

## Review Article

# Mysterious Hawaii Liver Disease Case – Naproxen Overdose as Cause Rather than OxyELITE Pro?

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## Abstract

A liver case was reported from a Honolulu medical center in 2013 and remained mysterious due to poorly documented case details and conflicting statements, necessitating a reanalysis of medical files containing redacted raw data of the female patient described as previously healthy. This actual reanalysis provides evidence of a patient with a remarkable multimorbidity associated with a significant present and past history of multimедication by abundant potentially hepatotoxic synthetic drugs and by some dietary supplements [DS]. Her liver disease now is best explained as recurrent toxic hepatitis by overdosed naproxen, a non-steroidal antiinflammatory drug [NSAID] with a well known and significant hepatotoxic potency. Actually, its reuse - five months after first disease onset - to treat daily headaches for a month unexpectedly caused a recurrence of the scleral icterus as at the initial onset. Additional diagnoses now include DILI by other used synthetic drugs; symptomatic acute acalculous cholecystitis associated with gallbladder sludge; acute hepatitis, preferentially prior not excluded hepatitis E virus infection, infections by HSV and VZV; and nonalcoholic fatty liver disease. Evidence is lacking that any of the four used DS was the culprit, including OxyELITE Pro [OEP] that initially was incriminated as the sole cause of liver disease by a team of investigators in Hawaii. The conclusion is reached that the case now loses its mystery and is best explained by overdosed naproxen, a NSAID with a known history of hepatotoxicity - rather than by any DS including OEP - affecting a multimorbid and multimедicated patient.

## ABBREVIATIONS

ADHD: Attention Deficit Hyperactivity Disorder; ALP: Alkaline Phosphatase; ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; BMI: Body Mass Index; CDC: Centers for Disease Control and Prevention; CIOMS: Council for International Organizations of Medical Sciences; CMV: Cytomegalovirus; DILI: Drug induced Liver Injury; DS: Dietary Supplement; EBV: Epstein Barr Virus; FDA: Federal Drug Administration in Washington DC, USA; HAV: Hepatitis A Virus; HBc: Hepatitis B core; HBs: Hepatitis B surface; HBV: Hepatitis B Virus; HDS: Herbal Dietary Supplement; HCV: Hepatitis C Virus; HEV: Hepatitis E Virus; HSV: Herpes Simplex Virus; HILI: Herb induced Liver Injury; LFTs: Liver Function Tests; N: Normal range as multiple of its upper limit; NAFLD: Non-alcoholic Fatty Liver Disease; NSAID: Non-Steroidal Anti-inflammatory Drug; OEP: OxyELITE Pro; PCP:

Primary Care Provider; PCR: Polymerase Chain Reaction; R: Ratio; RUCAM: Roussel Uclaf Causality Assessment Method; VZV: Varicella Zoster Virus.

## INTRODUCTION

Dietary supplements [DS] may be effective when used as slimming aids, but there is considerable concern regarding rare side effects including liver injury possibly attributable to few DS products [1-7]. In this context, the Centers for Disease Control and Prevention [CDC] published a preliminary report on a liver disease cohort of seven patients that emerged in Hawaii in the summer 2013 and remained a mystery [8]. This created uncertainty due in part to the reporting of inconsistent and incomplete data, associated with the lacking of an ascertained culprit. However, an assumed temporal association initially focused on OxyELITE Pro

[OEP], a popular over-the-counter DS intended for weight loss and muscle building, which was suspected as a single causative product for all patients of this unique disease cluster. A final CDC report has not yet been published, presumably due to continued uncertainties and ongoing scientific or regulatory investigations and discussions. Occurrence of this Hawaii liver disease cluster in primarily summertime is suggestive of a seasonal outbreak by some type of hepatitis infections, including hepatitis A or E [9], which so far might not have been excluded with the required scrutiny. It is also well recognized that patients taking herbal dietary supplements [HDS] tend to use these in overdoses and are under medication by several synthetic drugs and additional HDS, conditions considered as confounders [10-12].

Subsequently, another liver case of assumed connection with OEP use was reported, but some peculiarities and suspected confounders prevailed, questioning the proposed causal relationship a priori [13]. Actually, this case was characterized by a mild clinical course, absence of encephalopathy, only moderately elevated aminotransferases, virtually normal bilirubin values, and a hepatocellular rather than a cholestatic type of injury; complete recovery was surprisingly prolonged and only achieved within 85 days, whereas short-term restoration is to be expected under these favourable clinical conditions [13]. This called for additional intensified searches on alternative culprits to explain the liver disease, which initially was attributed to OEP with a highly probable causality [13] using the CIOMS scale [Council for International Organizations of Medical Sciences], also named RUCAM [Roussel Uclaf Causality Assessment Method] [14]. This unusual high causality grading is rarely awarded for assumed hepatotoxicity cases [15], unless case conditions were virtually perfect with fulfilment of all key CIOMS criteria, complete lack of confounders including comedication, and valid exclusion of alternative causes such as hepatitis A virus [HAV], hepatitis B virus [HBV], hepatitis C virus [HCV], hepatitis E virus [HEV], and infections by cytomegalovirus [CMV], Epstein Barr virus [EBV], herpes simplex virus [HSV], and varicella zoster virus [VZV], just to name a few examples [15-18]. In addition, this patient was not healthy as erroneously claimed [13]; prior to OEP use, she likely had morbid obesity and associated diseases including a metabolic syndrome, specifically with a hepatic metabolic syndrome and non-alcoholic fatty liver disease [NAFLD]. These conditions are well known risk factors for drug-induced liver injury [DILI] [19,20]. Morbid obesity often is associated with painful musculoskeletal disorders requiring management of the chronic multipain syndrome by synthetic drugs, mostly non-steroidal antiinflammatory drugs [NSAID] with their known hepatotoxic potency [21].

In face of these obvious uncertainties, the raw data of this complex case were reanalyzed for types of used DS products including their possible temporal associations, validity of presented case information, overall case data quality, confounding variables, complete exclusion of alternative causes, comorbidity, comedication, and firm causal attribution. The actual evaluation of this case follows recently published recommendations [15,22-24]. Due to lack of a valid diagnostic biomarker, the diagnosis of DILI and herb-induced liver injury [HILI] is a diagnosis of exclusion [24]. Our analysis now shows that naproxen used in overdose rather than OxyELITE Pro is the most likely cause of

this initially mysterious Hawaii liver disease case, affecting a multimorbid and multimedicated female patient.

