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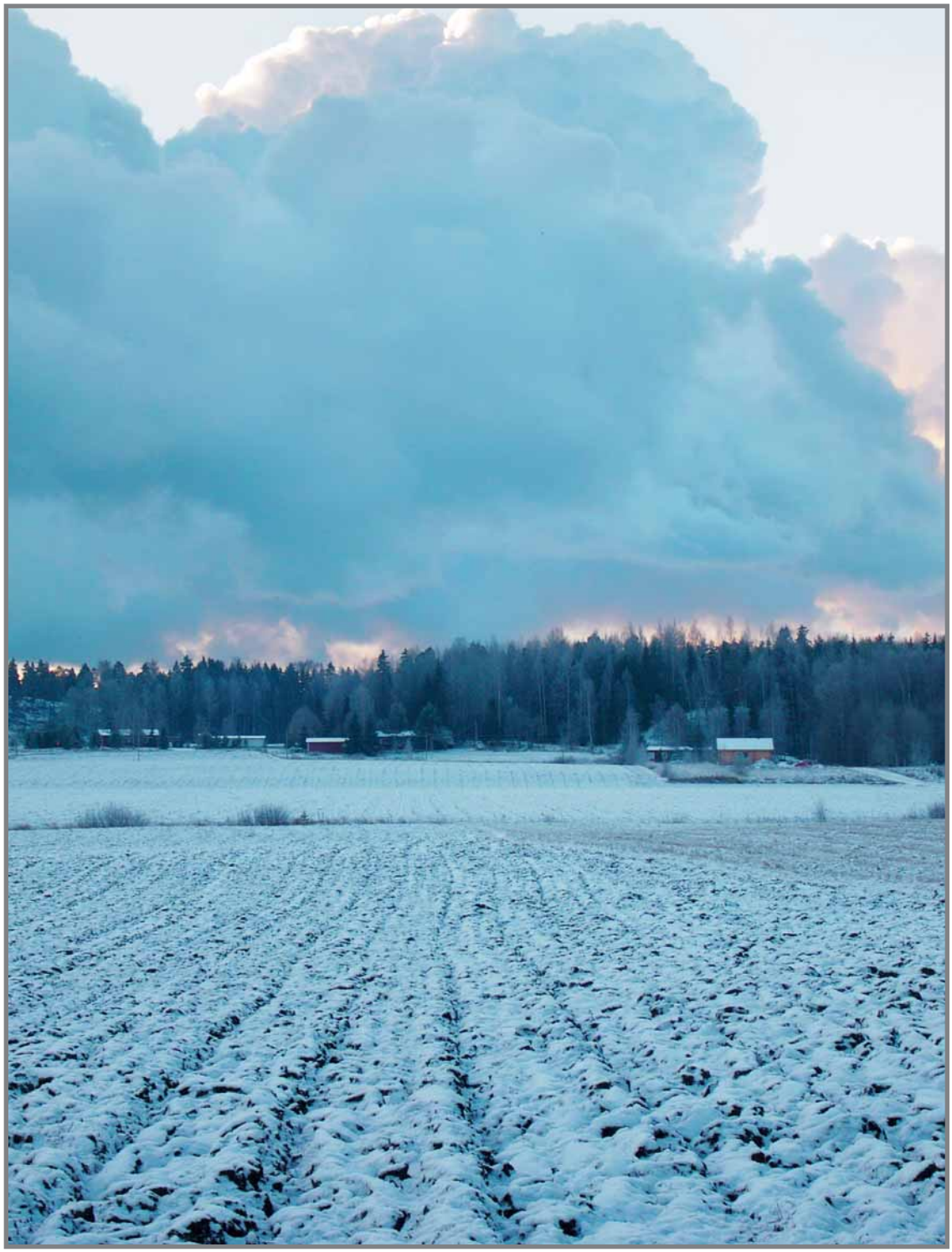
TABU

LÄÄKEINFORMAATIOTA LÄÄKELAITOKSELTA

LÄKEMEDELSINFORMATION FRÅN LÄKEMEDELSVERKET, FINLAND | DRUG INFORMATION FROM THE NATIONAL AGENCY FOR MEDICINES, FINLAND



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Sammandrag

Summary

Summary

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Forty years of European regulation of pharmaceuticals

A landmark in European regulation of pharmaceuticals will be reached on 26 January 2005. It is forty years since the first Directive on the regulation of medicinal products was adopted. Council Directive 65/65/EEC was published in the Official Journal of the EC on 9 February 1965.[1]

This fundamental Directive is a reflection of the reaction of the EEC and its six Member States to the world-wide disaster involving the use of thalidomide at the time. The marketing authorisation procedures even of many non-EEC countries, including those of Finland, for example, have their origins in the 1960s. The two options of the European system for the authorisation of medicinal products were even at that time the centralised and decentralised marketing authorisation procedures. However, the initial resolution focused only on harmonising the national procedures and the scientific evaluation criteria.

The first pharmaceutical directive was argumented by the need to safeguard public health and promote the internal markets – the most recent EU pharmaceutical legislation is also sustained by the same basic principles. The principles adopted forty years ago still largely remain the mainstay of the EU regulation of medicines. The most important principle of them all is perhaps the stipulation that a medicinal product cannot be sold or marketed unless it has a marketing authorisation approved by the authorities. Another essential principle is that issues relating to the efficacy, safety and quality of the product can be the sole grounds for considering a marketing authorisation.

It was as important 40 years ago as it is now that the authorities should have a carefully specified time limit within which to grant the marketing authorisation and that, once granted, the marketing authorisation cannot be cancelled other than on the grounds given in the directive. The incorporation of these principles in the national legislation took several years in many countries. In Finland, the principles were adopted in association with the EEA agreement in 1994.

With the enlargement of the EU through the decades the regulation of pharmaceuticals and the pharmaceutical legislation in Europe became more profound in many respects. The procedures of approval and regulation have become centralised, and closer collaboration between Member States has been established. The present EU regulation of medicines covers several specific categories of medicines. Examples of them include biotechnological medicinal products, orphan medicinal products, traditional herbal medicinal products and the proposed Regulation on paediatric medicinal products. Veterinary medicinal products are also an essential part of the regulation of medicines.

