



International Society for Complementary Medicine Research

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Newsletter Aim

The aim of the newsletter is to facilitate communication between members of the society, informing them about:

- The Society's strategies and future plans
- Future conferences
- Other similar networks
- Items of research interest and relevance to society members
- Items of political interest and relevance to society members.

Newsletter Process

PROCESS

The newsletter will be produced quarterly and distributed electronically to all Society members.

The newsletter will be edited and run by an Executive or Board member with the help of a small editorial group.

Comments welcome

George Lewith: g13@soton.ac.uk



From The President

The Society continues to grow and as you will see from Dr Zicks report on membership and our financial state we continue to be on track with a healthy membership growth. Please help us to recruit!

I encourage you all to consider attending the Munich conference, May next year, ISCMR membership offers substantial reductions for early bird booking. The website is <http://www.cmr-muc2007.de>. If any of you would like to volunteer to review and evaluate submitted abstracts then both ISCMR and the conference organising committee would be very grateful for your help and assistance in this matter please email us with your CV at info@iscmr.org. It would of course be something you can quite legitimately put on your academic CV as part of your academic portfolio.

We'd also like to announce the Australian Conference which we are sponsoring in 2008, there is an initial announcement from Professor Felix Wong and Alan Bensoussan within this Newsletter. We've not yet clarified exactly what reduction will be on offer to ISCMR members, but we hope to do that very soon.

You'll know doubt of noticed that newsflashes have effectively been divided into two: the usual newsflash that simply give people information and and 'Calls for Help'. Calls for Help are really for people who wish to advertise themselves for potential employment, research ideas, other academic call for research cooperation. These appear to have been a very successful addition to our electronic communication and I would really encourage those of you in need of collaborators, support, ideas and advice to use the 'Call for Help' please write to us at info@iscmr.org.

We have very importantly been discussing our association with one or more of the major academic journals in the area of CAM. We recently sent out a survey (which is on the next two pages) to the membership asking you which journal the society should associate with and if we should receive this journal via online access or as a hard copy in the mail. We also asked if you would be prepared to increase your membership fees to have a printed copy of the journal delivered to you by post.

We received 69 responses with 62 members indicating that they would be happy with only online access to the journal, and with the majority of respondents (54) not be willing to have their memberships fees increased to receive a print copy.

We had a clear choice of which journal the society should associate with being the Journal of Alternative and Complementary Medicine (JACM) with 37 votes. The second vote getter was Complementary Therapies in Medicine with 21 votes. We will be updating you on the progress with JACM in the coming months.

I look forward to seeing you all in Munich next May, if not before.

Good Luck and Kind Regards

George Lewith



Financial & Membership Update 19.9.06

Hello ISCMR Members. We are growing with leaps and bounds! The Edmonton Conference and immediately after it saw over 20 **new** ISCMR members join our ranks. During the rest of summer we have continued to see higher than expected levels of membership renewals and new members. My goal is to have over 200 members before the end of 2006. Talk to your colleagues and let them know about our current benefits and soon to be benefits of membership. Also, check out the ISCMR web-based membership list. You may find new research collaborators in your geographic or research area.

As of September, 19th 2006 we have 178 members! As before the majority of our members continue to come from the US (55), the UK (42) and Canada (24). We recently have members from including Saudi Arabia, Mexico and Liberia. Once again I like to make an appeal to those of you in countries other than the US, UK, and Canada to talk us up to friends and colleagues. Please, let them know that we would be excited to have more representation from around the globe. We have also, been gaining both more sustaining members (6) and low income members (12). We want to thank all of the sustaining members for making low income and student memberships possible.

Financially we are in excellent shape. We have almost \$11,000.00 in our checking account and have no major expenses pending. This should leave us with considerable monies with which to purchase online journal subscriptions for members (please see the article on the journal survey).

