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Journal of Hepatology 39 (2003) 62–67

Journal of Hepatology

www.elsevier.com/locate/jhep

Hepatitis induced by Kava (*Piper methysticum rhizoma*)

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***Background/Aims*: Botanical drugs are widely used and often contain highly active compounds. Kava root (*Piper methysticum rhizoma*), used frequently in Europe as a remedy against anxiety, contains kavapyrones with sedative effects. Seven case reports suggested the development of hepatitis after the intake of Kava.**

***Methods*: We analyzed 29 novel cases of hepatitis along with Kava ingestion which occurred between 1990 and 2002 in addition to the seven already published case reports using a clinical diagnostic scale established for adverse hepatic drug reactions.**

***Results*: Hepatic necrosis or cholestatic hepatitis were noticed with both alcoholic and acetonic Kava extracts. The majority of the 29 patients and the additional seven published reports were women (27 females, nine males). Both the cumulative dose and the latency to when the hepatotoxic reaction emerged were highly variable. Nine patients developed fulminant liver failure, of which eight patients underwent liver transplantation. Three patients died, two following unsuccessful liver transplantation and one without. In all other patients, a complete recovery was noticed after the withdrawal of Kava. Pathophysiologically, both immunoallergic and idiosyncratic factors may be responsible.**

***Conclusions*: The present report emphasizes the potentially severe hepatotoxicity of Kava which has recently led to the retraction of Kava-containing drugs by the pharmacovigilance authorities in Germany.**

***Keywords*: Drug-induced liver damage; Herbal medicine; Kava; Liver failure**

1. Introduction

Herbal drugs have become increasingly popular among patients and physicians [1,2]. This is, among other causes, due to the perception that drugs derived from plants are generally safe and devoid of side effects. However, numerous reports have emerged which showed hepatic adverse effects induced by plants containing pyrrolizidine alkaloids such as comfrey [3], preparations produced from germander [4], those containing chaparral extracts [5], and drugs made of Chinese herbs [6]. These plants may contain alkaloids that are biotransformed to toxins, such as the furanoditerpenoids contained in germander [7], or yet ill-defined hepatotoxins as exemplified by acute cholestatic hepatitis following the intake of Greater Celandine (*Chelidonium majus* [8]). With most herbals, hepatotoxic reactions were reversible after withdrawal, but occasionally lead to fulminant liver failure with subsequent death or liver transplantation.

Kava root (*Piper methysticum rhizoma*) is used as a traditional remedy for its psychotropic effects in Hawaii, Polynesia and the Fidji Islands. In industrialized countries, Kava-containing preparations are marketed as a sleeping aid and for the treatment of anxiety disorders and depression. The sedative action is exerted by kavapyrones, which are GABA receptor agonists through the inhibition of activating neurons in the reticular formation and the limbic system [9,10]. The therapeutic potential was carefully addressed in a recent systematic review and in a meta-analysis, which included the randomized, controlled trials with Kava for the treatment of anxiety. The results showed a significant anxiolytic effect as assessed by the Hamilton rating scale for anxiety [11]. Generally, the safety of Kava was considered

Received 27 January 2003; received in revised form 14 March 2003; accepted 27 March 2003

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0168-8278/03/$30.00
doi:10.1016/S0168-8278(03)00175-2

to be good and the rare typical side effects among frequent consumers comprise a yellowish skin discoloration and hair loss, a syndrome also termed *kavaism* [12]. Similarly, postmarketing trials in outpatients revealed good tolerability [13,14]. However, seven case reports describing hepatitis related to Kava ingestion have recently raised doubts over the safety of Kava products, which until recently were still available without prescription in Germany and elsewhere [15–21].

Here, we analyzed 29 so far unpublished cases of acute hepatitis which were finally reported to the German Federal Institute for Drugs and Medicinal Devices (BfArM), between 1990 and 2002, in addition to the seven already published cases.

2. Patients and methods

2.1. Patients

From 1990 until 2002, 39 cases of adverse hepatic reactions following the ingestion of Kava were reported to the German Department of Pharmacovigilance, Federal Institute for Drugs and Medicinal Devices (BfArM). Of these, sufficient retrospective data could be retrieved for 27 patients from the BfArM database. For the remaining 12 patients, either available data was insufficient or Kava could be excluded as the etiologic cause. Two additional cases which were recently treated in our hospitals as well as the seven already published cases were also included in the analysis.