The cost of developing a new innovative medicine is estimated at about 800 million US dollars. There has been an exponential rise in the research and development costs. At the same, the pharmaceuticals regulation and the internal market have improved. Important new innovations from the pharmaceutical industry, both in Europe and the USA, are not seen as often as they used to be. Justifiably, the question has been raised whether the research and development cost of a new medicine could be reduced and whether we should address the issue of the authorities' requirements for scientific and other evidence in association with marketing authorisations.[2]

It has also been suggested that the authorities appear to have 'ritualistic' requirements, the original grounds for which nobody any longer properly knows.

Unnecessary and groundless rituals in the authorisation of medicinal products – where they exist – should of course be abandoned. However, it makes sense and is preferable in general in the authorisation of medicines to pursue with caution rather than in a hazardous fashion. It appears that breakthrough innovations increasing the wellbeing of mankind are being made irrespective of the stipulations imposed by the regulation of medicines, or – at best – with the help of the stipulations.

[1] Council Directive 65/65/EEC of 26 January 1965 on the approximation of provisions laid down by law, regulation or administrative action relating to proprietary medicinal products. OJ No 22, 9.2.1965.

[2] Rawlins MD: Cutting the cost of drug development? Nature Drug Discovery 3:360-364, April 2004.

Summary

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Safety of dopamine agonists

Neurologists all over the world are concerned about the safety of the use of dopamine receptor agonists, since hitherto unknown and potentially life-threatening adverse effects have been described in association with drugs which have been in use for years (1). Dopamine agonists are used in the treatment of Parkinson's disease, restless legs syndrome, hyperprolactinaemia and acromegaly.

Bromocriptine, cabergoline and pergolide are ergot derivatives, whereas products such as quinagolide, pramipexole and ropinirole do not have an ergot radical. Clinical use of the drugs is based on the concept that they have an effect on the nerve tissue similar to that of dopamine. They are all D_2 receptor stimulants with varying effects on D_1 and D_3 (Table) and non-dopaminergic receptors. Ropinirole is selectively bound to dopamine receptors, pramipexole has a mild effect on noradrenergic alpha$_2$ receptors and ergot derivatives are also bound to noradrenergic (alpha$_1$ and alpha$_2$) and 5HT receptors.

Dopamine effect

The most common adverse effects of dopamine agonists are associated with their dopaminergic effects. These effects often occur at the start of treatment or are transient following an increase in the dose, and most of them are similar to one another. The adverse effects include nausea, vomiting, orthostatic hypotension, vertigo, somnolence and (in concomitant use with levodopa) dyskinesia (2). Common reactions also include insomnia, constipation, abdominal pain, indigestion and feeling weak. Dopamine like substances may on long-term use also cause confusion, hallucinations or paranoia, especially in individuals with impaired cognitive function. The rarer reactions include compulsive gambling and hypersexuality, priapism, reduced breast size and alopecia. Headache, nasal congestion and Raynaud's syndrome may also occur in patients on ergot derivatives. Efficacy and tolerability do not seem to vary considerably between the various dopamine agonists, even though, admittedly, comparisons have been made only with bromocriptine (3).

Some of the more recent adverse effects are discussed below.

Disturbances of alertness

Increased daytime sleepiness, increased frequency of nodding off and sudden sleep attacks have been reported with the use of dopamine agonists, especially in Parkinson's disease (4, 5). The problem has attracted special attention recently, since in 1999, a couple of patients were reported as having suddenly fallen asleep while driving.

In various studies (5) sleepiness has been reported in 18.3–32.4% of

Properties of dopamine agonists

	Bromocriptine	*Cabergoline*	*Pergolide*	*Quinagolide*	*Pramipexole*	*Ropinirole*
Receptor binding	D_1, D_2, D_3	D_1, D_2	D_1, D_2, D_3	D_2	D_2, D_3	D_2, D_3
Ergot derivative	*Yes*	*Yes*	*Yes*	*No*	*No*	*No*
Tmax (hours)	*1–2*	*0.5–4*	*1.5*	*0.5–1*	*2*	
T1/2 (hours)	*3–8*	*68*	*1–42*	*12–18*	*8–12*	*6*

patients on pramipexole and in 8.8–13.7% of patients on a placebo. It has been more common in patients using pramipexole than in the levodopa group of patients (17.3%) (6). Sleepiness was associated with ropinirole therapy in 36.2% of patients and in 4.8% of patients in the placebo group (7). It occurred mostly as the dose of medication was increased and at higher daily doses.

Despite the more prominent role of the more recent non-ergot agonists, there is a similar problem with the rest of the agonists (8, 9) and it seem apparently that the differences among the various drugs are not all that significant.

A sudden compulsive sleep attack, where falling asleep happens either without warning or so quickly that the person has no time to react properly, appears to be rarer than the irresistible need to fall asleep, where the person is able to react appropriately. In a study of 420 patients, Hobson et al. (10) reported sudden attacks of sleep in 16 patients while driving (3.8%), in three of whom (0.7%) this occurred without warning. The percentages are likely to show the overall tendency, and they correlate with the duration of the monitored period. If sudden sleep attacks occur, the patient should avoid driving. Patients should also be advised about it at the start of the treatment.

Oedema in the lower extremities

Oedema in the lower extremities ('pitting oedema') is a common problem associated with all dopamine agonists and in many patients has resulted, for example, in investigation for causes of cardiac origin. Among the more recent agonists, it is perhaps associated a little less with the use of ropinirole (11). The underlying biology of the problem is unknown, but it may be associated with the vasodilatory effect of dopamine.

Neuroleptic malignant syndrome

A condition similar to neuroleptic malignant syndrome may easily develop if medication is suddenly stopped. The clinical signs of this rare problem include fever, muscular rigidity, fluctuating level of consciousness and various disturbances of the autonomic nervous system (tachycardia, sweating, blood pressure changes, hypoventilation and elevated serum creatine kinase (12).

Adverse effects on the lungs and connective tissues

Ergot derivatives (bromocriptine, cabergoline and pergolide) have for a long time been known to cause pulmonary, pericardial and retroperitoneal pleuritis and fibrosis (13, 14). Upon discontinuation of the medication, the pleural fluid disappears, but fibrosis may result in reduced respiratory function.

The summaries of product characteristics give the impression that the problem is relatively rare, and according to the adverse drug reaction register the frequency with pergolide is about 1% in relation to the use of the drug (13). Between 1982 and 1995, in the Department of Neurology of Helsinki-Uusimaa Hospital District, 33 of the total of 185 long-term patients with Parkinson's disease receiving mainly bromocriptine or pergolide therapy were diagnosed as having pleuritis for an average period of 6 months (15). An ergot agonist was being used experimentally in four of the patients. The problem therefore appears to be far more common than is obvious from the adverse drug reaction register, and a conservative estimate shows that the risk in long-term treatment may be over 10%. It may be that Finns are especially sensitive; after all, the very first report of an adverse reaction was made in Finland in 1981 (16).