Suzanna Zick

Munich 2007

International Congress on Complementary Medicine Research

You can now submit abstracts and see the Program schedule and pre-conference workshops online. For further information please visit: <http://www.cmr-muc2007.de>

ISCMR Pre-conference Workshop

At the Munich conference in May of 2007 ISCMR will be presenting a workshop entitled “Challenges in Whole System Herbal Research”. This workshop is meant to raise ideas and promote discussion around the vital questions such as of: “What is a whole herbal system?”; “How might a whole herbal system appear and operate?”; and “How does examining and researching whole herbal systems impact future research?” We have four talks tentatively scheduled at this point including:

1. “Potential Frameworks for Researching Whole Systems of Herbal Medicine” presented by Tieraona Low Dog, MD, Director of Botanical Medicine for the Program in Integrative Medicine at the University of Arizona
2. “Tibetan Herbal Multicomponent Formulas: A round-trip from Tradition to Evidence” presented by Dr. Herbert Schwabl, from Padma Inc., Schwerzenbach, Switzerland
3. “Researching Herbal TCM Remedies as Part of the Whole TCM System” Andrew Flower, MBAC MRCHM, Research Associate, University of Southampton.
4. “Using Partial Functional Factorial Designs for Examining Complex Interactions in Whole System Herbal Research”, Suzanna Zick, ND MPH, University of Michigan, Department of Family Medicine

The workshop will be held on Friday May 11th from 1 to 5pm. We will be reserving at least half that time for group discussion and questions. We look forward to your participation. If you have any questions or know of a speaker that would be wonderful for this forum that we have not invited please contact Suzanna M. Zick at szick@umich.edu.



Australia 2008

**Preliminary announcement of
The 2008 International Congress on Complementary Medicine Research
March 29-31 2008, Sydney, Australia.**



This International Congress will be the third international meeting supported by the International Society for Complementary Medicine Research, as part of a three year rotation between North America (held in Edmonton 2006), Europe (to be held in Munich 2007) and Australia and Asia (to be held in Sydney 2008).

The program prepared by the scientific committee will be exciting, challenging and cater to a range of interests in complementary medicine. Major themes of the Congress will include evidence-based practice, women's health, cancer management, aged care and more. The organisation of the Congress will allow universities, hospitals, relevant industry groups and other research organisations to showcase

their research activities, and we anticipate significant contributions from China, Korea and Japan.

Sydney is an attractive, relaxed city surrounded by an extraordinary harbour and beaches, the Royal Botanical Gardens and the Opera House. The Congress will be held in the comfort of early autumn.

Further detail about research, sponsorships and preliminary announcements will be made through the ISCMR website: www.iscmr.org

*Felix Wong &
Alan Bensoussan*



N-of-1 – A new method for investigating CAM by K. Cramer & S. Vohra

With the desire to generate evidence-based approaches to complementary and alternative medicine (CAM), there is growing interest in research methods that meet the goals of both CAM and evidence-based medicine (EBM). To be accepted by both, methods for studying CAM have to incorporate its holistic approach and individualized treatment philosophy with methodological rigor. One method that is of particular interest is the N-of-1 trial, which is a randomized multiple crossover trial performed in a single participant. It has a long tradition in psychological research (1) and has been used in conventional Western medicine to generate treatment information when evidence from randomized controlled trials is not available or applicable (2). This method is suited for CAM research as it allows for an investigation of efficacy for an individual patient while maintaining the individualized approach central to CAM.

Three conditions should be fulfilled prior to beginning an N-of-1 trial (2). First, the condition under study should be chronic and stable (e.g. autism, irritable bowel syndrome, attention deficit disorder, diabetes, asthma). In situations where the condition is characterized by rapid or spontaneous improvement, there may be a false conclusion that the improvement is a result of the current treatment. Second, the intervention under study should have a quick onset and termination of effect and should not have an irreversible effect on the condition (e.g. cure). Quick onset and offset diminishes the need for long treatment periods and lengthy wash out periods between interventions. Third, outcomes need to be relevant to both the patient and their health care provider. Disease and patient specific questionnaires are typically developed for this purpose (3). Standardized measures are also used as outcomes when they have been validated for the condition and population under study.

