyspnea, rash, dark urine and pale stools	517	932	248	97	1.42		Hepatocellular
P9 (M/45/1)	Citalopram	NA	Nimesulide,clebopride, ketorolac, paracetamol, ketoprofen, diclofenac, amoxicillin/clavulanate	Asthenia, fatigue, lack of appetite, nausea and vomiting, joint aches, fever, dyspnea and pale stools	207	80	206	176	0.36	0.18	Mixed
P10 (F/88/1)	Trazodone	75 mg/d; >2 years	Amlodipine, bromazepam	Nausea, abdominal pain, dyspnea, jaundice, dark urine	433	212	66	145	1.7	0.6	Mixed
P11 (F/64/1)	Fluoxetine	20 mg/d; 4 months	Delorazepam, omeprazole, perindopril/indapamide, acetylsalicylic acid, paracetamol	Fatigue, lack of appetite, nausea and vomiting, abdominal bloating, joint aches, headache, dark urine	594	374	232	202		0.7	Mixed
P12 (F/48/1)	Duloxetine	30 mg/d; >2 years	Simvastatin	Asthenia, abdominal pain	696	319	103	122	0.9	0.2	Mixed

Table 1 continued

Patient (sex/age [y]/N. antidepressants)	Type of antidepressants	Dose; duration	Concomitant medications	Signs/symptoms of liver injury	ALT	AST	γ-GT	ALP	Indir. bilirubin	Dir. bilirubin	Type of liver injury[a]
P13 (F/80/1)	Sertraline	50 mg/d; >2 years	Lansoprazole, ambroxol, levothyroxine, ramipril, gliclazide, ticlopidine	Asthenia, fatigue, lack of appetite, vomiting	596				1.97		Hepatocellular
P14 (M/24/1)	Mirtazapine	30 mg/d; 10 months	Paracetamol, levothyroxine, bromazepam, folic acid, ciprofloxacin	Asthenia, fatigue, fever, nausea, joint aches, abdominal pain, dark urine	117						Hepatocellular
P15 (F/56/1)	Sertraline	50 mg/d; 18 months	Lansoprazole, metoclopramide, trimethoprim/sulfamethoxazole, beclometasone	Asthenia, fatigue, lack of appetite, nausea and vomiting, abdominal pain, jaundice, dark urine and pale stools	1514	1203	1559		4.71		Hepatocellular
P16 (F/50/1)	Paroxetine	20 mg/d; >2 years	Simvastatin, furosemide, ramipril, carvedilol, lansoprazole, lorazepam, levothyroxine warfarin, paracetamol	Epigastric pain, pre-syncope, sweating, nausea, abdominal bloating, dark urine	58	89	333	191	1.46		–
P17 (M/43/1)	Sertraline	50 mg/d; >2 years	Loperamide, ibuprofen, nimesulide	Fever, asthenia, lack of appetite, dyspnea, abdominal pain, dark urine	425						Hepatocellular

ALP alkaline phosphatase, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *γ-GT* γ-glutamyltransferase, *ULN* upper limit of normal range

[a] According to international consensus [11], liver injury has been classified as hepatocellular if ALT > 2 × ULN and ALP in normal range; cholestatic if ALP > 2 × ULN and ALT in normal range; mixed if ALT > 2 × ULN and ALP > ULN (any increase)

Based on criteria defined by an International Consensus Meeting of experts in hepatology (CIOMS) and recent evidence from literature [11, 12, 14, 17, 18], the pattern of liver injury was classified as hepatocellular in ten cases (58.8%), mixed in six cases (35.3%), and not assessable in one case (5.9%). Apart from amitriptyline, which was implicated in an increase over 2 × ULN of ALP, the other ADs were responsible for increases in ALT values, with or without small deviations of ALP. Specifically, out of 17 cases, 11 (65%) showed an increase of ALT more than 5 × ULN, while the remaining cases had concomitant increase of ALT, or AST and ALP or bilirubin >2 × ULN.

