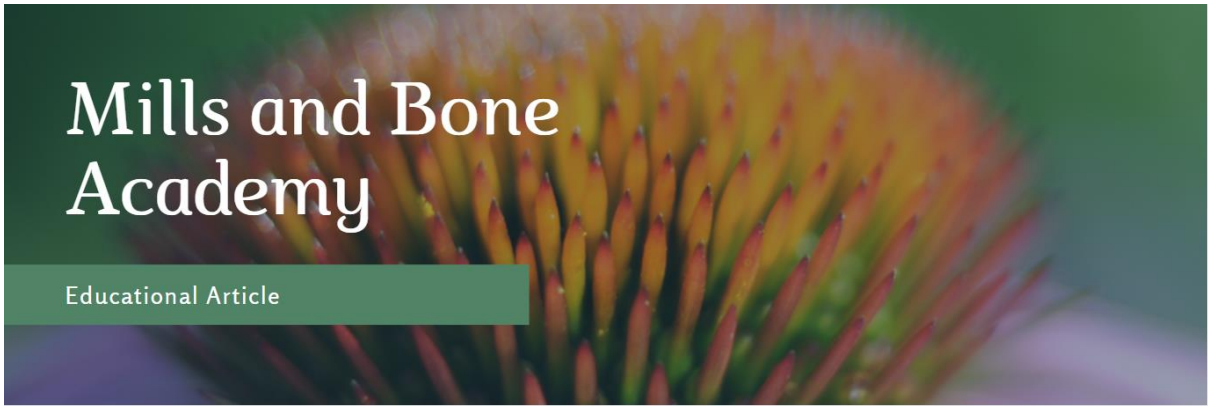

Black Cohosh: An Innocent Bystander – Kerry Bone

With all the valid negative publicity about the dangers of hormone replacement therapy (HRT), many women are seeking alternative solutions. One herb that is well proven in that regard and which has been featured in the media is black cohosh (*Actea* or *Cimicifuga racemosa*). Several clinical trials have demonstrated its benefit for the problems associated with menopause, including hot flushes. In fact, it is the best-proven and most used alternative to HRT. So we might begin to regard as suspicious that a black cloud is looming over the safety of this popular herb. This cloud on the horizon is the few reports of liver damage that have been linked to its use.

Where did this all begin? Well I hate to say it but it began with reports from Australia in 2002. By early 2006 there were around 50 adverse reaction reports on various health authority databases and several published case histories. In something like the "Domino Effect", the Australian authorities then decided that black cohosh products must carry a label warning about the potential for liver damage, and this was shortly followed by the UK and Canadian authorities.

How strong is this connection with liver damage? As mentioned earlier, in addition to the 5 published reports of 8 cases there are around 40 case reports of l

iver reactions to black cohosh which have been recorded by various government health authorities around the world. The European Medicines Agency Committee on Herbal Medicinal Products (HMPC) recently analysed all these cases. Based on their evaluations the HMPC concluded the following: [i]

"The HMPC evaluated 42 case reports of hepatotoxicity, collected from European National Competent Authorities (34 cases) as well as literature case reports (8 cases). Of these, only 16 cases were considered

sufficiently documented to allow the Committee to assess if use of Cimicifugae racemosae rhizoma (Black Cohosh, root) could be linked to the liver injuries. As a result of the assessment, 5 cases were excluded and 7 cases were considered unlikely to be related. In the remaining 4 cases (2 autoimmune hepatitis, 1 hepatocellular liver injury and 1 fulminant hepatic failure), there was a temporal association".

Of these four cases, only two were rated as "probable" by this expert committee using a recognised procedure for rating cause and effect. Not surprisingly these were two of the published cases.