The N-of-1 trial is gaining increasing interest and acceptance among the CAM and conventional

medical communities. To determine if this method can be easily be employed in practice the CARE program (Department of Pediatrics, University of Alberta, Stollery Children's Hospital, Edmonton, Alberta, Canada) has developed an N-of-1 CAM service. This clinical service assists patients and their providers with the design and implementation of an N-of-1 evaluation to determine if a specific CAM therapy is effective for a specific patient. In addition, to inform the development and conduct of N-of-1 trials, the CARE program is leading several systematic reviews on this topic. Specifically the objectives of these reviews are to identify the best methods for conducting, analysing, and meta-analyzing N-of-1 trials.

For more information on N-of-1 methods please refer to the following:

Backman CL, Harris SR. Case Studies, Single-Subject Research, and N of 1 Randomized Trials: Comparisons and Contrasts. *American Journal of Physical Medicine & Rehabilitation*. 1999; 78(2):170-176.

Cook DJ. Randomized Trials in Single Subjects: The N-of-1 Study. *Psychopharmacology Bulletin*. 1996; 32(3):363-367.

Guyatt G; Jaeschke R, and McGinn T. Therapy and Validity: N-of-1 Randomized Controlled Trials. *Users' Guides to the Medical Literature: A manual for Evidence-Based Clinical Practice*. Chicago, IL: American Medical Association; 2002; pp. 275-290.

Guyatt G; Keller J; Jaeschke R; Rosenbloom D; Adachi JD, and Newhouse MT. The N-of-1 Randomized Controlled Trial: Clinical Usefulness. Our Three-Year Experience. *Annals of Internal Medicine*. 1990; 112:293-299.

Guyatt G; Sackett D; Adachi J; Roberts R; Chong J; Rosenbloom D, and Keller J. A clinician's guide for conducting randomized trials in individual patients. *CMAJ*. 1988; 139:497-503.

References

1. Kazdin AE. *Single-Case Research Designs: methods for clinical and applied settings*. New York: Oxford U Pr, 1982.
2. Guyatt G, Sackett D, Adachi J *et al*. A clinician's guide for conducting randomized trials in individual patients. *CMAJ* 1988; 139:497-503.
3. Paterson C. Measuring outcome in primary care: a patient-generated measure, MYMOP, compared to the SF-36 health survey. *British Medical Journal* 1996;312:1016-20.



News from Korea *by Jongbae Park*

After more than 8 years' staying in the UK and USA, I spent a few months in my home country, South Korea. During the period, I have noticed several noteworthy changes related to complementary medicine research, which I intend to report in this newsletter.

In South Korea, two distinct medical systems, Western Medicine and Korean medicine, coexist as separate, yet parallel, systems. Both MDs (Medical Doctors) and KMDs (Korean Medicine Doctors) are trained under nationally standardized curricula for 6 years full time and their scopes of practice are clearly delineated. Although the scope of the KMD's practice overlaps with "CAM" in the West because it focuses on therapies such as acupuncture and herbal medicine, it differs from CAM in the US and Europe in that these therapies are united into one system. Nevertheless, like many CAM therapies in the US, Korean Medicine is politically and socially marginalized in relation to the dominant Western oriented medical system, resulting in tension between KMDs and MDs.

For simplicity, I report three Korean major news items only. First, since 1998, the size of government funding for R&D in Korean Medicine has been increasing to reach about 25 Million USD in 2005 alone. The research support was executed through the Ministry of Health and Social Welfare, Ministry of Science and Technology, Patent Office, and Ministry of Information and Communication. One outstanding project of these, Acupuncture & Meridian Science Research Center located at Kyung Hee University was granted one million every year for 9 years from 2005, and will be led by Prof. Hyejung Lee. This is unprecedented, and maybe due to high level of political pressure created by the public around 1993 and 1996.

Secondly, the government now faces counter-pressure to audit the use of those funds as the productivity of the R&D projects funded through

those schemes have been often questioned. In fact, the Korea Health Industry Development Institute held a public hearing to improve the efficiency of the government-funding project, and the Presidential Committee on Healthcare Industry Innovation hosted a panel of experts to brainstorm a solution to the aforementioned problem this October. I was lucky enough to attend both the meetings, and tried my best to get across what I believe in to amend the predicament, building the human research capacity.

