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An Evaluation of Case Report Studies Concerning Dietary Supplements Containing Aegeline and DMAA (1,3-Dimethylamylamine)

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ABSTRACT

With high obesity rates in the United States, consumers often turn to dietary supplements (DS) as a method to achieve weight loss. The more frequent use of these products has led to some speculation as to whether they are a frequent cause of liver injury. Case reports implicating herbs and DS as a cause of liver injury have, in some cases, caused controversial discussions. In Part 2 of a 3 Part series, published case reports related to aegeline, 1,3-dimethylamylamine (DMAA) and OxyELITE Pro and liver injury are examined and discussed in detail. Causality assessment methodology is also discussed. Further review suggests that at least in some cases, premature publicity regarding a claimed association between an ingredient or product and hepatotoxicity based only upon case reports may lead to erroneous claims of association between a DS and hepatotoxicity. A more thorough, objective and uniform method of diagnosing drug or herb-induced liver injury which also allows for correct attribution of a potential causal agent when multiple agents are used concomitantly/sequentially is critical to prevent such occurrences.

Keywords: Causality assessment, RUCAM, Bias, Subjectivity

INTRODUCTION

The prevalence of obesity is high in the United States population and continues to be a major health and economic concern [1-4]. Obesity is a serious illness due to comorbidities such as coronary heart disease, hypertension, diabetes mellitus type II, osteoarthritis, some cancers and certain types of liver disease [3,4]; obesity may, in fact, increase the risk of hepatotoxicity from drugs [5]. Perhaps not coincidentally, obese adults in the United States are known to use prescription medications, including those for hypertension, lipid-lowering, analgesia, and diabetes more frequently than normal weight adults [6]. Consumers suffering from obesity also often turn to dietary supplements (DS) for weight reduction, as evidenced by data showing a greater frequency of use compared to normal weight counterparts [7,8].

There is the general impression that the use of herbs and DS (HDS) may frequently be associated with liver injury, with some studies indicating an increased tendency. However, while an increase in proportional cases of liver injury may seem to indicate greater frequency of occurrence, this may simply be an indication of greater consumer and physician awareness of an association between HDS and liver injury and thus greater reporting. A true indication of an increase in cases would require an evaluation of incidence rates over time. Incidentally, the first U.S. based study to determine the rate of drug-induced liver injury (DILI) has recently been reported and includes potentially useful data in this regard, also serving as a baseline. Among a cohort in the U.S. state of Delaware, the total number of DILI cases was 20/729,779, corresponding to approximately 2.7 cases per 100,000 individuals in 2014; only 14 of these overall 20 subjects gave permission for further examination, of which 6 were determined to have been caused by HDS [9]. Unfortunately, such data do not allow for an accurate incidence rate to be calculated for HDS without assumptions; furthermore, the lack of differentiation between herbs and dietary supplements (DS) and missing case narratives including Roussel Uclaf Causality Assessment Method (RUCAM) scoring also places limitations on these data. An approach that is likely superior would include more detailed case information and RUCAM scoring, as others have done when examining inpatient cohorts and the frequency of herb-induced liver injury (HILI) in patients treated with Traditional Chinese Medicine [10]. Although the authors speculate that the data derived from this study likely

underestimate the true incidence rate of liver injury cases, there is overall, good evidence that liver injury by herbs and DS is likely a relatively rare event. For example, even if one assumes the unlikely scenario that the remaining 6 DILI subjects that refused further examination were all due to HDS, this would still be equal to an incidence rate of approximately 1.6 cases per 100,000 individuals (i.e., 12/729,779) [8]. This is in fairly good agreement with the estimated incidence rate of DILI due to HDS in Iceland from 2010-2011, which was approximately 3 cases per 100,000 individuals [11].

For the diagnosis of DILI or HILI, a definitive diagnostic biomarker does not exist [12,13]. This led to disagreement over causality assessment methods and differences in quality of case data evaluation, especially with respect to DS assumed to have caused liver injury [14-24].

The present review analyzes these discrepancies among initially suspected liver injury cases involving 1,3-dimethylamylamine (DMAA), aegeline and OxyELITE Pro. The conclusion is reached that these ingredients and formulations are unlikely to be hepatotoxic and such case reports are more likely the result of stimulated reporting and retrospective case seeking caused by intense media publicity and regulatory announcements concerning the product OxyELITE Pro. For the sake of clarity, the formula containing DMAA is referred to herein as OEP-OF (OxyELITE Pro-Old Formula), while that of the aegeline-containing versions are OEP-NF I-III (OxyELITE Pro-New Formula I-III).

Literature Search

As part of a general (non-systematic) review, PubMed and Google Scholar were searched for original research articles, reviews, reports, and letters to the editor which included an analysis of aegeline or 1,3-dimethylamylamine (DMAA) and hepatotoxicity or liver injury. Search terms included: DMAA, 1,3-dimethylamylamine, dietary supplements, OxyELITE Pro, OEP, aegeline, hepatotoxicity, liver, liver injury. Publications retrieved were analyzed with respect to any association between aegeline, DMAA or OxyELITE Pro and hepatotoxicity. Files received in response to a Freedom of Information Act (FOIA) request to the National Institutes of Health (NIH) were included for analysis of the U.S. DILIN authored publication.

Evaluation of Case Report Studies

U.S. Military Case Reports: Foley, et al., cover a series of 7 cases of what the authors indicate is DMAA-induced hepatotoxicity from individuals using OxyELITE Pro [25]. The dates for these cases are not given, but they were clearly reported by the authors after the publicity stemming from the attention surrounding the apparent association between a new formula of OxyELITE Pro, which did not contain DMAA (i.e., OEP-NF), and liver injury. Perhaps most importantly, these cases also demonstrate an example of stimulated reporting, with the name "OxyELITE Pro" being associated with hepatotoxicity in public announcements as the formulation implicated by Foley, et al., was not that of OEP-NF which contained aegeline, but rather, the old version containing DMAA [25]. Case reports are problematic when attempting to assign causality to a given agent [26,27], but the use of an at least somewhat objective causality assessment method such as the RUCAM is useful and is especially helpful for readers of publications as it provides data transparency for peer review and a scoring mechanism which considers the exclusion (or lack thereof) of alternative causes [13]. In the case of Foley, et al., no such causality assessment method was used making any claimed association particularly questionable [25,28]. The latency period of 2-3 years in some cases also indicates that OEP-OF is an unlikely cause [13]. In any event, it may be useful to point out the serious limitations of these published cases by Foley, et al., (Table 1) [25].

Table 1 Evaluation of cases details from Foley, et al., [25]

Case Number (Latency Period)	Viral Causes Excluded/ Method	Use of OTC Drugs & Other Dietary Supplements	Use of Prescription Medications	Other Potential Causes (e.g., Alcohol, Autoimmune Hepatitis, etc.) Excluded	Potential Causes Not Excluded	Causality Method (e.g., RUCAM) Used

One (2 Years)	Hepatitis A, B, C and D, cytomegalovirus (CMV) and Epstein-Barr virus (EBV) Method not Disclosed	None Listed Serum Acetaminophen Listed as Normal	None Listed	Alpha-1-antitrypsin, Wilson Disease, Autoimmune Hepatitis, Hemochromatosis	Hepatitis E, Varicella-Zoster Virus (VZV), Herpes Simplex Virus (HSV), Alcohol	None
Two (8 Weeks)	Not Specified	None Listed	None Listed	Wilson Disease, Autoimmune Hepatitis, Ischemic Hepatopathy	Unknown Due to Lack of Details Provided	None
Three (3 Years)	Hepatitis A, B, and C Method not Disclosed	C4 Extreme, Jack3D, Proprietary Sports Enhancement Blend	None Listed	Autoimmune hepatitis	Hepatitis E, VZV, CMV, EBV, HSV, Alcohol	None
Four (1 Month)	Not Reported	C4 Extreme	None Listed	Wilson Disease, Autoimmune Hepatitis Biliary Obstruction	Hepatitis A, B, C, E, VZV, CMV, EBV, HSV, Alcohol	None
Five (Not Specified)	Not Reported	RoxyLean	None Listed	Not Reported	Unknown Due to Insufficient Data	None
Six (1 Week)	Not Reported	None Listed	None Listed	Not Reported	Unknown Due to Insufficient Data	None
Seven (1 Year)	Only EBV Incorrectly Ruled Out Active Infection Present	None Listed	None Listed	Not Reported	Unknown Due to Insufficient Data	None

Overall, the lack of reporting for co-medication use in virtually all cases is difficult to reconcile with the fact that more than half of adults in the U.S. are known to use prescription medications [29] (Table 1). Furthermore, estimates indicate that 18% to 21% of individuals in the Air Force and Army use dietary supplements for bodybuilding and weight-loss purposes [30], while a more recent study indicated an overall use rate for dietary supplements of 67% in the military services (i.e., Army, Air Force, Navy, Marine Corps, and Coast Guard) with the Navy and Marine Core displaying the highest use rates of 71% and 74%, respectively [31]. Thus, it is reasonable to question whether an appropriate exclusion of prescription and over the counter medications, as well as other dietary supplements took place.

