



The American Academy of Clinical Toxicology

Uniting scientists and clinicians in the advancement of research, education, prevention and treatment of diseases caused by chemicals, drugs and other toxins.

American Academy of Clinical Toxicology Herbs & Dietary Supplements Special Interest Group Abstracting Service

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1. Liao WI, Lin YY, Chu SJ, Hsu CW, Tsai SH. Bradyarrhythmia caused by ginseng in a patient with chronic kidney disease. *Am J Emerg Med.* 2010;28(4):538 e5-6.
2. Hill GE, Ogunnaike B, Nasir D. Patients presenting with acute toxin ingestion. *Anesthesiol Clin.* 2010;28(1):117-37.
Organ toxicity caused by poisons or drug therapy is diverse and may not be commonly encountered clinically. In general, commonly encountered conditions caused by drug/toxin pharmacology can be classified into 7 categories by shared mechanisms of organ injury. This review of drug/toxin-induced injury discusses drug or toxin-induced pathology that the clinician may encounter and therapeutic approaches to these syndromes.
3. Bilgi N, Bell K, Ananthakrishnan AN, Atallah E. Imatinib and Panax ginseng: a potential interaction resulting in liver toxicity. *Ann Pharmacother.* 2010;44(5):926-8.
OBJECTIVE: To report a case of imatinib-induced hepatotoxicity after concurrent ginseng ingestion in a patient with chronic myelogenous leukemia (CML). CASE SUMMARY: A 26-year-old man with CML who had taken imatinib 400 mg daily for 7 years with no complications presented with right upper quadrant pain. Laboratory test results included alanine aminotransferase 1069 U/L, aspartate aminotransferase 481 U/L, alkaline phosphatase 124 IU/L, total bilirubin 1.4 mg/dL, albumin 4.0 g/dL, and international normalized ratio 1.08. Liver biopsy showed acute lobular hepatitis favoring a drug-induced etiology, and a diagnosis of imatinib-induced hepatotoxicity was made. The patient's only lifestyle modification prior to the diagnosis of

hepatotoxicity was daily ingestion of Panax ginseng via energy drinks for the past 3 months. Both imatinib and ginseng were discontinued, and the patient was treated with a short course of corticosteroids. Imatinib was later restarted at the same dose with no recurrent elevations in his liver enzyme levels. DISCUSSION: Imatinib-associated hepatotoxicity usually presents within 1-2 years of therapy initiation, with the median time to hepatotoxicity being 100 days. Ginseng is an herb that is not known to be hepatotoxic. In vivo, ginseng is known to inhibit CYP3A4, the primary enzyme involved in the metabolism of imatinib. We propose that our patient's late-onset imatinib-associated hepatotoxicity was due to an interaction between ginseng and imatinib through CYP3A4. Based on the Naranjo probability scale, it is probable that imatinib caused this patient's hepatotoxicity, and the Horn drug interaction probability scale also indicates a probable interaction between imatinib and ginseng. CONCLUSIONS: This case emphasizes the importance of continuous monitoring of liver function tests even after several years of imatinib therapy and the importance of advising patients to avoid ginseng and any other over-the-counter herbal supplements that may interact with imatinib.

4. Golka K, Hengstler JG, Marchan R, Bolt HM. Severe arsenic poisoning: one of the largest man-made catastrophies. *Arch Toxicol*. 2010.
5. Ehrman TM, Barlow DJ, Hylands PJ. In silico search for multi-target anti-inflammatories in Chinese herbs and formulas. *Bioorg Med Chem*. 2010;18(6):2204-18.
Chinese herbs were screened for compounds which may be active against four targets involved in inflammation, using pharmacophore-assisted docking. Multiple LigandScout (LS) pharmacophores built from ligand-receptor complexes in the protein databank (PDB) were first employed to select compounds. These compounds were then docked using LS-derived templates and ranked according to docking score. The targets comprised cyclo-oxygenases 1 & 2 (COX), p38 MAP kinase (p38), c-Jun terminal-NH(2) kinase (JNK) and type 4 cAMP-specific phosphodiesterase (PDE4). The results revealed that multi-target inhibitors are likely to be relatively common in Chinese herbs. Details of their distribution are given, in addition to experimental evidence supporting these results. Examples of compounds predicted to be active against at least three targets are presented, and their features outlined. The distribution of herbs containing predicted inhibitors was also analysed in relation to 192 Chinese formulas from over 50 herbal categories. Among those found to contain a high proportion of these herbs were formulas traditionally used to treat fever, headache,

rheumatoid arthritis, inflammatory bowel disorders, skin disease, cancer, and traumatic injury. Relationships between multi-target drug discovery and Chinese medicine are discussed.

