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RESEARCH ARTICLE

Drug-Induced Liver Injury during Antidepressant Treatment: Results of AMSP, a Drug Surveillance Program

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Abstract

Background: Drug-induced liver injury is a common cause of liver damage and the most frequent reason for withdrawal of a drug in the United States. The symptoms of drug-induced liver damage are extremely diverse, with some patients remaining asymptomatic.
Methods: This observational study is based on data of Arzneimittelsicherheit in der Psychiatrie, a multicenter drug surveillance program in German-speaking countries (Austria, Germany, and Switzerland) recording severe drug reactions in psychiatric inpatients. Of 184 234 psychiatric inpatients treated with antidepressants between 1993 and 2011 in 80 psychiatric hospitals, 149 cases of drug-induced liver injury (0.08%) were reported.
Results: The study revealed that incidence rates of drug-induced liver injury were highest during treatment with mianserine (0.36%), agomelatine (0.33%), and clomipramine (0.23%). The lowest probability of drug-induced liver injury occurred during treatment with selective serotonin reuptake inhibitors ([0.03%), especially escitalopram [0.01%], citalopram [0.02%], and fluoxetine [0.02%]). The most common clinical symptoms were nausea, fatigue, loss of appetite, and abdominal pain. In contrast to previous findings, the dosage at the timepoint when DILI occurred was higher in 7 of 9 substances than the median overall dosage. Regarding liver enzymes, duloxetine and clomipramine were associated with increased glutamat-pyruvat-transaminase and glutamat-oxalat-transaminase values, while mirtazapine hardly increased enzyme values. By contrast, duloxetine performed best in terms of gamma-glutamyl-transferase values, and trimipramine, clomipramine, and venlafaxine performed worst.
Conclusions: Our findings suggest that selective serotonin reuptake inhibitors are less likely than the other antidepressants, examined in this study, to precipitate drug-induced liver injury, especially in patients with preknown liver dysfunction.

Keywords: Adverse drug reaction, antidepressants, drug surveillance, elevation of liver enzymes

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Introduction

The liver, the central organ of biotransformation, is particularly prone to oral medication-related toxicity due to high concentrations of drugs and their metabolites in portal blood rather than in the actual target area of the central nervous system. It is, however, difficult to attribute liver damage to a specific medication in clinical practice (Meyer, 2000). The susceptibility of an individual to drug-induced liver injury (DILI) depends on multiple genetic and epigenetic factors, age, gender, weight, and alcohol consumption that influence the occurrence of hepatic adverse effects (Krähenbühl and Kaplowitz, 1996). Older patients seem more vulnerable, and women have a stronger tendency to toxic liver reaction than men (Meyer, 2000); ethnic differences have also been reported (Evans, 1986).

Genetic metabolic variability is the most significant susceptibility factor in drug-induced liver toxicity. Enzyme polymorphisms can cause a slowing or complete disruption of enzyme function, which in turn results in the inefficient processing of drugs (Shenfield and Gross, 1999). This may not always result in corresponding liver damage but does contribute to an increased toxicity of substances. The majority of drugs and almost all psychotropic drugs are metabolized by the enzyme CYP450. Due to genetically determined polymorphisms of CYP450-isoenzymes, individuals can be categorized as poor, intermediate, extensive, or superextensive metabolizers (Miners and Birkett, 1998; Shenfield and Gross, 1999; Wilkinson, 2004). If a poor metabolizer receives medication containing several substrates or inhibitors of the same isoenzyme, the risk of a toxic reaction increases owing to a slower drug metabolism. As most psychotropic drugs are a substrate of CYP2D6 (Ingelman-Sundberg, 2005), this cytochrome is especially significant in the pharmacokinetic interaction. Approximately 5% to 10% of Caucasians have reduced or nonexistent CYP2D6 activity and are therefore at risk of toxicity when receiving psychotropic treatment (Transon et al., 1996; Griese et al. 1998; Ingelman-Sundberg, 2005; Bernarda et al., 2006).

A further important consideration is whether patients with preexisting liver dysfunction have a higher risk of hepatotoxic reactions. Although little information from controlled studies exists, there are indications that patients with preexisting liver disorders generally do not display an increased risk of drug-induced hepatotoxicity. It is more likely that preexisting liver damage negatively affects the ability of the liver to regenerate in the case of a hepatotoxic reaction (Chang and Schiano, 2007).