The authors state vaguely that while other potential causes were negative, Epstein-Barr virus (EBV) capsid IgM and IgG were positive, but because the patient in Case 7, also had a positive EBV nuclear antibody, it made an acute infection from EBV an unlikely source of her abnormal liver tests. However, a positive result for all 3 of these parameters should be interpreted as a late primary infection or a reactivation of the virus and thus still as an active infection, albeit not acute [32]. However, an active infection is all that is required for the diagnosis of EBV hepatitis [33]. It is this type of error that makes transparency of clinical details important as Teschke, et al., have certainly demonstrated as well [12,20]. For example, if the authors would have vaguely stated that EBV was simply ruled out, there would be no way for others to review their work and conclusions. Some have also suggested that confirmation via polymerase chain reaction (PCR) testing should be performed as serology alone is unreliable when diagnosing viral hepatitis, at least when caused by hepatitis E virus (HEV), cytomegalovirus (CMV) or EBV [34]. A recent case also exemplifies the need for PCR testing for hepatitis C virus (HCV) in all cases of acute hepatitis of unknown cause, as antibody testing alone is unreliable [35], while also reaffirming the fact that patients are not always forthcoming with information regarding possible drug abuse; indeed the substantial rise in acute HCV infections in the U.S. is thought to be associated with the opioid epidemic and more specifically, intravenous opioid use [36].

The cases covered here, help illustrate the major shortcomings of not only case reports, but those involving

hepatotoxicity and the assignment of causality to a particular agent. Case reports are considered the lowest and least reliable form of evidence as they are not controlled for confounders or chance, while being particularly subject to bias (e.g., recall bias on the part of the patient and confirmation and information bias on the part of the clinician), confounders (i.e., are unlikely to contain all relevant data) and are subjective; they can't be subjected to hypothesis testing and are unable to actually demonstrate causality [26,27,37-39]. This is not to say they are devoid of any value (e.g., hypothesis generation); however, they must always be considered alongside their limitations. In the particular case of potential DILI or HILI, however, the possibilities for reaching erroneous conclusions increase substantially. For example, unlike many conditions, the diagnosis of DILI is one of exclusion, as there is no biological marker for a diagnosis [12,13]. DILI is known to mimic all forms of acute and chronic liver disease, including viral, genetic and autoimmune causes, biliary tract disease and even alcohol abuse [13]. To further confound matters, there are over 1,000 drugs and herbal products believed to cause DILI [40]. Yet, these are still only some of the confounders. For example, even obtaining an accurate prescription and over the counter medication history is difficult to obtain from patients; furthermore nearly 60% of those abusing opioids, obtain them without a prescription, often from friends or family members, making verification via prescription records extremely difficult; this is important to consider as many opioids are combined with acetaminophen [41,42]. Herbal and dietary supplements also provide difficulty in this regard [43]. Patients may forget what they are taking, confuse one drug for another, underreport or conceal their medication use (e.g., opioid/acetaminophen combinations) and deny or underreport the use dietary supplements and herbs as well as illicit or illegally obtained medications [41-50]. Additionally, it has been shown that a significant portion of consumers believe over the counter (OTC) pain relievers are completely safe; use more than the recommended dose and believe that side effects are always preceded by warning symptoms [51]. It has also been demonstrated that consumers (even including those with established liver disease) are not very knowledgeable about acetaminophen's hepatotoxicity, the appropriate daily dose or the fact that it's found in a wide variety of products [52,53]. In fact, as some have pointed out, while two-thirds of patients who have unintentionally taken excessively high doses of acetaminophen have done so because of habitual use of opioid/acetaminophen combinations, around one-third did so by consuming various OTC medications, many of which they were unaware contained acetaminophen [54].

With respect to DILI or HILI, while not always an easily achievable task, it becomes clear that cases must be thoroughly and exhaustively examined before an agent can be seriously considered as playing a role in liver toxicity [13]. Certainly, some have done more commendable work, relative to others [25,55,56]. Although even in cases with thorough diagnostic and exclusionary work, something as simple as a patient forgetting a medication or neglecting to mention/denying the use of a drug or herb for fear of ridicule or legal repercussions can lead to erroneous conclusions [41-50]. Self-reported information from patients should be thoroughly examined and ideally, should be considered a secondary source after obtaining medical and prescription records for evaluation. In some instances, such as Foley, et al., acetaminophen screening was considered, "normal" but acetaminophen concentrations decline fairly quickly and as others have pointed out, plasma acetaminophen may be undetectable and certainly in the therapeutic range or "normal" by the time a patient presents with symptoms of liver injury [25,57].

While the dates of the cases are not given in the Foley, et al., report, it is likely they came after the publicity considering both the date of submission for the publication and the reference to the public announcements. Thus, the fact that 7 cases were reported and apparently only after public announcements claiming an association between OxyELITE Pro and hepatotoxicity indicates these cases are likely background cases which were either idiopathic in nature or had unidentified/ignored alternative causes but were instead reported (i.e., as a result of media publicity causing biased reporting and conformational bias on the part of the physician) as being due to OxyELITE Pro with DMAA. The cases by Foley, et al., which lack transparency and vital clinical details, along with the lack of hepatotoxicity for DMAA with several lines of supporting evidence, if nothing else, serve as an example of the pitfalls of relying upon case reports as evidence of liver injury [25]. Indeed, up to 14% of cases of acute liver failure in adults are due to an indeterminate cause, while up to 18% of these cases were later determined to likely have been caused by acetaminophen toxicity [58,59]. Thus, case reports in general, sometimes neglect to consider that they, at least in some cases, may simply be reporting on a case without a truly identifiable cause, yet are attributing it to the only agent that was last used (i.e., temporal association). In other cases, the cause may be missed or ignored by the clinician. In a review by Bjornsson and Hoofnagle, out of 671 distinct drugs or drug entities implicated as causing hepatotoxicity on the LiverTox website, the authors found that while 53% had some level of evidence and were convincingly linked to liver injury, 47% had no convincing case reports indicating the agent had caused liver injury, with a large number

of case reports not fulfilling the criteria for causality by RUCAM [60]. Interestingly, Teschke et, al., found a similar proportion in a review of 573 cases of liver injury initially assumed to be due to herb-induced liver injury (HILI), with 48.5% demonstrating evidence for alternative causes [61]. Finally, it is worth noting that the aegeline-containing version of OxyELITE Pro, rather than the DMAA-containing version was apparently associated with hepatitis, further calling into question such case reports. As previously noted, multiple lines of available evidence, including animal data, randomized controlled trials, and epidemiological data demonstrate a lack of hepatotoxicity from DMAA (See Part 1). The contradictory nature of such case reports, however, may serve as an example of how a suggestion of a potential adverse event can lead to reporting bias and likely conformational bias on the part of the treating clinician [27,61-72].

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The cases published in a letter to the editor by Roytman, et al., effectively concluded that OEP-NF formulas were responsible for 8 cases of hepatitis; while 6 of these 8 had also used OEP-OF, the apparent closer temporal association with OEP-NF may have led the authors to implicate it instead [18,21]. As Teschke, et al., note, at least some of these cases were initially assumed to be related to DMAA but were subsequently stated in this publication to be caused by OEP-NF, which does not contain DMAA [21]. Teschke and colleagues have reviewed these cases in greater detail, demonstrating not only inconsistencies with the data reported, but effectively ruling out OEP-NF as a cause using RUCAM scoring, noting the inappropriate scoring by Roytman, et al., including the unfounded upgrading of scores [18,20,21].

U.S. DILIN

The paper published by Heidemann, et al., was a collection of cases from some authors of the Drug-Induced Liver Injury Network (DILIN) group which purported to demonstrate liver injury attributed to OEP-NF use [19]. While Teschke and Eickhoff have covered some issues of this paper, there are numerous issues that have not yet been addressed [22]. While even the initial entry of patients into the DILIN site seems biased (i.e., DILIN site providers are already given an implicated agent either by the referring physician or the patient themselves), the main issues in this publication are specific to these cases [74]. For example, while the RUCAM method was said to be applied to the use of OEP-NF, the reported RUCAM scores are not given for the other dietary supplements and medications that were being used concomitantly by some patients. Thus, whether the RUCAM scores of these other agents would have led to a different conclusion is unknown. It does not appear as though other viral causes such as hepatitis E, Herpes Simplex Virus (HSV), Varicella Zoster Virus (VZV), CMV and EBV were effectively or consistently ruled out. While CMV and EBV were said to be ruled out, there is no presentation of the results by Heidemann, et al. [19]. Furthermore, in cases which had little or only cursory serology at the time of illness, it is of questionable value to obtain serum many months after resolution and attempt to rule out a viral cause based upon a serology panel where it may be too late to detect an active or resolving infection. While most of the cases had obvious non-viral alternative causes other than OxyELITE Pro, if DILI is truly a diagnosis of exclusion, the lack of actually ruling out all potential viral causes in each case is unacceptable. Finally, it appears all of the cases were enrolled or analyzed after public announcements claiming an association between OEP-NF and liver injury, indicating biased reporting/stimulated reporting, along with some instances where inclusion criteria (i.e., enrollment within six months of DILI onset) were not apparently followed.