Lastly, the Ministry of Education & Human Resources Development and Ministry of Health and Social Welfare are jointly executing a plan to open a national school of Korean Medicine in March 2008. This is a very meaningful action in the education of Korean medicine in that it is the first time since the traditional system of medicine in Korea was abolished in 1894 followed by marginalization from then on.

In summary, South Korea, economically advanced, yet facing many challenging tasks, is certainly investing in R&D on its medical heritage for several reasons. Meanwhile, it is in urgent need of research capacity in human resources, methodology, and strategy.

Jongbae Park

Member of the ISCMR Board of Directors



Integrated Medicine in Australia *by Elizabeth Lew*

On our way to integration

There is a tremendous interest amongst younger physicians and also amongst older physicians in recovering the heart of medicine – the psychological and spiritual reasons why they went into medical practice – and moving away from the exclusively technological and biomedical base on which medicine is taught. I offer that as an indicator that there is a hunger in the medical community for responsible, integrative approaches, which is by no means limited to cancer. I think that hunger really reflects that fact that physicians are part of the culture as a whole and that the culture as a whole has a hunger for these integrative therapies.

In Australia all citizens receive health cover through a socialised healthcare system known as Medicare. A second tier of health cover known as Private Health Insurance, also exists. The Private Health Insurance industry is subsidized by the Australian Government, Australians with private health insurance cover receive a 30% rebate through the taxation system, a higher rebate is available for people over 65 i.e. 35% and for people over 70 the rebate is 40%. There are 4.6 million health insurance policies covering 9.9 million Australians, approximately 81% of Health Insurance Policies have ancillary cover. This represents 8,019,000 Australians. There are 41 private health insurers, in Australia.

National Chronic Disease Strategy

The Australian Department of Health and Ageing released the National Chronic Disease Strategy in March 2006. The strategy provides an overarching national framework for improving chronic disease prevention and care across Australia. The Strategy aims to strengthen Australia's capacity to meet the challenges arising from increasing prevalence of chronic disease, and improve health outcomes and reduce the impact of chronic disease on individuals, families, communities, and society. Improved outcomes will be achieved through enhanced effort and more consistent and integrated, evidence-based, practical and effective (including cost-effective), consumer-focussed approaches for improving the prevention, detection and management of chronic disease. In 2005 Medicare cover expanded its cover to include multidisciplinary care planning and access to allied health services. The new Chronic Disease Management system provides up to five consultations with an allied health provider per year. These payments are made through the Medicare system for services

organised through a care plan and delivered by allied health providers such as dieticians, occupational therapists, physiotherapists, chiropractors, osteopaths and psychologists. Current Medicare benefits paid to the primary healthcare sector from January 2004-December 2004 are in excess of \$2.9 billion.

Complementary and Alternative Medicines

According to the Complementary Healthcare Council, the proportion of Australians now using complementary services at least once a year has doubled in the past decade to about 60% of the population. Relatively large increases in the numbers of allied health professionals have been recorded in recent years. Between 1996 and 2001, the number of allied health professionals increased by 26.6% to 8,533. As with allied professions, there has also been a substantial recent increase, between 1996 and 2001 in the number of complementary healthcare practitioners, with the total number increasing by 31.2%. There are now more than 30 colleges offering courses to natural therapists. The Australian Traditional Medicine Society, which represents 65% of complementary health practitioners, now has 10,118 members. Ancillary cover which is available through private health insurance provides a fixed rebate for allied and complementary healthcare services. The types of services covered by ancillary health insurance are provided by a range of practitioners including: the traditional allied health professionals (dentists, physiotherapists, dietitians, orthotic providers and podiatrists); generally accepted alternative therapists such as osteopathic, naturopathic, acupuncture and remedial/rehabilitative massage practitioners; and alternative health practitioners. These practitioners cover treatments such as: Alexander technique, aromatherapy, kinesiology, massage, myotherapy, Shiatsu and western herbal treatments. The annual turnover in complementary healthcare is over \$2.1 billion per annum in Australia.

