

PUBLIC HEALTH RISK WITH HERBAL MEDICINES: AN OVERVIEW

Introduction

1. **There may be an erroneous perception in some quarters that the practice of herbal medicines poses few safety issues.** In fact, given that in some cases practitioners, who may be inexperienced, are supplying potentially powerful unlicensed herbal medicinal products, the range of opportunities for things to go wrong is significantly greater than is the case with many other complementary and alternative medicine therapies.
2. Many plants are **potent or toxic**. Indeed, many pharmaceutical medicines, ranging from aspirin to digoxin, have their origins in the isolation of active chemical constituents in particular plants. In considering issues of safety it is essential not to make the common mistake of confusing herbal medicine with homoeopathy.
3. It is important to note that use of herbal medicine is not restricted to the worried well or to use by people with minor or transient conditions. Studies show that complementary and alternative medicine (CAM) use in patients with cancer is high and that this usage is increasing. It has been reported that over 40% of breast cancer patients and over 20% of patients with lung cancer in Europe use CAM. In all of these surveys herbal medicine was the most commonly used form of CAM. There is clear evidence, e.g. from clinic leaflets and websites, that many practitioners **treat patients with serious medical conditions** including heart disease, cancer, diabetes and asthma. Some practitioners treat particularly **vulnerable groups**, such as babies and children, or the terminally ill. A substantial area of usage of herbal medicines is to treat or relieve the symptoms of chronic, difficult-to-treat conditions, for example eczema. This will often occur in cases where patients have not been satisfied with the results of conventional medication (e.g. they don't like the side effects) and therefore in some cases there may be **long term usage** of herbal medicine.
4. Surveys show that the use of herbal medicines by older patients is increasing and that typically more than one herbal product is used at a time, often concomitantly with prescription medicines. Older patients are often reluctant to tell their doctor that they are taking herbal products and so are at risk of potential drug-herb interactions.
5. This overview focuses mainly on the risks arising with unlicensed herbal medicines and in particular poor practice in the sourcing and supply to patients of such products.

6. Where products are subject to systematic regulation (having a marketing authorisation or a traditional herbal registration) many risks are avoided, notably those arising from low manufacturing standards and a lack of systematic patient information. There however, remains some residual risk, for example the patient may not read the authorised patient information leaflet and could consume the product inappropriately, despite the inclusion of suitable warnings and contraindications. As with licensed conventional medicines that have an effect on the body, there is the possibility of adverse reactions or interactions with other medicines. Where these possibilities are known they are included in the patient information leaflet for regulated products.
7. By the same token, many risks arising from practitioner activity will be considerably reduced where the practitioner is well qualified, responsible, and acts within the limits of their competence.
8. There are frequent references in this overview to problems associated with traditional Chinese medicine (TCM). In some cases it may be more accurate to regard some of the low grade products as “masquerading as TCM”, for example where there is inclusion of potent undeclared pharmaceutical ingredients.

Examples of major public health risks due to herbal products: What can go really seriously wrong?

9. There was a wake up call to the herbal medicine sector and to regulators in the mid 1990s. Women attending a slimming clinic in Belgium were given a herbal medicine containing the **wrong, toxic, herb** *Aristolochia* species, (which has been used in TCM). **Over 100 women developed kidney failure and many subsequently went on to develop cancer.** An EMEA report of 2005 notes that of 39 women who agreed to prophylactic surgery 18 were found to have urothelial carcinoma. The report also noted that in China out of 17 patients who had taken *Aristolochia manshuriensis* supplied under the common name Mu Tong 12 had died of renal failure. Despite a ban on this ingredient in many countries, including the UK, problems still recur with the accidental supply of products containing *Aristolochia* (it has a similar common name in Chinese and similar appearance to several other herbs).
10. **There is no reason to suppose that a major incident could not occur in the UK;** one difference is that it is less likely to be identified. Given the pattern of mostly small, dispersed herbal clinics across the UK it is likely that in a comparable example the treatment of resultant cases of kidney failure would be spread over a number of different renal units and simply not be picked up.

