AACT Herbal Dietary Supplements SIG Abstracts September 2017

1**. Natural products modulating the hERG channel: heartaches and hope.** Kratz JM, Grienke U, Scheel O, Mann SA, Rollinger JM.

Nat Prod Rep. 2017 Aug 2;34(8):957-980. doi: 10.1039/c7np00014f.

Covering: 1996-December 2016. The human Ether-à-go-go Related Gene (hERG) channel is a voltage-gated potassium channel playing an essential role in the normal electrical activity in the heart. It is involved in the repolarization and termination of action potentials in excitable cardiac cells. Mutations in the hERG gene and hERG channel blockage by small molecules are associated with increased risk of fatal arrhythmias. Several drugs have been withdrawn from the market due to hERG channel-related cardiotoxicity. Moreover, as a result of its notorious ligand promiscuity, this ion channel has emerged as an important antitarget in early drug discovery and development. Surprisingly, the hERG channel blocking profile of natural compounds present in frequently consumed botanicals (i.e. dietary supplements, spices, and herbal medicinal products) is not routinely assessed. This comprehensive review will address these issues and provide a critical compilation of hERG channel data for isolated natural products and extracts over the past two decades (1996-2016). In addition, the review will provide (i) a solid basis for the molecular understanding of the physiological functions of the hERG channel, (ii) the translational potential of in vitro/in vivo results to cardiotoxicity in humans, (iii) approaches for the identification of hERG channel blockers from natural sources, (iv) future perspectives for cardiac safety guidelines and their applications within phytopharmaceuticals and dietary supplements, and (v) novel applications of hERG channel modulation (e.g. as a drug target).

DOI: 10.1039/c7np00014f
PMID: 28497823 [Indexed for MEDLINE]

2. Clinical presentations and outcomes of bile duct loss caused by drugs and herbal and dietary supplements. Bonkovsky HL, Kleiner DE, Gu J, Odin JA, Russo MW, Navarro VM, Fontana RJ, Ghabril MS, Barnhart H, Hoofnagle JH; U.S. Drug Induced Liver Injury Network Investigators.

Hepatology. 2017 Apr;65(4):1267-1277. doi: 10.1002/hep.28967. Epub 2017 Feb 7.

Bile duct loss during the course of drug-induced liver injury is uncommon, but can be an indication of vanishing bile duct syndrome (VBDS). In this work, we assess the frequency, causes, clinical features, and outcomes of cases of drug-induced liver injury with histologically proven bile duct loss. All cases of drug-induced liver injury enrolled into a prospective database over a 10-year period that had undergone liver biopsies (n = 363) were scored for the presence of bile duct loss and assessed for clinical and laboratory features, causes, and outcomes. Twenty-six of the 363 patients (7%) with drug-, herbal-, or dietary-supplement-associated liver injury had bile duct loss on liver biopsy, which was moderate to severe (<50% of portal areas with bile ducts) in 14 and mild (50%-75%) in 12. The presenting clinical features of the 26 cases varied, but the most common clinical pattern was a severe cholestatic hepatitis. The implicated agents included amoxicillin/clavulanate (n = 3), temozolomide (n = 3), various herbal products (n = 3), azithromycin (n = 2), and 15 other medications or dietary supplements. Compared to those without, those with bile duct loss were more likely to develop chronic liver injury (94% vs. 47%), which was usually cholestatic and sometimes severe. Five patients died and 2 others underwent liver transplantation for progressive cholestasis despite treatment with corticosteroids and ursodiol. The most predictive factor of poor outcome was the degree of bile duct loss on liver biopsy.CONCLUSION: Bile duct loss during acute cholestatic hepatitis is an ominous early indicator of possible VBDS, for which at present there are no known means of prevention or therapy. (Hepatology 2017;65:1267-1277).

DOI: 10.1002/hep.28967
PMCID: PMC5360519 [Available on 2018-04-01]
PMID: 27981596 [Indexed for MEDLINE]

3. Safety assessment of the dietary supplement OxyELITE™ Pro (New Formula) in inbred and outbred mouse strains. Miousse IR, Skinner CM, Lin H, Ewing LE, Kosanke SD, Williams DK, Avula B, Khan IA, ElSohly MA, Gurley BJ, Koturbash I.