The Well Being Industry in Australia

The total 'Well being industry in Australia is estimated to generate \$12-\$15 billion in sales a year. There are forecasts that within seven years, Australians will spend more than \$60 billion a year on complementary medicines, weight loss programs, fitness centres, cosmetic surgery, functional foods and other new age products.' - *BRW June 2005*.

Elizabeth Lew, Epichealth

www.epichealth.com.au

Member of the ISCMR Board of Directors



The current situation of CAM/IM in East Asia *by Kazuhiko Atsumi*

First of all, I would like to introduce myself. I was a member of Science Council Japan (SCJ) and the director of the Section of Medicine, Dentistry and Pharmaceutics and organized “the symposia on Asian CAM” and “IM in Japan” and so on. My achievements in Tokyo University have focused on the promotion of “the research on Advanced Technology in Medicine” such as artificial heart, computerized medicine, laser surgery, bio-magnetism etc. When I visited NIH in 1995 as a Member of SCJ to negotiate the “US-Japan Science project”, I knew CAM would be one of the essential targets in future medicine. Since then, I have focused my efforts on the research of CAM and IM, and organized 2 academic societies. One is JACT (Japanese Association for Alternative, Complementary and Traditional Medicine) in 1998 and the other is JIM (Japanese Society for Integrative Medicine) in 2000. I have been appointed as the presidents of the both societies.

The following report is the information of the situation and activities in East Asia in the last decades with my own experiences and knowledge.

1) Japan

At present, several societies and research groups on CAM and IM have been organized. Among them, JACT, JIM, and JCAM (Japanese Society on CAM) are considered as the leading groups.

The information about these 3 major academic societies is as follows.

JACT: Japanese Association for Alternative, Complementary and Traditional Medicine. In JACT, 950 members have registered. They are mainly CAM practitioners. About 30% of them are some medical doctors. As activities, the annual meeting and 3-4 local meeting have been held, and the journals have been published quarterly.

JIM: Japanese Society for Integrative Medicine

In JIM, 700 members have registered. As activities, the annual meeting has been held, and the journal was published quarterly.

Recently, JACT and JIM have been communicated each other to promote IM and proposed the national budgets “National research on IM” with JPY 10 billion for 5 years to the Japanese government. Since 2002, the three supporting groups have been organized to promote IM, such as “Academic Association” (20 medical societies joined), “Senates Association (85 Senates registered) and “Cultural and Industrial Association (65 members registered).

At present, the three strong associations have been cooperating and started to achieve each activity to promote IM. Since 1999, the governor of Gifu prefecture, Mr. Taku Kajiwara made a plan to construct the “International Resort Center with CAM/IM therapies” and have held the annual International Symposium in the last 6 years. Leading researchers such as Dr. D. Eisenberg, Dr. F. Kronenberg, Dr. Haskel, and Dr. Melchart attended the symposium. Drs from China and India also joined. In 2004, February, the International symposium on Integrative Medicine was held in Tokyo, which organized by Dr. Kazuhiko Atsumi, Dr. A. Weil and Dr. F. Kronenberg. Researchers from China, Korea and India attended. In 2005, February, The International Symposium (Japan, China, Korea) “Towards IM” was held in Tokyo presided Dr. K. Atsumi, and the 2nd symposium will be held in Seoul in 9-10th November, 2006.

2) In Korea, The Korean CAM Society has registered about 2,000 membership presided by Dr. Min Mo Chun. The annual meeting was held in Seoul in 20 August this year and Dr. Lieu (China) and I were invited to give a lecture. Another group will organize the Korean IM in this October.

3) In China, about 20 years ago, the Society of Chinese Western Medicine started registered about 1,000 Members. The National and International Conferences and Symposia have been held. Recently, the Chinese Government wanted to promote the integrative medicine as the one of the national policy. Besides China, Taiwan also has been promoting IM aggressively.

4) In 2004, the symposium of CAM in IFMBE Congress held in Sydney, the Taiwanese and Japanese and American group attended and discussed.

As the forthcoming symposium the delegate from Korea, China, and Japan will get together in Seoul in November. We will discuss the future plan of the Asian Association on IM including the three countries and the other countries such as Singapore, Malaysia, Indonesia, Thailand and India. I would like to share the information at the next Congress in Munich, May 2007.