11. Another comparison showing the possibilities for larger incidents is a case in the UK of irreversible liver failure that was linked to a TCM slimming aid (Shubao) containing nitrosfenfluramine, a drug closely related to prescription only medicine, fenfluramine which is now banned. Reports from Japan indicate that in 2001 – 2002 more than 800 cases of serious liver damage and at least 4 deaths resulted from the use of Chinese slimming products containing fenfluramine or nitrosfenfluramine.

Areas of public health risk from practice of herbal medicine

12. The main areas of risk with herbal medicines (taken from real examples) include:

- **Delay in effective treatment** for serious condition (e.g. *TCM practitioner advertising that herbal remedy will obviate need for coronary artery bypass graft*).
- **Interference with vital treatment** (e.g. *Ayurvedic clinic advising patient to discontinue antipsychotic medication and take alternative Ayurvedic remedies*)
- **Exploitation of vulnerable groups such as children and the seriously ill** (e.g. *parents wanting baby/child to have "natural" cream for eczema, unaware that the products supplied actually contain undeclared steroids; patients with cancer have been prescribed large quantities of TCM*)
- **Overloading patient with multiple medications** (e.g. *16 year boy with acne on over 100 TCM tablets a day for several months; patient hospitalised with serious unexplained abdominal pain*)
- **Unexpected rare but serious liver toxicity of plants** (e.g. *Kava, Black cohosh leading to liver transplants in some cases*)
- **Toxic plants used** (e.g. *Senecio species used in TCM which may cause liver toxicity or liver cancer*)
- **Side effects** (as with any other medicine)
- **Interactions** with other medicines (e.g. *St John's Wort can interact with many prescribed medicines including contraceptive pill and immunosuppressant medicines. This has resulted in unwanted pregnancies and rejection of transplanted organs; ginkgo can interfere with the action of anaesthetics*)
- **Wrong, toxic, plant used** (either accidentally due to lack of expertise or intentionally due to practice in TCM of substituting one ingredient for another believed to have a similar action)
- **Adulteration with pharmaceutical substances.** (This is a frequent occurrence and has involved potent medicines such as anti-diabetics (glibenclamide), drugs for erectile dysfunction (sildenafil), appetite suppressants (sibutramine) etc)
- **Addition of analogues of pharmaceutical substances.** (This is a growing activity where a chemical derivative of a known pharmaceutical substance is included in a product e.g. nitrosfenfluramine, sildenafil (Viagra) analogues)

(homosildenafil, acetildenafil). The analogue is often more toxic than the parent molecule (e.g. nitrosildenafil) or is of unknown toxicity as in the case of many of the sildenafil derivatives)

- **Addition of heavy metals/toxic elements as ingredients** (e.g. TCM product in clinic found with 117,000 times level of mercury permitted in foods, leading to a number of hospital admissions. TCM and Ayurveda traditionally use heavy metals and other toxic elements as ingredients. These include realgar (arsenic sulphide), cinnabaris (mercuric sulphide), calomelas (mercurous chloride), hydrargyri oxydum rubrum (red mercuric oxide). The current Chinese Pharmacopoeia includes 48 products containing at least one of these ingredients)
- **Contamination** during manufacturing process (e.g. poor control on use of pesticides, mycotoxins, microbiological loads)
- **Confusion over standards** (e.g. in TCM sector over whether traditional formulae have or have not had known toxic ingredients removed)
- **Weak or missing information** (e.g. about safe use of products or other poor practices such as over labelling list of ingredients on product with a different list)
- **Communications** (Inability of practitioner to communicate in English – e.g. to find out whether patient has a serious medical condition, such as diabetes, is on other medication, or is pregnant, breastfeeding).