Food Chem Toxicol. 2017 Aug 23. pii: S0278-6915(17)30475-1. doi: 10.1016/j.fct.2017.08.025. [Epub ahead of print]

Herbal dietary supplements have gained wide acceptance as alternatives to conventional therapeutic agents despite concerns regarding their efficacy and safety. In 2013, a spate of severe liver injuries across the United States was linked to the dietary supplement OxyELITE Pro-New Formula (OEP-NF), a multi-ingredient product marketed for weight loss and exercise performance enhancement. The principal goal of this study was to assess the hepatotoxic potential of OEP-NF in outbred and inbred mouse models. In an acute toxicity study, significant mortality was observed after administering 10X and 3X mouse-equivalent doses (MED) of OEP-NF, respectively. Increases in liver/body weight ratio, ALT and AST were observed in female B6C3F1 mice after gavaging 2X and 1.5X MED of OEP-NF. Similar findings were observed in a 90-day feeding study. These alterations were paralleled by altered expression of gene- and microRNA-signatures of hepatotoxicity, including Cd36, Nqo1, Aldoa, Txnrd1, Scd1 and Ccng1, as well as miR-192, miR-193a and miR-125b and were most pronounced in female B6C3F1 mice. Body weight loss, observed at week 1, was followed by weight gain throughout the feeding studies. These findings bolster safety and efficacy concerns for OEP-NF, and argue strongly for implementation of pre-market toxicity studies within the dietary supplement industry.

DOI: 10.1016/j.fct.2017.08.025
PMID: 28843594

4. Acute liver failure induced by idiosyncratic reaction to drugs: challenges in diagnosis and therapy. Tujios SR, Lee WM.

Liver Int. 2017 Aug 3. doi: 10.1111/liv.13535. [Epub ahead of print]

Acute liver failure (ALF) requires urgent attention to identify etiology and determine prognosis, in order to assess likelihood of survival or need for transplantation. Identifying idiosyncratic drug-induced liver injury (iDILI) may be particularly difficult, but the illness generally follows a subacute course, allowing time to assess outcome and find a liver graft if needed. Not all drugs that cause iDILI lead to ALF; the most common are antibiotics including anti-tuberculous medications, non-steroidal anti-inflammatory agents and herbal and dietary supplements (HDS). Determining causality remains challenging particularly if altered mentation is present; identifying the causative agent depends in part on knowing the propensity of the drugs that have been taken in the proper time interval, plus excluding other causes. In general, iDILI that reaches the threshold of ALF will more often than not require transplantation, since survival without transplant is around 25%. Treatment consists of withdrawal of the presumed offending medication, consideration of N-acetylcysteine (NAC), as well as intensive care. Corticosteroids have not proven useful except perhaps in instances of apparent autoimmune hepatitis caused by a limited number of agents. Recently developed prognostic scoring systems may also aid in predicting outcome in this setting.

DOI: 10.1111/liv.13535
PMID: 28771932

5. Safety assessment of green tea based beverages and dried green tea extracts as nutritional supplements. Dekant W, Fujii K, Shibata E, Morita O, Shimotoyodome A.

Toxicol Lett. 2017 Aug 5;277:104-108. doi: 10.1016/j.toxlet.2017.06.008. Epub 2017 Jun 24.

The safety of green tea infusions and green tea extract (GTE)-based products is reviewed regarding catechins. Epigallocatechin 3-gallate (EGCG), the major catechin present in green tea, is suspected of being responsible for liver toxicity reported in humans consuming food supplements. Intake of EGCG with green tea infusions and GTE-based beverages is up to about 450mg EGCG/person/day in Europe and higher in Asia. Consumption of green tea is not associated with liver damage in humans, and green tea infusion and GTE-based beverages are considered safe in the range of historical uses. In animal studies, EGCG's potency for liver effects is highly dependent on conditions of administration. Use of NOAELs from bolus administration to derive a tolerable upper intake level applying the margin of safety concept results in acceptable EGCG-doses lower than those from one cup of green tea. NOAELs from toxicity studies applying EGCG with diet/split of the daily dose are a better point of departure for risk characterization. In clinical intervention studies, liver effects were not observed after intakes below 600mg EGCG/person/day. Thus, a

tolerable upper intake level of 300mg EGCG/person/day is proposed for food supplements; this gives a twofold safety margin to clinical studies that did not report liver effects and a margin of safety of 100 to the NOAELs in animal studies with dietary administration of green tea catechins.

DOI: 10.1016/j.toxlet.2017.06.008
PMID: 28655517 [Indexed for MEDLINE]

6. An Increase in Dietary Supplement Exposures Reported to US Poison Control Centers. Rao N, Spiller HA, Hodges NL, Chounthirath T, Casavant MJ, Kamboj AK, Smith GA.

J Med Toxicol. 2017 Jul 24. doi: 10.1007/s13181-017-0623-7. [Epub ahead of print]