Adverse effects on the connective tissues have also been reported in patients who have been given an ergot agonist for the suppression of prolactin (17) or for the treatment of restless legs (18). Fewer adverse effects in these reports could indicate that the problem is dose dependent.

Non-ergot agonists are not expected to be associated with the problem of fibrosis. Patients with Parkinsonism previously suffering from ergot-pleuritis (N=11) have been treated (15) with a non-ergot agonist (quinagolide) without difficulty for an average of 620 days followed by pramipexole therapy when it became available in the autumn of 1998. The phenomenon has not been shown in the use of pramipexole or ropinirole, except in some isolated cases with an unclear causal relationship.

Cardiac valve changes

Cardiac valve changes have very recently been reported in patients with Parkinson's disease treated with pergolide and carbergoline; some of the cases have been fatal (19-20). According to a review recently published (22), the problem may actually be very common. Baseman et al. (22) sent a letter to patients whom they knew to be using pergolide advising them to undergo cardiac examination. Forty-six of the recipients of the letter did as advised, and the researchers reported that 89% of the patients were suffering from some degree of cardiac valve regurgitation. Incidences of valvular regurgitation have been fewer in patients in Central-Europe compared with the USA, but the disorder still affects 33% of patients (23). Since migraine treatment with ergot derivatives (24) and the use of bromocriptine (25) have also been reported as having been associated with corresponding changes, a risk of a side effect characteristic of all ergot derivatives can be assumed, and all colleagues should be made aware of this. The actual extent of the problem will perhaps be revealed in the course of time.

Ergot pleuritis does not cause fever in the patients; the CRP and the ESR are elevated, but there is no leucocytosis. The authors have no information about laboratory results in patients with cardiac valve disorder.

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Cardiac QT interval prolongation and drugs

The cardiac action potential normally lasts for 200–300 milliseconds. As it is corrected according to the heart rate (QTc), the terms QT interval and QTc interval are used as synonyms in this article for the sake of simplicity. A QT interval prolongation over 440-460 milliseconds can cause ventricular fibrillation which, if left untreated, causes sudden death in about 20–25% of the patients. Ventricular fibrillation is in the ECG curve preceded by *torsades de pointes* type ventricular tachycardia.

There are two forms of the long QT syndrome, a congenital and an acquired one. The congenital form has seven different known predisposing genes, six of which are associated with the myocardial ion channels. The prevalence of the congenital form is estimated at less than 1/10000. Among the congenital forms, particular interest is focused on the potassium channel coded by the HERG gene located on chromosome 7 and with a key role in the normal electric cardiac activity. The potassium channel coded by the HERG gene is partly responsible for the return of the electric cardiac activity to the resting phase before the next myocardial electric activation process. Disturbed function will prolong the return to the resting phase, which is thought to be an essential part of the development mechanism of myocardial *torsades de pointes* tachycardia. There may also be a correlation between the strength of binding of the medicinal substance to the potassium channel coded by the HERG gene and prolongation of the QT interval.

When talking about an acquired QT prolongation, we mean the prolongation of the QT interval caused by drugs, examples of which include the effects of antiallergics such as astemizol and terfenadine. Even though several of the drugs affecting the QT interval are used only at certain seasons, the treatment periods may exceptionally be long-drawn-out. Another drug with QT interval prolonging properties recognised in the beginning of the 1990s, was cisapride. As it is difficult to predict the effects of various drugs on the QT interval, European drug regulation is focusing on the issue, and in future documentation on the effects of drugs on the QT interval even prior to the granting of a marketing authorisation will probably become part of drug safety procedures. In addition, interpretation of the effects is made difficult by the combined use of drugs, as a drug which may not have an effect on the QT interval when used alone may very well have one when used together with another medicinal product.

Drugs with a known effect on the QT interval include e.g. some antiarrhythmics, terfenadine and astemizol, and also some of the antidepressants, antipsychotics and antimicrobials (Table).

During 1981–2004 the NAM received a total of 58 reports on QT interval prolongation. Thirteen of the reports were on *torsades de pointes* ventricular tachycardia, 12 were on ventricular fibrillation, four on cardiac arrest, and one of the cases was fatal.

In addition, two reports were of a suspected interaction between terfenadine and itraconazole, and one on tamsulocine. There were two reports on cisapride, two on cetirizin, and one on ebastine used concomitantly with doxepine. According to ATC system, the most frequently suspected groups of drugs were antipsychotics (21 reports), antidepressants (11 reports) and sotalol (6 reports).

Several drugs have been withdrawn from the market due to the risk of arrhythmia. However, the relationship between the HERG gene, QT interval prolongation and torsades de pointes ventricular tachycardia is also complicated owing to the difficulty, if not the impossibility of assessment and prediction of the causal relationship. Despite the association which exists between the HERG gene, the potassium channel coded by it and the QT interval prolongation, there is at present no definitive proof of a link between these three factors. Obviously, as far as drug safety is concerned, drug effects such as severe cardiac arrhythmia are a major challenge to the medicinal product regulation system, especially in the light of precautionary measures. An example of an attempt to classify medicinal substances according to the QT interval prolongation they may possibly cause, is the website of the University of Arizona; The University of Arizona Health Sciences Center. http://www.qtdrugs.org/.

Most commonly reported drugs

Medicinal substances	*No of reports*
Sotalol	*6*
Sertindol	*6*
Risperidone	*6 **
Venlafaxine	*5*
Terodiline	*4*
Thioridazine	*4 ***

** three of the reports also included other suspected drugs*

*** two of the reports also included other suspected drugs*

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Macrolides and fluoroquinolones – target of improved monitoring

Over more than a decade the use of antimicrobials in out-patient care has fallen by about 10%. Despite the positive development overall, the use of antimicrobials in Finland still exceeds that in the other Nordic countries. The correct choice of antimicrobials in accordance with treatment recommendations and the length of the courses of treatment particularly need to be focused on. The targets for special monitoring are the use of macrolides and fluoroquinolones, including monitoring of the development of resistance.

The tendency of the total consumption of antimicrobials to decrease during the past decade is probably due to that courses of antiobiotics have been shortened. The variations in severity of the epidemics caused by viruses every winter is nevertheless immediately visible from the use of antimicrobials (1). Considerable annual fluctuations are consequently revealed by their use.