Compared with non-use, current use of overall ADs was associated with an increased risk of liver injury (adjusted OR, OR_{ADJ}, 1.84; 95% CI 1.02–3.32). When exploring different subclasses, because of the low number of exposed cases, we only focused the analyses on selective serotonin-reuptake inhibitors (SSRIs). Out of 17 cases and 99 controls, 11 cases and 66 controls were exposed to SSRIs, showing a potential but not significant association (OR_{ADJ} 1.25; 95% CI 0.60–2.59). Similarly, an increased risk of developing liver injury was observed in five subjects exposed to citalopram, but the risk became not significant when adjusted for several confounder factors, such as BMI, alcohol and smoking intake, pre-existing liver and cardiac disorders, and polypharmacy (OR_{ADJ} 1.82; 95% CI 0.60–5.53).

4 Discussion

Our results are to some extent consistent with preexisting findings that also hypothesized a potential DILI with ADs and, specifically, with SSRIs [1, 19]. According to Carvalho et al., the incidence of DILI among users of SSRIs and serotonin noradrenaline reuptake inhibitors is 0.5–1%. This adverse event usually occurs during the first 6 months of AD initiation treatment [20]. The occurrence of DILI can be linked to an idiosyncratic reaction, which can be a consequence of immuno-allergic or metabolic idiosyncratic DILI [1]. For drugs which underwent liver metabolism, a high risk of DILI can be observed, mainly related to drugs and their metabolites accumulating in portal blood. Also, genetic factors could explain the occurrence of DILI. For example, considering that ADs are mainly metabolized by CYP450, the presence of enzyme genetic polymorphisms can alter drug metabolism and, consequently, its accumulation in the body. Finally, DILI seems to be more frequent among women and the elderly [19]. According to this latter information, in our study, out of 17 patients with AILI, 14 were female and eight were older than 60 years.

Considering the seriousness of liver injury, all cases required hospitalization due to symptomatic increase of

liver enzymes. Since most of the implicated ADs, such as citalopram, sertraline, duloxetine, and clomipramine, showed a remarkable influence on ALT values (a fivefold increase of ULN was observed in 11 cases), aminotransferase monitoring may represent the most useful tool in order to detect AILI. Moreover, the results confirm the prevalence of a hepatocellular pattern for AILI, as previously reported in several case reports [1].

According to our results, several literature data demonstrated a correlation between our most involved ADs (citalopram, amitriptyline, sertraline, paroxetine, and trazodone) and liver injury occurrence. Among SSRIs, paroxetine has the highest number of clinical cases describing hepatotoxicity adverse events, including severe cholestatic and hepatocellular injury [21–26]. Several studies confirmed liver injury associated with trazodone, after either short- or long-term treatment [27–31]. Furthermore, liver toxicity was also observed in a patient treated with sertraline for 6 months, who had symptoms of DILI and elevated AST and ALT [32]. Similar cases describing sertraline-induced liver injury had common features: frequently, symptoms of DILI occurred from 2 weeks to 6 months after the initiation of sertraline therapy. Moreover, in all cases both ALT and AST elevation as well as administration of concomitant drugs were confirmed [4, 33]. On the contrary, citalopram seems to be the drug less frequently linked to occurrence of DILI [1]. According to data from literature, this drug was associated with DILI in a 39-year-old Asian woman affected by post-traumatic stress disorder and psychotic depression. The woman was previously treated with fluvoxamine and concomitantly treated with bupropion, clonazepam, and olanzapine, when hepatotoxicity, confirmed by both AST and ALT elevation, occurred [34]. A further case described the occurrence of liver injury in a 91-year-old woman treated with citalopram and donepezil, which recovered after donepezil discontinuation. In that case, authors suggested a possible role of drug–drug interaction [35]. Finally, as for citalopram, only few data on amitriptyline-induced DILI were found [36–38].