## APPROACHES OF CASE DATA ANALYSIS

Redacted files of the patient's medical records were analyzed for case data consistency, completeness of alternative cause exclusion, medication by synthetic drugs, use of DS, temporal association, clinical confounders, and causality assessment. The overall aim of this case analysis was to retrieve additional case data to clarify the possible culprit(s) of this mysterious liver disease [13]. Actual methods of analytical approaches were similar to those applied in previous assessments of HILI and DILI cases [15,22-24].

## CASE NARRATIVE

For an initial overview, some case details are extracted from the original but redacted medical files and summarized as short narrative (Table 1) and as tabular list (Table 2). This approach facilitates a comparative analysis of the case data derived from the original files with those already published [13].

This female patient was described as 35 years old and healthy in the published report [13], but the publicized clinical statement on her health condition was in no way corroborated by the facts documented in the raw data of the analyzed medical records that clearly described the patient as multimorbid and multimedicated (Tables 1 and 2). Other discrepancies between the publicized account and the facts found in the medical records are presented in detail (Table 2). Due to their strong initial focus on OEP as the only assumed culprit, the authors likely followed an unbalanced clinical approach and published a finally biased report [13], causing them to overlook even overt alternative causes. It is also unclear how the authors addressed key diagnostic questions in a setting of increased LFTs to resolve the liver disease cluster, and how they coped with apparent confounders. This reanalysis also found procedural shortcomings, since neither stringent diagnostic data sets nor relevant data were provided [13]. These are core elements to ensuring transparency of unbiased clinical and real scientific work. Also, other data appeared to have been ignored especially when they did not fit to the initial concept.

## Multimorbidity

The past medical history of this patient is a key feature of the clinical assessment. Actually, the present analysis of the medical files of this patient uncovered multiple diseases in her past years (Table 2), with exactly documented dates prior to her present liver disease. Notes in these files also confirm that physicians had regular access to the medical records prior to publication of their case report [13], since they had to sign intermittently their consent on the conclusions drawn from the documented details and on data correctness and completeness. Despite their knowledge of her multimorbidity, authors erroneously classified the patient as healthy in their publication [13], completely ignoring her multimorbidity and without mentioning even a single prior or coexisting disease (Table 2). Consequently, documented multimorbidity (Table 2) is at variance to the published report [13]. Disregarding relevant known morbidities in a case report does not fulfil requirements of valid mainstream medicine of data transparency and case evaluation; it rather reflects attempts

**Table 1:** Case narrative.

### Narrative, case details and analysis

The analyzed files contain documents of a female patient who experienced increased aminotransferases since 9/5/2013 of initially undetermined etiology. Her chronic multiplepain syndrome with headaches and intractable migraine also is well documented in the files, with headaches originating in her childhood. Consequently, an abundance of pain medications is documented which included naproxen, a non-steroidal anti-inflammatory drug (NSAID) and known for its potential hepatotoxicity; its typical dose is 250-500 mg taken orally twice a day. As recommended by her physician, the patient took naproxen at daily overdoses of at least 1500 mg, and this treatment now was identified as culprit of her liver disease. Actually, five months after the first disease onset, overdosed naproxen was reused to treat daily headaches for a month, and this treatment again caused scleral icterus as at the first disease bout, confirming this drug as the causative agent. Regarding the dose of naproxen and documented under current meds, the information is provided for the patient to take 2 Aleve tabs three times daily without identifying the amount of naproxen contained in each Aleve tablet, which may be 250 or 500 mg each; with only 250 mg each, 1500 mg of naproxen would have been used each day, which is more than the maximum recommendation of daily 1000 mg, while the daily amounts would be higher when tablets of 500 mg were used.

Apart from naproxen use, the documents reveal present and previous multimедication consisting of ibuprofen, ritalin, hydrocodone-acetaminophen, diazepam, claritin, and omeprazole, some of them are potentially hepatotoxic and also are candidates for DILI; details of drug use are rarely documented, except for some drugs that were discontinued on 9/30/2013. This implies drug use since 9/3/2013 or earlier. In addition, there are documented allergies by aspirin, celebrex, celeXa, doxycycline, NSAIDs, and penicillins.

Assessing conditions are further complicated by the use of DS. Documentation of DS use prior and subsequent to disease onset is inconsistent but includes four different DS at different times and in different combinations. Among these are GNC bleaching protein powder and GNC woman's active multivitamin, which were taken each for at least 2.5 years without any side effects, but the date of cessation is not documented. In addition, the well tolerated use of the first OEP product, subsequently called the old OEP, intended for weight loss, is documented for approximately 2.5 or 3 years with reported cessation sometime in 7/2013 and switching to a second OEP formula (OEP Super Thermogenic), subsequently called the new OEP. The patient stopped the use of the new OEP, because she was feeling unwell, possibly at around 9/3/2013 when she first noted dark urine and experienced symptoms of fatigue, nausea, abdominal pain, and anorexia, followed by jaundice of her skin and eyes on 9/7/2013. At first presentation to her PCP (primary care provider) on 9/5/2013, her LFTs were increased, with ALT 633 U/L, AST 329 U/L, ALP 123 U/L, and bilirubin 1.4 mg/dL. In the further course of the disease, ALT values were variable in a range between 105 U/L and 794 U/L, which represented a second peak, and normalized within 84 days on 1/7/2014. The variable ALT values are suggestive of an ongoing liver disease; of hepatitis E, which was forgotten to be excluded; of a not yet resolved acute acalculous cholecystitis with gallbladder sludge, which was suspected on clinical grounds, the positive Murphy sign, and the ultrasonic description of an abnormal appearance of the thickened gallbladder wall; of the action of still used synthetic drugs. Reuse of the new OEP was reported on 9/19/2013, but concurrent use of potentially hepatotoxic synthetic medications with their documented discontinuation only on 9/30/2013 impedes a valid assessment; in particular, the claimed positive reexposure test result for OEP is not substantiated due to these confounding variables. The patient's epilepsy with recurrent seizures and diazepam use is well documented in the files, but whether prolonged seizures recently occurred that might have caused the liver disease remains unanswered due to lack of actual specific details.

### CIOMS assessment

CIOMS based causality for the new and old OEP was unlikely or excluded, and excluded for the GNC bleaching protein powder and the GNC woman's active multivitamin. Lack of appropriate drug use details impedes a valid CIOMS based assessment of causality for drugs, although for overdosed use of naproxen a temporal association with an icteric bout exists and is suggestive of a causal relationship.