INTRODUCTION: The objective of this study was to investigate the epidemiology of dietary supplement exposures in the USA. METHODS: A retrospective analysis was conducted of out-of-hospital dietary supplement exposures reported to the National Poison Data System from 2000 through 2012. RESULTS: There were 274,998 dietary supplement exposures from 2000 through 2012. The annual rate of dietary supplement exposures per 100,000 population increased by 46.1% during 2000-2002, decreased 8.8% during 2002-2005, and then increased again by 49.3% from 2005 to 2012. These trends were influenced by the decrease in ma huang exposures starting in 2002. Miscellaneous dietary supplements accounted for 43.9% of all exposures, followed by botanicals (31.9%), hormonal products (15.1%), and other supplements (5.1%). The majority of dietary supplement exposures (70.0%) occurred among children younger than 6 years old and were acute (94.0%) and unintentional (82.9%). Serious medical outcomes accounted for 4.5% of exposures and most (95.0%) occurred among individuals 6 years and older. Ma huang products, yohimbe, and energy products were the categories associated with the greatest toxicity. CONCLUSIONS: There was an overall increase in the rate of dietary supplement exposures from 2000 through 2012. Although the majority of these exposures did not require treatment at a health care facility or result in serious medical outcomes, exposures to yohimbe and energy products were associated with considerable toxicity. Our results demonstrate the success of the FDA ban on ma huang products and the need for FDA regulation of yohimbe and energy products in the USA.

DOI: 10.1007/s13181-017-0623-7
PMID: 28741126

7. Direct and indirect risk associated with the use of dietary supplements among persons with dementia in a Norwegian memory clinic. Risvoll H, Giverhaug T, Halvorsen KH, Waaseth M, Musial F.

BMC Complement Altern Med. 2017 May 12;17(1):261. doi: 10.1186/s12906-017-1765-5.

BACKGROUND: The use of dietary supplements (DS) is common among persons with dementia. Direct risks associated with DS use include adverse events and DS-drug interactions. A direct risk is a risk caused by the treatment itself. Indirect risks are related to the treatment setting, such as the conditions of use, and not to the treatment itself. Because dementia symptoms may reduce a person's ability to cope with the administration of DS, the use of DS may pose a threat to safety as an indirect risk. The aim of this study was to describe the extent of DS use among persons with dementia in ambulatory care and to identify some relevant direct and indirect risks related to DS use. METHODS: We conducted a survey among 151 persons with dementia attending an outpatient memory clinic in Northern Norway. Study measurements included: the participants' characteristics, cognitive functioning, functioning in the activities of daily living (ADL), and the use of DS and prescription drugs (PD). We assessed direct risks by evaluating potential DS-drug interactions and indirect risks by evaluating the conditions under which it was used. RESULTS: Forty-six percent (n = 70) of the persons with dementia used DS. Ninety-seven percent (n = 147) used PD. We found potentially clinically relevant DS-drug interactions representing a direct risk in eight persons with dementia (11% of users). While only 36% (n = 26) of the participants received assistance with the administration of DS, 73% (n = 106) received assistance with the administration of PD. Persons with dementia living alone were at risk of not receiving assistance, as home care service seldom was involved in DS administration. Data indicated that assistance with DS administration was not provided for all persons with dementia in need, representing an indirect risk to these persons. Only one-third of the persons with dementia and half of the caregivers were aware of the general risks of adverse events and interactions associated with the use of DS. CONCLUSIONS: Persons with dementia use DS frequently, yet DS use may be associated with direct and indirect risks to patient safety as potentially clinically relevant interactions were discovered and DS intake often was unsupervised.

DOI: 10.1186/s12906-017-1765-5
PMCID: PMC5427606
PMID: 28494750 [Indexed for MEDLINE]

8. Dietary supplement use in the older population of Iceland and association with mortality. Ólafsdóttir B, Gunnarsdóttir I, Nikulásdóttir H, Eiríksdóttir G, Harris TB, Launer LJ, Guðnason V, Halldórsson TI, Einarsdóttir K.

Br J Nutr. 2017 May;117(10):1463-1469. doi: 10.1017/S0007114517001313. Epub 2017 Jun 13.

Dietary supplements are often used by the elderly to improve their nutritional status. However, intake above the recommended dietary levels may be detrimental, and uncertainty exists on the potential health benefits of supplementation in this population. The aim of this study was to describe supplement use among Icelandic older adults and to assess its association with total mortality and CVD-related mortality. This study used data from the Age Gene/Environment Susceptibility-Reykjavik study, which recruited 5764 participants aged 66-98 years in 2002-2006. Intake of vitamins and minerals from dietary supplements was estimated from interviews. Hazard ratios (HR) for mortality were estimated in multivariate analyses with follow-up ending in 2009. The results showed that most (77 %) of the participants used supplements. Overall, the consumption of vitamins and minerals from supplements was moderate although 22 and 14 % of users exceeded the upper recommended intake levels for vitamin B6 and Zn, respectively. Supplement users followed in general a healthier lifestyle than non-users. There were 1221 deaths including 525 CVD-related deaths during the follow-up period. When comparing multivitamin users with non-users in multivariable models, no associations with total mortality (HR 0·91; 95 % CI: 0·77, 1·08) or CVD-related mortality (HR 0·91; 95 % CI 0·70, 1·18) were observed. In conclusion, users of supplements generally lead healthier lifestyles than non-users and supplements did not confer any added advantage or harm relative to mortality risk. However, the intake of vitamin B6 and Zn from dietary supplements exceeded the recommended daily intake for almost a quarter of the supplement users.