So what were these two "probable" cases? They were both from the US. The first report describes the development of autoimmune hepatitis which the authors claim was triggered by the use of black cohosh (Case 1).[ii] A 57-year-old diabetic woman presented with a 2-week history of lethargy and fatigue. Her medications (all of which had been used for more than 2 years) included labetalol, fosinopril, verapamil, metformin, aspirin and insulin. Three weeks before presentation, the patient began taking black cohosh tablets (unknown brand or dose) for hot flushes. Drug-induced autoimmune hepatitis, attributed to the black cohosh, was diagnosed. Tests for hepatitis A, B and C were negative. The black cohosh was discontinued, and a tapering steroid course was instituted. Complete resolution of symptoms occurred within 2 weeks, and resolution of the abnormal liver function tests (LFTs) occurred within 9 weeks. Follow-up liver chemistries remained normal 2 months after steroids were discontinued. However, at 4 months the woman returned with a complaint of jaundice and fatigue and her LFTs were abnormal again. The patient experienced rapid improvement on a second course of steroids and long-term azathioprine was begun. The authors claimed that none of the patient's other medications have ever been implicated as triggers for autoimmune hepatitis, but provided no information as to whether these drugs were maintained or withdrawn from the patient. Rechallenge with black cohosh was not undertaken.

The next case report (Case 2) was that of a 50-year-old woman suffering from acute onset jaundice.[iii] The provisional diagnosis was autoimmune hepatitis, since tests for hepatitis A, B and C, cytomegalovirus and Epstein-Barr virus were all negative. In the 5 months prior to the onset of jaundice the patient was taking black cohosh 500 mg daily for menopausal symptoms and was not on any other medications. The patient

underwent liver transplantation after she failed to respond to initial treatment and the explanted liver showed features of acute hepatitis. No further details concerning the black cohosh usage by the patient (or its cessation) were provided.

As you can probably already see, these two published case histories are full of flaws. Not the least of these was that neither study reported the brand of black cohosh being used by the women. Added to this was the fact that black cohosh was not positively identified as the true ingredient of the products they were using.

The issue of the botanical authenticity of black cohosh products in the US has been highlighted by a recent publication.[iv] Of 11 black cohosh products tested, 3 were found to be from the wrong species (Asian species of Actea) and one was a mixture of both black cohosh and an Asian Actea species. For the 7 products containing only authentic black cohosh, there was significant product-to-product variability in phytochemical constituents.

There are many other flaws and evidence of bias in these two "probable" cases. In Case 1 the authors claimed that none of the drugs the patient was taking have been linked to autoimmune hepatitis. Yet a simple search on PubMed revealed several cases where labetalol may have indeed caused idiosyncratic autoimmune hepatitis, including one overview report of 11 cases from the US FDA.[v,vi,vii]

In Case 2, the authors justify their attribution of black cohosh as the cause of the patient's liver injury on the basis of the two flawed Australian publications (which were dismissed as unlikely by the expert committee). In their discussion they attribute to black cohosh the presence of hepatotoxic alkaloids and salicylates. Such attributions are nonsensical, are unsupported by the literature[viii] and above all cast doubt on the credibility and diligence of their overall analysis of the case. So even the "probable" cases as rated by the expert committee are in fact highly improbable. If these two cases represent the best evidence there is that black cohosh causes liver damage, then we must give it a clean bill of health.

So what might be going on here? Is this evidence of an anti-herbal conspiracy? Probably not an overt one, but there may be an unconscious bias at work. Research in several countries has found that one of the most serious causes of liver damage is

unknown. Around about one-third of all liver transplants are due to a disorder known as idiopathic or non-A non-B hepatitis.[ix,x] The demographics of idiopathic hepatitis (female, late 30s to early 50s) and black cohosh use strongly overlap. Hence there is a distinct possibility that some patients who develop idiopathic hepatitis might also be coincidentally taking black cohosh, given that this herb is so popular. The herb could then be mistakenly attributed as the cause. So the most likely and rational explanation of some of the cases described is that they are idiopathic hepatitis, mistakenly attributed to black cohosh because of the common use of this herb. Once one mistaken case is described in the literature, however poor its quality, it is likely that others will follow in a process akin to a self-fulfilling prophecy. Separate or confounding issues are the common adulteration of black cohosh products with Asian species of Actea and the co-administration of many drugs that are known to cause liver damage. The association of authentic black cohosh and liver damage remains unproven on the current evidence.

References

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