Drugs, OTCs, Herbals and Hepatotoxicity

Drug-induced toxicity is the leading cause of acute liver failure and acute hepatitis in the United States. Prescription drugs such as amoxicillin-clavulanic acid, troglitazone, antiretrovirals, angiotensin receptor blockers (ARBs), angiotensin-converting enzyme inhibitors (ACE-I), anti-diabetic agents (acarbose, gliclazide, metfomin, and insulin), anticonvulsants, antiepileptics, and other psychotropics (e.g. selective-serotonin reuptake inhibitors [SSRIs]) have all been implicated in liver damage. Most prescription anti-inflammatory drugs (COX-2 inhibitors) have been completely pulled off the market, and even the most common over-the-counter (OTC) drugs – non-steroidal, anti-inflammatory drugs (NSAIDs) – are being linked with increasing prevalence to hepatotoxicity. The effects of overusing aspirin, ibuprofen, naproxen, etc… are increasingly being linked with organ distress. Even renal (kidney) damage is being linked to toxic levels of NSAID use. Some scientists speculate that this is one of the underlying factors related to kidney and liver problems in professional athletes. This subset of the population is notorious for abusing NSAIDs due to the daily strains of athletic performance. According to the National Kidney Foundation 10% of kidney failures are associated with substantial overuse of NSAIDS. Professional athletes including Alonzo Morning, Sean Elliot, and Kenny Ezeasley all attribute their kidney problems to NSAID abuse.

In an effort to shy away from the negative effects of prescription drugs and OTC drugs, many individuals have turned to herbal supplements and other "natural" remedies for ailments and disease prevention. For example, the Women's Health Initiative indicated that estrogen and progesterone hormone replacement increased the risk of cardiovascular events. In response, a plethora of post-menopausal women have looked for alternative treatment for symptoms. Black cohosh for example, is one common herb used to treat the symptoms specific to post-menopause and has been linked to several case reports associated with hepatitis and culminant hepatic failure. Lynch et al. reported a case study of one woman who required a liver transplant following acute hepatic failure that was directly attributed to her use of the herbal supplement.

Most individuals are uninformed to the fact that the herbal and supplement industry is unregulated, and many who understand that it is unregulated do not comprehend what this means. Even though dietary and herbal supplements are governed under the DSHEA act of 1994, they are not regulated by the Food and Drug Administration (FDA) and their safety profiles are not documented. These products are not standardized with regard to their contents, checked for purity or content, and unlike OTC medications are not required to be proven safe before being sold. Consistent reports suggest that there is a very large variability of ingredients from one bottle to another, and this is even true of the same product from the same company. This

especially occurs with crude herbals that are commonly formulated as a mixture or "proprietary blend" resulting in an ambiguous list of ingredients and even potentially harmful contaminants. The surge in the sale and usage of herbal remedies has been catalyzed by the notion that all herbal products are safe and effective; the fact that consumers are more prone to self-treatment; and the high availability of these products due to a lack of regulation. As a result, reports of hepatotoxicity due to herbal use are on the rise.

Pittler et al. of the Peninsula Medical School in the U.K. reported in 2005 that ephedra (and all ephedrine containing supplements), Paullinia cupana, guar gum, Plantago psyllium, Ilex paraguariensis, and Pausinystalia yohimbe have been associated with adverse events including hepatic injury and death. Ephedra was also linked to psychiatric, autonomic and gastrointestinal events, and cardiac palpitations. They concluded that "although [they] couldn't justify definitive attribution of causality in most cases…the reported risks are sufficient to shift the risk-benefit balance against the use of most of the reviewed herbal weight loss supplements." Ephedra alkaloids were banned in 2004 but are once again available in the free market. Although ephedra is listed as a hepatotoxic agent, the mix with caffeine and aspirin make it even more risky for some individuals. Herbal items banned in the United States are available for purchase online; this includes illegal steroids and hormone precursors.

Due to the fact that an estimated 30% of adults are obese and 65% are overweight, $55.4 billion was spent in the U.S. for weight-loss and diet control last year alone. In another study conducted by Pittler's group the effectiveness of several OTC weight-loss supplements were reviewed in an attempt to determine if the risk of hepatic, cardiac, and other events is justifiable for weight-loss. The results were negative for the supplement business. They concluded that "the evidence for [these] dietary supplements as weight reducers is not convincing." Authors suggested that none of the reviewed dietary supplements can be recommended for OTC use due to questions of efficacy and/or safety. The herbals studied here were chitosan, chromium picolinate, ephedra sinica, garcinia cambogia, glucomannan, guar gum, hydroxymethyl-butyrate, plantago psyllium, pyruvate, yerba mate, and yohimbe.

Another scientific review by Dara et al. of the Department of Medicine, Griffin Hospital in conjunction with Yale University School of Medicine, elucidated the dangers of the common weight-loss supplements. Several components to weight loss supplements have been linked to hepatotoxicity yet the underlying mechanisms were poorly understood. For example, the specific components of weight loss supplements implicated in liver toxicity include G. Cambogia, Chromium, and the green tea root extract Camellia Sinensis.

G. Cambogia is a fruit native to southeastern Asia and western Africa. Its main component is hydroxycitric acid (HCA) – an inhibitor of the citrate cleavage enzyme which results in a blockage of component-synthesis of fatty acids. This results in a suppression of appetite. A recent case of fatal liver failure was attributed

to a patient's use of HCA and montelukast. Montelucast is a leukotriene receptor antagonist (LTRA) used for asthma and to relieve symptoms of seasonal allergies, suggesting a synergistic hepatotoxic effect of these two agents.

Chromium is an essential trace element required as a cofactor for insulin. Due to its carcinogenic properties when inhaled, this element has been heavily studied and the National Academy of Sciences (NAS) established an "estimated safe and adequate daily dietary intake" range of between 50-200 mg for the metal. It is used as a weight loss supplement due to purported effects of decreasing body fat and increasing basal metabolic rate (BMR). Clinical trials have not supported these claims. There are reported cases of hepatotoxicity, thrombocytopenia, and renal failure due to environmental and supplemental consumption of chromium. For reference, one serving of Hydroxycut contains 133mg of the metal, which is supposed to be taken 3 times daily resulting in a daily intake of more than twice the NAS safe maximum dose.

Finally, C. Sinensis is the botanical name for green tea. Producers advertise its anti-cancer effects, its potential for weight reduction, and its antioxidant properties. There are 17 published cases of C. Sinensis in the literature that describe acute hepatotoxicity due to herbal use. Physiological insult was mainly attributed to large ingestion of green tea. For this reason, the herb has been banned in France and Spain.

The list of unregulated herbs with an increasing number of cases describing adverse events is growing. Mau Huang and yohimbine are potentially toxic. Hoodia Gordini has also been implicated in liver toxicity and Zalestrim represent another potentially toxic herbal mix containing cohosh and green tea extract. An estimated 80% of the world population uses herbal medicines. Although this is largely outside of the U.S., American use is on the rise and with it, reports of complications associated with their usage. Most of these products have not been rigorously studied through placebo-controlled, blinded, randomized trials. Although policy shifts resulting in regulation by the FDA may solve some of the inherent problems of the industry, public awareness of these dangers and educating healthcare professionals is at the forefront of possible solutions. The use of supplements is often not queried by physicians and other healthcare providers. Most consumers take supplements with complete ignorance to the compounds they contain or the efficacy or more commonly lack of efficacy demonstrated in clinical trials. Education is the best remedy currently available to combat the negative effects of over-consuming hazardous herbs.