Kazuhiko Atsumi

Member of the ISCMR Board of Directors



News from the International Symposium on Pharmacovigilance (London, April 26-28 2006)

From Wednesday, April 26 to Friday, April 28 the international symposium “Pharmacovigilance of herbal medicines: Current state and future directions” took place in London. ANME visited this conference, as information on the views on regulatory and safety issues on various herbs was to be expected.

Adverse effect reporting systems

The major topic of the conference was the organisation of data collection systems including adverse event reports from herbal remedies. In Germany herbal remedies are subject to drug regulatory processes anyway, and a working adverse event reporting system is already in place. This is, however, not the case in most other countries where herbals are sold as food supplements or unregulated health products. Thus, the focus of the conference was clearly on how underreporting of adverse events from herbals might be avoided and how reporting systems can be developed.

A large number of systems were presented, e.g. the adverse event database of the WHO, the Yellow Card System of the British MHRA, systems established by the BfArM, the EMEA, the ESCOP, the German producers of antroposophic medicines, the system installed by the Chinese drug regulatory authorities (perfectly structured and transparent, but in Chinese). Most systems are installed in parallel and do not interact, mostly due to differences in terminology and coding. As the organisations partly communicate adverse effect reports to each other, an increase of duplicate entries and thus the danger of false signals is to be expected.

Still, all organisations claim that there is a considerable degree of underreporting, as most patients do not believe that herbs might be harmful and an incidence as high as 90% was suggested. However, what was not discussed is the degree of underreporting pharmaceuticals. The high degree of underreporting was attributed to the work overload of general practitioners, which would also apply to pharmaceuticals. Our experience is that adverse events from chemical entities are often not reported when the possibility of such effects is already mentioned in the product leaflet. However, there is no doubt that there is a need for improvement of pharmacovigilance systems, regardless of the nature of the products.

Drug quality and adverse effects

Major improvements of existing reporting systems were not discussed. Logic would suggest we address the impact of quality as a factor contributing to drug safety. However, this is never done, although all examples of herbal adverse

drug reactions discussed in the conference were in fact related to drug quality:

- St. John’s Wort (*Hypericum perforatum*) interactions are clearly related to the content of hyperforin. Patients taking products high in hyperforin are at risk, patients with traditional products or regular extract qualities not artificially enriched in hyperforin are not. Several experts from the audience tried to raise this issue, but obviously there is no place for quality in pharmacovigilance.

- *Aristolochia* and aristolochic acid are clearly recognized as the causative factors for Chinese herb nephropathia. However, the use of *Aristolochia* can be traced back to a substitution of the safe plant *Stephania tetrandia*, which has the same vernacular name, but is non-toxic. Still, there does not seem to be a future even for *Stephania* on the herb market.

- *Cimicifuga racemosa* (Black Cohosh) has been linked to hepatotoxicity in a number of case reports (of doubtful quality). A major case report was only recently demonstrated to have been based on deliberately omitted facts speaking in favour of Black Cohosh. Generally, potential liver toxicity is only known from poorly controlled products from countries where the sale is unregulated. As according to the presentations in London 97% of the raw material of Black Cohosh is collected by wild crafting, the danger of substitutions and adulterations is high and should be countered by proper analytical controls. Such controls are established for companies where *Cimicifuga* preparations are registered and prepared under GMP. The question of drug quality was not taken into consideration by the pharmacovigilance system.

- A striking example of bad quality presented in the conference was the business conducted by Panpharma in Australia. This producer was finally closed down by the regulatory bodies, based on fraudulent management of herbs and analytical protocols. The safety problems that resulted from the criminal actions of the company are, however, still linked to the herbs.

In conclusion, the discussion of herbal drug safety can easily become artificial, especially when problems relating to the quality of one specific product become related to all preparations containing the herb. A basic principle of pharmacovigilance is doubt. Scientists would argue that when the culprit is identified, there is no reason to suspect the plant itself. People involved in pharmacovigilance seem not to agree. As long as there is no proof that the regular quality of the plant does not and never causes



the defined adverse event, it seems its safety must still be in doubt. The magic word is “precaution”.