2.2. Methods

Data of all patients were analyzed systematically according to a clinical diagnostic scale (CDS) which has recently been developed and evaluated for the diagnosis of drug-related liver damage in routine settings [22]. Following these criteria, drug-induced hepatotoxicity is likely when: [1] the time from drug intake to the apparent onset of the reaction is 'suggestive' (5–90 days from initial drug intake) or 'compatible' with drug hepatotoxicity (less than 5 or more than 90 days from initial drug intake and not more than 15 days of drug withdrawal for a hepatocellular reaction and not more than 30 days of drug withdrawal for a cholestatic reaction); [2] the course of the reaction after cessation of the drug is 'very suggestive' (when liver enzymes decrease by at least 50% of the excess over the upper limit of normal within 8 days) or 'suggestive' (when liver enzymes decrease by at least 50% within 30 days for a hepatocellular reaction and 180 days for a cholestatic reaction); [3] alternative causes of liver damage have been excluded by detailed investigations, including a liver biopsy [4]; there is a positive response to rechallenge (at least a doubling of liver enzymes) when such information is available. The causality between a drug and a drug-related adverse reaction is classified as 'certain' if all criteria are met. If only the first three criteria apply, i.e. with a positive rechallenge reaction unavailable, the hepatotoxic reaction ought to be classified as 'probable' [23]. An adverse hepatic reaction with a reasonable time relation to administration of the drug, but which can also be explained by concurrent disease or comedication, should be considered as 'possible'.

3. Results

The relevant data of all patients are displayed in Tables 1 and 2. In patients, where histology was available (24 out of 36), the histologic picture was compatible with drug-induced liver damage. The most frequent liver injury was hepatic necrosis ($n = 16$), seven patients developed cholestatic hepatitis and one patient had lobular hepatitis.

Table 1
Published case-reports on Kava-associated hepatotoxicity

Author	Patient (age in years/ gender)	Dosage (daily) (mg)	Duration of intake	Laboratory findings	Comedication	Histology	Outcome	Causality
Strahl et al., 1998 [15]	60/female	120	6 months	AST 921, ALT 1305, Bilir. 513, INR > 4	Paroxetin estrogens	Hepatic necrosis	Full recovery after 4 months	Probable
Brauer et al., 2001 [20]	22/female	240	4 months	AST 519, Bilir. 179.5	None	Hepatic necrosis	Liver failure transplantation alive	Probable
Russmann et al., 2001 [18]	33/female	210	3 weeks	AST 2430, ALT 2450, Bilir. 393.3	None	Cholestatic hepatitis	NR	Certain (lymphozyte proliferation +)
Humbertston et al., 2001 [21]	14/female	NR	6 months	NR	NR	Hepatic necrosis	Liver failure, transplantation alive	Certain (positive rechallenge)
Saß et al., 2001 [19]	50/female	60	7 months	AST 3129, ALT 2046, GGT 56, AP 371, Bilir. 511, INR 2.8	Glimepirid estrogens	Hepatic necrosis	Liver failure transplantation death	Probable
Kraft et al., 2001 [17]	60/female	480 Overdose	NR	AST 970, ALT 1139, GGT 60, INR > 4	Piretanide etilefrine	NR	Liver failure transplantation alive	Possible
Escher et al., 2001 [16]	50/female	210	2 months	AST and ALT > 1000 Bilir. 427, INR > 4	None	Hepatic necrosis	Liver failure transplantation alive	Probable

NR – not reported; LTX – liver transplantation; bilirubin levels are expressed as μmol/L (upper limit of normal [ULN], 17 μmol/L [1.0 mg/dL]). ALT-(alanine-aminotransferase; ULN, 17 IU), AST-(aspartate-aminotrans-ferase; ULN, 15 IU), GGT-(γ-glutamyltranspeptidase; ULN, 18 IU), AP-(alkaline phosphatase; ULN 170 IU)-levels are given as international units/liter (IU/L). INR, international normalized ratio. ANA, antinuclear antibodies. AMA, antimitochondrial antibodies. SMA, smooth muscle antibodies