Case 1

This case was attributed by the authors as being likely due to the Celsius product, rather than OxyELITE Pro with DMAA. Although, interestingly, the authors assigned a DILIN score of 5 (unlikely) to whey protein, despite a case report implicating it as playing a role in hepatotoxicity [75]. If nothing else, this demonstrates the inconsistencies amongst case reports for apparent hepatotoxicity. Clearly, this case, which took place in 2011 and was enrolled in 2012, was actively searched for after publicity. This also suggests that these cases were either actively sought by the authors or they were the result of stimulated reporting. Interestingly, Case 1 appears to have been reported in another publication where it was the only instance of OEP being implicated as a cause of liver injury (Table 1, Case 111); this same Case 1 also appeared to be one of the cases in 2011 listed as being a case of OEP-induced liver injury [73,76]. The fact that the same case was implicated twice before finally being ruled out is troubling, but also brings up the issue of possible case duplication.

Case 2

This case presents a patient with a recent history of alcohol abuse, yet it does not appear that serum ethanol was assessed by physicians nor was there any examination for other possible drugs of abuse such as opioids in combination with acetaminophen. The patient had a history of mental illness (i.e., anxiety) but no medications are listed; however, enrollment forms indicate the use of zolpidem and alprazolam. The authors state that Case 2 presented to the emergency room in May of 2013, after using OxyELITE Pro for 4 months. This would make it impossible that this patient was using the version of OxyELITE Pro with aegeline (i.e., OxyELITE Pro New Formula or OEP-NF). Instead, the patient in Case 2 would have started using OxyELITE Pro in January of 2013, which would have been the old formula containing DMAA; indeed, her symptoms, in this case, began on April 1, 2013, thus this couldn't have been OEP-NF. This patient also reported taking OxyELITE Pro in 2011 for 3 months without any adverse effects; the same formula that was used in January 2013. The authors assigned a DILIN score of 2 (highly likely) to OxyELITE Pro but only a 4 (possible) to the other supplement, Stacker 3, which the patient in Case 2 was taking at the same time. The authors do not elaborate on why the Stacker 3 supplement was given only a "possible" ranking, but it is implied in the supplemental report that it was because it had been used for several years (i.e., since 2010) without any apparent side effects. First, the lack of implicating a given product or agent because it had been used for a long period of time without issue is confusing, considering that OxyELITE Pro fits the same criterion in many of these cases. Nonetheless, this completely ignores the fact that Stacker 3 has not been a fixed formula over the years with ingredients changing, along with different iterations [77-79], with green tea extract in a previous formula and green tea combined with *Garcinia cambogia*, both of which have been known to cause hepatotoxicity [16,55,56,80-84]. The authors make no attempt to confirm the formulas used and the ingredients. The patient was female, positive for anti-nuclear (ANA) antibodies (1:320 and rising to 1:1280) and had an ALP: AST/ALT ratio less than 1.5. Unfortunately, immunoglobulin G was not assessed, nor were biopsy results of the explanted liver reported, making it difficult to exclude autoimmune hepatitis (AIH) [85,86]. Corticosteroids were administered to the patient prior to transplant, with no positive response; this, however, does not exclude AIH [85,86]. Finally, the patient was noted to have fatty liver at presentation (via computed tomography scan) and ultrasound revealed a heterogeneous hepatic echotexture. Despite this evidence of chronic liver disease (and history of alcohol abuse), possible AIH or serological overlap (e.g., viral hepatitis, alcoholic or non-alcoholic fatty liver disease) and use of the Stacker supplement, Heidemann, et al., again implicate OEP-NF despite clear evidence of alternative causes [19]. Furthermore, the DILI onset date of May 7, 2013, indicates deviation from the enrollment of cases within 6 months of onset as the case was enrolled on February 25, 2014, which is beyond 6 months and more importantly well after public announcements were made. At the time the case was enrolled, hepatitis A, B, and C, as well as CMV, were ruled out. Hepatitis E, VZV, EBV, and HSV do not appear to have been ruled out after review of the DILIN enrollment form.

Case 3

The first issue in Case 3 is yet again the timing of use and formula availability. It states in Table 1 of the paper that she presented in June 2013, yet she had been using the product for 11 weeks. If April 2013 was the first time the formula with aegeline was available [73], this indicates the patient was using the old formula (OEP-OF) with DMAA. The authors also state that she stopped taking OEP during the pregnancy (this formula would thus have been the old formula) and resumed taking it postpartum. It is presumed that she continued taking the supplement from the same bottle; here again, this would have been the old formula, the same formula she had taken for 2 years without any adverse effects. Importantly, there are major discrepancies between what was published in the Heidemann, et al., paper and what was submitted on enrollment forms by the DILIN group [19]. For example, case-patient 3 was actually noted to have been taking two contraceptives from the time she gave birth until DILI onset; norethindrone (i.e., December 29, 2012, until June 15, 2013) along with a combination contraceptive, levonorgestrel/ethinyl estradiol starting in early May of 2013 around one month before onset. It is unclear why two contraceptives were used concomitantly and more importantly, why these data were not provided in the Heidemann, et al., publication, but it is especially troubling because these contraceptive products are known to cause hepatotoxicity and have been previously given DILIN causality scores of 3 (probable), even in cases of presumed azithromycin-induced liver injury [19,87]. Finally, it appears as though case 3 was enrolled on December 14, 2013, 1 day short of the 6 month cutoff for enrollment but still clearly occurring only after publicity suggesting that OEP-NF was a cause of hepatotoxicity. During the course of hepatitis and at the time the case was enrolled, hepatitis A, B, and C, as well as CMV were ruled out. Hepatitis E, VZV, EBV, and HSV do not

appear to have been ruled out as no testing or results are reported for the DILIN enrollment form. Liver biopsy results indicated acute hepatitis and cholestasis.

Case 4

This particular case also is missing many critical details. For example, common assays to exclude other conditions were not performed; while hepatitis B and C were ruled out, hepatitis A, hepatitis E, EBV, VZV, CMV, and HSV were apparently not [88]. In addition, neither ANA nor smooth muscle antibodies (SMA) were assayed [88]. The long latency of 745 days makes this case highly unlikely to have been caused by OEP, while also confirming that this was the DMAA-containing version being implicated, not OEP-NF. Heidemann, et al., confusingly speculate that because this patient as well as case 5 had taken OEP formulations in the past without adverse effects prior to 2013, these cases may have been the result of switching to the reformulated product in 2013 [19]. Yet, such speculation demonstrates the inconsistent nature of the authors' opinions. If the DMAA-containing formulation is not thought to be hepatotoxic in case 4, how is it hepatotoxic in cases such as 2 or 3 where the patients were taking OEP when an aegeline-containing formulation was not yet on the market? Furthermore, the authors admit that they have no information as to what formula any patient was using. Thus, such speculation appears unwarranted. Finally, this patient was believed not to have been taking any other medications, but whether any other supplements were being used concomitantly is not reported. The lack of actual exclusion for alternative causes is problematic, while the long latency and incorrect formula (i.e., OEP-OF) suggest this case was unlikely to have been related to the use of OEP.