The clinical symptoms of DILI are extremely diverse, with some patients remaining asymptomatic. Possible symptoms are tiredness, lack of appetite, nausea, vomiting, fever, a feeling of pressure in the upper right region of the abdomen, joint and muscle pain, pruritus, rashes, and jaundice; the latter is the only symptom directly indicative of the liver's involvement (Chang and Schiano, 2007).

To diagnose asymptomatic toxic liver damage early, a minimum of laboratory testing is required. This involves the measurement of the glutamat-oxalat transaminase (GOT), glutamat-pyruvat-transaminase (GPT), and gamma-glutamyl-transferase (γ-GT) in serum which, if found to be normal, indicates that there has been no disruption to liver function. GOT and GPT are also well known as the enzyme aspartate aminotransferase (AST) and alanine aminotransferase (ALT), respectively. It is important to consider the possibility of DILI when prescribing psychotropic drugs and to record a detailed history of all medication taken by the patient, with particular attention paid to the length of use, the dose, and the time between the intake of medication and appearance of symptoms. The latency period involved here can vary between a few days and some months and, as liver damage may result from other causes such as viral, autoimmune, alcohol-induced hepatitis, and acute Morbus Wilson, the diagnosis of drug-induced toxic liver-damage is often a diagnosis of exclusion (Norris et al., 2008). Recently, Chalasani et al. (2014) developed practice guidelines for diagnosing and managing DILI.

The hepatic pattern of damage can be classified as predominantly hepatocellular, predominantly cholestatic, or a hepatocellular/cholestatic mixture and is important, as these patterns are of varying severity. The drugs also cause drug-specific patterns of liver damage revealing increased values of transaminases (GOT and GTP) and/or cholestasis (γ-GT, alkaline phosphatase [Zimmerman, 1999; Andrade et a., 2004]). A slight increase in transaminases or γ-GT levels to twice the norm without a rise in bilirubin is often of no clinical significance and in spite of continued medication, can simply disappear. This is a phenomenon often observed in antiepileptic or mood-stabilizing therapy (Yatham et al., 2002). These small functional changes must still be checked and in the case of a further elevation in liver enzyme levels medication must be discontinued (Voican et al., 2014). The prognosis of DILI is generally good, and less severe forms heal quickly and completely (Hayashi and Fontana, 2014). It is difficult to obtain figures regarding hepatotoxic drug reactions, as systematic epidemiological analyses are seldom done and observations are not conducted for a long enough period to have any true validity. Adverse effects are also not reliably reported or registered.

Drug surveillance programs permit an early detection of adverse drug reactions (ADRs) and this may minimize consequences. The Arzneimittelsicherheit in der Psychiatrie (AMSP) study is one such program in the field of psychiatry systematically evaluating severe ADRs of psychotropic medication in inpatients. The AMSP produces a database of these ADRs registered in the participating psychiatric clinics in Austria, Germany, and Switzerland (for details on AMSP methods, see Grohmann et al., 2004, 2013 Konstantinidis et al., 2012). In the present study, we have used this database to analyze the elevation of liver enzymes with a particular focus on sociodemographic data and the significance of clinical manifestations as well as transaminase levels measured during antidepressant (AD) monotherapy and combination therapies.

Methods

The AMSP program aims for a continuous detection of severe ADRs resulting from psychotropic treatment. These are evaluated during inpatient treatment. In our study, we analyzed data from 80 university, municipal, or state psychiatric hospitals or departments participating in the AMSP program in 1993 to 2011. Information on severe ADRs is collected from clinicians on a regular basis by psychiatrists as drug monitors who use a standardized questionnaire to document cases. The drug monitors get in touch with ward psychiatrists at regular intervals and severe adverse drug reactions are reported at weekly meetings of the medical staff (Grohmann et al., 2004). Information is collected on the details of adverse events as well as on patient demographics and nonpsychotropic drug intake. It includes alternative hypotheses on the causes of the ADR, relevant risk factors, measures undertaken, and previous exposure to the drug. Senior doctors of each hospital involved review the cases

that are later discussed at central and regional case conferences, which take place 3 times per year. Participants comprise hospital drug monitors, representatives from the national authorities regulating drugs, and drug safety experts from the pharmaceutical industry. Following discussions and analyses, ADR probability ratings are assigned and sent to the relevant authorities, and pharmaceutical companies receive the case questionnaires, which are also stored in the AMSP central database.