Table 2
Unpublished cases of Kava-associated hepatotoxicity

No.	Gender	Age (years)	Indication	Dose (daily) (mg)	Duration of intake	Laboratory (AST/ALT/AP/GGT/Bilir.)	Histology	Comedication	Comorbidity	Course	Causality
1	Female	69	Restlessness	120	8 weeks	920/1056/605/473/485.6	ND	Aspirin bumetizide pentoxifylline	Ischemic heart disease arteriosclerosis	Remission (4 months)	Possible
2	Male	35	Anxiety	120	4 months	397/574/224/298/923	ND	None regular alcohol	None	Remission (NR)	Possible
3	Female	39	Anxiety	100	12 weeks	1048/2305/307/246.4	Cholestatic hepatitis	L-thyroxine contraceptive	None	Remission (6 weeks)	Probable
4	Female	68	Depression	100	2 years	617/596/220/280/764.4 ANA 1:5120	Cholestatic hepatitis	St. John's wort	None	Remission (1 year)	Possible
5	Female	50	Anxiety	300	2 months	1120/1012/249/231/525	Necrotizing hepatitis	Atenolol hydrochlorothiazide terfenadine	Hypertension atopic eczema	Remission (4 weeks)	Possible
6	Female	72	Restlessness	50	2 years	104/137/913/1719/291	Cholestatic hepatitis	B-vitamins ursodeoxycholic acid, prednisone	Rheumatoid arthritis	Remission (6 weeks)	Possible
7	Female	81	Anxiety	230 Overdose	10 months	1990/1394/366/95/583	Necrotizing hepatitis eosinophilic infiltrate	None	Hypertension	Fulminant liver failure death	Probable
8	Female	33	Depression	700 Overdose	4 months	720/665/370/187/438 SMA 1:160	Necrotizing hepatitis	None	None	Remission after prednisolone	Probable
9	Female	35	Depression	120	3 months	721/964/135/156/171 INR 3.0	ND	St. John's wort	Multiple sclerosis	Remission (3 months)	Probable
10	Female	59	Anxiety	240 Overdose	4 months	1094/1972/252/459/350	ND	Estrogen	Migraine multiple allergies	Remission (2 months)	Possible
11	Female	21	Depression	>1000 Overdose	7 months	703/997/218/60/545.5/INR2.7	Necrotizing hepatitis	None	None	Remission (6 months)	Probable
12	Male	38	Restlessness	100	2 weeks	453/774/198/102/68	Necrotizing hepatitis	Penicillin regular alcohol	Tonsillitis	Remission (3 months)	Probable
13	Male	39	Restlessness	100	2 weeks	667/1002/229/164/116	Cholestatic hepatitis	None	None	Remission (6 months)	Probable
14	Female	57	Anxiety	120	5 months	106/299/normal/24/normal	Lobular hepatitis	Thyroxine candesartan estrogen	Hypertension hypothyreosis	Remission	Certain (positive rechallenge)
15	Female	34	Restlessness	120	1 month	113/840253/92/34	ND	None	None	Remission (3 months	Probable
16	Male	32	Restlessness	240 Overdose	3 months	1473/1969/489/265/660 AMA 1:1280	Necrotizing hepatitis	None	None	Liver failure LTX, re-LTX	Probable
17	Male	36	Mood swings	100	6 weeks	1369/1208/425/213/204	Necrotizing hepatitis	None	None	Remission (4 months)	Probable
18	Male	39	Depression	120	6 months	968/1170/388/101/664	ND	Interferon-β	Multiple sclerosis	Remission (4 months)	Possible
19	Male	45	Restlessness	120	3 months	724/952/243/245/94	Cholestatic hepatitis	None	None	Remission (2 months)	Probable
20	Male	55	Anxiety	120	3 months	589/738/256/125/174	Cholestatic hepatitis	Glibenclamide	Diabetes	Remission (3 months)	Probable
21	Female	45	Depression	120	4 months	700/1000/361/245/685	ND	None	None	Remission (4 months)	Possible
22	Female	61	Restlessness	120	2 months	997/2431/242/408/357	Necrotizing hepatitis	Omeprazole gingko	None	Liver failure LTX death	Probable
23	Female	46	Restlessness	360	4 weeks	683/1442/325/229/65	ND	None	None	Remission (1 month)	Possible
24	Female	38	Stress	120	1 week	220/572/325/229/65	ND	Diclofenac sulfasalazine rechallenge with either drug negative	Rheumatoid arthritis	Remission (3 months)	Probable
25	Female	41	Restlessness	120	10 months	595/1005/264/136/1001	ND	None	None	Remission (10 months)	Possible
26	Female	45	Anxiety	120	4 months	712/620/400/139/443 INR 3.2, ANA 1:320	Necrotizing hepatitis	None	None	Liver failure LTX alive	Probable
27	Female	24	Panic attacks	120	5 months	1020/1483/382/229/396	ND	None	None	Remission (10 months)	Possible
28	Female	49	Stress	120	1 month	1815/1950/393/690/295	Necrotizing hepatitis	None regular alcohol	None	Remission after prednisolone	Probable
29	Male	33	Restlessness	100	2 weeks	920/2100/315/148/578	Necrotizing hepatitis	None regular alcohol	None	Remission (8 months)	Probable