Case 5

The most significant issue with case 5 is the disregard for trimethoprim-sulfamethoxazole (TMP/SMZ) as a potential cause of the hepatotoxicity. The authors only assign it a DILIN score of 4 (possible), while OxyELITE Pro is given a score of 3 (probable). The authors apparently justified this reasoning by noting that the patient reported having taken TMP/SMZ in the past without adverse events. Thus, this would not have been a cause. However, despite noting that this patient is not a great historian of her supplement use, the authors do not indicate if they corroborated the patient's claim of prior TMP/SMZ use. Furthermore, prior use of TMP/SMZ or SMZ alone without adverse events does not rule out adverse reactions with subsequent use. In fact, there are several published papers demonstrating hepatotoxicity from TMP/SMZ or SMZ alone occurring in individuals who had been previously exposed to these drugs without adverse events [89-91]. Furthermore, it is strange that the logic used here, i.e., if TMP/SMZ had been used in the past without adverse events, it is unlikely to be the cause, is never similarly applied to cases of OEP. This statement from the patient is also problematic, "She reported taking one tablet of OxyELITE Pro daily on an intermittent basis for about two years to enhance her energy level. She noted that her eyes would occasionally become icteric after she had been taking the medication for an extended period of time, which would prompt her to discontinue OxyELITE until icterus resolved." The statement above would mean that she experienced hepatitis from both the formula with DMAA and aegeline if this occurred over a period of nearly 2 years. This is highly unlikely and contradicts the authors' conclusions in other cases that the lack of the previous hepatotoxicity from continued use, only for it to suddenly change after an extremely long latency period is explained by a formulation switch from DMAA to aegeline [13]. Her story about occasionally having her eyes appear icteric may in fact simply have been an observation from previous treatment with TMP/SMZ or another medication or supplement. Here again, the authors neglect to mention when exactly, she had used TMP/SMZ in the past and did not attempt to see if that coincided with icterus. As noted in a case by Faria, et al., who also had a woman who had previously used TMP/SMZ without issue, only to later experience hepatitis from it: "The time interval between drug discontinuation and initiation of symptoms in the present case was quite long (30 days) [89]. However, we could not rule out the possibility of the presence of mild symptoms before they became severe enough to be noticed by the patient." The patient in case 5 was also taking several medications around the time of the liver injury, some of which may cause hepatotoxicity; albeit in rare instances [92,93]. The fact that OxyELITE Pro was used for over 700 days (i.e., used from November 4, 2011 to October 14, 2013) without issue, while her symptoms began only two days after completing a seven day course of TMP/SMZ (i.e., used from October 15, 2013, to October 22, 2013, with onset of symptoms on October 24, 2013) is indicative of the latter being the cause. Incidentally, while TMP/SMZ is the most obvious cause, also not reported was this patient's use of presumably significant quantities of xylitol as a means of improving bone health for 4 months prior to the onset of illness. While xylitol is a common food additive generally regarded as quite safe for humans, there are reports, albeit inconsistent, suggestive of potential hepatotoxicity in some animals and even humans when large

amounts are administered intravenously [94-99]. While oral (as opposed to intravenous for parenteral nutrition) intake of even large amounts of xylitol seems unlikely as a cause or contributor, such details should have been reported for transparency rather than disregarded entirely. Finally, case 5 appears to have been enrolled on March 4, 2014, well after the media and regulatory publicity. This is yet another case where in fact a DMAA-containing formula is actually implicated rather than OEP-NF. Hepatitis A, B, C and CMV appear to have been ruled out, but it doesn't appear as though VZV, EBV and HSV were ruled out.

Case 6

In this case, similar to case 5, the authors inexplicably implicate OxyELITE Pro with a DILIN score of 3 (probable), while assigning a score of only 4 (possible) to azithromycin. The authors state that "She also completed a 10-day course of azithromycin for a sinus infection 2 weeks before presentation." They then state that after being seen, "She discontinued the supplements and her symptoms and serum enzyme abnormalities resolved within a few weeks".

The authors offer no reasoning as to why azithromycin was considered only, "possible". This is especially concerning as azithromycin induced hepatotoxicity has been studied by the DILIN group [87]. They have stated that "azithromycin-induced liver injury typically occurs within 2-3 weeks of exposure" and "recovery was usually prompt, averaging 2 to 5 weeks and usually followed by complete resolution with completely normal serum enzymes and no symptoms or signs of persistent liver disease." Considering that this patient was exposed to azithromycin 2 weeks prior to presentation and her symptoms and liver enzymes returned to normal within a "few" (2-5 weeks), this fits exactly with the time course described by the DILIN group [87]. Considering that OEP was used for 4 months without issue and the timing of azithromycin onset and resolution matched that found in the DILIN study, it shows a clear bias by these particular study authors. Additionally and of concern is the fact that several medications which this patient was taking, along with pertinent clinical details were not included in the Heidemann, et al., paper [19]. For example, the patient was taking bupropion, venlafaxine, oral contraceptives (norgestimate and ethinyl estradiol), and Mucinex Fast-Max Cold and Sinus (containing acetaminophen). A more thorough detailing of the case's experience is also worth covering. On October 14, 2013, the patient was started on a 10-day course of azithromycin for a sinus infection. From October 15, 2013, to October 19, 2013, she was also taking Mucinex Fast-Max Cold and Sinus (containing acetaminophen). She had also been taking OxyELITE Pro since June of 2013. Her liver enzymes had been normal but were noted to be mildly elevated at a visit with her primary care physician on October 29, 2013. After symptoms had onset (November 06, 2013) on November 08, 2013, her liver enzymes had risen more and continued to rise on November 12, 2013 (i.e., onset date according to DILIN protocol) and November 19, 2013, before her symptoms and liver enzymes began to improve on December 03, 2013 after which they were essentially normal by December 17, 2013. Thus, this patient had been taking OEP for 4 months, yet her liver enzymes only rose after she had taken a course of azithromycin, which followed the typical course of latency and recovery. Yet, confusingly, the authors implicate OEP as the causal agent. Interestingly, this case also appears to be enrolled on November 20, 2014, over a year from the date of DILI onset, once again indicating that these authors did not follow the DILIN inclusion criteria and also indicating once again that this case was reported only after media and regulatory attention. Incidentally, during the course of hepatitis and at the time the case was enrolled, hepatitis A, B and C, as well as CMV were ruled out. Hepatitis E, VZV, EBV, and HSV do not appear to have been ruled out as no testing or results are reported for the DILIN enrollment form.

Case 7

In this case, even ignoring the chronic hepatitis B, the authors again inexplicably ignore or assign lower causality scores to other agents, while OEP is given a score of 3 (probable) which was used from March 2013 to October 2013. In this case, the patient was said to be consuming products called, "Ravage" and "Hydroxycut". Hydroxycut has a long history of being implicated in causing liver toxicity in the primary literature, even after formula changes [100-104]. In fact, in a 2014 paper covering herb and dietary supplement liver injury cases up to March of 2013 in the drug-induced liver injury network (DILIN), Hydroxycut was implicated frequently [76]. Despite this history with old and new formulas, Hydroxycut was given a causality score of 5 (unlikely). While the authors do not explain this discrepancy, this could possibly be because the authors referenced a 2016 formula of Hydroxycut, as opposed to reviewing ingredients present in a product from 2013 or potentially because the last reported use occurred in May 2013, while the date of onset was December 3, 2013. Similarly, the "Ravage" product was given a causality score of

4 (possible) and was reportedly used from April 20123 to September 2013. This product contains Chinese Skullcap Root Extract (*Scutellaria baicalenis*) and *Acacia catechu*, which have been implicated in causing hepatotoxicity [10,105-109]. Here again, however, the authors inexplicably assign only a score of 4 (possible). Also not apparently considered by Heidemann, et al., this patient was also using a Whole Body Vitapak product (a product noted in other publications) which featured a joint health formula also consisting of *Acacia catechu* and Chinese Skullcap Root Extract (*Scutellaria baicalenis*) which was used from April 2013 to November 2013 [19,20]. This lack of consideration for a product by the authors is concerning, but also represents a circumstance which likely occurs rather frequently where patients consume multiple products which may contain some of the same ingredients, unwittingly consuming quantities much larger than anticipated. Finally, though not reported by the authors, this patient was also using the product N.O.-Xplode which had previously been implicated in causing liver injury as well [110]. This patient similar to others, began using OxyELITE Pro before OEP-NF (i.e., March 15, 2013) was on the market, thus it is yet another case where it was the DMAA-containing formula being implicated. This patient also had been diagnosed with migraine, dysthymia and as well as alcohol-related liver disease in January 2012. Hepatitis E, VZV, EBV, HSV and CMV does not appear to have been ruled out. Hepatitis C was not ruled out via HCV RNA analysis upon admission, but was negative post-transplant; however approximately 8 months later it was positive. Medications used prior to illness onset also included ibuprofen (presumably for migraine) and entecavir (chronic hepatitis B infection). This case was enrolled on November 20, 2014, nearly 1 year after DILI onset (December 03, 2013), again indicating deviation from normal inclusion criteria and enrollment after media and regulatory publicity.

It is revealing that at least 6 (cases 1, 2, 3, 4, 5, and 7) out of the 7 cases reported would have used the DMAA-containing version or OEP-OF, which is somewhat consistent with the data by Klontz, et al., who reported that approximately 55% of cases reporting had used OEP-OF, containing DMAA as well as those of Foley, et al., where all 7 cases were attributed to OEP-OF containing DMAA [25,73]. This is in contrast to Johnston, et al., who found that the majority (75%) of reports indicated consuming a DMAA-free formulation or OEP-NF [111]. This clearly demonstrates the contradictory nature of the reports with most implicating the wrong formula; such contradictions also serve as evidence of biased reporting towards a name, OxyELITE Pro, rather than an ingredient or formulation.

This case series showed a high degree of bias, including the lack of important clinical details, inclusion of cases only after media and regulatory publicity specifically implicating the product as being a cause of hepatitis, the lack of consideration for alternative causes, inclusion or enrollment of cases which should have been excluded based upon the authors' own defined inclusion criteria, apparent retrospective case-seeking by the authors, and inconsistent (subjective) causality scoring.