### Primary diagnosis

Recurrent toxic hepatitis by naproxen (Aleve) overdose 8-9/2013 and 4/2014, with lacking causality for all dietary supplements including the two OEP products. Several alternative diagnoses are suggested, documented multimorbidity and overt multimедication are clear confounders (see Table 2).

### Commentary

The overall poor quality of case data contained in the analyzed medical files is unexpected for a major medical center in search of culprits in a mysterious liver disease cluster.

**Abbreviations:** ALP: Alkaline Phosphatase; ALT: Alanine aminotransferase; AST: Aspartate Aminotransferase; CIOMS: Council for International Organizations of Medical Sciences; LFTs: Liver Function Tests; NSAID: Non-steroidal antiinflammatory Drug; OEP: OxyELITE Pro; PCP: Primary Care Provider.

to suppress essential clinical features and again raises the question to what extent their overall assessment was due to bias. Therefore, failure to recognize, handle, evaluate, and publish the extraordinary multimorbidity [13] is a major annoying pitfall of evaluation of this complex case, basically preventable in a normal clinical setting (Table 2).

## MULTIMEDICATION

### Synthetic drugs

In line with ignoring the patient's multimorbidity, aspects of comedication also were disregarded in this as healthy classified patient (Table 2) [13]. Actually, significant prior and present medications of synthetic drugs were documented in the analyzed

**Table 2:** Comparison of documented versus published case details.

Documented information	Analysis of present study	Publication of Roytman et al. [13]	Commentaries
Age	Redacted files.	34	Important: Age as published.
Gender	Female.	Female.	Consistency.
BMI (kg/m <sup>2</sup> )	BMI 37, or 40-45; morbid obesity with peak weight of 240 pounds. Lost 70 pounds under DS use.	BMI 37, overweight, obesity. Weight loss under DS not published.	Morbid obesity is more severe and critical for overall case assessment.
General health	Multimorbidity.	"Healthy individual".	Obvious inconsistency, major scientific neglect and not meeting requirements of a sound case report.
Past medical history	Morbid obesity, nonalcoholic fatty liver disease (NAFLD); Attention deficit hyperactivity disorder (ADHD); schizophrenia; multipain syndrome, headaches, migraine (intractable); phobia; epilepsy and recurrent seizures; asthma; chronic otitis externa right ear; obstructive sleep apnea syndrome; latent tuberculosis; multiple tattoos; kidney stones; menorrhagia; esophageal reflux; lumbar disc degeneration; surgical history of insert posterior spine process distract device, spinal cord stimulator, laminectomy decompressive up to two lumbar segments; two surgeries L 3-4, L 4-5, L5-S1; partial meniscectomy left knee; and others.	Overweight/obesity, otherwise ignored.	Striking inconsistency, differences of case data presentations and deleting comorbidity details in the published report are obvious and difficult to reconcile. Careful listing of diseases is a key item and part of a correct and honest case report. Neglect of significant comorbidities impedes careful clinical search of drug therapy for the listed disorders, with the consequence that information on daily doses and duration of drug therapy is not appropriately captured to be used to validly evaluate DILI by synthetic drugs as culprits for the liver disease under discussion.
Previous and present drug medication	Naproxen, ibuprofen, ritalin, hydrocodone-acetaminophen, diazepam, claritin, and omeprazole. Documented allergies by aspirin, celebrex, celeXa, doxycycline, NSAIDs, and penicillins.	None declared.	Obvious inconsistency, difficult to reconcile. Neglect of assessing and reporting comedication by synthetic drugs impedes a careful case analysis regarding possible culprits.
Presenting symptoms	Fatigue, nausea, abdominal pain, anorexia, scleral and skin icterus.	Fatigue, nausea, abdominal pain, anorexia, jaundice.	Consistency.
Disease severity	Mild.	Mild.	Consistency.
Use of new OEP	Since sometime of 7/2013, during 4-8 weeks until symptoms at around 9/3/2013; undocumented daily dose.	4 weeks, daily dose and exact dates not published.	Some consistency. Daily dose unknown due to poor case documentation in the files.
Use of old OEP	3 or 2.5 years until sometime in 7/2013 and until 4-8 weeks prior to symptoms, with undocumented daily dose.	24 months, but daily dose and exact dates not published.	Inconsistency. Daily dose unknown due to poor case documentation in the files.
Other concomitant HDS	GNC bleaching protein powder and GNC woman's active multivitamin, each used for at least 2.5 years, but daily dose and date of cessation not documented.	Under the specific section "Other concomitant herbal DS", none declared.	Inconsistency due to the omission to publish the two other herbal DS that were used as documented in the medical files. Daily dose unknown.
ALT (IU/L)	794	633	Variable time points.
ALP (IU/L)	123	123	Consistency.
Bilirubin	1.4	1.4 – 1.0	Consistency.
ALT dechallenge	+	+	Consistency.
ALT normalization	+	+	Consistency.
Liver and biliary tract imaging	Fatty liver. Positive Murphy sign and thickening of the gallbladder wall, suggestive of edema, acute and chronic cholecystitis, and various other conditions. Bile ducts normal.	Imaging data were not published, not discussed, and ignored as major differential diagnosis.	Inconsistency. Symptomatic acute cholecystitis as possible major diagnosis was clinically missed. In the further clinical course, cholecystitis was not any more assessed by imaging reevaluation. Fatty liver was not published.
HAV	Excluded.	Nothing declared.	
HBV	Anti-HBs positive [Immunization?]	Nothing declared.	Inconsistency.



