Potential liver toxicity of herbal supplement NMDA relief Exendo®

Introduction

The herbal supplement NMDA Relief® from the manufacturer Exendo is available in drug stores and web shops. The product contains glidwort (Skullcap, genus Scutelaria), L-theanine and Ginkgo biloba. According to the information on the website glidwort *helps with mental pressure and effort* and l-theanine *improves concentration and focus, promotes calm and relaxation and reduces anxiety* (1).The product has no registration as a (traditional herbal) medicine through the Dutch Medicines Evaluation Board, but falls under the Dutch Commodities Act (2).

Reports

Pharmacovigilance centre Lareb received two reports of liver toxicity associated with use of herb supplement NMDA relief Exendo® in 2018. Both serious reports were reported by a gastroenterologist/hepatologist.

Table 1: Reports on NMDA relief Exendo®

Reportnumber Patient, Sex, Age, Reporter	**Drug Indication for use**	**Concomitant medication**	**Suspected adverse drug reaction MedDRA term**	**Time to onset, Action with drug outcome**
A, 00266543/ 00276683* Female, 41-50 years specialist doctor	NMDA Relief Exendo®	vitamin D3 Holland & Barret® Glycine Mg Exendo® B-complex Biovital®	Acute liver failure	6 weeks Drug withdrawn Liver transplant
B, 00306040 Male, 31-40 years specialist doctor	NMDA relief Exendo® Kudzu Exendo® Mentalis stress®		Hepatitis	2 months 1 month 3 months Drugs withdrawn Recovering

*** duplicated reports; reported by a co-assistant and the specialist doctor**

Patient A concerns a female, aged 41-50 years with menopausal symptoms. For her complaints she visited a women's clinic. She was advised to use the herbal supplement NMDA relief®. After 6 weeks she experienced influenza like symptoms. The supplement was withdrawn and she was admitted to the hospital. Echo of the abdomen showed signs of acute liver failure with portal hypertension, splenomegaly and ascites. Subsequently she developed hepatic encephalopathy. Liver biopsy revealed extensive necrosis involving around 80% of the liver parenchym, best suited to an acute liver failure. Liver laboratory- tests showed bilirubin > 347µmol/l, decreased factor V and INR>6. After hospitalisation the kidney function decreased, probably related to lower intake and hepatorenal syndrome. She developed multi-organ failure. Her medical condition fulfilled King's College criteria and she underwent a liver transplant. After the transplantation the recovery was delayed due to a respiratory infection with persistent pleural exudate, reactivation of CMV and gastroparesis. Seven months after transplantation the patient was diagnosed with posttransplant lymphoproliferative disorder (PTLD) for which she is still treated.
Preliminary to the onset of complaints the patient used for the period of 6 weeks beside the NMDA Relief® also supplement vitamin D3 Holland & Barrett®, Glycine magnesium Exendo®, and B-complex brand Biovital®. Those supplements were also withdrawn. The last weeks before the hospitalization the patient used occasionally also paracetamol, maximal twice daily 1000mg. In respect to the medical history it is mentioned that she has asthma. She doesn't use recreational drugs or tobacco, occasionally she drank 1 glass of wine.

Patient B concerns a male aged 31-40 years. Because of symptoms of stress the patient started to use supplement Mentalis stress®, 1 tablet daily. After approximately 1 month also two tablets of

NMDA relief® per day were added. Finally, one month later also Kudzu Optimum® was started. After 1 month the patient developed hepatitis and was hospitalized. The drugs were withdrawn. The laboratory- tests showed bilirubin 150µmo/l, bilirubin not conjugated 120µmol/l, ASAT 2600U/l, ALAT 4100U/l, LD 570mEq/l, alkaline phosphatase 288 U/l, gamma-glutamyltransferase 200U/l, albumins 42g/l and INR 1,1. After the conservative treatment, not specified reported, the patient recovered. He has no medical history.