Based on the AMSP study guidelines (Grohmann et al., 2004) and recommendations of Hurwitz and Wade (1969) and Seidl et al. (1965), probability ratings were performed. The ADR probability rating system defines the following grades of probability beginning with Grade1, in which ADR is possible, that is, the risk of ADR is not known or the probability of another cause other than the drug in question is >50%. Grade 2 is defined as probable, with a known reaction, time course, and dosage for a specific drug. The likelihood of alternative causes is <50%. Grade 3 is categorized as definite, meaning a reexposure to the drug again causes the ADR. Grade 4 signifies questionable or not sufficiently documented.

In cases where an ADR results from a pharmacodynamic interaction of 2 or more drugs, each drug is given a rating of possible, probable, or definite according to the given facts.

Furthermore, drug-use data are collected twice per year from all hospitals participating in the AMSP program; the number of all inpatients and the mean treatment duration of all patients per year are also recorded.

The data presented in this study refer only to elevated liver enzymes due to "probable" (grade 2) and "definite" (grade 3) ADRs. Documentation of ADRs occurs when the value for one of the liver enzymes (GOT/AST, GPT/ALT, γ-GT, or alkaline phosphatase) exceed 5 times the upper normal values ("severe" as defined by the AMSP, based on the judgment of hepatologic experts) or when there are severe clinical symptoms and/or cholestasis. The threshold of 5 times the upper limit of normal GOT and GPT values have been proposed in the literature to avoid unnecessary withdrawal of substances (Aithal et al., 2011). Maximal levels of each liver enzyme are recorded in the AMSP in all DILI cases; mean maximum values per drug were evaluated for this analysis. Only drugs prescribed more than 2000 times within the overall study population were included in the analyses.

Our retrospective analysis employs data extracted from the anonymized databank of the AMSP drawn from all 80 participating hospitals between 1993 and 2011. Detailed information on the hospitals participating in the program can be found online (www.amsp.de). The informed consent of participants was not required, as the data analyzed were derived from an anonymized databank.

The AMSP drug surveillance program was approved by the leading boards of each participating institute prior to implementation, and the Ethics Committee of the University of Munich formally approved evaluations based on the AMSP databank.

Statistical Analysis

Incidence rates of hepatotoxicity were calculated as the percentage of inpatients receiving a specific AD or AD subclass and presented together with their 95% CIs. Regarding the low actual number of cases and the significant number of inpatients involved, the CI was calculated employing the exact method rather than one of the approximate methods (Vollset, 1993). The statistical program R was used to generate the figures (R Core Team, 2014). Q-square tests were calculated using the SPSS system Version 22.0. Significance was set at $P < .05$.

Results

Social Demographic and Illness-Related Data

From 1993 to 2011 the AMSP program monitored 390252 inpatients in 80 hospitals. A total of 184234 inpatients were treated with antidepressants. In 147 inpatients (and 149 cases, as 2 inpatients suffered from DILI twice) a severe hepatic ADR was observed (0.08%). Within 27 of 149 cases, clinical symptoms appeared (18.1%). In 104 inpatients, only ADs were imputed with the remaining inpatients suffering toxicity from an AD in combination with other psychotropic drugs. The majority of all monitored inpatients treated with antidepressants (56.5%) were suffering from depression. A total 75.9% were aged <65 years. Inpatients under surveillance were predominantly female (63.1%). A total 75.2% of inpatients suffering from DILI were diagnosed with depression, followed by 9.4% with the diagnosis of schizophrenia (Table 1). Thus, DILI patients differed significantly in their diagnostic distribution from the total AD population. Age and sex distribution, on the other hand, did not differ in DILI patients from all monitored AD patients.

Table 1. Age, Sex, and International Classification of Diseases Version 10 (ICD-10) Diagnosis of Patients Monitored during the Period of 1993–2011 Suffering from DILI Due to ADs and the Total Population under Surveillance (149 cases of DILI)

	All AD Patients Monitored, n (% of all n = 184.234)	Patients with DILI, n (%) of 149 Cases	DILI in % of all AD-Patients	*P*
Diagnosis (ICD-10)				
Organic disorders (F0)	14.192 (07.7)	5 (03.4)	0.035	χ^2=25.161,df=5,
Addiction (F1)	7.681 (04.2)	0 (00.0)	0.000	p<0.001
Schizophrenia (F2)	25.670 (13.9)	14 (9.4)	0.055	
Depression (F3)	104.096 (56.5)	112 (75.2)	0.107	
Neuroses/PP (F6)	27.377 (14.9)	13 (08.7)	0.047	
Others (F4, F7)	5.218 (02.8)	5 (03.3)	0.096	
Age (y)				
<65	139.795 (75.9)	115 (77.2)	0.082	χ^2=0.224, df=1, p=0.636
≥65	44.439 (24.1)	34 (22.8)	0.076	
Sex				
Male	68.004 (36.9)	56 (37.6)	0.082	χ^2=0.029, df=1, p=0.865
Female	116.230 (63.1)	93 (62.4)	0.080	

Abbreviations: DILI, drug-induced liver injury; AD, antidepressant; n, number.