The precautionary principle

The problem with this line of arguments and especially with the “precautionary principle” is that a complete absence of any given phenomenon cannot be guaranteed scientifically. Science can only demonstrate effects, but never the absence of an effect. Therefore, pharmacovigilance can be abused by regulatory bodies for political reasons. Recent examples are the discussions about Kava, St. John’s Wort and Greater Celandine (*Chelidonium majus*). Based on the argument of a negative risk-benefit ratio of any given herb a single adverse event can be sufficient to cause the ban of preparations from this plant all over Europe.

The benefit itself is defined by the outcome of modern clinical trials. Even though there is a huge number of clinical trials on herbals, almost all of them are not compliant with modern standards in clinical research (the question is, of course: how many chemical compounds are tested according to these modern standards, especially among the “older” drugs?). When only the most recent standards are accepted – which is currently the case for Kava and Greater Celandine – only a handful of plants would have attributable clinical benefits. With >90% of herbs falling under traditional use, and with traditionally used herbs by definition being used without clinical proof of efficacy, there is a constant threat that the herb might be withdrawn deliberately and quite arbitrarily – all in the name of consumer safety.

Figures outweigh causality

Another major problem with pharmacovigilance is the importance of data. Numbers of case reports are in fact more important than causality assessments or the calculation of incidence rates. The WHO pharmacovigilance database contains a large number of entries which do not reflect causality. “Signals” indicative for potential problems are entirely based on numbers of case reports, not on assessments of individual cases. As was discussed in London, a signal based on case numbers instead of facts can be misleading.

The WHO currently has >3.6 million case reports of adverse events in total. A total of >41,000 cases involved herbals, 17,000 of which was use of herbals in monotherapy. The small percentage of herbals in the total database might (according to WHO representatives) point to underreporting. However, underreporting would also have to be expected for pharmaceuticals, so that perhaps

herbs genuinely do not create substantial numbers of adverse events. I personally interpret the figures as a general proof of safety – the deduction of a potential problem from figures giving no real evidence that such a problem exists. Overregulation only leads to a decrease of quality, which then may cause problems in the sense of a self-fulfilling prophecy. Who protects the consumer from the consumer-protectors?

Current signal generation

The plants mostly involved in herbal adverse event reporting were *Hypericum perforatum*, *Ginkgo biloba*, *Echinacea sp.*, *Serrenoa serrulata*, *Mentha piperita* and *Plantago ovata* – with figures of reports ranging up to 600/plant (for ginkgo). This would represent a very small risk, however, according to the speaker even the tiniest risk might be intolerable without a clear benefit. Currently, the WHO sees a signal for hypertension by *Cimicifuga racemosa* and *Panax ginseng* (based on single reports from three sources), but not by *Eleutherococcus senticosus*. WHO also detects a potential signal for white blood cell changes with *Hypericum perforatum* from approximately 5 sources worldwide.

Kava

In most presentations Kava was not mentioned – deliberately, as it seems. I had the impression that Kava makes the regulators uneasy, as if they knew exactly that the signal of toxicity they argue does exist might in fact be false positive. The topic of Kava was even largely avoided in the presentation of Prof. Hagemann, former head of the pharmacovigilance department of the German BfArM and responsible for the decisions taken about Kava.

- In his only direct mention of Kava he explicitly said that Kava was traditionally used as a beverage and never in the form of extracts for the treatment of anxiety. Implicitly this reflects his opinion that Kava has no effect, respectively the rather strange view that scientifically the effects of the aqueous Kava drink must be separated from the effects of ethanolic extracts.

- Hagemann states that adverse effect reports are thoroughly examined by the staff of his department, taking into account the possibility of underlying diseases, proper use and quality. However, this is exactly what we found to be insufficiently addressed in the drug safety protocol. Questions related to the differences in the quality of raw materials, and hints to other possible causes of the reported adverse events (e.g. underlying hepatic disease!) were never taken into consideration,



and the line listings with tabulated adverse events prepared by the BfArM contain a high amount of factual errors.