DOI: 10.1017/S0007114517001313
PMID: 28606218 [Indexed for MEDLINE]

9. Sources, distribution, bioavailability, toxicity, and risk assessment of heavy metal(loid)s in complementary medicines. Bolan S, Kunhikrishnan A, Seshadri B, Choppala G, Naidu R, Bolan NS, Ok YS, Zhang M, Li CG, Li F, Noller B, Kirkham MB.

Environ Int. 2017 Aug 23;108:103-118. doi: 10.1016/j.envint.2017.08.005. [Epub ahead of print]

The last few decades have seen the rise of alternative medical approaches including the use of herbal supplements, natural products, and traditional medicines, which are collectively known as 'Complementary medicines'. However, there are increasing concerns on the safety and health benefits of these medicines. One of the main hazards with the use of complementary medicines is the presence of heavy metal(loid)s such as arsenic (As), cadmium (Cd), lead (Pb), and mercury (Hg). This review deals with the characteristics of complementary medicines in terms of heavy metal(loid)s sources, distribution, bioavailability, toxicity, and human risk assessment. The heavy metal(loid)s in these medicines are derived from uptake by medicinal plants, cross-contamination during processing, and therapeutic input of metal(loid)s. This paper discusses the distribution of heavy metal(loid)s in these medicines, in terms of their nature, concentration, and speciation. The importance of determining bioavailability towards human health risk assessment was emphasized by the need to estimate daily intake of heavy metal(loid)s in complementary medicines. The review ends with selected case studies of heavy metal(loid) toxicity from complementary medicines with specific reference to As, Cd, Pb, and Hg. The future research opportunities mentioned in the conclusion of review will help researchers to explore new avenues, methodologies, and approaches to the issue of heavy metal(loid)s in complementary medicines, thereby generating new regulations and proposing fresh approach towards safe use of these medicines.

DOI: 10.1016/j.envint.2017.08.005
PMID: 28843139

10. Ayurvedic plumbism. Sadler M, Bell S.

Intern Med J. 2017 Jul;47(7):823-825. doi: 10.1111/imj.13478.

Ayurveda is a traditional medicine native to India but is used in many parts of the world as an alternative or adjunct to standard medicine. Preparation can involve incorporation of heavy metals, including lead. We report the case of a 64-year-old man presenting with malaise, abdominal pain, anaemia and very high lead levels. He was found to be taking ayurvedic medicines to help his diabetic control. Analysis of the ayurvedic medications showed several with very high lead content. Following treatment with an oral chelating agent, the patient's symptoms and blood abnormalities resolved. This case highlights the need to be aware of potentially toxic alternative medications patients take and the efficacy of oral treatment choices in lead poisoning.

DOI: 10.1111/imj.13478
PMID: 28677317

11. Acute Alopecia: Evidence to Thallium Poisoning. Senthilkumaran S, Balamurugan N, Jena NN, Menezes RG, Thirumalaikolundusubramanian P.

Int J Trichology. 2017 Jan-Mar;9(1):30-32. doi: 10.4103/ijt.ijt_82_16.

Thallium is a toxic heavy metal often involved in criminal poisonings and occasionally in accidental poisoning. Here, we report a case of acute, nonintentional thallium poisoning due to thallium-contaminated alternative medicine for its rarity and to create awareness about the combination of rapid, diffuse alopecia with neurologic and gastrointestinal symptoms among practitioners, professionals, public, and policymakers.

DOI: 10.4103/ijt.ijt_82_16
PMCID: PMC5514793
PMID: 28761262

12. Common Herbal Dietary Supplement-Drug Interactions. Asher GN, Corbett AH, Hawke RL.

Am Fam Physician. 2017 Jul 15;96(2):101-107.

Nearly 25% of U.S. adults report concurrently taking a prescription medication with a dietary supplement. Some supplements, such as St. John's wort and goldenseal, are known to cause clinically important drug interactions and should be avoided by most patients receiving any pharmacologic therapy. However, many other supplements are predicted to cause interactions based only on in vitro studies that have not been confirmed or have been refuted in human clinical trials. Some supplements may cause interactions with a few medications but are likely to be safe with other medications (e.g., curcumin, echinacea, garlic, Asian ginseng, green tea extract, kava kava). Some supplements have a low likelihood of drug interactions and, with certain caveats, can safely be taken with most medications (e.g., black cohosh, cranberry, ginkgo, milk thistle, American ginseng, saw palmetto, valerian). Clinicians should consult reliable dietary supplement resources, or clinical pharmacists or pharmacologists, to help assess the safety of specific herbal supplement-drug combinations. Because most patients do not disclose supplement use to clinicians, the most important strategy for detecting herb-drug interactions is to develop a trusting relationship that encourages patients to discuss their dietary supplement use.