Drugs Involved in DILI

In 147 inpatients (and 149 cases), 19 single substances were solely held responsible for DILI. In all other cases, combinations of several drugs were imputed. DILI frequencies for the different single substances as well as classes of ADs are given in Table 2 and Figures 1 and 2.

As for AD classes, the subgroup of tricyclic and tetracyclic ADs showed the most unfavorable profiles in terms of DILI, while the subgroup of serotonin reuptake inhibitors (SSRIs) had the lowest rates of DILI (all cases as well as SSRIs alone cases).

As for single drugs, mianserine, agomelatine, and clomipramine showed the highest frequencies of DILI with 0.36%, 0.33%, and 0.23%, respectively. Escitalopram, citalopram, and fluoxetine performed best. Trazodone (the only serotonin antagonist and reuptake inhibitor), serotonin norepinephrine reuptake inhibitors (SNRIs), and noradrenergic and specific serotonergic antidepressant (NaSSA) obtained similar results in between. Mianserine was added to the tricyclic and tetracyclic ADs according to existing literature (Benkert et al., 2010), as its side effects profile is similar to the latter. Nevertheless, this can be argued, as some authors add it towards the NaSSA group due to its similar chemical structure.

In 104 of 149 cases, ADs were imputed to be solely responsible for DILI, 96 cases were registered where only one AD was imputed, and 8 cases where 2 ADs or more were imputed in combination. The drugs listed as "other tricyclic antidepressants" (9 cases of DILI) were amitriptylinoxid (1 case), desipramine (1 case), dibenzepine (6 cases), and imipramine (1 case). The substances mentioned as "other ADs" were nefazodone (1 case) and bupropion (1 case). The group of monoaminooxidase (MAO) inhibitors consisted of tranylcypromine (3 cases) and moclobemide (no case). The substances metioned in "other TCAs" (tricyclic antidepressants), "other Ads," and MAO inhibitors were prescribed <2000 times; hence, these single drugs were not included in the analyses of the present study. An exception was made for agomelatine, due to the particular interest in this drugs hepatotoxicity. The results of agomelatine, however, have to be interpreted with caution, as it was not introduced until April 2009. Therefore, the observation period for agomelatine was significantly shorter than for all other drugs observed since 1993.

Dose-Dependent Aspects of Involved Drugs

As presented in Table 2, there were differences in the median dosages between the drugs deemed responsible for DILI and those for all monitored inpatients treated with ADs. Within the SSRI subgroup, escitalopram, citalopram, and sertraline were prescribed at double the dosage compared with all monitored

Table 2. Incidence of DILI and Median Dosages among Drug Classes (N=149 Cases of DILI and 184.234 Patients Monitored Overall, Respectively)

Drug class / substance	Patients monitored, n	Median dosage (mg/d) all patients (n=22.665)	Number of cases with DILI, n all cases (drug / group imputed alone)	Median dosage (mg/d) patients with DILI	Frequency, all cases in %
Monitored overall	**184.234**		**149 (104)**		**0.08**
SSRI	**70.060**		**22 (8)**		**0.03**
Citalopram	20.476	20	4 (2)	40	0.02
Escitalopram	18.549	10	2 (1)	20	0.01
Fluoxetine	4.682	40	1 (0)	40	0.02
Fluvoxamine	3.991	100	2 (0)	100	0.05
Paroxetine	9.494	30	6 (4)	30	0.06
Sertraline	12.868	100	7 (1)	200	0.05
SNRI	**36.636**		**28 (15)**		**0.08**
Duloxetine	8.015	60	3 (3)	90	0.04
Venlafaxine	28.621	150	25 (12)	225	0.09
NaSSA	**43.902**		**39 (21)**		**0.09**
Mirtazapine	43.902	30	39 (21)	45	0.09
NARI	**3.251**		**1 (0)**		**0.03**
Reboxetine	3.251	8	1 (0)	12	0.03
MAO Inhib.	**3.869**		**3 (1)**		**0.08**
SARI	**6.844**		**1 (1)**		0.01
Trazodone	6.844	150	1 (1)	100	0.01
TCAs+Tetra	**50201**		**71 (50)**		**0.14**
Amitriptyline	12.347	100	10 (8)	150	0.08
Clomipramine	5.657	125	13 (9)	150	0.23
Doxepine	12.412	100	7 (2)	150	0.06
Nortriptyline	2.016	100	2 (1)	175	0.09
Trimipramine	11.876	100	18 (13)	125	0.15
Maprotilin	3.097	100	2 (1)	52,5	0.06
Mianserine	2.796	60	10 (7)	90	0.36
Other TCAs*			9 (7)		NA
Melatonergic	**1.504**		**5 (2)**		**0.33**
Agomelatine	1.504	50	5 (2)	50	0.33
Other ADs*	**3.104**		**2 (0)**		**0.06**