6. Caubet-Kamar N, Tubery M, Garrouste C, Lauque D, Kamar N. Harmful effect of saline infusion in a patient with glycyrrhizic acid poisoning. *CJEM*. 2010;12(3):224-5.
Alcohol-free licorice beverages contain glycyrrhizic acid. Excess glycyrrhizic acid is a well-known cause of excess mineralocorticoid syndrome. We report a case of glycyrrhizic acid poisoning in an abstinent alcoholic complicated by severe pulmonary edema following excessive hydration with intravenous normal saline.
7. Anderson B, Ke X, Klein-Schwartz W. Potential for erroneous interpretation of poisoning outcomes due to changes in National Poison Data System reporting. *Clin Toxicol (Phila)*. 2010.
Background/Objective. In 2006, the annual report of poison centers in the United States changed the method of reporting profiles for generic substance categories from all exposures to single-substance exposures only. The objective of this study is to describe the potential impact of this reporting change on longitudinal analysis of outcomes. Methods. Generic substance categories with data available for all years of the study were manually extracted from Table 22 of the National Poison Data System (NPDS) annual reports for 2002-2007. For each generic substance category, the following data were extracted for each of the 6 years: total number of substance mentions (2002-2005) or single-substance exposures (2006-2007), reason (unintentional or intentional), pediatric exposures (children age <6 years), and outcomes of major effect and death. Data were compared using descriptive analysis (Wilcoxon signed-rank test) and negative binomial regression. Results. There were 65 generic substance categories (30 drug categories and 35 nondrug categories) that had data in all study years. For drug categories the average annual number of reported deaths by substance category decreased by 80.8%, from 2,229 in year 2002-2005 to 428 after the 2006 reporting change ($p < 0.0001$). The average annual number of reported major outcomes by substance category dropped by 76.0% ($p < 0.0001$). The impact on nondrug categories was similar: the annual average number of deaths and major effects by substance category decreased by about 50% from 394 and 4,639 per year during 2002-2005 to 198 deaths ($p < 0.0001$) and 2,357 major effects ($p \leq 0.0001$) during 2006-2007. After controlling for potential covariates, multivariate regression showed that there were significant decreases in average rates of reported

deaths (61.7 and 35.9%) and major effects (36.3 and 11.2%) for drug categories and nondrug categories, respectively ($p < 0.01$ for all). Conclusions. Overall rates of major outcomes and deaths reported to poison control centers from 2002 to 2007 have remained constant. The new method of describing demographic data in Table 22 results in outcomes that are different from those reported in previous NPDS annual reports. Comparing NPDS generic substance outcome data before and after the reporting change in 2006 will yield inaccurate results if the change in reporting methodology is not taken into account.

8. Chinnakaruppan NR, Marcus SM. Asymptomatic congenital lead poisoning - case report. *Clin Toxicol (Phila)*. 2010.
Context. Congenital lead poisoning is uncommon and there is no consensus on the management of the newborn. Case Details. A female infant was born to a lead-burdened woman identified by screening just prior to delivery. Maternal blood lead level (BLL) was 58 mug/dL. The infant's BLL on the second day of life was 72 mug/dL with a free erythrocyte protoporphyrin level of 175 mug/dL. The child was managed by an exchange transfusion followed by chelation. The BLL 6 h after exchange transfusion was 11.4 mug/dL. Follow-up 2 years later showed a BLL of 9 mug/dL and normal development. Discussion. We present the details of a case of congenital lead poisoning treated aggressively which appears to have resulted in a favorable outcome.
9. Krenzelok EP. Datura poisoning and the use of physostigmine. *Clin Toxicol (Phila)*. 2010.
10. Nader R, Mathieu-Daude JC, Deveaux M, Faure K, Hayek-Lanthois M, de Haro L. Child cyanide poisoning after ingestion of bitter almonds. *Clin Toxicol (Phila)*. 2010.
11. Panzeri C, Bacis G, Ferri F, Rinaldi G, Persico A, Uberti F, et al. Extracorporeal life support in a severe *Taxus baccata* poisoning. *Clin Toxicol (Phila)*. 2010;48(5):463-5.
INTRODUCTION: Yew (*Taxus baccata*) is a conifer known to be toxic since ancient times. Taxine A and taxine B, the toxic alkaloids of *Taxus*, block cardiac sodium and calcium channels causing nausea, vomiting, abdominal pain, cardiac arrhythmias, respiratory distress, coma, seizures, and death in yew poisoning. CASE REPORT: A 44-year-old male farmer was admitted to the hospital because of a suspected myocardial infarction. First bradycardia and then ventricular tachycardia were present and a severe right ventricular dilatation with