PMID: 28762712 [Indexed for MEDLINE]

13. Update on the Pharmacology and Legal Status of Kratom. Prozialeck WC.

J Am Osteopath Assoc. 2016 Dec 1;116(12):802-809. doi: 10.7556/jaoa.2016.156.

Kratom (Mitragyna speciosa) is a plant indigenous to Southeast Asia. Its leaves and the teas brewed from them have long been used by people in that region to stave off fatigue and to manage pain and opioid withdrawal. In a comprehensive review published in 2012, Prozialeck et al presented evidence that kratom had been increasingly used for the self-management of opioid withdrawal and pain in the United States. At the time, kratom was classified as a legal herbal product by the US Drug Enforcement Administration. Recent studies have confirmed that kratom and its chemical constituents do have useful pharmacologic

actions. However, there have also been increasing numbers of reports of adverse effects resulting from use of kratom products. In August 2016, the US Drug Enforcement Administration announced plans to classify kratom and its mitragynine constituents as Schedule 1 controlled substances, a move that triggered a massive response from kratom advocates. The purpose of this report is to highlight the current scientific and legal controversies regarding kratom.

DOI: 10.7556/jaoa.2016.156
PMID: 27893147 [Indexed for MEDLINE]

14. Kidney toxicity related to herbs and dietary supplements: Online table of case reports. Part 3 of 5 series. Brown AC.

Food Chem Toxicol. 2017 Sep;107(Pt A):502-519. doi: 10.1016/j.fct.2016.07.024.

BACKGROUND: No tabular summary of potentially life-threatening, kidney-toxic dietary supplements (DS; includes herbs) based on PubMed case reports is currently available online and continually updated to forewarn United States consumers, clinicians, and companies manufacturing DS. The purpose of this review was to create an online research summary table of kidney toxicity case reports related to DS. METHODS: Documented PubMed case reports (1966 to May 2016, and cross-referencing) of DS appearing to contribute to kidney toxicity were listed in "DS Toxic Tables." Keywords included "herb" or "dietary supplement" combined with "kidney" to generate an overview list, and possibly "toxicity" to narrow the selection. Case reports were excluded if they involved herb combinations (some exceptions), Chinese herb mixtures, teas of mixed herb contents, mushrooms, poisonous plants, self-harm, excessive doses (except vitamins/minerals), legal or illegal drugs, drug-herbal interactions, and confounders of drugs or diseases. Since commercial DS often include a combination of ingredients, they were treated separately; so were foods. A few foods with kidney-toxic effects were listed in a fourth table. The spectrum of herbal or DS-induced kidney injuries included kidney stones, nephritis, nephrotic syndrome, necrosis, acute kidney injury (AKI; previously known as acute renal failure [ARF]), chronic kidney disease, kidney transplant, and death. RESULTS: Approximately 7 herbs (minus 4 no longer for sale) and 10 dietary supplements (minus 3 excluded due to excessive doses + germanium that is no longer sold) have been related to kidney injury case reports published in PubMed (+crosslisting) in the last 50 + years (1966 to May 2016). The implicated herbs include Chinese yew (Taxus celbica) extract, impila (Callilepis laureola), morning cypress (Cupressus funebris Endl), St. John's wort (Hypericum perforatum), thundergod vine (Tripterygium wilfordii hook F), tribulus (Tribulus terrestris) and wormwood (Artemisia herba-alba). No longer sold in the United States are chocolate vine or mu tong (Caulis aristolochiae), guang fang ji (Aristolochia fangchi), ma huang (Ephedra sinica), and Tenshin Tokishigyaku-ka-goshuyu-shokyo-to. The DS include bile (sheep), chlorella, chromium (Cr), CKLS, creatine, gallbladder (fish), glucosamine, hydrazine, N.O.-Xplode, Spanish fly, and excess intakes of vitamins A, C, and D. Germanium (Ge) is not available for sale. The top two DS with the largest number of reported publications, but not always case reports, in descending order, were the aristolochic acid-containing herbs guang fang ji (mistaken identity) and chocolate vine or mu tong. The remaining DS featured one to three publications over a 50+ year period. Numerous case reports were reported for kidney-toxic foods: djenkol bean, gallbladders (carp fish, pufferfish, & snake), and star fruit (only in chronic kidney disease patients), and uncooked yam powder or juice. CONCLUSION: This online "DS Toxic Table" provides clinicians, consumers, and manufacturers with a list of herbs that could potentially contribute to kidney injuries.

DOI: 10.1016/j.fct.2016.07.024
PMID: 28755953

15. Overview of regulation of dietary supplements in the USA and issues of adulteration with phenethylamines (PEAs). Pawar RS, Grundel E.

Drug Test Anal. 2017 Mar;9(3):500-517. doi: 10.1002/dta.1980. Epub 2016 Jun 3.