*Other TCAs: amitryptilinoxid, desipramine, dibenzepin, imipramine.
**No case of milnacipran and tianeptin; multiple nominations possible.

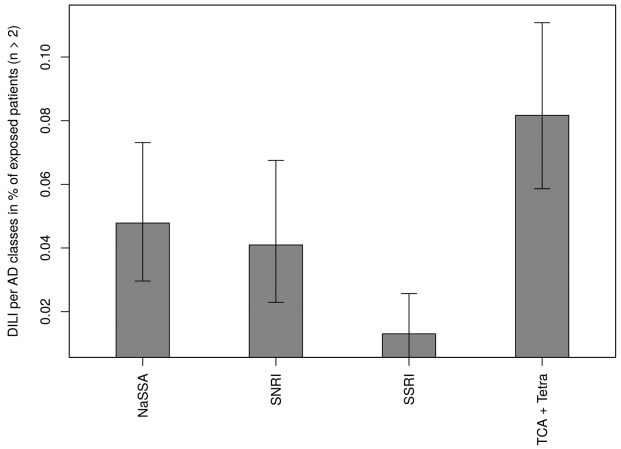

Figure 1. Drug-induced liver injury (DILI) per antidepressant (AD) classes/subgroups in percent of exposed patients, only cases where AD subgroups were imputed alone for DILI, and only substance classes imputed 3 times or more (except agomelatine due to its delayed implementation, which was imputed 2 times).

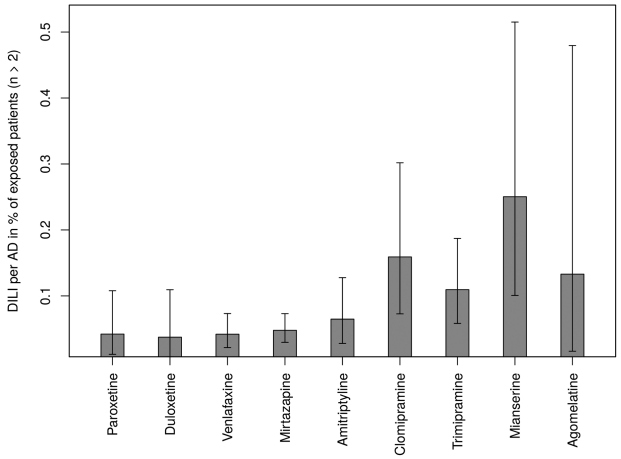

Figure 2. Drug-induced liver injury (DILI) per antidepressant (AD)/single substance in percent of exposed patients, only cases where single ADs were imputed alone, and just substance classes imputed 3 times or more were included (except agomelatine due to its delayed implementation, which was imputed 2 times).

inpatients at the time when DILI appeared. Also within the SNRI, noradrenalin reuptake inhibitor, and NaSSA subgroups, higher dosages compared with the median dosage for all patients monitored were observed when DILI occurred. Within the tricyclic and tetracyclic class, only maprotiline was prescribed at a lower dosage at the moment of DILI, while all the other substances of this subgroup were prescribed at higher dosages in cases of DILI.

Combination Treatment and DILI

The most prevalent drug class combination was the one of ADs and antipsychotic drugs (APs), in 31 cases within our study. First, olanzapine was implicated in DILI (6 cases), followed by clozapine (3 cases), and other APs held responsible for DILI in only 1 to 2 cases (haloperidol, melperone, chlorprothixene, quetiapine, perazine, levomepromazine, promethazine, and risperidone). Second, anticonvulsant drugs were combined with ADs (7 cases). Valproic acid was responsible for 3 DILI cases followed by carbamazepine, galantamine, pregabaline, and lamotrigine, implicated in only one case each.