For abbreviations, see table 1; ND – Not done

Histologic pictures of the two predominant liver injuries are displayed in Figs. 1 and 2.

When the above mentioned criteria are applied to the patients in the present report and those which have been published previously, an association between Kava ingestion and liver injury can be considered certain in three cases. In 21 patients, Kava is the probable cause of the observed liver damage. In 12 additional patients, a causal role of Kava is at least possible, but other confounders, such as comorbidities or comedications may also be responsible.

A total of nine patients developed fulminant hepatic failure of which three eventually died. Of the former, eight patients underwent orthotopic liver transplantation, of which five were successful and one was successful after retransplantation. Two transplanted patients died subsequently due to postsurgical infectious complications. One of the two patients who died from fulminant liver failure was too old (81 years) for undergoing liver transplantation. The majority of all patients were women (27 females/nine males) and the mean age was 46.7 years (median, 39 years; range 14–81). The latency from the first intake of Kava until the onset of symptoms varied between 2 weeks and 2 years with a median of 4.5 months. Other possible etiologies of hepatitis were ruled out in all patients. However, in some individuals, regular alcohol consumption ($n = 4$) and comedication ($n = 20$) were present which includes the possibility of either liver damage due to alcohol or the administered comedication or hepatotoxicity related to drug interactions. All patients except for those with fulminant hepatic failure recovered completely after the withdrawal of Kava.

4. Discussion

In the present report, 29 so far unpublished cases of severe hepatotoxicty following the ingestion of Kava preparations are described and evaluated in terms of causality. From these data, in addition to the already published cases, three patients died from Kava-related acute liver failure. So far, our report constitutes the largest series of patients with Kava-induced adverse hepatic reactions which impressively demonstrates the potential of Kava preparations to cause severe liver damage.

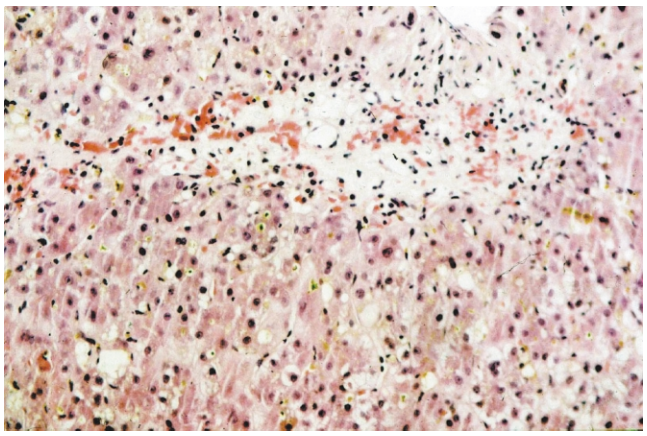

Fig. 1. Liver histology of a patient with Kava-Kava-associated cholestatic hepatitis (case 28) with surrounding lymphocytic infiltration in zone 3 (H&E stain, magnification 400-fold).

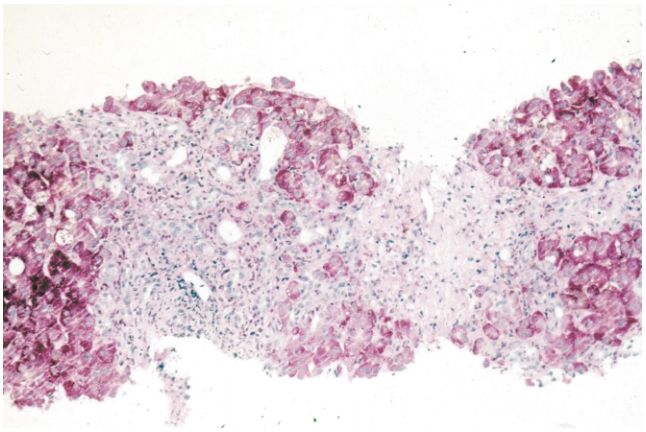

Fig. 2. Massive pericentral hepatic necrosis, inflammatory infiltration and bile duct proliferation (periodic acid stain [PAS], magnification 160-fold).