The multi-billion dollar dietary supplement industry is global in reach. The industry has been criticized for problems related to poor quality control, safety, misbranding, and adulteration. In this review, we describe how the US Food and Drug Administration (FDA) regulates dietary supplements within the framework of the Federal Food, Drug, and Cosmetic Act (FD&C Act). The Dietary Supplement Health and Education Act of 1994 (DSHEA), which amended the FD&C Act, gave the FDA the authority to promulgate Good Manufacturing Practices for dietary supplements and required that manufacturers provide the FDA

information supporting a conclusion that the ingredients are reasonably expected to be safe if the dietary ingredients were not marketed in the USA before 15 October 1994. Recent amendments to the FD&C Act require that serious dietary-supplement-related adverse events be reported to the FDA and provide the agency with mandatory recall authority. We discuss the presence of naturally occurring (e.g. Ephedra, Citrus aurantium, Acacia) and synthetic (e.g. β-methylphenethylamines, methylsynephrine, α-ethyl-phenethylamine) biologically active phenethylamines (PEAs) in dietary supplements and of PEA drugs (e.g. clenbuterol, fenfluramine, sibutramine, lorcaserin) in weight-loss products. Regulatory actions against manufacturers of products labelled as dietary supplements that contain the aliphatic amines 1,3-dimethylamine and 1,3-dimethylbutylamine, and PEAs such as β-methylphenethylamine, aegeline, and Dendrobium illustrate the FDA's use of its authority under the FD&C Act to promote dietary supplement safety. Published 2016. This article is a U.S. Government work and is in the public domain in the USA.

DOI: 10.1002/dta.1980
PMID: 27259162 [Indexed for MEDLINE]

16. Serotonergic medications, herbal supplements, and perioperative serotonin syndrome. Warner ME, Naranjo J, Pollard EM, Weingarten TN, Warner MA, Sprung J.

Can J Anaesth. 2017 Jun 30. doi: 10.1007/s12630-017-0918-9. [Epub ahead of print]

PURPOSE: Perioperative use of serotonergic agents increases the risk of serotonin syndrome. We describe the occurrence of serotonin syndrome after fentanyl use in two patients taking multiple serotonergic agents. CLINICAL FEATURES: Two patients who had been taking multiple serotonergic medications or herbal supplements (one patient taking fluoxetine, turmeric supplement, and acyclovir; the other taking fluoxetine and trazodone) developed serotonin syndrome perioperatively when undergoing outpatient procedures. Both experienced acute loss of consciousness and generalized myoclonus after receiving fentanyl. In one patient, the serotonin syndrome promptly resolved after naloxone administration. In the other patient, the onset of serotonin syndrome was delayed and manifested after discharge, most likely attributed to the intraoperative use of midazolam for sedation. CONCLUSION: Even small doses of fentanyl administered to patients taking multiple serotonergic medications and herbal supplements may trigger serotonin syndrome. Prompt reversal of serotonin toxicity in one patient by naloxone illustrates the likely opioid-mediated pathogenesis of serotonin syndrome in this case. It also highlights that taking serotonergic agents concomitantly can produce the compounding effect that causes serotonin syndrome. The delayed presentation of serotonin syndrome in the patient who received a large dose of midazolam suggests that outpatients taking multiple serotonergic drugs who receive benzodiazepines may require longer postprocedural monitoring.

DOI: 10.1007/s12630-017-0918-9
PMID: 28667541

17. Trends in Use of High-Dose Vitamin D Supplements Exceeding 1000 or 4000 International Units Daily, 1999-2014. Rooney MR, Harnack L, Michos ED, Ogilvie RP, Sempos CT, Lutsey PL.

JAMA. 2017 Jun 20;317(23):2448-2450. doi: 10.1001/jama.2017.4392.

DOI: 10.1001/jama.2017.4392
PMID: 28632857 [Indexed for MEDLINE]

18. Trends in the Diagnosis of Vitamin D Deficiency. Basatemur E, Horsfall L, Marston L, Rait G, Sutcliffe A.

Pediatrics. 2017 Mar;139(3). pii: e20162748. doi: 10.1542/peds.2016-2748. Epub 2017 Feb 3.

BACKGROUND: Vitamin D has attracted considerable interest in recent years, and health care providers have reported large increases in vitamin D test requests. However, rates of diagnosis of vitamin D deficiency in clinical practice have not been investigated. We examined trends in diagnosis of vitamin D deficiency in children in England over time, and by sociodemographic characteristics. METHODS: Cohort study using primary care records of 711 788 children aged 0 to 17 years, from the Health Improvement Network database. Incidence rates for diagnosis of vitamin D deficiency were calculated per year between 2000 and 2014. Rate ratios exploring differences by age, sex, ethnicity, and social deprivation were estimated using

multivariable Poisson regression. RESULTS: The crude rate of vitamin D deficiency diagnosis increased from 3.14 per 100 000 person-years in 2000 (95% confidence interval [CI], 1.31-7.54) to 261 per 100 000 person-years in 2014 (95% CI, 241-281). After accounting for changes in demographic characteristics, a 15-fold (95% CI, 10-21) increase in diagnosis was seen between 2008 and 2014. Older age (≥10 years), nonwhite ethnicity, and social deprivation were independently associated with higher rates of diagnosis. In children aged <5 years, diagnosis rates were higher in boys than girls, whereas in children aged ≥10 they were higher in girls. CONCLUSIONS: There has been a marked increase in diagnosis of vitamin D deficiency in children over the past decade. Future research should explore the drivers for this change in diagnostic behavior and the reasons prompting investigation of vitamin D status in clinical practice.