Elevation of Liver Enzymes and Involved Drugs

Maximum gamma-GT and transaminase (glutamat-oxalat-transaminase [GOT] and glutamat-pyruvat-transaminase [GPT]) values per DILI case were evaluated for the time period from 2003 to 2011 (values for agomelatine from 2009 to 2011, as agomelatine was introduced in 2009). As there are small deviations in terms of maximum GOT (also known as aspartate-aminotransferase or AST), GPT (also known as alanin-aminotranferase or ALT), and alkaline phosphatase values across the participating institutions, a 5-fold increase in enzyme values was determined as DILI. From 2003 on, measurement of liver enzymes was done at all participating hospitals at a temperature of 37°C. Prior to this, measurement was done at 15 to 20°C, resulting in lower values for varying time periods at the different hospitals.

Duloxetine, clomipramine, and paroxetine were mainly responsible for high GPT values, while mirtazapine affected GPT values least. In terms of GOT values, duloxetine and clomipramine performed worst, and again mirtazapine had the least influence on GOT values. Regarding γ-GT, duloxetine performed best, while trimipramine, clomipramine, as well as venlafaxine increased γ-GT values most (Figure 3a-c). The duration of treatment when DILI occurred was different among the antidepressants; mianserine was taken for 22 days on average, while mirtazapine was taken for 40 days. Trimipramine had the longest time span with 43.8 days on average until DILI occurred. Bilirubin was elevated in 5 of 149 cases.

Elevation of Liver Enzymes in Preexisting Liver Damage and Clinical Symptoms

For inpatients with no preexisting liver damage, the mean maximum values for γ-GT, GOT, and GPT were 240, 202, and 285 U/L, respectively, when DILI was diagnosed. Cases with preknown liver damage presented maximum γ-GT, GOT, and GPT mean values of 525, 402, and 564 U/L, respectively. This indicates that preknown liver damage inpatients had more than doubled mean maximum values for γ-GT transaminases than subjects with normal liver status at the time when DILI appeared. In our study sample, risk factors were documented in 57% (85 of 149 cases). Preexisting hepatic injury was the most common risk factor by far (59 cases), followed by substance abuse, mostly alcohol (20 cases). Furthermore, predisposition to adverse reactions occurred in 10 cases.

The most common clinical symptoms were nausea, fatigue, loss of appetite, and abdominal pain. A total of 27 inpatients showed clinical symptoms, while the majority did not show any. In 8 cases, the AD treatment remained and dosage was reduced, while in all other cases the drug was withdrawn after DILI was assessed. Within 55 cases, DILI disappeared totally, while in 85 cases DILI improved. Within 9 cases the course was unknown.

Single Case of Acute Liver Failure

In our study sample of 149 liver enzyme elevations, only one case of acute liver failure occurred in a 20-year-old woman with a predamaged liver resulting from an overdose of paracetamol. At the time of admission to the psychiatric ward, the transaminase values were normal. She had been on a medication of 150 mg doxepine (for 3 days) and 10 mg olanzapine (for 6 days). The patient's liver enzymes increased rapidly, and clinical symptoms such as vomiting, nausea, and epigastric pain set in. In the following laboratory analysis, a hepato-toxicity was identified (bilirubin 3.8 mg/dL, GPT 8827 U/L, GOT 7363 U/L, lactate

