Complementary and alternative therapies (CAM)

- Medical and health care systems, practices, and products that are not generally considered part of conventional medicine
  - http://nccam.nih.gov/about/

(2) Complementary and alternative therapies (CAM)

- Acupuncture
- Ayurveda
- Biofeedback
- Chelation therapy
- Chiropractic or osteopathic manipulation
- Deep breathing exercises
- Diet-based therapies
- Energy healing
- Guided imagery
- Homeopathic treatment
- Hypnosis
- Massage
- Meditation
- Movement therapies
Complementary and alternative therapies (CAM) (3)

- Natural products, including botanicals
- Naturopathy
- Progressive relaxation
- Qi gong
- Tai chi
- Traditional healers
- Yoga

Outline

- Scope of herbal use
- Regulatory aspects of herbs in U.S.
- Unmet medical needs in epilepsy: why botanicals?
- Harvard Epilepsy Botanical Program

Scope of use of herbs by epilepsy patients

- Herbs taken include ginseng, St. John’s wort, melatonin, gingko biloba, garlic and black cohosh
- Reasons: treat seizures (<10%), other symptoms (20%), and general health (>70%)

Peebles et al., Epilepsy Behav 2000; 1: 74-7
Easterford et al., Epilepsy Behav 2005; 6: 59-62
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U.S. regulation of herbs

- Herbal products are generally classified by the U.S. government as dietary supplements, not pharmaceuticals
- Dietary supplements in the U.S. are regulated by the 1994 Dietary Supplement and Health Education Act (DSHEA), whereas prescription drugs must meet the most rigorous requirements of the Federal Food, Drug, and Cosmetic Act

U.S. regulation of herbs (2)

Standards set forth by the DSHEA:
- Manufacturers of herbal products are responsible for the truthfulness of labeling claims
- However, no government agency, including the FDA, independently reviews and verifies the claims and supporting evidence
- Manufacturers are responsible for controlling product quality and verifying safety of herbal supplements
U.S. regulation of herbs (3)

Therefore,

- Herbal products could potentially be contaminated with microorganisms, pesticides, or toxic metals, and adulterated with other herbs or drugs; and
- The potency and amount per pill/capsule may vary significantly within the same bottle or from batch to batch, or from one branded product to another.

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Unmet medical need in epilepsy

- 1% -2% of the world’s population experience recurrent seizures (epilepsy)
  - 60 million worldwide
  - 40 million not on any therapy = treatment gap
- Significant proportion have mood and cognitive disorders
Unmet medical need in epilepsy (2)

- 2 out of 3 patients have unsatisfactory results from current drug treatments
  - Half continue to have seizures
  - Half have intolerable side effects
- Most drugs have a negative impact on memory; none improve memory
- No drug prevents epilepsy in patients at risk (Head injury, Stroke, Alzheimer’s disease)

Why botanicals?

- Botanicals have a rich history as a source of compounds for therapeutic use
- Substantial number of prescription drugs contain natural product derivatives
- Latest example – Razadyne (Ortho-McNeil)
  - Galantamine (Galanthus nivalis; Common snowdrop)
  - Possibly the herb “moly” in Homer’s Odyssey

Why botanicals? (2)

- A large number of Asian, African and South American herbs have been historically used singly and in combinations to treat seizures
- A number of herbal medicines have been shown to have mechanisms of action that are relevant to epilepsy
- Systematic study of botanicals as sources for new epilepsy therapies appears promising
East Asian literature: herbs for epilepsy

- Search strategy
  - A literature search was carried out using PubMed, Embase, PsychInfo, AltHealth (from inception to March 2005), the Chinese Medicine Database, the Korean Medical Database, and the Korean Drug Research Information Center;
  - Bibliographies of initially identified articles were also checked
  - All clinical studies, including case reports, that reported the results of treating epilepsy with herbal formulas were included

East Asian literature: herbs for epilepsy (2)

- 71 studies in the East Asian medical literature report clinical effects of herbs for epilepsy, including:
  - 3 randomized controlled trials
  - 5 non-randomized controlled trials
  - 6 case control studies
  - 57 observational studies, including case reports
  - Over 135 different herbs were used singly or in combination formulas

Why botanicals?

- The FDA has a guidance for INDs and NDAs for "botanical drug products" such as extracts
  - [http://www.fda.gov/cder/guidance/4592.html](http://www.fda.gov/cder/guidance/4592.html)
- On 11/9/06, the FDA approved an extract of green tea for topical treatment of genital warts caused by human papilloma virus (brand name – Veregen Ointment)
Alternative Therapies
Steven C. Schachter, M.D.

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Harvard epilepsy botanical program

- Goals
  - Find herbal medicine extracts with promising activity in animal epilepsy models and in vitro assays relevant to epilepsy
  - Isolate compounds from these extracts and then retest them in the same models and assays
  - Conduct the necessary pre-clinical studies and then proceed to early stage clinical studies
  - Partner to develop and commercialize the compounds and extracts as FDA-approved
Harvard epilepsy botanical program (2)

- Global team
  - Herbal experts
  - Natural product chemists
  - Neuroscientists with expertise in testing botanical products
  - Animal experimentalists

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The process
Step 1: identify

- Methods for selecting botanicals
  - Use in epilepsy
  - Relevant mechanism of action
  - Review of TCM textbooks
  - Opinion of herbal medicine experts
  - Original literature (e.g., Chinese, Japanese)
  - English literature

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The process
Step 2: acquisition

- Acquisition of herbal medicine extracts (water based, methanol based, etc.)
  - Herbal experts in the field
- Authentication
  - Analytic laboratories
  - Methods range from visual inspection to DNA fingerprinting

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The process
Step 3: *in vivo* and *in vitro* models

- Animal epilepsy models are highly predictive of efficacy in humans
  - Maximal electroshock (MES): Generalized tonic-clonic seizures
  - Subcutaneous Metrazole (ScMET): Generalized myoclonic seizures
  - 6-Hz: Refractory limbic (mesial temporal) seizures
- *In vitro* studies (e.g., patch clamp) may help explain underlying mechanisms

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The process
Step 4: compound isolation and testing

- Isolate compounds from extracts with activity in *in vivo* and/or *in vitro* studies
- Test compounds in animal epilepsy models and *in vitro* assays

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The process
Step 5: clinical trials

- Pre-clinical safety studies
- Phase I
- Phase II
- Phase III

Applies to extracts and compounds
Alternative Therapies
Steven C. Schachter, M.D.

• Medical and health care systems, practices, and products that are not generally considered part of conventional medicine have been used as treatments for epilepsy for centuries
• Further research into their safety and efficacy is needed to better understand their potential risks and benefits for patients with epilepsy
• Herbal products hold particular promise and are under active pre-clinical evaluation at present