DOI: 10.1542/peds.2016-2748
PMCID: PMC5337117 [Available on 2017-09-01]
PMID: 28159871 [Indexed for MEDLINE]

19. Costs of vitamin D testing and prescribing among children in primary care. Basatemur E, Hunter R, Horsfall L, Sutcliffe A, Rait G.

Eur J Pediatr. 2017 Aug 12. doi: 10.1007/s00431-017-2986-9. [Epub ahead of print]

Vitamin D has attracted considerable interest in recent years, with a marked increase in diagnosis of vitamin D deficiency seen among children in clinical practice in the UK. The economic implications of this change in diagnostic behaviour have not been explored. We performed a cohort study to examine longitudinal trends in healthcare expenditure arising from vitamin D testing and prescribing for children in primary care in England, using the electronic healthcare records of 722,525 children aged 0-17 years held in The Health Improvement Network database. Combined costs of vitamin D tests and prescriptions increased from £1647 per 100,000 person-years in 2008 (95% CI, £934 to £3007) to £28,913 per 100,000 person-years in 2014 (95% CI, £26,361 to £31,739). The total cost of vitamin D prescriptions and tests for children in primary care at the national level in England in 2014 was estimated to be £4.31 million (95% CI, £2.96-£6.48 million).CONCLUSION: There has been a marked increase in healthcare expenditure on vitamin D tests and prescriptions for children in primary care over the past decade. Future research should explore the drivers for this change in diagnostic behaviour and the reasons prompting investigation of vitamin D status in clinical practice. What is Known: • Vitamin D deficiency has attracted considerable interest in recent years, with a marked increase in diagnosis seen in children. • The economic implications of this change in diagnostic behaviour have not been explored. What is New: • There has been a large increase in healthcare expenditure on vitamin D tests and prescriptions for children in primary care in England over the past decade (> 15 fold between 2008 and 2013). • Screening of vitamin D status in children without specific risk factors or clinical features of deficiency may represent avoidable healthcare expenditure.

DOI: 10.1007/s00431-017-2986-9
PMID: 28803270

20. A rare case of iron-pill induced gastritis in a female teenager: A case report and a review of the literature. Meliţ LE, Mărginean CO, Mocanu S, Mărginean MO.

Medicine (Baltimore). 2017 Jul;96(30):e7550. doi: 10.1097/MD.0000000000007550.

RATIONALE: The treatment of iron-deficiency anemia with oral iron supplements can present side-effects on the GI tract mucosa including necrosis, ulceration, or ischemia. The particular endoscopic findings and the histopathological exam will establish the diagnosis of erosive gastritis with iron deposits in the gastric mucosa. PATIENT CONCERNS: We present the case of a 14-year-old female admitted in our clinic for upper digestive hemorrhage, nausea, melena, and abdominal pain. Her personal history revealed iron deficiency anemia receiving oral iron supplements for approximately 2 weeks. DIAGNOSIS: The laboratory tests at the moment of admission pointed out anemia, increased level of serum iron, increased liver transaminases, a decreased level of ferritin, but with normal levels of both total iron-binding capacity and transferrin. INTERVENTIONS: The eso-gastro-duodenoscopy revealed multiple brown deposits on the surface of the gastric mucosa and multiple hemorrhagic lesions, under the aspect of erosions all over the gastric mucosa, but more severe in the antral part, and the histopathological exam confirmed the presence of iron deposits at this level. CONCLUSION: Iron-pill induced gastritis is a rare, under-diagnosed entity that can be present even at pediatric ages with potential severe clinical impact.

DOI: 10.1097/MD.0000000000007550
PMID: 28746201 [Indexed for MEDLINE]

21. Facial eschar following a single application of black salve. Laskey D, Tran M.

Clin Toxicol (Phila). 2017 Aug;55(7):676-677. doi: 10.1080/15563650.2017.1312428. Epub 2017 Apr 20.

A previously healthy 86-year-old male was transported by ambulance to the trauma bay of the emergency department (ED) for profuse bleeding from the left temple. The ambulance crew raised concern that the volume and force of the bleed may suggest arterial involvement. The patient reported having applied a natural topical remedy to a mole two weeks prior at the recommendation of a naturopath. The patient described progressive blackening and swelling of the area in the days following the single application of the product. After gaining control of the bleeding in the ED, the area was found to have a raised, 2 cm eschar.