HCV	Excluded.	Nothing declared.	
HEV	Not done, not excluded.	Nothing declared.	Forgetting to exclude HEV in this case signifies lack of a valid conceptual approach to case analysis and differential diagnoses.
CMV	Excluded.	Nothing declared.	
EBV	Excluded.	Nothing declared.	
HSV	Not done, not excluded.	Nothing declared.	HSV remains a candidate culprit for this case.
VZV	Not done, not excluded.	Nothing declared.	VZV remains a candidate culprit for this case.
Past and present medication by synthetic drugs	Abundantly documented.	Nothing declared.	Inconsistency. Poor clinical and scientific approach.
Use of dietary supplements others than OEP	Use of 2 other DS documented, taken together with old or new OEP product.	Nothing declared.	Inconsistency.
Recovery	≤ 85 days.	≤ 85 days.	Consistency.
RUCAM/CIOMS score for old OEP for new OEP	Score -5, excluded causality. Score +1, unlikely causality.	Not assessed. Score +10, highly probable causality.	Score +10 for new OEP is not justified due to existing alternative cause and a reexposure test invalidated due to comedication by synthetic drugs.
for Protein DS for Vitamin DS	Score -4, excluded causality. Score -4, excluded causality.	Not assessed. Not assessed.	
<b>Diagnoses</b>	<p><b>Established diagnosis</b> Recurrent toxic hepatitis by naproxen overdose 8-9/2013 and 4/2014.</p> <p><b>Alternative and other relevant diagnoses</b></p> <ol style="list-style-type: none"> <li>1. Symptomatic acute acalculous cholecystitis associated with gallbladder sludge;</li> <li>2. Acute hepatitis, preferentially suspected hepatitis E (not yet excluded);</li> <li>3. Nonalcoholic fatty liver disease (NAFLD) due to morbid obesity with BMI 40-45 kg/m<sup>2</sup>;</li> <li>4. Suspected DILI by one of the abundant used synthetic drugs;</li> <li>5. Well documented multimorbidity;</li> <li>6. Chronic multipain syndrome, headaches, and intractable migraine;</li> <li>7. DILI with excluded or unlikely causality for all used DS including new and old OEP;</li> <li>8. Lacking exclusion of HSV and VZV and therefore candidates for liver disease.</li> <li>9. Possible prolonged seizures in the context of the patient's epilepsy with documented recurrent seizures as cause of severe liver disease.</li> </ol>	<p><b>Proposed diagnosis</b> Acute hepatotoxicity by new OEP.</p> <p><b>Alternatives diagnoses</b> None analyzed, none mentioned, none discussed.</p>	<p>Hepatotoxicity by the old OEP is excluded since liver disease emerged 4-8 weeks after discontinuation of the old OEP, substantiating lack of a temporal association. Based on CIOMS criteria, causality for the new OEP is unlikely and for the Protein DS and Vitamin DS excluded. For details of the established diagnosis and the alternative diagnoses see also Table 1.</p>

Abbreviation: ADHD: Attention Deficit Hyperactivity Disorder; ALP: Alkaline Phosphatase; ALT: Alanine Aminotransferase; BMI: Body Mass Index; CIOMS: Council for International Organizations of Medical Sciences; CMV: Cytomegalovirus; DILI: Drug Induced Liver Injury; DS: Dietary Supplement; EBV: Epstein Barr Virus; HAV: Hepatitis A Virus; HBV: Hepatitis B Virus; HDS: Herbal Dietary Supplement; HCV: Hepatitis C Virus; HEV: Hepatitis E Virus; HSV: Herpes Simplex Virus; HILI: Herb Induced Liver Injury; LFTs: Liver Function Tests; N: Normal range as multiple of its upper limit; NAFLD: Non-alcoholic Fatty Liver Disease; NSAID: Non-Steroidal Antiinflammatory Drug; OEP: OxyELITE Pro; PCR: Polymerase Chain Reaction; PCP: Primary Care Provider; Protein DS: GNC bleaching protein powder; RUCAM: Roussel Uclaf Causality Assessment Method; VZV: Varicella Zoster Virus; Vitamin DS: GNC woman's active multivitamin.

files and are now listed (Table 2), but not a single drug was mentioned in the publication [13]. Due to her multimorbidity, past and present therapy by synthetic drugs is abundant and a crucial issue, with multimедication consisting mostly of potentially hepatotoxic drugs. DILI by one of the used and listed synthetic drugs is a reasonable candidate for the observed liver disease, but identifying a single drug as culprit is almost impossible, with the exception of naproxen. This drug can be hepatotoxic at normal doses causing DILI or at higher doses leading to toxic hepatitis

due to overdosage [21]. For the actual patient, these different aspects of naproxen hepatotoxicity are worth of consideration (Table 1). Naproxen may have been used for headaches (Table 1), intractable migraine, otitis externa right ear, menorrhagia, partial meniscectomy left knee, or pains by lumbar disc degeneration, surgical history of insert posterior spine process distract device, spinal cord stimulator, laminectomy decompressive up to two lumbar segments, and two surgeries L 3-4, L 4-5, L5-S1 (Table 2). Since ibuprofen also is found on the medication list (Table 2), the

patient may have accidentally pursued a combined treatment with naproxen to cope with her chronic multipain syndrome. Risk factors for DILI by naproxen in this patient include high doses of the drug [25], preexisting liver disease such as NAFLD [19,20], and comedication by several synthetic drugs [26]. Details of drug use are poorly documented in the files, a remarkable finding for medical records (Tables 3 and 4).

### Dietary supplements

The analyzed files documented the use of four different DS, always taken as combinations (Table 2). Based on these files, the new OEP, corresponding to the product named OEP Super Thermogenic, was used for 4-8 weeks just prior to emerging symptoms, replacing the old OEP. This was taken before for 3 or 2.5 years, while GNC bleaching protein powder [Protein DS in short] and GNC woman's active multivitamin [Vitamin DS in short], each was consumed for at least 2.5 years prior to symptoms (Table 2). Whereas the files clearly documented four DS, the published report unexpectedly restricted its information to two DS only, namely the new and old OEP, forgetting the Protein DS and Vitamin DS (Table 2) [13]. No exact time frames with dates of first and last use were provided for the new and old OEP, mentioning merely 24 months and 4 weeks, respectively [13]. Daily doses of all four DS were not documented in the files (Table 2), and those of both OEP products also were not published [13]. Consequently, details are poorly documented in the files and fragmentarily published, impeding valid causality assessments due to inconsistent and unclear data presentation. The poorly documented details of the used DS in the analyzed files are unusual for medical records (Tables 3 and 4).