A review of the results of the MIKSTRA Program carried out during 1998–2002 is under way. Once the review is ready, it will reveal more detailed information on the use of antimicrobials and the indications for which they have been used in Finland. It is already known that there has been no reduction in their use for the treatment of acute bronchitis (2). Acute bronchitis is still often unnecessarily treated with antimicrobials despite the fact that it is a viral disease. But the treatment recommendations relative to urinary tract infections, in particular with respect to the choice of drug, have been closely followed (3).

Penicillins

According to the Finnish Statistics on Medicines (www.nam.fi/) significant changes have taken place in the various uses of antimicrobials during the 1980s and 1990s (Fig. 1). The use of penicillin V has been reduced by a half during a little over a decade. Its use may have been replaced mostly by amoxicillin. This has all been in line with the current treatment recommendations, since the treatment recommendations, especially for acute otitis and maxillary sinusitis, now also include amoxicillin alongside penicillin as the primary drug. The easier use of amoxicillin, especially in the treatment of infections in children, may also have contributed to its increased use.

An increase in the use of amoxicillin-clavulanic acid also has been seen in recent years. In the treatment recommendations, however, this is distinctly treated as a secondary drug. The increased use may be explained by the fact that respiratory tract infections are considered by doctors more often to be caused by bacteria which produce betalactamase. The production of betalacta-

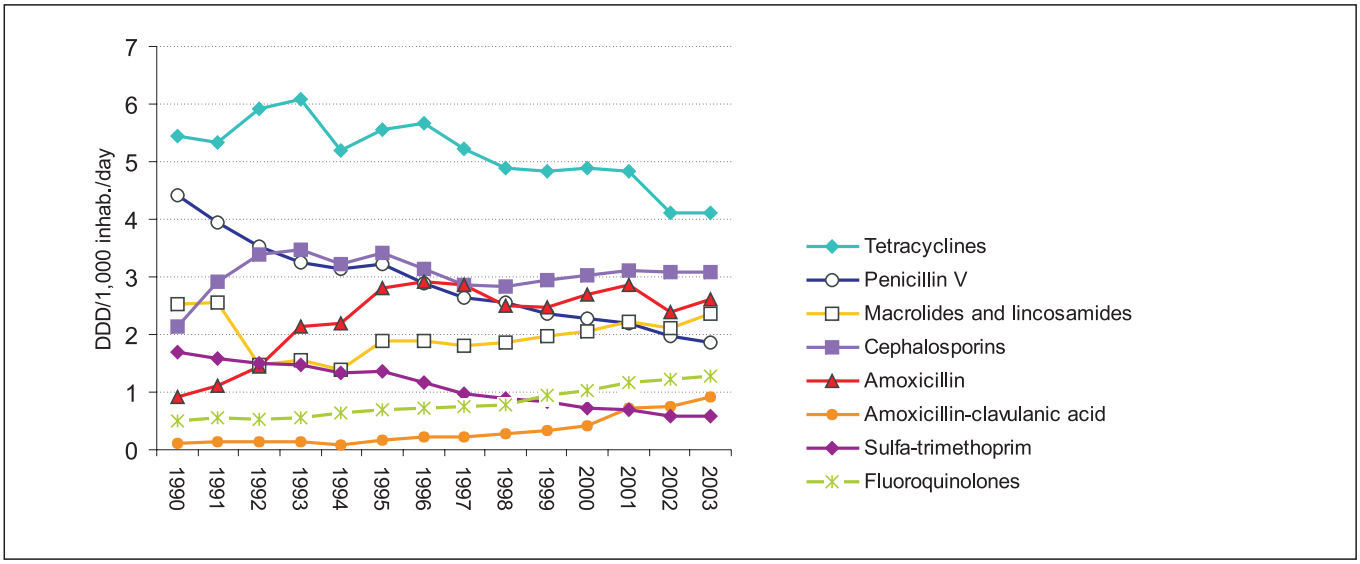

Fig. 1. Consumption of most common antimicrobials in Finland 1990–2003

mase by bacteria such as *Haemophilus influenzae* and *Moraxella catarrhalis* has not, however, increased during the past seven years, but rather diminished (www.ktl.fi/extras/fire). The efficacy of amoxicillin-clavulanic acid against pneumococcus is equal to that of amoxicillin alone. Grounds for the increased use of amoxicillin-clavulanic acid are therefore difficult to find.

Cephalosporins

Cephalosporins are rather widely used in Finland, compared with other European countries (http://www.ua.ac.be/main.asp?c=*ESAC). The consumption profile is, however, totally different compared to that of other European countries. The ones used in Finland are mainly first-generation cephalosporins concentrating on the treatment of infections of the skin and of the respiratory tract. The treatment of skin infections with first-generation cephalosporins mainly follows the current treatment recommendations. In the treatment of respiratory tract infections, however, first-generation cephalosporins do not have primary indications. Their efficacy against pneumococcus is not superior to that of amoxicillin or penicillin V, and the efficacy against *Haemophilus* is poorer than that of amoxicillin. In the treatment of tonsillitis, first-generation cephalosporins have often been regarded as a primary drug equivalent to penicillin. At the present time they are still defined as a secondary choice in the current treatment recommendations.

Second- and third-generation cephalosporins are hardly ever used in out-patient care in Finland. This is excellent. Their clinical efficacy in the treatment of out-patient infections is not superior to that of the primary drugs included in the treatment recommendations. Furthermore, their oral administration is associated with a host of gastrointestinal adverse effects. The avoidance of these drugs has also delayed the development of bacterial resistance.

Sulfa-trimethoprimes

Products containing sulfonamide alone were quietly withdrawn from the Finnish market around the mid-1990s. That marked the end of the journey as far as its use went as an independent product of the first antimicrobial developed by humans. The use of the sulfa-trimethoprim combination is also modest. The fear of the serious adverse effects of sulfonamides and the development of resistance are the main reasons for the decreased use. Sulfa-trimethoprim is nevertheless still an important secondary or third alternative in the treatment for otitis and perhaps even for sinusitis. The situation with regard to the sensitivity of respiratory pathogens is also somewhat improved compared with that five years ago.