Analyses of the products

Samples of the supplements used by both patients were collected and sent to the National Institute for Public Health and the Environment (RIVM) for analysis. The samples were examined using UPLC-QTOF-MS / MS on the presence of pharmacologically active substances (3;4).

Results of the analysis of the NMDA Relief Exendo® sample used by the patient A:
The sample of NMDA Relief Exendo® contains baicalin with a content of 166 mg per dosage unit and baicalein. There are also strong indications for the presence of wogonin and wogonoside. Baicalin, baicalein, wogonin and wognoside are well-known components of blue glidewort (*Scutellaria lateriflora*). There are no indications for the presence of substances from Teucrium.

Results of the analysis of the NMDA Relief Exendo® and Kudzu Optimum Exendo epigenomics sample from the patient B:
In the sample of the NMDA Relief Exendo® baicalin and baicalein have been found and are strong indications for the presence of wogonoside and wogonin. The presence of baicalin and baicalein has been confirmed with a reference standard. Baicalin is also determined semi-quantitatively. Baicalin is the glucuronidated variant of baicalein and was found in an amount of 232 mg per dosage unit. Wogonoside is the glycosylated variant of wogonin. Baicalin, baicalein and wogonin are naturally richly present in blue glidewort (*Scutellaria lateriflora*) Blue glidewort is declared on the supplied NDMA relief packaging. There are no indications for the presence of substances from Teucrium.

No indications were found with the method used for the presence of pharmacologically active substances in the sample of Kudzu Optimum Exendo.

Product information
The main ingredient in the product NMDA Relief Exendo® is Skullcap (*Scutelaria lateriflora*). The genus Scutellaria in the family Lamiaceae has over 350 species, many of which are medicinally active. *Scutellaria baicalensis* and *Scutellaria lateriflora* are the most widely studied medicinal plants (5-7). *Scutellaria baicalensis* (Chinese skullcap) is related to *Scutellaria lateriflora* (American Skullcap) and even though they are not the same, both are often referred to as Skullcap or scutellaria, making differentiation difficult. They are both commonly used as a relaxant (8).
The information about the species of Skullcap, used in the product NMDA Relief® is confusing. Consulting The Federal Public Service (FPS) Health, Food Chain Safety and Environment of Belgium revealed that here are 2 different products notified (9):
NMDA Relief (*Scutellaria lateriflora*, L theanine, Magnesium-bisglycinaat and Ginkgo biloba) and NMDA Relief B (*Scutellaria baicalensis*, L-theanine, Magnesium-bisglycinaat and Vitamin B12
But the official website from Exendo provides the ingredients notified as NMDA Relief B® under the product name NMDA Relief® (1).

Table 2. The ingredients as declared on the package of the product used by patient A and patient B (image appendix)

Ingredients	Weight	Extract/ADH
Glidkwort (Scutellaria lateriflora)	200 mg	98% baicaline extract
L-theanine	200 mg	98,5% L theanine

Magnesium-bisglycinaat	200 mg	22 mg elemental magnesium
Ginkgo biloba	50 mg	24% ginkgo glycosides, 6% ginkgo carrot lactones, less than 5ppm ginkgoic acids

Ingredients of the concomitant supplements used by the patient B:
Kudzu Exendo® (10) contains per 1 vegetarian capsule of 600 mg (daily dose) :

- Kudzu extract (roots of Pueraria lobata) 500 mg (40% isoflavones)
- Ginkgo biloba extract (leaves) 100 mg (24% ginkgo flavonglycosides = 24 mg, 6% ginkgo seeder lactones =6mg, less than 5 ppm of ginkgoic acids)

Mentalis Stress Trenker® (11) contains per capsule:

- 300 mg extract of ashwagandha (Withania somnifera L.), magnesium
- vitamin B3, superoxide dismutase (SOD 15000 IU / g) of melon (Cucumis melo L.).
- B5, B6, B2, B1, B9, B8, B12