To further illustrate the subjectivity and bias of the scoring applied by the authors, for example, one may look at other publications by some of the authors from the group, including a paper focused on the examination of a cohort of azithromycin-induced DILI [87]. In this study, azithromycin, following time-courses that fall within the same timeframe as that seen with Case 6, was assigned a causality score of no lower than a 3 (probable) and often a 2 (highly likely) [87]. In fact, out of 18 cases in the cohort, 8 (~44%) were rated as 3 (probable), 9 (50%) were rated as 2 (highly likely) and 1 (~6%) was rated as 1 (definite); not a single case was rated as 4 (possible). Yet, in the Heidemann, et al., paper, azithromycin was rated only as 4 (possible) [19]. Considering that OEP was used for 4 months without issue and the timing of azithromycin-induced DILI onset (i.e., liver enzymes rose only after azithromycin treatment) and resolution matched that found in the DILIN study, it shows a clear bias by these particular study authors.

In yet another interesting sign of bias and subjectivity, in the azithromycin study, some of the cases had patients who took other medications concomitantly. In these cases, the authors assigned DILIN causality scores to them as well. Interestingly, not one of those other medications included a score of 4 (possible). Instead, they were all given a score of 3 (probable) or higher. These other medications included ibuprofen (score of 2-highly likely); MRC-6, a weight loss supplement (score of 3--probable), drospirenone and ethinyl estradiol (score of 3-probable); additionally, cases involving other implicated medications included TMP and TMP/SMZ. TMP alone was given a causality score of 3 (probable) while TMP/SMZ received a score of 2 (highly likely) and 3 (probable). Here again, TMP or TMP/SMZ never received a score of less than 3 (probable) even in cases where azithromycin was also implicated. The authors in some cases had multiple medications (e.g., TMP and azithromycin) both receiving the same causality score of 2 (highly likely) in the same patient or both azithromycin and TMP receiving a causality score of 3 (probable) in the same patient [87]. Yet, inexplicably, the authors of Heidemann, et al., rated TMP/SMZ as only a 4 (possible) while rating OxyELITE Pro as a 3 (probable) [19].

Case 7 (i.e., concomitantly used supplements with known hepatotoxic ingredients were given scores of 4-possible and 5-unlikely or not scored at all) also contrasts with the previous actions in the azithromycin-DILIN paper, where they gave a dietary supplement, MRC-6, a score of 3 (probable), despite the fact that it doesn't appear to contain any known hepatotoxic constituents with the possible exception of kelp, which has a single case report of hepatotoxicity from a tea containing kelp [87,112]. In any event, it reveals bias and subjectivity by Heidemann, et al., who assigned such low scores to products containing substances associated with hepatotoxicity and gave elevated scores to OEP [19]. Of course, in many cases, other medications that patients were taking in these cases (as well as pertinent patient history) weren't even reported, let alone given a causality score.

The cases presented by Heidemann, et al., demonstrate the vulnerability of case studies and "causality scoring methods" such as that used by the DILIN group [19]. Of course, it is difficult for opinion not to enter into the realm of causality determination when multiple agents are used concomitantly/sequentially [113]; as was the case in Heidemann, et al. [19]. For example, one group found it effectively impossible to objectively determine causality with various assessment methods in such cases [113]. While the RUCAM method is intended to inject a modicum of objectivity by using a standardized algorithm based scoring method, without an objective biomarker, any causality method can never be truly assessed for validity (i.e., accuracy) because every possible cause is highly unlikely to be excluded [13,28,114,115]. Ultimately, the use of the term "causality" in such models should be considered tenuous as these cases aren't subject to hypothesis testing and can't be validated; they are probably best viewed as non-validated screening tools. The DILIN method, in particular, relies heavily upon, "expert opinion" which ultimately is vulnerable to subjectivity and bias that may result in an incorrect attribution of causality [28,71,116]. A Bayesian approach is likely superior to the RUCAM or DILIN method but has its own limitations and may not be practical [28]. In any event, as others have noted, beliefs and experiences, regardless of expertise are not a reliable source of knowledge when assessing causality as cognitive biases are inherent to us all [64]; there is a body of research demonstrating that this occurs with physicians in particular [67-72]. In the case of OEP, it is clear that it was already assumed to be hepatotoxic even before cases were analyzed and preconceived opinions (bias) are a known issue with such assessments [28]. Ultimately, one is left with case reports which have serious limitations [27,39]; in the case of DILI/HILI, it is subject to an even greater number of confounders including underreporting or lack of consideration for other supplements, over the counter drugs and prescription medications, by the patient and clinician, respectively [12,41-53,61]. This is in addition to ruling out other known conditions which may be confused for DILI/HILI, including viral infections, alcoholic liver disease, autoimmune hepatitis (AIH), genetic disorders (e.g., Wilson disease and alpha-1-antitrypsin deficiency), non-alcoholic steatohepatitis (seen with obesity), ischemic hepatitis and biliary diseases [12]. As noted previously, the incorrect attribution of causality for given agents without a thorough examination of all available case details either through ignorance or neglect has been demonstrated by others in cases of DILI and HILI, with nearly 50% of cases neglecting alternative causes or failing to meet causality as determined by RUCAM scoring [60,61]. Implicating the wrong agent could cause the patient to receive an incorrect treatment, unnecessary and potentially harmful treatment, or no treatment at all [72,117]. Others have noted, while discussing the deficiencies pointed out by Teschke and Eickhoff, regarding the cases put forth by Heidemann, et al., that such cases may represent instances where a causality scoring method may need to be "overridden" by expert opinion if the results are not in line with the expectation of causality [19,22,118]. However, such a line of reasoning not only calls into question the point of using such scoring methods altogether if they can simply be overridden but as importantly, the notion of a need for overriding scored results itself, clearly demonstrates a bias of assuming causality beforehand [27,62-72]. Furthermore, while case studies themselves are unable to be subjected to hypothesis testing, such reasoning is also antithetical to a basic tenet of science, which is to test the notion that there is no association between two variables (i.e., the null hypothesis).

Heidemann, et al., seem to place great emphasis on the fact that many cases reportedly occurred during the specified timeframe (e.g., May 2013 to late 2013) of the outbreak as defined by regulatory and public health agencies in public announcements [19,22]. Yet, consistent with the data published by Klontz, et al., it is clear that regardless of when the hepatitis or date of onset occurred, these cases were not reported as being related to OEP-NF until after these public announcements [73,119], a clear indication of stimulated reporting and retrospective case seeking, where cases which were either idiopathic in nature or due to alternative causes were instead associated with OEP-NF. For example, analyzing case information and enrollment forms obtained through a Freedom of Information Act (FOIA) request to the National Institutes of Health in order to obtain information not detailed in the published report, in cases 1, 2, 3, 5,

6 and 7 (the dates of enrollment or inclusion for OEP-NF-related hepatotoxicity analysis for case 4 is unknown) it is clear they were enrolled or included for analysis only after the public announcements in September 2013 and those subsequent to it. Indeed, except for case 1 which was clearly reexamined after the fact (and ultimately ruled out as a cause regardless) and case 4, for which the enrollment date is unknown (although considering the illness date in August, it too was likely reported after September 2013), the remaining cases were enrolled by authors of the paper no earlier than November 2013 and much later in some cases. Thus, the reporting of cases which fit the defined timeframe after public announcements is not surprising as patients and physicians may retrospectively examine their use or cases which happened to consume OEP during the timeframe specified in public reports and assume their case is associated, leading to reporting. The fact that these cases were evaluated only after publicity is also significant as the causality assessment method primarily employed by the authors is ultimately based upon opinion and thus is particularly prone to subjectivity and bias (preconceived opinion) [28,116].

Finally, it should be noted that in at least some cases, clinicians may be encountering patients for the first time and for various reasons may not have access to a centralized system for medical history, prescriptions (i.e., most states have databases which track only potentially abused prescription drugs rather than all prescription drugs-only 1 currently requires reporting of all dispensed prescription drugs to a central database) and reported dietary supplement intake (e.g., as recorded by a primary care provider or other specialists), forcing them to rely exclusively upon the patient for such information. This represents a potential area for improvement as well.

CONCLUSION

Case studies which have been published to date are likely the result of stimulated reporting and retrospective case seeking; lack evidence and critical information for interested readers to truly assess the likelihood of causality and contradictorily, implicate the wrong formulation of OxyELITE Pro (i.e., OEP containing DMAA). The initial group reporting cases locally in Hawaii did not utilize an adequate approach to evaluate potential causality, failing to accurately report important details of the patients, their medical history, and other medications and dietary supplements being used where alternative causes were evident; most concerning was the intentional upgrading of causality scores to fit with personal beliefs. Some authors have also produced biased and contradictory reports with causality assessment methods that are prone to bias and subjectivity. This highlights the disadvantages and erroneous conclusions one can reach when relying exclusively on case studies to implicate a given agent. A more uniform, thorough and objective method of diagnosing DILI/HILI allowing correct attribution of a causal agent when multiple agents are used concomitantly/sequentially, as opposed to reliance upon each individual physician's discretion and subjective judgment is needed. Ultimately, the discovery of the ever elusive DILI/HILI biomarker is also needed; in the meantime, it seems the RUCAM, while also imperfect, is preferred.