biventricular dysfunction was observed but with normal coronary arteriography. He was resistant to conventional therapy and, 6 h after hospital admission, extracorporeal support with membrane oxygenation was applied. The patient recovered. Nine days later, a large number of yew leaves were unexpectedly observed in his feces. Botanical and laboratory analysis confirmed the poisoning. Blood (651 ng/mL) and urinary (5.6 mcg/mL) levels of 3,5-dimethoxyphenol (metabolite of taxicatine) were greater than previously reported in lethal cases. The patient was transferred to a psychiatric unit 17 days after admission. CONCLUSIONS: Intensive treatment of severe cardiovascular symptoms with antiarrhythmic drugs, temporary pacemaker, intra-aortic balloon pump, extracorporeal membrane oxygenation, and extracorporeal life support can be life-saving even after a potentially lethal ingestion of *T. baccata* leaves.

12. Zhuo Q, Yuan Z, Chen H, Wu T. Traditional Chinese herbal products for stable angina. *Cochrane Database Syst Rev.* 2010;5:CD004468. BACKGROUND: Stable angina pectoris is a common condition, worldwide. Traditional Chinese herbal products (TCHP) are developed for treating stable angina pectoris in China. OBJECTIVES: To assess the effectiveness and safety of TCHP in patients with stable angina. SEARCH STRATEGY: We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library Issue 4, 2006), MEDLINE (1995 to June 2008), EMBASE (1995 to June 2008), the Chinese Biomedical Database (CBM) (1995 to June 2008), Chinese Science and Technique Journals Database (VIP) (1994 to June 2008) and Chinese National Knowledge Infrastructure (CNKI) (1995 to June 2008). We handsearched the relevant Chinese journals. We also contacted researchers in the field and authors of studies evaluated in this review for more information. No language restrictions were applied. SELECTION CRITERIA: Randomised controlled trials comparing TCHP with placebo, various other TCHP preparations, or with other regimes commonly used currently in the treatment of stable angina. DATA COLLECTION AND ANALYSIS: Quality of studies was assessed independently by two authors. Data were extracted by one author and checked by the other one. MAIN RESULTS: Three studies each with the number of participants ranging from 60 to 80, and a total of 216 participants, were included in this review. The interventions used in the included studies were different from one another. One study compared TCHP with nitrates and was of good methodological quality whereas the remaining two trials compared one preparation with another preparation and one was of poor methodological quality. As such, we were unable to perform a summary meta-analysis. Only one trial with

small patient numbers showed positive results favouring TCHP treatment compared with nitrates, in improved angina symptoms. Two of the trials stated that adverse reactions occurred but detailed data could not be obtained. AUTHORS' CONCLUSIONS: There is currently insufficient evidence for effectively treating stable angina pectoris with any of the examined TCHP in this review, due to the small number of included studies and participants. Therefore, TCHP should be used with caution. High quality randomised trials with similar interventions are required to strengthen the evidence for the effectiveness and safety of Chinese medicinal herbs in angina pectoris.

13. Lopez-Moreno JA, Lopez-Jimenez A, Gorriti MA, de Fonseca FR. Functional interactions between endogenous cannabinoid and opioid systems: focus on alcohol, genetics and drug-addicted behaviors. *Curr Drug Targets*. 2010;11(4):406-28.
Although the first studies regarding the endogenous opioid system and addiction were published during the 1940s, addiction and cannabinoids were not addressed until the 1970s. Currently, the number of opioid addiction studies indexed in PubMed-Medline is 16 times greater than the number of cannabinoid addiction reports. More recently, functional interactions have been demonstrated between the endogenous cannabinoid and opioid systems. For example, the cannabinoid brain receptor type 1 (CB1) and mu opioid receptor type 1 (MOR1) co-localize in the same presynaptic nerve terminals and signal through a common receptor-mediated G-protein pathway. Here, we review a great variety of behavioral models of drug addiction and alcohol-related behaviors. We also include data providing clear evidence that activation of the cannabinoid and opioid endogenous systems via WIN 55,512-2 (0.4-10 mg/kg) and morphine (1.0-10 mg/kg), respectively, produces similar levels of relapse to alcohol in operant alcohol self-administration tasks. Finally, we discuss genetic studies that reveal significant associations between polymorphisms in MOR1 and CB1 receptors and drug addiction. For example, the SNP A118G, which changes the amino acid aspartate to asparagine in the MOR1 gene, is highly associated with altered opioid system function. The presence of a microsatellite polymorphism of an (AAT)_n triplet near the CB1 gene is associated with drug addiction phenotypes. But, studies exploring haplotypes with regard to both systems, however, are lacking.
14. Parolaro D, Rubino T, Vigano D, Massi P, Guidali C, Realini N. Cellular mechanisms underlying the interaction between cannabinoid and opioid system. *Curr Drug Targets*. 2010;11(4):393-405.
Recently, the presence of functional interaction between the opioid and