Other sources of information

Literature

In literature a few case-reports of hepatotoxicity related to the use of skullcap have been described (8;12-15). Skullcap has been implicated in rare instances of clinically apparent liver injury, although in most cases multiple herbal medications were being taken and the role of skullcap in the hepatic damage was unclear. In reported cases, the onset of symptoms and jaundice occurred within 6 to 24 weeks of starting skullcap, and the serum enzyme pattern was typically hepatocellular. Immunoallergic and autoimmune features were usually absent, although low titers of autoantibodies were not infrequent. Recovery was rapid once the herbal was discontinued, but some cases have resulted in acute liver failure. Chinese skullcap is a different species, but may also have adverse effects on the liver. There have been several reports and small case series of acute liver injury with jaundice arising after 1 to 3 months of starting herbals or dietary supplements with Chinese skullcap (Scutellaria biacalensis), the liver injury resembling that associated with North American skullcap (Scutellaria lateriflora) (16).

Furthermore, in some instances phytochemical analysis has identified significant adulterants with germander (Teucrium) or mislabelling in cases of suspected skullcap hepatotoxicity. *Teucrium canadense L*. and *T. chamaedrys L*. (Lamiaceae), contain potentially hepatotoxic neoclerodane diterpenes such as teucrin. The hepatotoxicity of germander arises from the bioactivation of teucrin A by cytochrome P450 to create reactive metabolites (17-19).

Discussion and conclusion

Herbal and dietary supplement use is common. Most marketed products consist of complex mixtures. Although they are perceived as safe, instances of hepatotoxicity attributable to these products underscore their potential for injury, but the exact component that is responsible for injury is difficult to discern (20). Their efficacy, safety, and claims are not assessed by regulatory agencies, and there is uncertainty about their reported and unreported contents (21).

The mechanisms through which herbal dietary supplements cause hepatoxicity are variable and specific to the substance consumed. In Herb- Induced Liver Injury (HILI), it is important to note that substances may be safe in their ‘natural’ form but highly concentrated preparations and synthesized chemicals, although marketed as natural, may be associated with toxicities (22).

Discerning the exact toxic substance in a supplement is sometimes difficult as herbal supplements may also be contaminated with herbs or synthetic substances that are not mentioned on the label. Therefore remnants of NMDA Relief ® from both our patients have been collected and sent to the National Institute for Public Health and the Environment (RIVM) for analysis. By analyzing the samples

we can demonstrate or exclude the presence of the contamination and also control the amount of active parts declared by the manufacturer. In the samples of te product NMDA Relief Exendo® from both patients only the active substances from the Skullcap, were found: baicalin, baicalein, wogonin and wognoside which are well-known components of blue glidewort (Scutellaria lateriflora), declared on the labeling. There was remarkable difference (40%) in the amount of baicalin between the samples: sample A contained 166mg and sample B 232mg baicalin per dosage. According the labeling one dosage unit should content 200mg glidewort with 98% baicalin extract. There was no indications for the presence of substances from germander such as hepatotoxic verbascoside However, in literature also a possible liver toxicity of baicalin has been described (16).

It should be mentions that both our patients used more than one supplement in the period previously to hospitalization. It is not possible to exclude a role of these supplements with certainty. Nevertheless, we regard this relationship as very likely, bear up on that the only common product used by both patients was NMDA Relief Exendo®. The latency between start of the use and signs of the liver injury in both cases fits the reported latency time for onset of hepatotoxicity in the literature, which is 1-3 months (16). The liver biopsy of the patient A fits drug- induced liver toxicity and there have been several supportive case-reports in the literature, describing association between liver injury and exposition to skullcap.

In conclusion: the two cases reported to the Pharmacovigilance centre Lareb shows a possible relation between the use of herbal product NMDA Relief® from the manufacturer Exendo and the liver toxicity. Further investigation of this association is warranted. The big difference in the amount of active ingredients per dosage unit also deserves attention.

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This signal was updated on March 4, 2019. It is possible that in the meantime other information became available.

Appendix