Scale of risk

13. Internationally, no one, whether regulator authority or academic, has been able to overcome the obstacles in the way of making reliable estimates of ill health caused by herbal medicines, including the likely significant distinction in levels of risk between herbal medicine practised (a) responsibly and (b) irresponsibly. Principal obstacles affecting the UK are that:

- A perception that **natural equates to safe** and therefore many herbal medicine users would not realise that a herbal remedy may be responsible for symptoms they have experienced
- Survey evidence shows that most people don't tell their doctor that they are taking a herbal remedy (and most doctors don't ask) and so the **doctor would have no reason to suspect that ill health was linked to consumption of a herbal remedy**; survey evidence also shows that patients are much less likely to report to their doctor the suspected side effect of a medicine if they believe it may be linked to a herbal medicine
- It is a regular occurrence that cases of ill health are linked to consumption of low grade products containing **undeclared ingredients**. In this situation the chance of detection of any specific individual case is very low indeed

- Many issues arise from low standards – e.g. sourcing from unreliable suppliers operating to low standards; in these circumstances the degrees of **adulteration/contamination/substitution of one species for another are random and erratic**
- Herbal practitioners are largely supplying unlicensed products on a private basis; there may therefore be an **inbuilt disincentive for less responsible practitioners to report patient side effects** lest this affects adversely on them personally and at a wider level, undermines the business.

14. There are, however, pointers to what may lie beneath the surface:

- The MHRA currently receives about **70** suspected adverse drug reaction reports relating to herbal medicines each year. This is believed to represent only a small proportion of cases (e.g. in a year when there was considerable publicity about St John's Wort interacting with other medicines, reporting doubled). The expectation is that over time with better publicity and following the recent extension of the reporting scheme to patients, self reporting will increase
- There have been a **handful of identified UK deaths** associated with use of herbal medicines; there is a **small but reasonably steady flow of cases entailing very serious illness** such as kidney or liver failure requiring transplant; and other cases (e.g. coma) involving prolonged hospitalisation. A high proportion of such cases have only come to light because of the actions of very alert clinicians who have taken the time to investigate causation of ill health and/or perhaps refer the case to a poisons unit
- **There are a much higher number of cases where MHRA recover from the market dangerous unlicensed products (typically sold in, or destined for, clinics) which pose a clear risk to public health.** These include products with hazardous levels of heavy metals, highly potent or even banned pharmaceuticals, products which may be associated with infectivity e.g. containing human placenta or bat excrement. **In some cases the product seizures or recalls have been on substantial scale – e.g. products destined for distribution through nationwide chains of TCM clinics. The MHRA believes that it identifies and recovers only a small proportion of dangerous products; consequently many will have been used by the public.** A recent example was a **seizure in May 2008 by the MHRA and Police in a joint operation of nearly 500 boxes containing bottles of an unlicensed “herbal” lotion containing steroids.** The issue had been brought to our attention by a paediatric dermatologist concerned about the use of the product by parents on babies.

15. Worldwide, there is increasing study and scientific understanding of herbal medicines; also improved sharing of information between regulators. It is therefore predictable that over time new safety areas will be identified as well as further examples of known existing problems.

Variations in risk across the UK sector

16. Such has been the frequency of findings with low grade products in the **TCM** sector that on several occasions the MHRA has issued general alerts about patchy standards in the sector.

17. Issues of risk in the TCM sector can be complex and present difficult handling issues. For example, there are many traditional formulae in TCM. In some of these the old formulae includes a potentially dangerous ingredient such as a heavy metal or a toxic herb. Responsible operators in the sector would like to reach agreement with the MHRA that it is acceptable to use new versions of these formulae minus the potent ingredient. The issue in a largely unregulated environment then becomes whether it is possible to rely on a voluntary agreement to protect the public – and what to do about the likelihood that other players who are not part of such an agreement would continue to supply the former versions of the formulae.

18. With typical **western herbal medicines**, e.g. found in health food shops, supermarkets, etc the most frequent area of concern in the unlicensed sector is lack of systematic patient information. Some products fall short of what is desirable in terms of information about safe usage. With **Ayurvedic** medicines the most frequent problems are the illegal inclusion of heavy metals; also illegal product claims.