DECLARATIONS

Conflict of Interest

The author has served as a consultant to USPlabs, the manufacturer of OxyELITE Pro and is a defendant in ongoing litigation related to OxyELITE Pro. USPlabs was not involved in the conception, writing, or editing of this article. The views expressed here are those of the author.

REFERENCES

[1] Ogden, Cynthia L., et al. "Prevalence of childhood and adult obesity in the United States, 2011-2012." *JAMA,* Vol. 311, No. 8, 2014, pp. 806-14.

[2] Hales, Craig M., et al. *Prevalence of obesity among adults and youth: United States, 2015-2016*. US Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Health Statistics, 2017.

[3] Corey, Kathleen E., and Lee M. Kaplan. "Obesity and liver disease: the epidemic of the twenty-first century." *Clinics in Liver Disease,* Vol. 18, No. 1, 2014, pp. 1-18.

[4] Zhang, Yi, et al. "Obesity: pathophysiology and intervention." *Nutrients,* Vol. 6, No. 11, 2014, pp. 5153-83.

[5] Massart, Julie, et al. "Role of nonalcoholic fatty liver disease as a risk factor for drug-induced hepatotoxicity." *Journal of Clinical and Translational Research,* Vol. 3, No. 1, 2017, pp. 212-32.

[6] Kit, Brian K., Cynthia L. Ogden, and Katherine M. Flegal. "Prescription medication use among normal weight, overweight, and obese adults, United States, 2005-2008." *Annals of Epidemiology,* Vol. 22, No. 2, 2012, pp. 112-19.

[7] Blanck, Heidi Michels, et al. "Use of nonprescription dietary supplements for weight loss is common among Americans." *Journal of the American Dietetic Association,* Vol. 107, No. 3, 2007, pp. 441-47.

[8] Pillitteri, Janine L., et al. "Use of dietary supplements for weight loss in the United States: results of a national survey." *Obesity,* Vol. 16, No. 4, 2008, pp. 790-96.

[9] Vega, Maricruz, et al. "The incidence of drug-and herbal and dietary supplement-induced liver injury: preliminary findings from gastroenterologist-based surveillance in the population of the State of Delaware." *Drug Safety,* Vol. 40, No. 9, 2017, pp. 783-87.

[10] Melchart, Dieter, et al. "Herbal Traditional Chinese Medicine and suspected liver injury: A prospective study." *World Journal of Hepatology,* Vol. 9, No. 29, 2017, pp. 1141-57.

[11] Björnsson, Einar S., et al. "Incidence, presentation, and outcomes in patients with drug-induced liver injury in the general population of Iceland." *Gastroenterology,* Vol. 144, No. 7, 2013, pp. 1419-25.

[12] Teschke, Rolf, et al. "Drug-induced liver injury: accuracy of diagnosis in published reports." *Annals of Hepatology,* Vol. 13, No. 2, 2014, pp. 248-55.

[13] Danan, Gaby, and Rolf Teschke. "RUCAM in drug and herb-induced liver injury: the update." *International Journal of Molecular Sciences,* Vol. 17, No. 1, 2015, p. 14.

[14] Appelhans, Kristy, Najeeullah, Raushana, and Frankos, Vasilios. "Retrospective reviews of liver□related case reports allegedly associated with Herbalife present insufficient and inaccurate data". *Alimentary Pharmacology and Therapeutics*, Vol. 37, No. 7, 2013, pp. 753-754.

[15] Reddy, K. R., and C. Bunchorntavakul. "Retrospective reviews of liver□related case reports allegedly associated with Herbalife present insufficient and inaccurate data–authors' reply." *Alimentary Pharmacology and Therapeutics,* Vol. 37, No. 7, 2013, pp. 754-55.

[16] Teschke, Rolf, et al. "Herbal hepatotoxicity: analysis of cases with initially reported positive re-exposure tests." *Digestive and Liver Disease,* Vol. 46, No. 3, 2014, pp. 264-69.

[17] Teschke, Rolf, et al. "Herbalife hepatotoxicity: Evaluation of cases with positive reexposure tests." *World Journal of Hepatology,* Vol. 5, No. 7, 2013, pp. 353-63.

[18] Roytman, Marina M., et al. "Outbreak of severe hepatitis linked to weight-loss supplement OxyELITE Pro." *The American Journal of Gastroenterology,* Vol. 109, No. 8, 2014, pp. 1296-98.

[19] Heidemann, Lauren A., et al. "Severe acute hepatocellular injury attributed to OxyELITE Pro: a case series." *Digestive Diseases and Sciences,* Vol. 61, No. 9, 2016, pp. 2741-48.

[20] Teschke, Rolf, and Axel Eickhoff. "The Honolulu Liver disease cluster at the Medical Center: Its mysteries and challenges." *International Journal of Molecular Sciences,* Vol. 17, No. 4, 2016, p. 476.

[21] Teschke, Rolf, et al. "The mystery of the Hawaii liver disease cluster in summer 2013: A pragmatic and clinical approach to solving the problem." *Annals of Hepatology,* Vol. 15, No. 1, 2016, pp. 91-109.

[22] Teschke, Rolf, and Axel Eickhoff. "Suspected liver injury and the dilemma of causality." *Digestive Diseases and Sciences,* Vol. 62, No. 4, 2017, pp. 1095-98.

[23] Zambrone, Flávio Ailton Duque, Cristiana Leslie Corrêa, and Ligia Mesquita Sampaio do Amaral. "A critical analysis of the hepatotoxicity cases described in the literature related to Herbalife (r) products." *Brazilian Journal of Pharmaceutical Sciences,* Vol. 51, No. 4, 2015, 785-96.

[24] Teschke, Rolf, et al. "Mysterious Hawaii Liver Disease Case-Naproxen Overdose as Cause Rather than OxyELITE Pro." *Journal of Liver and Clinical Research*, Vol. 2, 2015, p. 1013.

[25] Foley, Sean, et al. "Experience with OxyELITE pro and acute liver injury in active duty service members." *Digestive diseases and sciences,* Vol. 59, No. 12, 2014, pp. 3117-21.

[26] Grimes, David A., and Kenneth F. Schulz. "Descriptive studies: what they can and cannot do." *The Lancet,* Vol. 359, No. 9301, 2002, pp. 145-49.

[27] Nissen, Trygve, and Rolf Wynn. "The clinical case report: a review of its merits and limitations." *BMC Research Notes,* Vol. 7, No. 1, 2014, p. 264.

[28] Agbabiaka, Taofikat B., Jelena Savović, and Edzard Ernst. "Methods for causality assessment of adverse drug reactions." *Drug Safety,* Vol. 31, No. 1, 2008, pp. 21-37.

[29] Kantor, Elizabeth D., et al. "Trends in prescription drug use among adults in the United States from 1999-2012." *Jama,* Vol. 314, No. 17, 2015, pp. 1818-31.

[30] Austin, Krista Gail, et al. "Use of dietary supplements containing 1, 3 dimethylamylamine by military personnel." *FASEB Journal*, Vol. 26, No. 1, 2012, p. 415.

[31] Knapik, Joseph J., et al. "Dietary Supplement Use in All United States Military Services." *The FASEB Journal,* Vol. 31, No. 1, 2017, p. 647.

[32] De Paschale, Massimo, and Pierangelo Clerici. "Serological diagnosis of Epstein-Barr virus infection: problems and solutions." *World Journal of Virology,* Vol. 1, No. 1, 2012, pp. 31-43.

[33] Gallegos-Orozco, Juan Fernando, and Jorge Rakela-Broedner. "Hepatitis viruses: not always what it seems to be." *Revista Médica de Chile,* Vol. 138, No. 10, 2010, pp. 1302-11.

[34] Hyams, Catherine, et al. "Serological cross-reactivity to CMV and EBV causes problems in the diagnosis of acute hepatitis E virus infection." *Journal of Medical Virology*, Vol. 86, No. 3, 2013, pp. 478-83.

[35] Hovaida, M., E. Torrazza-Perez and D. McCarthy. "Liver function tests "gone viral": acute hepatitis of uncertain cause." *Digestive Diseases and Sciences*, Vol. 63, No. 1, 2018, pp. 32-35.

[36] Zibbell, Jon E., et al. "Increases in acute hepatitis C virus infection related to a growing opioid epidemic and associated injection drug use, United States, 2004 to 2014." *American Journal of Public Health*, Vol. 108, No. 2, 2018, pp. 175-81.

[37] OCEBM Levels of Evidence Working Group. The Oxford Levels of Evidence 2. Oxford Centre for Evidence-Based Medicine, http://www.cebm.net/index.aspx?o=5653.

[38] Howick, Jeremy, et al. "Explanation of the 2011 Oxford Centre for Evidence-Based Medicine (OCEBM) levels of evidence (background document)." *Oxford Center for Evidence-Based Medicine,* 2011.