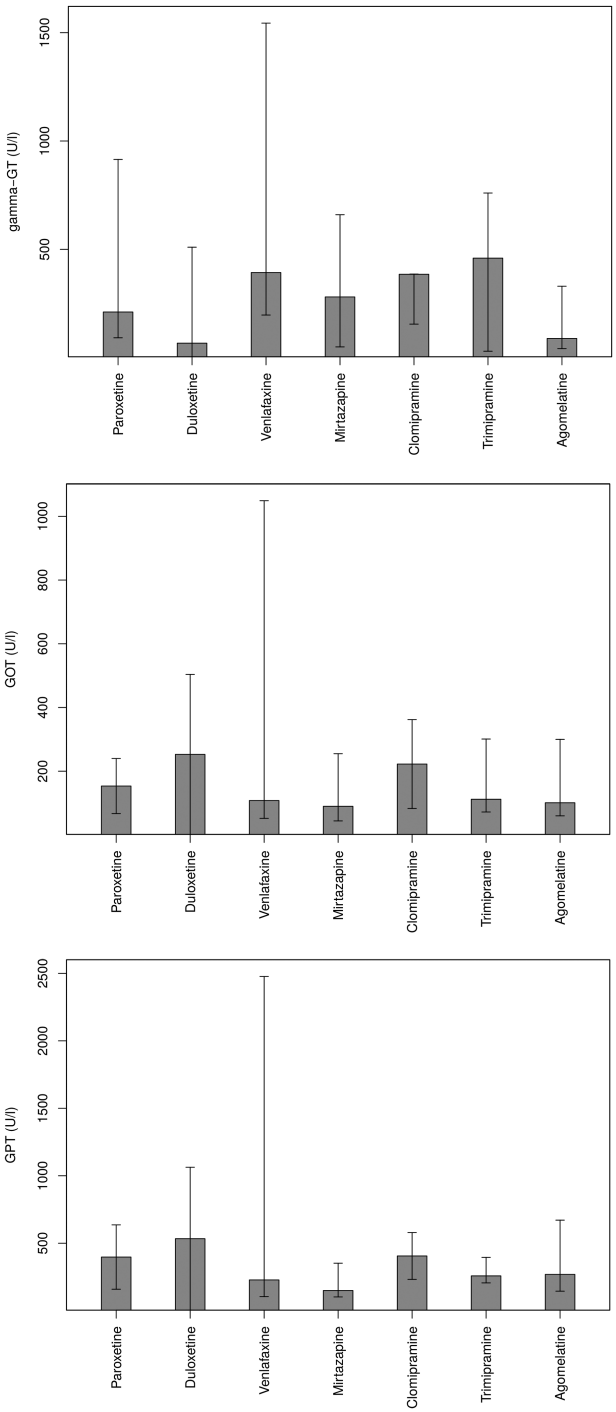

Figure 3. (a) Gamma-Glutamyl-Transferase (Gamma-GT) mean maximum values of single substances (imputed alone for a minimum of 3 times except agomelatine due to its delayed implementation, which was imputed 2 times). (b) Glutamat-oxalat-transaminase (GOT; also known as aspartate-aminotransferase [AST]) mean maximum values of single substances (imputed alone for a minimum of 3 cases, except agomelatine due to its delayed implementation, which was imputed 2 times). (c) Glutamat-pyruvat-transaminase (GPT; also known as alanin-aminotransferase [ALT]) mean maximum values of single substances (imputed alone for a minimum of 3 cases except agomelatine due to its delayed implementation).

dehydrogenase 4321 U/L). As soon as acute liver failure was diagnosed, the patient was transferred to the intensive care ward where she was under the care of the transplantation consulting team. All medication was discontinued and the patient received electrolyte infusions. As her liver function recovered rapidly, a liver transplantation was no longer necessary. The hepatotoxic effects of doxepine and olanzapine have been discribed in previous literature, but to our knowledge such a severe case has not been presented so far.

Discussion

To date, studies on the occurrence of the elevation of liver enzymes during psychotropic treatment have generally been based on case reports. A systematic drug surveillance program, however, increases the methodological accuracy significantly, and several such programs have shown links between ADRs and a range of psychotropic drugs (Grohmann et al., 2004, 2013; Gallego et al., 2012; Lettmaier et al., 2012).

In our study, mianserine, agomelatine, and clomipramine showed the highest frequencies of DILI. This result regarding the TCAs is in accordance with the previous results of the AMSP and Arzneimittel-Überwachungs-Programm in der Psychiatrie (German Drug Surveillance in Psychiatry) study group. The AMSP group published a manuscript on severe ADRs of ADs in the year 2004 (Degner et al., 2004). ADs were classified according to receptors and their diverse action profiles, and TCAs were linked to increased levels of liver enzymes. Classical TCAs have a significantly higher potential for inducing hepatic ADRs than newer ADs. Predominantly, these ADRs provoke cholestatic liver damage with prolonged cholestasis, and hepatocellular necrosis may also occur (Zimmerman, 1999). In an intensive drug monitoring study by the Arzneimittel-Überwachungs-Programm working group, elevated liver values were observed in 13.8% of inpatients taking TCAs, but the majority of inpatients presented with only minor increase in transaminases (eg, GPT and AP in one-third of cases observed) (Grohmann et al., 1999, 2004; Degner et al., 2004). Most TCAs do not induce or inhibit CYP-450-isoenzymes. As a substrate of these enzymes, however, they may be affected by interactions, a point that is of interest due to their relatively restricted therapeutic index (Chou et al., 2000; Kalra, 2007).

In our study population, up to 0.02% of inpatients receiving long-term therapy with fluoxetine showed elevated liver enzymes. While severe hepatotoxic reactions are rare, the literature reported some ADRs linked to fluoxetine and a few to paroxetine and sertraline (Grohmann et al., 1999, 2004; Charlier et al., 2000; Degner et al., 2004). Many new ADs inhibit CYP-450 enzymes; for example, both fluoxetine and paroxetine are inhibitors of CYP2D6. In combination with TCAs, severe intoxications may occur, and in those involving 3 or more substances, the likelihood of toxicity is even higher (Gillman et al., 2007).