### Initial symptoms and clinical course

Patient's symptoms are well documented and include fatigue, nausea, abdominal pain, anorexia, dark urine [since 9/3/2013], and jaundice of her skin and eyes [since 9/7/2013]. At first presentation to her PCP on 9/5/2013, her LFTs were increased, with alanine aminotransferase [ALT] 633 U/L, aspartate aminotransferase [AST] 329 U/L, alkaline phosphatase [ALP] 123 U/L, and bilirubin 1.4 mg/dL. In the further course, ALT values were variable within a broad range between 105 U/L and 794 U/L that included a second ALT peak and final ALT normalization on 1/7/2014. These variable ALT values suggest an ongoing liver or biliary disease or the action of still used hepatotoxic drugs. The initial symptom of scleral icterus reemerged after half a year in association with reused naproxen in overdose; in retrospect, this recurrence is highly suggestive of naproxen as the causative hepatotoxic agent also for the initial disease period, whereas OEP or another DS does not appear to be involved in the disease development; naproxen is a drug known for its hepatotoxic potential [21], characteristics not described for OEP before.

### Laboratory hepatotoxicity criteria

Laboratory-based criteria of hepatotoxicity are defined by ALT and/or ALP values, expressed as N in multiples of the upper limit of their normal range [24]. For ALT, recommendations are at >5N or at 3N if total bilirubin values exceed 2N; for ALP, values of >2N are considered diagnostic. Based on the initial assessment with ALT 633 U/L [normal range 0-41 U/L] and ALP

123 U/L [normal range 35-129 U/L], the diagnostic criteria of hepatotoxicity are fulfilled for this patient [13].

### Liver injury pattern

Classification of the liver injury pattern is mandatory in cases of assumed DILI and HILI to choose the correct CIOMS scale for assessment [24]. Based on specific laboratory constellations, differentiation of the hepatocellular, cholestatic or mixed form of hepatotoxicity is feasible by comparing serum activities of ALT and ALP. Enzyme activity is expressed as a multiple of the upper limit of the normal range [N], and the ratio [R] of ALT/ALP is calculated. Liver injury is classified as hepatocellular, if ALT > 2N alone or  $R \geq 5$ ; cholestatic, when there is an increase of ALP > 2N alone or when  $R \leq 2$ ; of the mixed type if ALT > 2N, ALP is increased, and  $2 < R < 5$ . Calculation for this patient provides an R value of 16.7 and thereby a hepatocellular type of liver injury, confirming published data [13]. This form is also observed in DILI by naproxen [21].

### Liver and biliary tract imaging

According to the analyzed files, initial ultrasound examinations revealed a fatty liver and a positive Murphy sign, associated with a significant, not quantified thickening of the gallbladder wall (Table 2). These findings were interpreted as gallbladder wall edema with potential tumefactive gallbladder sludge, gallbladder polyps or other processes, whereas a mass or gallstones were not excluded at that time. Given the gallbladder wall thickening and the reported sonographic Murphy sign, symptomatic acute cholecystitis is not excluded. Gallbladder wall thickening could also be associated with chronic cholecystitis, acute hepatitis/liver disease, right heart failure, or other systemic etiology.

Improvement of the gallbladder wall thickening was not documented in the files. Ultrasound reexaminations in the further course were obviously not done according to the analyzed medical files. Therefore, the gallbladder disease evidently was of little clinical interest even at a time when the etiology of the increased LFTs was still unknown and a symptomatic acute cholecystitis associated with gallbladder sludge was a likely primary diagnosis. Any possible transition from acute to chronic cholecystitis therefore is not documented. Although this biliary disease represented a significant alternative diagnosis (Table 2), it remained unreported in the publication [13].

### Hepatitis and autoimmune serology

Hepatitis exclusion was confined to infections by CMV and EBV and to hepatitis A and C (Table 4), but HBs antibodies were positive while not documented whether this result is due to prior vaccination. Not considered and therefore not excluded were infections by HEV, HSV, and VZV, being additional potential culprits of the patient's complex disease. Firmly excluded were autoimmune and genetic liver diseases.

Neglecting HEV exclusion in a setting of a summer liver disease cohort is a major clinical omission in this case (Table 4), since HEV is a typical seasonal infection disease [9] and often not recognized in cohorts in which DILI was initially diagnosed, but these patients actually had HEV, not DILI [27,28]. The results of these clinical studies suggest that cases should not be defined as

**Table 3:** Overview of documented information on drug and DS use.

Documented information	All Products	Synthetic drugs (all)	Naproxen	New OEP	Old OEP	Protein DS	Vitamin DS
Brand name	+	+	+	+	+	+	+
Daily product dose	-/+	-/+	+	-	-	-	-
Date of product start	-/+	-/+	+	-/+	+	+	+
Date of product end	-/+	-/+	+	+	+	+	-/+
Time on product	-/+	-/+	+	+	+	+	+
Time to onset	-/+	-/+	+	+	-	-/+	-/+
Temporal association	-/+	-/+	+	+	-	-/+	-/+

**Abbreviations:** DS: Dietary Supplement; OEP: OxyELITE Pro; Protein DS: GNC protein powder; Vitamin DS: GNC woman's multivitamin.

**Table 4:** Overview of case data information.

Individual case item	Documented information	Published information [13]
Brand name	+	-/+
Daily product dose	-/+	-
Date of symptoms	+	-
ALT value	+	+
ALP value	+	+
Hepatotoxicity criteria	+	+
Liver injury pattern	+	+
ALT dechallenge	+	+
ALT normalization	+	+
Liver and biliary tract imaging	+	Not published: Fatty liver and thickening of gallbladder wall.
HAV	+	-
HBV	+	-
HCV	+	-
HEV	Not done.	-
CMV	+	-
EBV	+	-
HSV	Not done.	-
VZV	Not done.	-
Autoimmune parameters	+	-
Comedication synthetic drugs	+	-
Comedication dietary supplements	+	-

Symbols: +, information sufficiently documented; -, information missing; -/+, information only partially provided. Abbreviation: ALP: Alkaline Phosphatase; ALT: Alanine Aminotransferase; CMV: Cytomegalovirus; EBV: Epstein Barr Virus; HAV: Hepatitis A Virus; HBV: Hepatitis B Virus; HCV: Hepatitis C Virus; HEV: Hepatitis E Virus.

DILI unless HEV is safely excluded. HEV exclusion is thus a core item of the updated CIOMS scale [15,24] and should not have been ignored [13]. Although HEV antibody tests are not FDA approved [28,29], HEV-PCR methods are worldwide available.