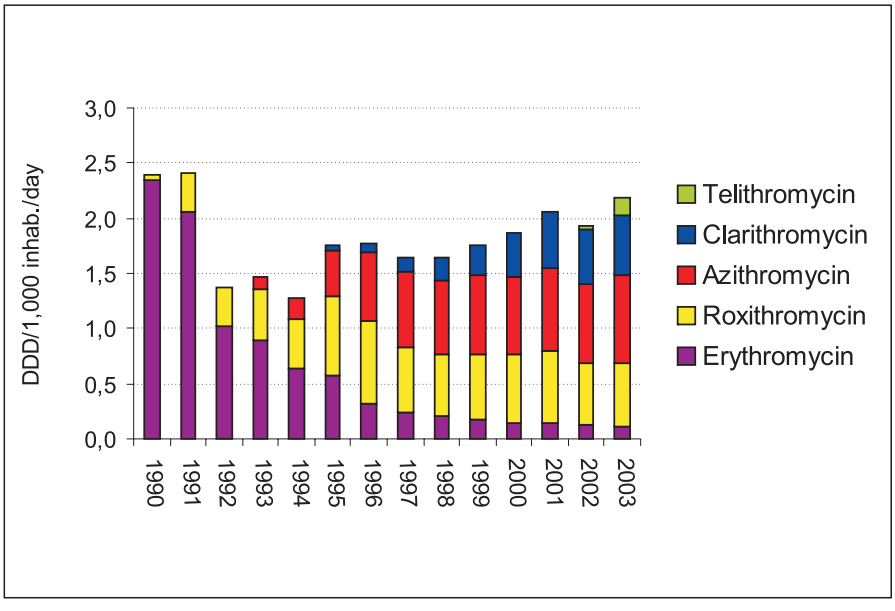

Fig. 2. Consumption of macrolides in out-patient care in Finland 1990–2003

Trimethoprim has retained its position as a primary drug in urinary tract infections (3). The sensitivity to trimethoprim of *E. coli* separated from urinary samples has also increased rather than decreased. Trimethoprim, side by side with mecillinam, is the drug most commonly used in urinary tract infections.

Tetracyclines

As with penicillin V and sulfa-trimethoprim, the use of tetracyclines has also declined during recent years. Tetracyclines are the conventional drugs in the treatment of respiratory tract infections. The use of tetracyclines has been replaced partly by macrolides and partly by amoxicillin. The sensitivity to tetracyclines of bacteria causing respiratory tract infections still remains good, however, despite their continuous use for decades. The position of tetracyclines could therefore be reviewed in the next update of the current treatment recommendations, especially in regard to the treatment of adult otitis and sinusitis. This would reduce the pressures to use macrolides and other secondary drugs.

Macrolides

The use of macrolides was cut by almost a half during 1992–1994 as a result of the recommendations given in association with the increase in the macrolide resistance of Streptococcus A bacteria (Fig. 2). For now, the use of macrolides has reverted to almost the same level as that at which it was during 1990–1991. It remains to be seen whether the considerable increase recently reported in the macrolide resistance of pneumococci has any effect on drug use (4, 5). In order to halt the increase in the resistance of pneumococci, the use of macrolides should be significantly decreased in the treatment of infections caused by pneumococci. The preconditions for this are good, since macrolides are only rarely used as primary drugs in the treatment of infections in out-patient care. Together with the increase in the macrolide resistance, the efficacy of these drugs against pneumococci is

also reduced. The use of macrolides and the development of the situation regarding bacterial resistance will continue to be closely monitored in the years to come.

Fluoroquinolones

The increased use of fluoroquinolones is a result of the increase in the use of both levofloxacin and ciprofloxacin (Fig. 3). The use has nevertheless remained relatively steady during the last four years. Norfloxacin and ciprofloxacin are probably mostly used in the treatment of urinary tract infections. In urinary tract infections fluoroquinolones are nevertheless a secondary drug group, in which position they have also remained according to the results of MIKSTRA.

According to the Finnish Statistics on Medicines 2003, 43% of the levofloxacin used is used in out-patient care. A closer study on the indications for use is not available at present. However, levofloxacin remains a drug in reverse for the treatment of respiratory infections and it should only be used in special cases.

The increase in the use of fluoroquinolones is already apparent in some areas in the form of an increased resistance of urinary tract *E. coli* bacteria. The fluoroquinolone resistance of *Neisseria gonorrhoea* in 2003 was approximately 20%. A large proportion of *Campylobacter* are resistant to fluoroquinolones, and the degree of sensitivity of *Salmonella* is also falling. According to experience in other parts of the world, the increased use of fluoroquinolones in the treatment of respiratory infections has also been apparent in the level of resistance of pneumococci. Consequently, the use of fluoroquinolones and the state of the resistance to them are also closely monitored in Finland.

Conclusion

The changes in the use of antimicrobials reflect in many ways the spirit of the current treatment recommendations in Finland. Positive changes include the reinforced position of amoxicillin for otitis and sinusitis and the recommended treatment practice for urinary tract infections.

Negative developments include the increased use of macrolides and the increase in the macrolide resistance of pneumococci. The use of fluoroquinolones has also more than doubled, already with associated emerging problems of resistance.

The position of tetracyclines in the treatment of respiratory infections could be reviewed, especially since the level of resistance to other drugs used for these infections is gradually making those less effective.

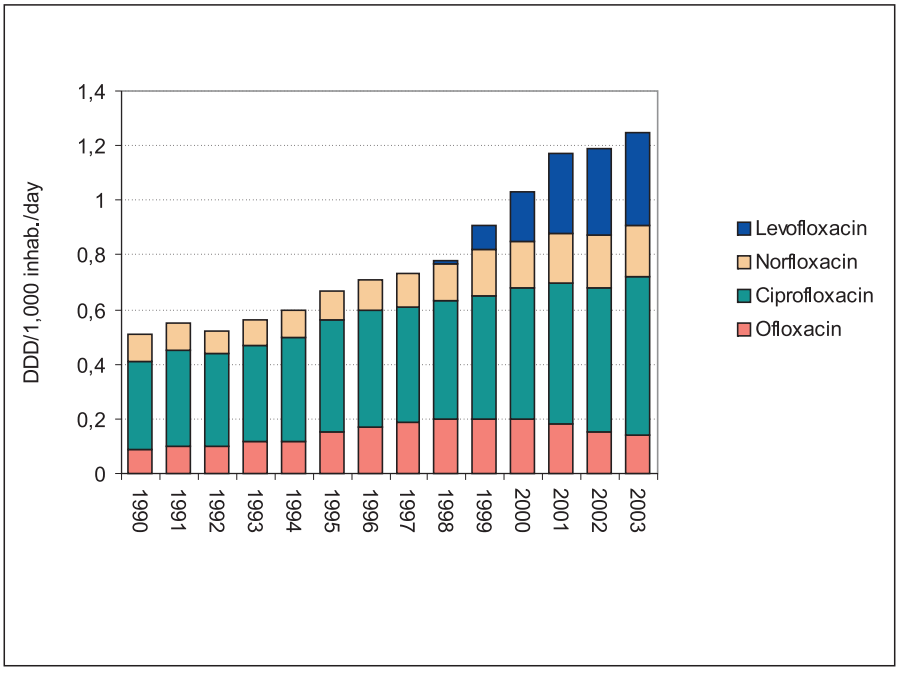

Fig. 3. Consumption of most common quinolones in Finland 1990–2003

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Complementary medicine in Australia