In our setting, liver injury occurred within the summary of product characteristics recommended therapeutic dosage range for each AD agent. However, concomitant hepatotoxic medication use and elderly age may lead to an increase of plasmatic levels of AD, even if taken at the therapeutic dosage range. Thus, we cannot exclude a potential dose-dependent mechanism of antidepressant-induced liver injury [1, 39].

Apart from the effects of concomitant medications on ADs plasmatic levels, their hepatotoxicity profile should also be considered as a potential confounder. According to a recent analysis of 185 patients diagnosed with DILI, the most commonly involved drugs in DILI occurrence are antibiotics, NSAIDs, immunosuppressant agents, statins, anti-platelets, and anti-psychiatric drugs [40]. Furthermore, other DILI studies confirmed that among the most common drugs associated with DILI, antibiotics as well as drugs acting on the cardiovascular, central nervous and endocrine systems play a key role [41]. For this reason, given that all 17 patients who had AILI in our study population received the above-mentioned drugs, all analyses have been adjusted for concomitant therapies in order to reduce the influence of such medications on the risk of AILI.

Another potential limitation to be considered is that increased incidence of nonalcoholic fatty liver injury plays a crucial role for high frequency detection of mild or moderate elevation of ALT, leading to false positives for DILI [42]. However, all the analyses have been controlled for potential risk factors such as BMI or statins use, as proxy variables for obesity and hyperlipidemia, respectively. Finally, although other possible causes of hepatic disease, if known, have been accurately excluded to prevent a potential misclassification bias, residual confounders cannot be completely excluded from our analysis. In fact, some symptoms are non-specific for hepatic injury and may represent underlying depressive symptoms for which they are being treated with ADs. No INR (International Normalized Ratio) values are provided and not all types of hepatitis (such as hepatitis E or acute hepatitis C), which has been shown in recent publications to mimic DILI, are specifically excluded. Moreover, listing gallstones or cholecystectomy as a chronic liver disease is significantly different to nonalcoholic liver injury, chronic viral hepatitis, or significant fibrosis, which are typically considered as examples of chronic liver injury.

In attempt to quantify the risk of AILI, as added value, this study shows that the likelihood of developing acute liver injury in AD users is 84% higher than in non-users. Likewise, in line with results of adverse drug reaction spontaneous reporting analysis [43], we estimated a similar probability (82%) in patients exposed to citalopram, even if not significant. Nonetheless, the lack of significance, rather than the absence of risk, reflects an insufficient exposure to quantify any risk of liver injury, suggesting therefore the need to evaluate this risk in wider antidepressant user settings. Lastly, since we cannot exclude the influence of concomitant medications or underlying diseases, as confirmed by adjusted analyses, our results need to be interpreted with caution.

5 Conclusions and Implications for the Future

The use of antidepressants is not safe in terms of liver injury as expected; instead, the risk of antidepressant-induced liver injury is likely underestimated. Therefore,

reinforcing the existing recommendations, abnormalities of liver enzymes need to be evaluated in patients treated with these antidepressants. Nevertheless, since routinely monitoring liver function tests during AD therapy is unlikely, clinicians should at least be aware of the potential role of antidepressants in developing liver injury. Moreover, while educating patients to recognize and promptly report symptoms of liver toxicity, they are recommended to consider possible withdrawal of the drug when there is suspicion of hepatotoxicity, because it could be reversible.

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Conflict of interests Carmen Ferrajolo, Cristina Scavone, Monia Donati, Oscar Bortolami, Giovanna Stoppa, Domenico Motola, Alfredo Vannacci, Alessandro Mugelli, Roberto Leone, and Annalisa Capuano have no conflicts of interest that are directly relevant to the content of this study.

Ethical approval The study protocol was independently approved by ethics committees for each participant hospital.

Patient consent Each patient was informed about the aim of the study and written informed consent was signed before the interview.

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