As seen in short-term studies, mirtazapine elevates liver enzymes up to 3 times of the norm in 2% of patients, but in most cases patients do not develop significant liver damage, with some patients' values even recovering in spite of continued medication (Hui et al., 2002; Biswas et al., 2003). Two cases have been documented, however, in which mirtazapine induced severe cholestatic hepatitis (Dodd et al., 2001; Hui et al., 2002). Within our study sample, mirtazapine did not perform worse than SNRIs, especially in terms of GPT and GOT values, where it actually showed a favorable profile.

In our study in cases of DILI, the most prevalent drug class combination was the one of ADs and APs, with most cases concerning a combination of AD with olanzapine or clozapine. Most classical APs are metabolized via CYP2D6. A total of 5% to 10% of patients are slow metabolizers and show both high plasma levels and a high risk of a hepatotoxic reaction (Kevin

et al., 2007). There is little information available on the newer generation of APs regarding hepatotoxic side effects, but extreme hepatotoxicity seems to occur very rarely. Clozapine and risperidone induced liver damage, and even acute liver failure associated with clozapine has been documented (Macfarlane et al., 1997). Olanzapine seems to trigger a hypersensitivity reaction with involvement of the liver (Mansur et al., 2008). Clozapine causes a mild and mostly temporary increase in transaminases in 37% of patients (Grohmann et al., 1989; Macfarlane et al., 1997).

Our results are to some extent consistent with preexisting findings as summarized in a recent review of antidepressant-induced liver injury published in 2014, which also indicated a greater risk of hepatotoxicity for TCAs and agomelatine and the least potential for DILI with SSRIs (Voican et el., 2014). The latter review claimed aminotransferase surveillance (GPT) as the most useful tool for detecting DILI. In accordance with Voican et al. (2014), duloxetine and TCAs such as clomipramine had the least favorable influence on GPT values.

Furthermore, antidepressant-induced liver injury is considered to be dose independent. This is in agreement with our findings; in our sample, the median dosage when DILI occurred was higher than the overall median dosage in 7 of 9 substances. Additionally, compared with existing findings, age was not significantly related with the occurrence of DILI. Nefazodone and MAO-inhibitors were often described as highly responsible for DILI in previous studies, which cannot be confirmed within the results of this surveillance program, as single MAO inhibitors as well as nefazodone were only rarely prescribed and therefore could not be reliably compared with other drugs.

Conclusions

Our findings suggest that SSRIs are less likely than the other antidepressants examined in this study to precipitate DILI. Preknown liver damage inpatients are more at risk and had more than doubled mean values for γ-GT and transaminases than subjects with healthy liver status, at the time when DILI appeared in our data. Thus, special attention should be given to these inpatients when prescribing antidepressants with potential adverse effects affecting the liver. Given the huge sample size in our observational naturalistic study, the present findings may contribute significantly to the existing literature and help to prevent antidepressant-induced adverse hepatic events.

Limitations

The findings from the present study reflect data obtained from inpatients who are likely to be more severely ill and have higher antidepressant dosages or more polypharmacy compared with outpatients. Second, the detection of DILI was dependent on increased liver enzyme values and hence on blood examination tests. Regular blood tests are taken at the time of admittance to the hospital; however, there is no standardized regimen for laboratory testing after admittance that might influence the detection of DILI, especially in cases of asymptomatic drug-induced liver dysfunction. Small differences in surveillance habits of liver enzymes across the 80 hospitals participating in the AMSP program may further contribute to the aforementioned problem. The AMSP program focuses on only severe ADRs (Grohmann et al., 2004) with at least 5-fold increase of liver enzymes. This leads to a lower incidence rate of DILI compared with other studies using GPT values 3 times and GOT values 2-fold above the normal value as indicative of DILI. Furthermore, reporting bias cannot be ruled out due to the nature of the surveillance program. To prevent discrepancies among reported cases, the latter are discussed and examined in a systematic way at regional and international meetings within the AMSP group. In terms of the results for agomelatine, it has to be mentioned that there was an awareness of possible liver ADRs from the beginning of the surveillance. The so-called “dear doctor letters” (product safety information) might have influenced the detection of agomelatine-induced liver enzyme elevations due to this sensitization prior to the onset of DILI.

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Statement of Interest

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