'Complementary therapies' or 'Alternative therapies' were not always known as complementary or alternative. In the past these were the only available therapeutic agents. Traditionally plant, sometimes animal or mineral derived products were used for therapeutic purposes. In many developing countries patient care still relies extensively on herbal or similar preparations. The World Health Organization estimates that the extent of this reliance is as high as 80%. (1).

In the public debate of the pros and cons of various medications it is often forgotten that many modern drugs are derived from herbs and plants (table 1).

With the emergence of modern chemistry the active ingredients of medicinal plants, such as those above, were extracted and purified. Consequently for the last century there has been an emphasis on the use of purified or purpose made preparations to achieve predictable therapeutic goals. This approach has been extremely effective and has facilitated an unforeseen development of new therapies. Nevertheless, there is a worldwide resurgence of "*traditional*" therapies.

These trends are clearly evident also in Australia. Complementary medicine, is now gaining the attention of the broader health care sector and the regulatory agencies. The Australian Medical Association (AMA) defines the term complementary medicine as *a wide range of non-prescription products with health claims such as herbal medicines, homoeopathic medicines, nutritional and other supplements such as vitamins and minerals.*

Complementary therapies" include acupuncture, chiropractic, osteopathy, naturopathy, aromatherapy, reflexology, iridology, kinesiology and meditation" (2). Often the term complementary medicine refers to both complementary medicines and therapies.

The Therapeutic Goods Administration of Australia (TGA) defines complementary medicine as "*a regime for the prevention or alleviation of a disease or ailment, or for the maintenance of health, and which does not necessarily rely on evidence of efficacy based on Western medical practice*" (3).

These definitions are in line with the World Health Organization, who defines complementary and alternative medicine (CAM) as a *broad set of health-care practices that are not part of a country's own tradition and not integrated into the dominant health care system* (1). Whilst this definition may be accurate, soon it may need to be revised as the use of complementary medicine continues to increase and in some countries exceeds the use of conventional medicine.

Table 1. Examples of drugs derivated from herbs

Salicylates ('aspirin')	*Willow bark (Salix sp.)*
Opium (morphine, codeine)	*Poppy (Papaver somniferum)*
Digitalis	*Foxglove (Digitalis purpurea)*
Scopolamine	*Angels trumpets (Brugmansia suaveolens)*
Atropine	*Belladonna (Atropa belladonna/Deadly nightshade)*
Colchicine	*Colchicum (Colchicum autumnale)*
Cocaine	*Coca leaves (Erythroxylum coca)*

Historic transition to modern therapies

The pharmacological treatment of disease emerged long ago with the use of herbs (4). Herbs were an important part of traditional folk healing throughout the world. By definition *traditional use* of herbal medicines, implies significant historical use. Complementary medicines have maintained their popularity for historical and cultural reasons irrespective of efficacy. However, these products have become much more widely available commercially, especially in developed countries. The commercial marketing of complementary medicines has led to uses that were never contemplated in the traditional healing systems. The use of ephedra (*Ephedra sinica*, Chinese Ephedra, *Ma huang*) for weight loss or athletic performance is a good example of this (5).

Resurgence of complementary medicines and therapies

Whilst complementary medicine has maintained its place in all regions of the developing world for historical reasons but also out of necessity, in the industrialized countries the rapid growth of their use is occurring for other reasons (table 2).

Use of complementary medicine in Australia

There has been a sharp increase in the expenditure for complementary

medicine in Australia. Over 52% of the population use complementary medicines and 23% visit practitioners for complementary therapy. It is estimated that in 2000 the Australian public outlaid $1,671 million on complementary medicines, when by comparison they outlaid $688 million for prescription medications. Figure compares the out of pocket expenses of Australians on complementary therapies, complementary medicine and prescription medication in Australia. Based on the figure it appears that there has been a ~2-fold increase in total expenditure on prescription medicines between 1993 and 2000, and a ~3-fold increase in expenditure on complementary medicines for the same period. This data highlights the increase in use and popularity of complementary medicines in Australia.

A significant proportion of complementary medicines used in Australia are herbal products. Table 3 shows the top 10 selling herbs by pharmacies and supermarkets in Australia for 2000–2001. This usage pattern is very much in line with the USA and other western countries.

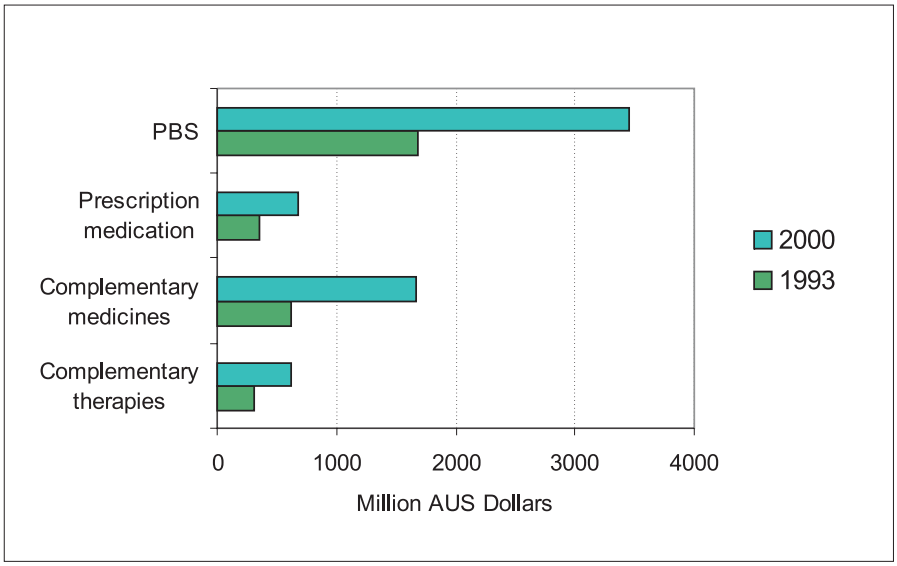
Adverse effects

One of the greatest problems with complementary medicine is that many people consider them to be intrinsically safe because they are derived from natural sources. In the study conducted by MacLennan (7), 90% of people who used complementary medicines considered them to be safe. This belief in their safety remains largely intact even though there are 150–200 cases of adverse reactions per year reported to the Australian Government Adverse Drug Reactions Advisory Committee (ADRAC) (8). The main types of adverse reactions reported to ADRAC include headaches, skin rashes, dizziness, nausea and gastrointestinal upsets (10).