### CASE DATA QUALITY AND CONFOUNDING VARIABLES

Documented case data in the analyzed files are incomplete and open for both discussions and speculations (Tables 1-4). This invalidates the published case report with its major

inconsistencies, found by comparing data of the present files with those published earlier (Table 2) [13]. Analysis of the files (Tables 1-4) and the published report [13] uncovers numerous confounding variables that impede a robust case presentation (Table 5). The mysterious disease cluster has received a high publicity in print and TV media [8,13,30] and is of major regulatory interest [8], which may confound case assessment by fostering biased rather than balanced evaluations. Resulting problems likely lead to case overreporting and causality upgrading by favouring quantity over quality, i.e., high case numbers over high

**Table 5:** Confounding variables and their consequences.

Confounding variables	Consequences for validity of case assessment
General health status	Describing the patient as healthy by neglecting significant comorbidities [13], which are well documented in the files, confounds case assessment and impairs credibility and validity of overall case assessment.
Medication	Ignoring significant medication by synthetic drugs with known hepatotoxic potency and deleting this important information from the published report [13] invalidates and confounds case evaluation.
Old OEP	Information of its use for 24 months without defining last day of use [13] does not allow correctly assessing dechallenge features of ALT decline and confounds case assessment.
New OEP	Information of its use for 4 weeks without defining first and last day of its use [13] impedes evaluation of latency period and possible dechallenge criteria, considering also the reported anorexia of the patient that might have reduced the DS intake.
GNC bleaching protein powder	Ignoring use of this DS in the published report confounds case assessment [13]; DS use of at least 2-1/2 years is clearly documented in the medical charts.
GNC woman's active multivitamin	Deleting this DS in the published report questions validity of case assessment [13], although use of this DS for 2-1/2 years is well documented in the medical charts.
Daily doses	With respect to old and new OEP, no exact daily doses are provided in the report [13] or in the analyzed medical files provided for the present analysis, indicating lack of thorough case management.
Temporal association and anorexia	Patient reported anorexia that questions regular use of OEP products, the other DS, and synthetic drugs; anorexia impairs robust assessment of any temporal association and any dechallenge features. Past and present medication by synthetic drug was not captured and not documented.
Poor medical chart quality	Details in medical charts are poorly documented, seldom analyzed, rarely and insufficiently summarized, and not considered in the context of possible alternative diagnoses.
HEV	Lacking HEV exclusion invalidates DILI or HILI diagnoses.
Alternative causes	Differential diagnoses were not extracted from the documenting files, not published and not discussed in the published report [13].
Clinical diagnostic concept	Lack of a convincing clinical concept to diagnose HILI or DILI prospectively is a major confounding variable.
Bias	Documents imply focus on OEP as the only single culprit, allowing merely a biased clinical and analytical approach open for further scientific discussions.
Selective data presentation	Withholding important case data causes unjustified upgrades of case numbers and causality levels and questions the credibility and validity of case management and data evaluations.
Media attention and regulatory strategy	The highly publicized topic of the mysterious disease cluster [8,13,30] in TV and print media and the straight regulatory strategy [8] are conditions to foster clinical and scientific bias and confound case evaluation.

Abbreviations: DILI: Drug Induced Liver Injury; HEV: Hepatitis E Virus; HILI: Herb Induced Liver Injury; OEP: OxyELITE Pro.

data quality.

## RISK FACTORS

Several risk factors may have contributed to the disease development of this patient (Table 6) and are of relevance for patients with obesity, NAFLD, DS use, and drug therapy, since most risk factors with the exception of genetic predisposition can be eliminated or attenuated. Crucial points include high individual amounts of synthetic drugs which carry an increased risk of DILI [25], but this condition can be reduced by choosing drugs which are effective already with smaller amounts rather excessive doses as needed for treatment by naproxen. Comedication with several synthetic drugs should be avoided in face of the known increased risk of DILI [26]. Drugs with a low metabolic rate also require special attention due to their risk of high cumulative doses in the course of treatment.

Whether DS are specific risk factors of DILI has not yet been investigated, but their uses over years without cessation periods are irresponsible and should be resisted. Combined use of several DS also is not recommended due to possible accumulation of specific ingredients derived from any of the used DS. Comedication by synthetic drugs has been reported in elder individuals consuming DS [5] but not in young athletes [6,7].

## Causality evaluation

To quantify the causality grading for all four DS used by this patient (Table 7), the updated CIOMS scale was applied [15]. Causality for the new OEP was unlikely and excluded for the old OEP, Protein DS [GNC bleaching protein powder], and Vitamin DS [GNC woman's active multivitamin] (Table 7). Individual scoring was impeded by poor and inaccurate data of challenge periods prior to disease unfolding and the uncertainty over which time periods DS and drugs still have been taken at the time of presentation to the PCP and thereafter. Since none of the evaluated DS had a past record of ascertained liver injury, appropriate scores could not be provided (Table 7). For the old OEP, which was well tolerated for at least 2.5 years, the long interval between cessation and start of symptoms provides lack of a temporal association that also excludes any causal association. Failure to disregard other relevant alternatives such as HEV, HSV, and VZV add to the problem of attempting to erroneously establish DS hepatotoxicity as a diagnosis of exclusion. Lack of appropriate drug use details impedes a valid CIOMS based assessment of causality for drugs, although for overdosed reuse of naproxen a temporal association with the icteric reappearance exists in favor of a causal relationship.

## DIAGNOSIS AND DIFFERENTIAL DIAGNOSES

The data documented in the medical files are highly



**Table 6:** Risk factors for hepatotoxicity by naproxen.

Possible risk factor	Consequences for case assessment	References
Genetic predisposition	Patient could be at risk for DILI by naproxen due to genetic susceptibility as discussed for various drugs.	Chalasanani and Björnsson, 2010 [31]
Multimedication by synthetic drugs	Multimedication by synthetic drugs increases the risk of DILI by synthetic drugs, may be applicable to naproxen.	Sgro et al., 2002 [26]
High daily doses	Naproxen was used in extremely high daily doses of at least 1500 mg. High doses are risk factors of DILI.	Lammert et al., 2008 [26]
High cumulative doses	Metabolic degradation of naproxen is slow, which could be a risk factor of DILI by naproxen in a setting of high cumulative doses.	LiverTox, 2015 [21]
NAFLD	New clinical data provide evidence that preexisting liver disease including NAFLD are risk factors of DILI by synthetic drugs, applicable to the patient with her NADFL documented in the analyzed files.	Chalasanani et al., 2015 [19] Teschke and Andrade, 2015 [20]
Dietary supplements	It is unclear whether dietary supplements were risk factors of DILI by synthetic drugs in the present case. In cases with DS use, comedication was described in some elder patients but not in young athletes.	Teschke et al., 2013 [5] Alevar-Escobar et al., 2012 [6] Timcheh-Hariri et al., 2012 [7]

Abbreviations: DILI: Drug Induced Liver Injury; NAFLD: Non-alcoholic Fatty Liver Disease.