- The question of the alleged inefficacy was again raised, although not directly related to a specific herb. Hagemann said: “If there is no benefit, you have to take it off the market”. This reflects a general problem of pharmacovigilance in Europe: The definition of benefit and risk is far from being consistent. Whereas in the very same conference 80.000 causal case reports with Vioxx (also banned) were claimed to be in an acceptable range in view of the benefits millions of users experienced (less than 1 case report of stroke or cardiac infarction in 10,000 patients stood against an anti-inflammatory efficacy) the same moderate view is not attributed to Kava (less than 1 case report of hepatotoxicity in 10,000,000 patients!). Here, the benefit is simply not accepted, despite the existence of >35 clinical trials and several positive meta-analyses for Kava.

- Pinpointed to Kava, Hagemann stated in the discussion that the number of adverse effect reports (and thus the incidence) is less important than the severity of the adverse reaction. Hepatotoxicity of Kava clearly outweighs the low number of reports (almost verbatim). The problem with this kind of argument it is entirely based on an arbitrary judgement: What is an acceptable threshold of severity? Severe adverse events are linked to any plant or agent, and have to be expected for any plant or agent once in a while. The argument used by Hagemann demonstrates that in fact the question of incidence rates, (the number of case reports with Kava is by far lower than the natural occurrence of liver disease without any link to drugs or toxins) does not seem to be relevant to the German BfArM.

As Hagemann has to defend his highly questionable decision on Kava (there are liabilities at stake – the question of indemnity is still open), a retraction from him seems unlikely. However, the general attitude in the audience was one of disbelief, even from regulatory people from other countries such as Switzerland – even though these countries also banned Kava.

Re-evaluations of Kava

One of the reasons why Kava was not mentioned by the representatives of the MHRA and the WHO was the pending review. In both cases I was told in discussions in the coffee break that the result of the review of the MHRA is to be expected imminently possibly in May. In fact the MHRA re-evaluation has meanwhile been published, confirming the established view of the risk-benefit profile of Kava. However, the situation in the United Kingdom cannot be compared with the one

encountered in Germany or Switzerland. In the UK, Kava was mostly used in the form of unregulated health products, whereas the few Kava preparations registered as drugs were not intended for the treatment of anxiety disorders, but rather bladder discomfort. This indication, formerly mentioned in pre-war pharmacopoeias, has never been substantiated in clinical trials.

The review of the WHO seems to be almost finished, and will also be published in the near future. From this report, we may reasonably expect a much better view on Kava than the one held by Hagemann/Thiele from the BfArM. Rumours from insiders say that Kava hepatotoxicity might be seen as a consequence of a quality problem, which might open a way to demonstrate that the quality issue has been effectively solved with the Kava exporting states of the South Pacific.

Requirements for CTDs

- Until 2011, all herbs currently on the market which are not in the process of drug registration will have to be registered under the rules of traditional use. Drugs not being registered after that date cannot be traded any longer.

- An application for “traditional use” is needed in any EU member state or through the EMEA, which in the case of the EMEA requires the creation of a monograph, and in the case of a national registration a full documentation by the producer. In both cases work will have to be done to compile the necessary documentation. I was again told in London that London lacks the personnel and the funding to properly perform its task to create lists of traditionally used plants. It is now quite obvious that EMEA will not be able to provide much support for a high number of herbs. Producers will have to act, and to act soon, or otherwise they will lose their market.

- Any registration of a traditional herbal product will have to be accompanied by a quality dossier according to CTD (Common Technical document) part 3.2. This part of the CTD includes sophisticated analyses on the levels of the herb, the preparation and the finished product. The major topics to be addressed are identity, purity (e.g. lack of adulterants, mycotoxins, heavy metals or microbiological contaminations) and stability. Traceability of the herbal raw material is also a major topic. All tests have to be validated. Again, producers will have to act soon, especially since stability testing takes up to 5 years. Products without a CTD will not be accepted on the market any longer.

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Dr. Mathias Schmidt

(For the ANME/EFCAM)



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