Whilst the figure of 150–200 is only a small proportion of the 12,000 adverse reactions reported to the ADRAC annually, it should be noted that complementary medicines have only been recently added to the ADRAC list. Other reasons for the low number of adverse effects

Table 2. Observations regarding the increase in use and popularity of complementary medicines according to the WHO (6)

- *25% of modern medicines are made from herbs first used traditionally.*
- *In China, traditional herbal preparations account for 30–50% of the total medicinal consumption.*
- *In Ghana, Mali, Nigeria and Zambia, the first line of treatment for 60% of children with high fever resulting from malaria is the use of herbal medicines at home.*
- *In Europe, North America and other industrialized regions, over 50% of the population have used complementary or alternative medicine at least once.*
- *In San Francisco, London and South Africa, 75% of people living with HIV/AIDS use complementary medicines.*
- *70% of the population in Canada have used a complementary medicine at least once.*
- *In Germany, 90% of the population have used a natural remedy at some point in their life. In Germany between 1995 and 2000, the number of doctors who had undergone special training in natural remedy medicine had almost doubled to 10,800.*
- *In the United States, 158 million of the adult population use complementary medicines and according to the USA Commission for Alternative and Complementary medicines, US $17 billion was spent on traditional remedies in 2000.*
- *In the United Kingdom, annual expenditure on alternative medicine is US$ 230 million.*
- *The global market for herbal medicines currently stands at over US $ 60 billion annually and is growing steadily.*



The trends in out of pocket expenses for complementary therapies, medicines and prescription medication in Australia from 1993 to 2000. *The total cost of the Pharmaceutical Benefits Scheme (PBS) is given as a comparison (the PBS is what the government in Australia contributes to the cost of prescription medications).*

Table 3. Combined retail sales data for supermarkets and pharmacies in Australia for 2000 and 2001. *Adapted from Wohlmuth et al. (9)*

Herbal product	*AUS Dollars*	*% Share of herbals*
Echinacea (Echinacea sp.)	*15,500,000*	*13*
Phytoestrogens	*11,000,000*	*9*
Evening Primrose Oil (Oenothera biennis)	*10,000,000*	*8*
Garlic/Horseradish (Allium sativum/Radicula rusticana)	*7,500,000*	*6*
Valerian (Valeriana officinalis)	*6,500,000*	*5*
Ginko (Ginkgo biloba)	*6,500,000*	*5*
Hypericum (Hypericum perforatum)	*6,500,000*	*5*
Guarana	*4,500,000*	*4*
Celery (Apium graveolens)	*4,500,000*	*4*
Garlic (Allium sativum)	*4,000,000*	*3*

reported include the ease of access to products, lack of knowledge by many practitioners and members of the public as to what constitutes an adverse effect. Self medication with complementary medicines may also lead to under-reporting of adverse effects. However, the low number of adverse reactions reported in relation to complementary medicines cannot be taken as an indicator of safety.

Causes of adverse effects

The increased use of complementary remedies in western cultures has resulted in their unregulated marketing and use. In some cases this has lead to tragic consequences. In 1993 over 100 cases of irreversible nephropathy were reported in young women attending a slimming clinic in Belgium. The nephrotoxicity was traced to the accidental substitution of *Stephania tetandra* with the highly toxic *Aristolochia fangchi*. The misidentification of other *Aristolochi*a species has occurred in the United Kingdom, China and France (11). Substitution of one ingredient with another may be accidental due to misidentification or deliberate.

Deliberate substitution with other herbal products or illegal "*fortification*" with medicinal substances may have dire consequences. The addition of corticosteroid in creams for the treatment of eczema, fenfluramine in a slimming product and prescription medicines such as sildenafil, glibenclamide, warfarin and alprazolam in herbal products have all been reported (11).

In the modern mass marketing of complementary medicines quality standards in manufacturing are important. Poor manufacturing standards are a health threat to the consumer. In January 2003, questions into the manufacturing and quality control processes were raised by the TGA with respect to a very large Australian manufacturer of generic and complementary medicines. Initially it was found that the content of the active ingredient (hyoscine hydrobromide) in motion sickness tablets varied from 0–700% of the listed dose. Under further scrutiny a large number of irregular practices emerged affecting both generic and complementary products. Table 4 summarizes the findings of the expert committee from the TGA that investigated the manufacture plant. In April 2003, there was a large-scale recall of medicines involving as many as 219 products. The manufacturing license was subsequently suspended and now the company has gone into liquidation.

There are many examples of heavy metal contamination of complementary medicines. Heavy metal content may arise from contaminated raw materials, from processing and manufacturing practices or be added deliberately. In the latter case it may be declared as a constituent of complementary medicines. The Chinese Pharmacopoeia lists formulations for nearly fifty products that include heavy metals such as arsenic or mercury.

"Tainted herbal tablets poison baby

The item above is of a case of heavy metal contamination of complementary medicines reported in an Australian newspaper:
"Doctors measured the highest yet recorded lead level in a newborn baby after a woman who had been taking contaminated herbal tablets gave birth in an Adelaide hospital. The girl was born critically ill but survived despite having a blood lead concentration 25 times the maximum acceptable level.

Her 24-year-old mother, who recently emigrated from India, had for nine years been taking herbal tablets prescribed to her by a doctor skilled in Eastern medicine to treat a stomach complaint. In the nine months of her pregnancy, the woman's lead intake was estimated to be at least 50 times the average weekly intake of Western populations. The baby was born with an abnormal brain condition known as encephalopathy." *(The Age 19/08/2002)*

Another significant concern with complementary medicines is that they are, by their nature, self-administered and consequently patients may not seek medical advice for potentially severe medical conditions.