**Table 7:** Causality assessment by the updated CIOMS scale.

Items	Score	New OEP	Old OEP	Protein DS	Vitamin DS
<b>1. Time to onset from the beginning of the DS</b>					
• 5 – 90 days	+2	+2	-		
• < 5 or > 90 days	+1		-	+1	+1
<b>2. Time to onset from cessation of the DS</b>					
• ≤ 15 days	+1		-		
<b>3. Course of ALT after cessation of the DS</b>					
• Decrease ≥ 50 % within 8 days	+3	+3			
• Decrease ≥ 50 % within 30 days	+2				
• No information	0		-	0	0
• Decrease ≥ 50 % after the 30th day	0				
• Decrease < 50 % after the 30th day or recurrent increase	-2				
<b>4. Risk factor ethanol</b>					
• Alcohol use (drinks/d: > 2 for woman, > 3 for men)	+1				
• No alcohol use (drinks/d: ≤ 2 for woman, ≤ 3 for men)	0	0	0	0	0
<b>5. Risk factor age</b>					
• ≥ 55 years	+1				
• < 55 years	0	0	0	0	0
<b>6. Concomitant drug(s)</b>					
• None or no information	0				
• Concomitant drug with incompatible time to onset	0				
• Concomitant drug with compatible or suggestive time to onset	-1				
• Concomitant drug known as hepatotoxin and with compatible or suggestive time to onset	-2	-2	-2	-2	-2
• Concomitant drug with evidence for its role in this case (positive rechallenge or validated test)	-3				

<b>7. Search for non drug causes</b>					
<b>Group I (6 causes)</b>					
● Anti-HAV-IgM		-	-	-	-
● Anti-HBc-IgM / HBV-DNA		-	-	-	-
● Anti-HCV-IgM / HCV-RNA		-	-	-	-
● Hepato-biliary sonography / colour Doppler sonography of liver vessels		+ result	+ result	+ result	+ result
● Alcoholism (AST/ ALT ≥ 2)		-	-	-	-
● Acute recent hypotension history (particularly if underlying heart disease)		-	-	-	-
<b>Group II</b>					
● Complications of underlying disease(s) such as sepsis; or: autoimmune hepatitis, chronic hepatitis B or C, primary biliary cholangitis or sclerosing cholangitis, genetic liver diseases		-	-	-	-
● Infection suggested by PCR and titre change for					
CMV (Anti-CMV-IgM / IgG)		-	-	-	-
EBV (Anti-EBV-IgM / IgG)		-	-	-	-
HEV (Anti-HEV-IgM / IgG)		missing	missing	missing	missing
HSV (Anti-HSV-IgM/IgG)		missing	missing	missing	missing
VZV (Anti-VZV-IgM / IgG)		missing	missing	missing	missing
<b>Evaluation of group I and II</b>					
● All causes - group I and II - reasonably ruled out	+2				
● The 6 causes of group I ruled out	+1				
● 5 or 4 causes of group I ruled out	0	0	0	0	0
● Less than 4 causes of group I ruled out	-2				
● Non DS cause highly probable	-3	-3	-3	-3	-3
<b>8. Previous information on hepatotoxicity of the drug</b>					
● Reaction labelled in the product characteristics	+2				
● Reaction published but unlabelled	+1				
● Reaction unknown	0	0	0	0	0
<b>9. Response to readministration</b>					
● Doubling of ALT with the DS alone	+3				
● Doubling of ALT with the DS and drugs already given at the time of first reaction	+1	+1			
● Increase of ALT but less than N in the same conditions as for the first administration	-2				
● Other situations	0		0	0	0
<b>Total points for patient</b>		+1	-5	-4	-4

Causality assessment was achieved using the updated scale of CIOMS (Council for International Organizations of Medical Sciences), considering the items for the hepatocellular type of liver injury [15,24]. In the above section 6 of concomitant drug(s), naproxen was considered but not other drugs with their poor data details. In the section 7 (search for none drug causes), the symbol of - denotes that the obtained result was negative and that of + was positive, whereas lack of a symbol indicates that assessment was not performed; Anti-HBs was positive tested in the patient, possibly due to immunization. Abbreviations; ALT; Alanine Aminotransferase, AST: Aspartate Aminotransferase; DS: Dietary Supplement; HAV: Hepatitis A Virus; HBc: Hepatitis B core; HBs: Hepatitis B surface; HBV: Hepatitis B Virus; HCV: Hepatitis C Virus; CMV: Cytomegalovirus; EBV: Epstein Barr Virus; HSV: Herpes Simplex Virus; OEP: OxyELITE Pro; PCR: Polymerase Chain Reaction; VZV: Varicella Zoster Virus. Total points / causality: ≤ 0 = excluded; 1-2 = unlikely; 3-5 = possible; 6-8 = probable; ≥ 9 = highly probable.

**Table 8:** Details of diagnoses

**Verified diagnosis**

**Recurrent toxic hepatitis by naproxen (Aleve) overdose**

Naproxen is a potentially hepatotoxic drug, even when used at recommended daily doses of up to 1000 mg/d. For this patient, prescribed doses were 2 tablets three times daily as documented; assuming each tablet contained only 250 mg and not 500 mg, the daily use would be 1500 mg, representing an overdose with a risk of toxic hepatitis as observed in 8-9/2013. Naproxen was discontinued on 9/30/2013 and then used on an off and on basis. Scleral icterus recurred in 4/2014 when she again used an overdose of Aleve to treat daily headaches for a month in the absence of any OEP use.

**Alternative and other relevant diagnoses**

**1. Symptomatic acute acalculous cholecystitis associated with gallbladder sludge**

The sonographic Murphy's sign was positive and indicates acute cholecystitis, in line with imaging results of gallbladder wall thickening, the suggestions made by the clinical staff of the medical center, and clinical features. Further work up was not done to exclude for instance chronic cholecystitis, expressing a poor clinical care of the patient and clinical negligence. Tenderness of the right upper abdominal quadrant persisted even in 2014.