cannabinoid system has been shown in various pharmacological responses. Although there is an increasing interest for the feasible therapeutic application of a co-administration of cannabinoids and opioids in some disorders (i.e. to manage pain, to modulate immune system and emotions) and the combined use of the two drugs by drug abusers is becoming largely diffuse, only few papers focused on cellular and molecular mechanisms underlying this interaction. This review updates the biochemical and molecular underpinnings of opioid and cannabinoid interaction, both within the central nervous system and periphery. The most convincing theory for the explanation of this reciprocal interaction involves (i) the release of opioid peptides by cannabinoids or endocannabinoids by opioids, (ii) the existence of a direct receptor-receptor interaction when the receptors are co-expressed in the same cells, and (iii) the interaction of their intracellular pathways. Finally, the cannabinoid/opioid interaction might be different in the brain rewarding networks and in those accounting for other pharmacological effects (antinociception, modulation of emotionality and cognitive behavior), as well as between the central nervous system and periphery. Further insights about the cannabinoid/opioid interaction could pave the way for new and promising therapeutic approaches.

15. Robledo P. Cannabinoids, opioids and MDMA: neuropsychological interactions related to addiction. *Curr Drug Targets*. 2010;11(4):429-39.

3,4-methylenedioxymethamphetamine (MDMA, "ecstasy") is an amphetamine derivative with psychostimulant properties. This substance is widely used around the world by young adults in recreational settings. One of the most remarkable characteristic of ecstasy users is the concurrent consumption of several other drugs of abuse including psychostimulants, alcohol, tobacco, LSD, cannabis and opioids. This poly-drug pattern of use is now prompting research towards understanding how the combination of MDMA with cannabis and opioids could affect neuropsychobiological processes related to addiction. As with other drugs of abuse, behavioural evidence has been presented supporting the role of the endocannabinoid system as a modulator of the rewarding/reinforcing properties of MDMA. On the other hand, the neurochemical substrate for the complex interactions between the endocannabinoid system and MDMA is poorly understood. MDMA also modulates the activity of the dynorphinergic and enkephalinergic systems in several brain structures related to addiction, as it has been shown for other psychostimulants. The work regarding the contribution of micro- and delta-opioid receptors in the

rewarding effects of MDMA shows differential results in pharmacological studies in rats, with respect to studies using knock-out mice. The present review describes the behavioural and neurochemical interactions between MDMA, cannabinoids and opioids with respect to addiction processes.

16. Bambico FR, Nguyen NT, Katz N, Gobbi G. Chronic exposure to cannabinoids during adolescence but not during adulthood impairs emotional behaviour and monoaminergic neurotransmission. *Neurobiol Dis.* 2010;37(3):641-55.
The pathophysiological neural mechanism underlying the depressogenic and anxiogenic effects of chronic adolescent cannabinoid use may be linked to perturbations in monoaminergic neurotransmission. We tested this hypothesis by administering the CB(1) receptor agonist WIN55,212-2, once daily for 20 days to adolescent and adult rats, subsequently subjecting them to tests for emotional reactivity paralleled by the in vivo extracellular recordings of serotonergic and noradrenergic neurons. Chronic adolescent exposure but not adult exposure to low (0.2 mg/kg) and high (1.0 mg/kg) doses led to depression-like behaviour in the forced swim and sucrose preference test, while the high dose also induced anxiety-like consequences in the novelty-suppressed feeding test. Electrophysiological recordings revealed both doses to have attenuated serotonergic activity, while the high dose also led to a hyperactivity of noradrenergic neurons only after adolescent exposure. These suggest that long-term exposure to cannabinoids during adolescence induces anxiety-like and depression-like behaviours in adulthood and that this may be instigated by serotonergic hypoactivity and noradrenergic hyperactivity.
17. Li XZ, Ramzan I. Role of ethanol in kava hepatotoxicity. *Phytother Res.* 2010;24(4):475-80.
Kava is known for its recreational, ceremonial and medicinal use in the Pacific. The aqueous non-alcoholic drink of kava rhizome produces intoxicating, relaxing and soothing effects. While kava's medicinal effects receive worldwide recognition, kava-containing products came under scrutiny after over 100 reports of spontaneous adverse hepatic effects. Many mechanisms have been postulated to explain the unexpected toxicity, one being pharmacokinetic interactions between kavalactones and co-administered drugs involving cytochrome P450 enzyme system. Alcohol is often co-injected in kava hepatotoxicity cases. This review evaluates the possible hepatotoxicity mechanisms involving alcohol and kava.