[39] Brighton, Brian, et al. "Hierarchy of evidence: from case reports to randomized controlled trials." *Clinical Orthopaedics and Related Research*, Vol. 413, 2003, pp. 19-24.

[40] Weiler-Normann, Christina, and Christoph Schramm. "Drug-induced liver injury and its relationship to autoimmune hepatitis." *Journal of Hepatology,* Vol. 55, No. 4, 2011, pp. 747-49.

[41] Barritt, A. Sidney, Joseph Lee and Paul H. Hayashi. "Detective work in drug-induced liver injury: sometimes it is all about interviewing the right witness." *Clinical Gastroenterology and Hepatology*, Vol. 8, No. 7, 2010, pp. 635-37.

[42] Han, Beth, et al. "Prescription opioid use, misuse, and use disorders in US adults: 2015 National Survey on Drug Use and Health." *Annals of Internal Medicine*, Vol. 167, No. 5, 2017, pp. 293-301.

[43] de Boer, Ynto S., and Averell H. Sherker. "Herbal and dietary supplement–induced liver injury." *Clinics in Liver Disease*, Vol. 21, No. 1, 2017, pp. 135-49.

[44] Hensrud, Donald D., Dean D. Engle and Sidna M. Scheitel. "Underreporting the use of dietary supplements and nonprescription medications among patients undergoing a periodic health examination." *Mayo Clinic Proceedings*, Vol. 74, No. 5, 1999, pp. 443-47.

[45] Hser, Yih-Ing. "Self-reported drug use: results of selected empirical investigations of validity." *NIDA Research Monograph*, Vol. 167, 1997, pp. 320-43.

[46] Pratt, Daniel S. and Marshall M. Kaplan. "Evaluation of abnormal liver-enzyme results in asymptomatic patients." *New England Journal of Medicine*, Vol. 342, No. 17, 2000, pp. 1266-71.

[47] Delaney-Black, Virginia, et al. "Just say "I don't": lack of concordance between teen report and biological measures of drug use." *Pediatrics*, Vol. 126, No. 5, 2010, pp. 887-93.

[48] Pergolizzi, Joseph, et al. "The role of urine drug testing for patients on opioid therapy." *Pain Practice*, Vol. 10, No. 6, 2010, pp. 497-507.

[49] Bond, G. Randall, Mona Ho and Randall W. Woodward. "Trends in Hepatic injury associated with unintentional overdose of paracetamol (*Acetaminophen*) in products with and without opioid." *Drug Safety*, Vol. 35, No. 2, 2012, pp. 149-57.

[50] Lee, Sean S., W. U. Zhang and Yiming Li. "The antimicrobial potential of 14 natural herbal dentifrices." *The Journal of the American Dental Association*, Vol. 135, No. 8, 2004, pp. 1133-41.

[51] Wilcox, C. Mel, Byron Cryer and George Triadafilopoulos. "Patterns of use and public perception of over-the-counter pain relievers: focus on nonsteroidal anti-inflammatory drugs." *The Journal of Rheumatology*, Vol. 32, No. 11, 2005, pp. 2218-24.

[52] Herndon, Christopher M. and Dawn M. Dankenbring. "Patient perception and knowledge of acetaminophen in a large family medicine service." *Journal of Pain and Palliative Care Pharmacotherapy*, Vol. 28, No. 2, 2014, pp. 109-16.

[53] Saab, Sammy, et al. "Limited knowledge of acetaminophen in patients with liver disease." *Journal of Clinical and Translational Hepatology*, Vol. 4, No. 4, 2016, pp. 281-87.

[54] Lee, William M. "Acetaminophen (APAP) hepatotoxicity-Isn't it time for APAP to go away?" *Journal of Hepatology*, Vol. 67, No. 6, 2017, pp. 1324-31.

[55] Lunsford, Keri E., et al. "Dangerous dietary supplements: garcinia cambogia-associated hepatic failure requiring transplantation." *World Journal of Gastroenterology*, Vol. 22, No. 45, 2016, pp. 10071-76.

[56] Smith, Rosemary J., Christina Bertilone and Andrew G. Robertson. "Fulminant liver failure and transplantation after use of dietary supplements." *The Medical Journal of Australia*, Vol. 204, No. 1, 2016, pp. 30-32.

[57] Davern, Timothy J., et al. "Measurement of serum acetaminophen-protein adducts in patients with acute liver failure." *Gastroenterology*, Vol. 130, No. 3, 2006, pp. 687-94.

[58] Khandelwal, Niraj, et al. "Unrecognized acetaminophen toxicity as a cause of indeterminate acute liver failure." *Hepatology*, Vol. 53, No. 2, 2011, pp. 567-76.

[59] Fontana, R. John, et al. "The role of hepatitis E virus infection in adult Americans with acute liver failure." *Hepatology*, Vol. 64, No. 6, 2016, pp. 1870-80.

[60] Björnsson, Einar S. and Jay H. Hoofnagle. Categorization of drugs implicated in causing liver injury: critical assessment based on published case reports." *Hepatology,* Vol. 63, No. 2, 2015, pp. 590-603.

[61] Teschke, Rolf, et al. "Herbal hepatotoxicity: suspected cases assessed for alternative causes." *European Journal of Gastroenterology & Hepatology*, Vol. 25, No. 9, 2013, pp. 1093-98.

[62] Sica, Gregory T. "Bias in research studies." *Radiology*, Vol. 238, No. 3, 2006, pp. 780-89.

[63] Yarritu, Ion, Helena Matute and David Luque. "The dark side of cognitive illusions: when an illusory belief interferes with the acquisition of evidence-based knowledge." *British Journal of Psychology*, Vol. 106, No. 4, 2015, pp. 597-608.

[64] Matute, Helena, et al. "Illusions of causality: how they bias our everyday thinking and how they could be reduced." *Frontiers in Psychology*, Vol. 6, 2015, p. 888.

[65] Yarritu, Ion and Helena Matute. "Previous knowledge can induce an illusion of causality through actively biasing behavior." *Frontiers in Psychology*, Vol. 6, 2015, p. 389.

[66] Vadillo, Miguel A., Helena Matute and Fernando Blanco. "Fighting the illusion of control: how to make use of cue competition and alternative explanations." *Universitas Psychologica*, Vol. 12, No. 1, 2013, pp. 261-70.

[67] Klein, Jill G. "Five pitfalls in decisions about diagnosis and prescribing." *BMJ,* Vol. 330, No. 7494, 2005, pp. 781-83.

[68] Hall, Katherine H. "Reviewing intuitive decision-making and uncertainty: the implications for medical education." *Medical Education,* Vol. 36, No. 3, 2002, pp. 216-24.

[69] Tschan, Franziska, et al. "Explicit reasoning, confirmation bias, and illusory transactive memory." *Small Group Research,* Vol. 40, No. 3, 2009, pp. 271-300.

[70] Casarett, David. "The science of choosing wisely-overcoming the therapeutic illusion." *New England Journal of Medicine,* Vol. 374, No. 13, 2016, pp. 1203-05.

[71] Guzelian, Philip S., et al. "Evidence-based toxicology: a comprehensive framework for causation." *Human and Experimental Toxicology,* Vol. 24, No. 4, 2005, pp. 161-201.

[72] Berner, Eta S. and Mark L. Graber. "Overconfidence as a cause of diagnostic error in medicine." *The American Journal of Medicine,* Vol. 121, No. 5, 2008, pp. S2-23.

[73] Klontz, Karl C., et al. "The role of adverse event reporting in the FDA response to a multistate outbreak of liver disease associated with a dietary supplement." *Public Health Reports,* Vol. 130, No. 5, 2015, pp. 526-32.

[74] Fontana, Robert J., et al. "Drug-induced liver injury network (DILIN) prospective study." *Drug Safety,* Vol. 32, No. 1, 2009, pp. 55-68.

[75] Whitt, Kerry, et al. "Cholestatic liver injury associated with whey protein and creatine supplements." *Seminars in Liver Disease,* Vol. 28, No. 2, 2008, pp. 226-31.

[76] Navarro, Victor J., et al. "Liver injury from herbals and dietary supplements in the U.S. Drug-Induced Liver Injury Network." *Hepatology,* Vol. 60, No. 4, 2014, pp. 1399-408.

[77] Expert Rated Reviews. Stacker 3 XPLC Review-is Stacker 3 XPLC Safe? Expert Rated Reviews. 2017, http://expertratedreviews.com/stacker-3-xplc-review-is-stacker-3-xplc-safe/.

[78] eVitamins. NVE Pharmaceuticals Stacker 3 XPLC-60 capsules. eVitamins, 2017, https://www.evitamins.com/stacker-3-xplc-nve-pharmaceuticals-5971

[79] Walgreens. Stacker 3 Herbal Dietary Supplement Capsules. Walgreens, 2017. https://www.walgreens.com/store/c/stacker-3-herbal-dietary-supplement-capsules/ID=prod1420290-product.