**2. Acute hepatitis, preferentially suspected hepatitis E (not yet excluded)**

Exclusion of hepatitis E as a typical seasonal disease in summertime was forgotten, although the diagnosis of suspected hepatitis was well documented by the physicians in the patient's charts. The undulating ALT course in September 2013 is in line with an infectious disease with flares until complete resolution.

**3. Nonalcoholic fatty liver disease (NAFLD) due to morbid obesity with BMI 40-45 kg/m<sup>2</sup>**

Any chronic liver disease including NAFLD is a risk factor of DILI by any drug with an increased risk especially for this patient who used abundant synthetic drugs.

**4. Suspected DILI by one of the abundant used synthetic drugs**

Candidates are apart from naproxen (Aleve) also ibuprofen, ritalin, hydrocodone-acetaminophen, diazepam, claritin, and omeprazole, all documented with past or present history of drug medication.

Documented were allergies by aspirin, celebrex, celexa, doxycycline, NSAIDs, and penicillins.

**5. Well documented multimorbidity**

The list of diseases is exorbitant and comprises many disorders causing pains and requiring medications which mostly are potentially hepatotoxic, including acetaminophen and NSAIDs: multimorbidity includes attention deficit hyperactivity disorder (ADHD); schizophrenia; migraine (intractable); phobia; epilepsy and recurrent seizures; asthma; chronic otitis externa right ear; obstructive sleep apnea syndrome; latent tuberculosis; multiple tattoos; kidney stones; menorrhagia; obesity, BMI 40-45; nonalcoholic fatty liver disease (NAFLD); esophageal reflux; lumbar disc degeneration; surgical history of insert posterior spine process distract device, spinal cord stimulator, laminectomy decompressive up to two lumbar segments; two surgeries L 3-4, L 4-5, L5-S1; partial meniscectomy left knee.

**6. Chronic pain syndrome, headaches, and intractable migraine**

There have been accidents with bone fractures and poorly healing wounds, major problems with the lumbar areas, headaches since childhood, and an intractable migraine; it appears that all these conditions required a substantial amount of pain medications to relieve the symptoms.

**7. DILI with unlikely causality for several used DS including OEP**

Documented past or present history of multiple dietary supplement and multivitamin use: Old OxyELITE Pro (OEP) taken for the last 3 years until sometime in 7/2013; GNC bleaching protein powder and GNC woman's active multivitamin, each used for at least 2.5 years, but date of cessation remained undocumented. Old OEP lacks a past history of potential hepatotoxic adverse effects in the scientific literature, which was confirmed in the present patient who used the old OEP for three years without any adverse hepatotoxic reactions. In addition, OEP use was confounded by an exorbitant comedication of potentially hepatotoxic synthetic drugs which more likely are causes of the liver disease as compared to OEP. The new OEP was used from somewhere in 7/2013 likely until around 9/3/2013. There is the note of an assumed positive reexposure test result due to an unintentional reuse of this new OEP on 9/19/2013 under unclear conditions of potentially hepatotoxic drug comedications, considered as confounders since these medications including naproxen, hydrocodone-acetaminophen, ritalin, and diazepam were stopped only on 9/30/2013. The ALT course after first presentation was undulating, suggesting the action of confounding variables, such as various drugs as comedication, or flare of the basic liver disease.

**8. Lacking exclusion of HSV and VZV and candidates for liver disease.**

Both virus infections were not excluded and are therefore culprit candidates.

**9. Possible prolonged seizures as cause of severe liver disease**

Documented as PMH is epilepsy with recurrent seizures and use of diazepam. It is unclear whether the patient experienced prolonged seizures which can cause severe liver disease.

Abbreviations: ADHD: Attention Deficit Hyperactivity Disorder; ALT: Alanine Aminotransferase; HBV: Hepatitis B Virus; CMV: Cytomegalovirus; EBV: Epstein Barr Virus; HSV: Herpes Simplex Virus; NAFLD: Non-alcoholic Fatty Liver Disease; NSAID: Non-Steroidal Antiinflammatory Drug; OEP: OxyELITE Pro; PMH: Past Medical History; VZV: Varicella Zoster Virus.

suggestive of recurrent toxic hepatitis by naproxen overdose as the primary diagnosis (Table 8). There are good arguments also for other diagnoses of potential relevance in this case (Table 8), with details summarizing key findings for reasons of transparency (Tables 1-7) but not substantiating the published claim of another diagnosis related to OEP [13]. In analogy to other cases of DILI and HILI, this patient presented a challenging complex disease (Tables 2 and 8) which normally requires clinical expertise, intuition, commitment, professional case management, and valid criteria to establish the diagnosis to some degree of certainty. Cases like the present one (Tables 1-8) with a thorough diagnostic approach in search of the culprit are of great interest in any clinical and regulatory setting for the scientific community, but this requires an impartial detailed case analysis.

## COMMENTARY AND RECOMMENDATION

Expectations on case reports published by members of an otherwise well reputed medical center are high, but the presently analyzed case report of this patient is disappointing [13]. Certainly, the overall documentation in the medical charts was not on a high medical level, with evident problems related to the multimorbidity and polymedication with missing treatment details of the used drugs and DS. However, numerous essential data of the medical records have not or incorrectly been transferred to the publication (Table 2) [13]. Selective data presentation favoring an initial unsubstantiated proposal and ignoring data to the contrary led to erroneous conclusions [13] that are by no means acceptable (Table 2).

The actual analysis shows an irresponsible management of and by the patient who consumed three DS concomitantly over several years without any intermission. This inevitably leads to the recommendation for potential DS consumers and their PCP, if reduced caloric intake and sport activities have been unsuccessful losing weight and DS are under potential consideration, individuals should be on the safe side by taking one single DS instead of several ones concomitantly and restricting the use to two months with subsequent cessation for one month. Drug therapy preferentially should be limited to short term use under strict indication to reduce potential health hazards. DS manufacturers are responsible for safe use of their products, assisted by extending efforts of regulatory authorities to ascertain not only safety but also efficacy of product use.

## CONCLUSIONS

The mysterious Hawaii liver case initially created concern due to inconsistencies associated with an undetermined causality, but this case is now best explained by recurrent and overdosed naproxen rather than any DS including OEP products. Present assessment was supported using all available case data rather than selective ones.

## DISCLOSURES

Rolf Teschke received an honorarium by Merz Pharmaceuticals and Max Zeller Pharmaceuticals for lectures at scientific

meetings and by Covington & Burling LLP Washington DC for consultation. None of the other authors received honoraria or has a conflict of interest.

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