An increasing number of herbal remedies have been identified as potential hepatotoxins precipitating liver damage ranging from mild liver enzyme elevations to a severe and even lethal outcome [24]. In this setting, it is often difficult to clearly prove the causal role of incriminated herbals. The ultimate proof is given when the clinical picture recurs after a voluntary or accidental reexposure to the drug, as could be seen in patient no. 14.

The active components in Kava extracted by alcohol or acetone are kavapyrones which are also used for standardization. The major constituents within aqueous, ethanolic and acetonic extracts include kavain, dihydrokavain, methysticin, dihydromethysticin, yangonin, and desmethoxyyangonin, all of which are lipophilic styrylpyrones displayed in Table 3 [25]. By the time Kava was issued marketing approval, animal toxicity studies had shown no evidence for potential hepatotoxicity of the entire extract or monosubstances contained within and the monograph of the commission E of the German pharmacovigilance authorities did not list liver damage as a possible adverse effect.

From the available data, it remains speculative as to what mechanism was responsible for hepatotoxicity in the observed 36 cases, but both immunoallergic and idiosyncratic reactions may be responsible. The obvious lack of dose-dependency and the marked eosinophilic infiltrate in some liver biopsies, support this assumption. Furthermore, two patients (no. 8 and 28) showed rapid improvement after prednisolone, which is compatible with drug-induced autoimmunity. Both cases were reported anonymously to German pharmacovigilance authorities (BfArM) and only written histology reports were available in which a notion on the kind of cellular infiltrate is unfortunately lacking. So,

Table 3
Content of kavapyrones in Kava-root (*Piper methysticum rhizoma*). Numbers are given in grams (g)

Kavapyrone (g)	Aqueous extract (100 ml)	Ethanolic extract[a]	Acetonic extract[b]
Kavain	2.2	29.4	17.8
Dihydrokavain	8.1	31.2	11.1
Methysticin	1.2	14.2	16.4
Dihydromethysticin	1.5	16.8	10.5
Yangonin	0.3	18.1	8.1
Desmethoxyyangonin	0.5	9.5	4.4
Total (daily dose)	13.8	119.2	68.3

[a] Kava ratiopharm forte®, 120 mg.
[b] Laitan®, 100 mg (Ref. [25]).

only assumptions can be made over the decision to treat the patients with prednisolone. At least in patient 8, an anti-SMA titre of 1:160 is suggestive of the involvement of autoimmune mechanisms which may justify the administration of steroids. Three further patients revealed elevated levels of autoantibodies, namely ANA, AMA, and SMA. Slightly to moderately elevated ANA and SMA titres are known features of immunoallergically precipitated hepatitis [8]. Another diagnostic measure that comes close to a proof of causality of a drug to precipitate an immunoallergic adverse hepatic reaction is a positive lymphocyte transformation test as it was performed in the case report by Russmann and associates [18]. Unfortunately, this in vitro test is not very sensitive and often yields false negative results. However, its specificity is satisfactory, especially when necessary precautions are fulfilled [26]. Apart from drug-induced hypersensitivity, the long latency period, the absence of features of autoimmunity in many patients, as well as the fact that the dosage exceeded several times the recommended dose of 120 mg per day, embody the possibility of individual metabolic idiosyncrasy. In their case report, Russmann and colleagues have recently found a poor-metabolizer phenotype of cytochrome P450 2D6 (CYP2D6) in individuals who experienced Kava-induced hepatitis and they suggested that this condition may be a risk factor for developing Kava-related liver damage [18]. A CYP2D6 deficiency phenotype is well known to be associated with perhexiline hepatotoxicity [27]. Therefore, it may add to a mechanistic understanding to genotype of all patients who experienced Kava-induced liver damage for CYP2D6 polymorphisms which are known to produce the above mentioned poor-metabolizer phenotype [28]. However, contacting and recruiting the patients from the BfArM database for genotype analysis would have conflicted with patients' data protection.