[80] Mezera, Vojtech, et al. "The effect of epigallocatechin gallate on hepatocytes isolated from normal and partially hepatectomized rats." *Canadian Journal of Physiology and Pharmacology,* Vol. 92, No. 6, 2014, pp. 512-17.

[81] Galati, Giuseppe, et al. "Cellular and *in vivo* hepatotoxicity caused by green tea phenolic acids and catechins." *Free Radical Biology and Medicine,* Vol. 40, No. 4, 2006, pp. 570-80.

[82] Lambert, Joshua D., et al. "Hepatotoxicity of high oral dose (-)-epigallocatechin-3-gallate in mice." *Food and Chemical Toxicology,* Vol. 48, No. 1, 2010, pp. 409-16.

[83] Kim, Young-Je, et al. "Garcinia *Cambogia attenuates* diet-induced adiposity but exacerbates hepatic collagen accumulation and inflammation." *World Journal of Gastroenterology,* Vol. 19, No. 29, 2013, pp. 4689-701.

[84] Teschke, Rolf, et al. "Herbal hepatotoxicity: a tabular compilation of reported cases." *Liver International,* Vol. 32, No. 10, 2012, pp. 1543-56.

[85] Alvarez, Fernando, et al. "International autoimmune hepatitis group report: review of criteria for diagnosis of autoimmune hepatitis." *Journal of Hepatology,* Vol. 31, No. 5, 1999, pp. 929-38.

[86] Manns, Michael P., et al. "Diagnosis and management of autoimmune hepatitis." *Hepatology*, Vol. 51, No. 6, 2010, pp. 2193-213.

[87] Martinez, Melissa A., et al. "Clinical and histologic features of azithromycin-induced liver injury." *Clinical Gastroenterology and Hepatology,* Vol. 13, No. 2, 2015, pp. 369-76.

[88] LiverTox. Summary of Case 19262. LiverTox. 2017, https://livertox.niddk.nih.gov/Home/ReferenceCases/oxyelite_pro/19262.

[89] Faria, Luciana C., et al. "Severe and prolonged cholestasis caused by trimethoprim-sulfamethoxazole: a case report." *Clinics,* Vol. 64, No. 1, 2009, pp. 71-74.

[90] Dujovne, Carlos A., Chao H. Chan and Hyman J. Zimmerman. "Sulfonamide hepatic injury: review of the literature and report of a case due to sulfamethoxazole." *New England Journal of Medicine,* Vol. 277, No. 15, 1967, pp. 785-88.

[91] LiverTox. Case 2. Cholestatic Hepatitis Due to TMP/SMZ, https://livertox.nih.gov/SulfamethoxazoleTrimethoprim.htm. Accessed 11 Jul. 2017.

[92] Bessone, Fernando, et al. "Hepatotoxicity induced by coxibs: how concerned should we be?" *Expert Opinion on Drug Safety,* Vol. 15, No. 11, 2016, pp. 1463-75.

[93] Johnson, A. G. and R. O. Day. "The problems and pitfalls of NSAID therapy in the elderly (part I)." *Drugs and Aging,* Vol. 1, No. 2, 1991, pp. 130-43.

[94] Sakai, T., et al. "Toxic effects of xylitol in mice." *Bulletin of the College of Agriculture and Veterinary Medicine, Nihon University,* Vol. 47, 1990, pp. 1-10.

[95] Xia, Z., Y. He, and J. Yu. "Experimental acute toxicity of xylitol in dogs." *Journal of Veterinary Pharmacology and Therapeutics,* Vol. 32, No.5, 2009, pp. 465-69.

[96] Schumer, William. "Adverse effects of xylitol in parenteral alimentation." *Metabolism,* Vol. 20, No. 4, 1971, pp. 345-47.

[97] Sestoft, Leif, and Allan Gammeltoft. "The effect of intravenous xylitol on the concentration of adenine nucleotides in human liver." *Biochemical Pharmacology,* Vol. 25, No. 23, 1976, pp. 2619-21.

[98] Schneider, Andrea S., et al. "Assessment of xylitol serum levels during the course of parenteral nutrition including xylitol in intensive care patients: a case-control study." *Clinical Nutrition,* Vol. 33, No. 3, 2014, pp. 483-88.

[99] Dunayer, Eric K., and Sharon M. Gwaltney-Brant. "Acute hepatic failure and coagulopathy associated with xylitol ingestion in eight dogs." *Journal of the American Veterinary Medical Association,* Vol. 229, No. 7, 2006, pp. 1113-17.

[100] Fong, Tse-Ling, et al. "Hepatotoxicity due to Hydroxycut: a case series." *The American Journal of Gastroenterology,* Vol. 105, No. 7, 2010, pp. 1561-66.

[101] Haimowitz, Stephanie, et al. "Liver failure after hydroxycut™ use in a patient with undiagnosed hereditary coproporphyria." *Journal of General Internal Medicine,* Vol. 30, No. 6, 2015, pp. 856-59.

[102] Adike, Abimbola, et al. "Hydroxycut-related vanishing bile duct syndrome." *Clinical Gastroenterology and Hepatology,* Vol. 15, No. 1, 2017, pp. 142-44.

[103] Araujo, James L. and Howard J. Worman. "Acute liver injury associated with a newer formulation of the herbal weight loss supplement Hydroxycut." *BMJ Case Reports,* Vol. 2015, 2015.

[104] Kaswala, D. H., et al. "Hydroxycut-induced Liver Toxicity." *Annals of Medical and Health Sciences Research*, Vol. 4, No. 1, 2014, pp. 143-45.

[105] Papafragkakis, Charilaos, et al. "Acute hepatitis after ingestion of a preparation of Chinese skullcap and black catechu for joint pain." *Case Reports in Hepatology,* Vol. 2016, 2016, pp. 1-3.

[106] Woo, H. Jung, et al. "Drug-induced liver injury: a 2-year retrospective study of 1169 hospitalized patients in a single medical center." *Phytomedicin*e, Vol. 22, No. 13, 2015, pp. 1201-05.

[107] Wang, Jir-You, et al. "Herb-induced autoimmune-like hepatitis in C57BL/6J mice." *Liver International,* Vol. 34, No. 4, 2013, pp. 583-93.

[108] Ong, E. Shi, et al. "Proteomic analysis of mouse liver for the evaluation of effects of *Scutellariae radix* by liquid chromatography with tandem mass spectrometry." *Rapid Communications in Mass Spectrometry,* Vol. 18, No. 21, 2004, pp. 2522-30.

[109] Yang, Leslie, et al. "Herbal hepatoxicity from Chinese skullcap: a case report." *World Journal of Hepatology,* Vol. 4, No. 7, 2012, pp. 231-33.

[110] Martin, Donald J., Brett J. Partridge, and William Shields. "Hepatotoxicity associated with the dietary supplement NO-XPLODE." *Annals of Internal Medicine,* Vol. 159, No. 7, 2013, pp. 503-04.

[111] Johnston, David I., et al. "Hepatotoxicity associated with the dietary supplement OxyELITE Pro™ - Hawaii, 2013." *Drug Testing and Analysis,* Vol. 8, No. 3-4, 2015, pp. 319-27.

[112] Viswanathan, Lavanya and Anish Patel. "Hepatotoxicity associated with herbal tea containing kelp." *ACG Case Reports Journal,* Vol. 1, No. 1, 2013, pp. 55-57.

[113] Lim, Roxanne, et al. "A challenge for diagnosing acute liver injury with concomitant/sequential exposure to multiple drugs: can causality assessment scales be utilized to identify the offending drug?" *Case Reports in Pediatrics,* Vol. 2014, 2014, p. 156389.

[114] Wilke, Russell A., et al. "Identifying genetic risk factors for serious adverse drug reactions: current progress and challenges." *Nature Reviews Drug Discovery*, Vol. 6, No. 11, 2007, pp. 904-16.

[115] Davern, Timothy J. "Drug-Induced Liver Disease." *Clinics in Liver Disease,* Vol. 16, No. 2, 2012, pp. 231-45.

[116] García-Cortés, Miren, et al. "Causality assessment methods in drug-induced liver injury: strengths and weaknesses." *Journal of Hepatology,* Vol. 55, No. 3, 2011, pp. 683-91.

[117] Graber, Mark. "Diagnostic errors in medicine: a case of neglect." *The Joint Commission Journal on Quality and Patient Safety*, Vol. 31, No. 2, 2005, pp. 106-13.

[118] Shahbaz, Omar, Sandeep Mahajan and James H. Lewis. "Highlights of drug - and herb-induced liver injury in the literature from 2016: how best to translate new information into clinical practice?" *Expert Opinion on Drug Metabolism and Toxicology*, Vol. 13, No. 9, 2017, pp. 935-51.

[119] Timbo, Babgaleh B., et al. "A review of dietary supplement adverse event report data from the FDA center for food safety and applied nutrition adverse event reporting system (CAERS)." *Annals of Pharmacotherapy,* Vol. 52, No. 5, 2017, pp. 431-38.