DOI: 10.1080/15563650.2017.1312428
PMID: 28426257 [Indexed for MEDLINE]

22. Adverse event due to a likely interaction between sodium aescinate and ginkgo biloba extract: a case report. Ji H, Zhang G, Yue F, Zhou X.

J Clin Pharm Ther. 2017 Apr;42(2):237-238. doi: 10.1111/jcpt.12500. Epub 2017 Feb 1.

WHAT IS KNOWN AND OBJECTIVE: Drug-induced nephrotoxicity is potentially lethal. When sodium aescinate is given to surgical inpatients to treat postoperative inflammation and oedema, adverse drug reactions and drug-drug interactions must be closely monitored. CASE DESCRIPTION: We report a case of a 58-year-old man with phalangeal fractures who suffered from acute kidney injury that was most likely induced by the drug interaction between sodium aescinate and ginkgo biloba extract due to the protein-binding and metabolic characteristics of these drugs. WHAT IS NEW AND CONCLUSION: Close monitoring and the prompt discontinuation of drugs that have high protein-binding capacity and hepatic metabolism are necessary to avoid drug-drug interactions in patients who are treated with sodium aescinate.

DOI: 10.1111/jcpt.12500
PMID: 28144968 [Indexed for MEDLINE]

23. The Effect of Prolonged Glucosamine Usage on HbA1c Levels and New-Onset Diabetes Mellitus in Overweight and Obese Middle-Aged Women. Gommans YMM, Runhaar J, Jacobs ML, Bierma-Zeinstra SMA.

Am J Med. 2017 Jun;130(6):731-737.e6. doi: 10.1016/j.amjmed.2016.11.038. Epub 2016 Dec 21.

OBJECTIVE: The aim of the present study was to evaluate the effect of a 2.5-year glucosamine sulfate intervention on hemoglobin A1c (HbA1c) levels and the incidence of new-onset diabetes mellitus over 6.5 years in middle-aged women with a body mass index ≥27 kg/m(2). METHODS: In total, 407 women were randomized into either oral crystalline glucosamine sulfate or placebo. At baseline, 1 year, 2.5 years, and 6.5 years, a blood sample for the HbA1c level was drawn and questionnaires were taken. After 6.5 years there were missing data for some variables, therefore, multiple imputation was used. With the imputed data, a generalized estimating equation was performed to analyze the effect of glucosamine sulfate usage over 6.5 years. Finally, these analyses were rerun for the 2 subgroups of participants with and without high HbA1c level (≥42 mmol/mol) at baseline. RESULTS: There was no significant effect of a 2.5-year glucosamine sulfate intervention on mean HbA1c level or on obtaining a high HbA1c level or new-onset diabetes mellitus over 6.5 years. The subgroup analyses of participants with and without high HbA1c level at baseline were also not statistically significant. However, participants with a high HbA1c level at baseline had higher odds ratios compared with the participants with a normal HbA1c at baseline. CONCLUSIONS: There was no effect of glucosamine sulfate on mean HbA1c level nor on obtaining a high HbA1c level or new-onset diabetes mellitus over 6.5 years, especially in participants with a normal HbA1c level at baseline.

DOI: 10.1016/j.amjmed.2016.11.038
PMID: 28011309 [Indexed for MEDLINE]

24. A Case Report of Fatal Desmethyl Carbodenafil Toxicity. Bakota EL, Kelly AT, Walterscheid JP, Phatak DR.

J Anal Toxicol. 2017 Apr 1;41(3):250-255. doi: 10.1093/jat/bkw128.

We present the case report of a 34-year-old Hispanic male who was found unresponsive in the carport of his residence. Surveillance video footage from a security camera showed that he collapsed as he was walking to his vehicle. The decedent had no medical history and no history of illicit drug use. Initial toxicology testing revealed no alcohol or illicit drugs. Autopsy findings indicated a need for additional toxicological analysis due to a lack of trauma and the paucity of pathophysiologically significant natural disease. Liquid chromatography time-of-flight mass spectrometry of postmortem blood revealed the presence of two large peaks corresponding to desmethyl carbodenafil, an unapproved sildenafil analogue and its hydroxy metabolite. Species that are probable desmethyl and hydroxydesmethyl metabolites of desmethyl carbodenafil were also found. The mass and retention time of the parent compound in the decedent's sample were matched to those of a commercial standard. Based on this preliminary match, a method was developed and validated to quantify desmethyl carbodenafil in human blood. This is the first known case of fatal intoxication by desmethyl carbodenafil, a phosphodiesterase-5 inhibitor that is not approved for use in the United States. Over the past several years, retailers have issued voluntary recalls for dietary supplements marketed as sexual performance enhancers on the basis that these supplements may contain undeclared desmethyl carbodenafil.

DOI: 10.1093/jat/bkw128
PMID: 27999095 [Indexed for MEDLINE]