In two patients, the adverse hepatic reaction occurred after an intake of 2 years (patients no. 4 and 6). As can be seen from Table 2, these two patients took rather low doses of Kava, which may explain the long latency until the onset of symptoms. In patient no. 4, the high ANA titres disappeared after discontinuation of Kava intake which excludes genuine autoimmune hepatitis. Unfortunately, there was no documentation on autoantibodies prior to Kava ingestion.

Several patients also took other drugs that are known to potentially induce adverse hepatic reactions, such as interferon-β and glibenclamide, in patients no. 18 and 20, respectively, or might have influenced the tolerability of Kava, such as St. John's wort in patients no. 4 and 9. Interferon-β administered for treating multiple sclerosis has occasionally led to the induction of autoimmune hepatitis requiring treatment discontinuation [29,30]. However, direct hepatotoxicity is extremely rare and in patient 18, the elevated liver enzyme levels normalized although interferon-β medication was continued and, therefore, interferon can be excluded as the precipitating drug. Since glibenclamide, in patient 20, was taken for several years before hepatitis occurred and hepatitis subsided following Kava withdrawal, glibenclamide toxicity can also be excluded. Preparations containing St. John's wort have repeatedly led to adverse drug interactions, e.g. with ciclosporine, due to its potential to induce CYP3A4, which in turn may be inhibited by Kava. However, kavalactones are almost entirely degraded by CYP2D6. An interaction via inhibition of CYP3A4 should rather affect the clinical efficacy of St. John's wort than increase the toxicity of Kava. This case was labelled as possible.

It cannot be ruled out that other components than those mentioned above within the Kava preparation might have been the cause. It is a constant problem in herbal medicine, in particular traditional Chinese and Indian herbal medicine, that combinations of herbs are administered, making the identification of the crucial compound that is either therapeutic or causes toxicity almost impossible [31]. In our report, liver damage could be observed along with numerous different Kava preparations available on the German drug market (Antares®, Kavacur®, Kava ratiopharm®, Kavasedon®, Kavosporal®, Kavatino®, Laitan®, Limbao®, and others), which is highly suggestive that Kava itself produced toxicity. It seems noteworthy that both alcoholic and acetonic extracts led to liver damage implying the toxicity of kavapyrones rather than manufactural characteristics. Kava-containing preparations were used extensively in Germany and its estimated annual sales reached about 650,000 packages resulting in 13 million daily doses. Like with many other herbal drugs, no prescription was required and, therefore, most patients ingested the drug in self-medication and consequently unmonitored by a professional health care provider. The finding of 33 cases of hepatitis due to Kava in Germany alone, therefore, suggests significant underreporting in other countries. The incidence for Kava-associated adverse hepatic events has recently been calculated during the implemented federal reevaluation of the drug, resulting in 0.24 cases/1,000,000 daily doses for doses $\leq$120 mg (95% confidence interval 0.09–0.53) and 0.26/1,000,000 daily doses for doses $\geq$120 mg (95%

confidence interval 0.12–0.49), indicating a lack of dose-dependence. The present report clearly shows the potential of Kava to cause severe liver damage and a presumed immunoallergic mechanism in at least some of the patients renders the associated risk extremely unpredictable. We are particularly concerned about the three patients who died from hepatic failure or associated complications. In the light of the emerging hazards along with this botanical, the risk-benefit-ratio is certainly negative. In Europe, the awareness towards Kava-associated hepatotoxicity has increased as indicated by recent reports [32,33]. Consequently, on June 14th 2002, the Federal Institute of Drug and Medicinal Devices has banned the marketing and sale of all Kava-containing drugs except for homeopathic preparations in Germany.

Acknowledgements

The authors would like to express their gratitude to Dr Hans-Jörg Horst from the German Federal Institute of Drugs and Medicinal Devices (BfArM), Bonn for excellent co-operation in collecting some of the data and consulting over legal issues.

This work was supported in part by a grant from the *Fonds für Forschung und Lehre – ELAN-Programm* (No. 01.03.14.1) of the University of Erlangen-Nürnberg.

F.S. is a recipient of a research grant from *Interdisziplinäres Zentrum für klinische Forschung* (*IZKF*) of the University of Erlangen-Nürnberg.

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