Other causes of adverse reactions may be the consumption of products such as infusions of comfrey, which may contain pyrrolizidine alkaloids.

Complementary therapies themselves rather than complementary medicines have also been a cause of adverse events. Most of the adverse

Table 4. Findings from the TGA's investigations into the Australian manufacturer (12)

- *Misidentification of raw material, especially herbal materials, which could lead to severe organ damage, including renal and hepatic damage*
- *Cross-contamination or substitution of ingredients due to inadequate operating procedures and poor compliance with existing procedures could lead to severe allergic reactions including anaphylaxis*
- *Microbiological contamination through poor raw material sourcing and handling, poor cleaning practices, and inadequate operating procedures, potentially leading to infections*
- *Substitution of shark cartilage for bovine cartilage which could cause seroius allergic reactions, including anaphylaxis, in fish-protein sensitive individuals*
- *Substitution of bovine cartilage for shark cartilage where the bovine cartilage has been sourced without any assurance that it is TSE-free, and the country of origin is unknown*
- *Bovine colostrum obtained from non-approved suppliers where the raw material may have been sourced from a TSE 'at risk' country, and where the source is unknown*
- *Manipulation of assay results of finished products in order to comply with specifications*
- *Fabrication of assay results of a finished vitamin product for export in order to comply with specifications*

effects are associated with acupuncture and include systemic infections, endocarditis, septicemia, hepatitis B, HIV, osteomyelitis, myositis, peritonitis and pleural emphysema (13).

Complementary and Western medicines

It has been well documented that complementary medicines can interact with western medicines, these interactions can cause adverse effects. The concurrent use of complementary and western medicine is reported to be as high 30% in Australia (7). Therefore based on this estimate as many as 1.8 million to 4 million Australians may be effected by such interactions in 2004 (14).

The potential for adverse effects including interactions is compounded by the patients not disclosing the use of complementary medicines to their doctors. An American study revealed that 63–72% of patients did not tell their doctors about their use of complementary medicines and therapies (15). Reasons given by the patients included "*it's not important for the doctor to know*" (61%), "*the doctor never asked*" (60%) "*it was none of the doctors' business*" (31%) and "*the doctor would not understand*" (20%). In Australia also the reported level of undisclosed concurrent use of complementary medicines with western medicine is as high as 57% (7).

"Bush medicine"

Traditional medicines derived from the Australian aborigines have received relatively little attention. The Australian aboriginal medicine is more commonly referred to as *bush medicine*. The Australian aboriginal people have a holistic view towards health and the following definition has been adopted by the National Aboriginal Health Strategy (NAHS) health is "*not just the physical but the social emotional and cultural well being of the whole community. This is the whole-of-life view and it also includes the cyclical concept of life-death-life.*"

Australian aborigines have occupied the land for over 40,000 years and over time they have acquired good knowledge of their surroundings and the benefits of the flora and fauna. Webb (16) showed that many of the traditional bush medicines did in fact contain biologically active constituents. Several examples include Bitter Bark (*Alstonia constricta*) which contains reserpine (a tranquilliser and antihypertensive) and the Native Daisy (*Spilanthe* spp.) which contains anaesthetic spilanthol.

Over half the world's supply of the drugs hyoscine and scopolamine come from the Australian native tree *Duboisia*, which has been traditionally used by aborigines as an emu and fish poison (17). There are certain to be many other *bush medicines* that are yet to be investigated, however much of the aboriginal traditional knowledge may have been lost in more recent times.

Regulation of complementary medicines

The product mobility and international access to products makes regulation of these products difficult. While in some countries, complementary medicines are subject to rigorous manufacturing standards, this is not so everywhere. In the USA most herbal products are marketed and regulated as dietary supplements. This means that products do not require approval under the Federal Food, Drug, and Cosmetic Act. The only requirement is that these products meet the standards of the 1994 Dietary Supplement and Health Education Act. This means that herbal products are not regulated by the Food and Drug Administration (FDA) and are not manufactured to comply with Good Manufacturing Practice (GMP). Under the relevant act claims can be made that a product affects the structure or function of the body, as long as there is no claim of effectiveness for the prevention or treatment of a specific disease.

In sharp contrast to the USA, in Germany for example, where herbal products are sold as *phytomedicines*, they are subject to the same criteria for efficacy, safety and quality assurance as are other medicinal products.

In April 2004, the European Union introduced *Directive 2004/24/EC on Traditional Herbal Medicinal Products (18)*. This directive requires traditional herbal medicines to meet specific standards of safety and quality and for the products to be accompanied by the necessary information for the product to be used safely. The normal requirement for medicines to demonstrate efficacy will be replaced by a requirement to demonstrate traditional use.

Regulation in Australia

Australia is one of few individual countries to have implemented reforms in the area of complementary medicine. The Complementary Medicines Reform Package was released in January 1999. It was designed to *provide more timely market access for complementary healthcare products, while continuing to ensure that products are safe, of high quality, and that they do what they claim they will do*.

The reform packages has two key policies review of advertising arrangements, including the code and guidelines; and enhancement of post-market vigilance.

The Office of Complementary Medicines (OCM) is a body within the Therapeutic Goods Administration (TGA) that regulates complementary healthcare products. Another body, the Complementary Healthcare Consultative Forum (CHCF) is a high level forum aimed at facilitating consultation between government, the complementary health care industry and consumers.

In Australia, the TGA regulates proprietary medicines which includes complementary medicines. This means that all products sold must be listed or registered with the TGA and labelled with an "AustL" or "AustR" number. (AustL products have been assessed for quality and safety, AustR products have been assessed for quality, safety and efficacy). In December 1997 the Complementary Medicines Evaluation Committee (CMEC) was established. This is an expert committee that evaluates and reviews new complementary medicines and new substances for complementary healthcare products.

Whilst the products are regulated

by the Federal Government, the States and Territories regulate practitioners. The Chinese Medicine Registration Act 2000 was passed by the Victorian Parliament. In passing this act, Victoria became the first state to introduce statutory regulation of Chinese medicine. Currently New South Wales is reviewing their regulations of Chinese Medicine.

Health insurance and complementary medicines

The extent of financial contributions by health insurance bodies is relevant to the availability and use of complementary medicines. Expenses for complementary medicines are generally covered by the patient in Australia. Private health insurance may cover the cost of some treatments and therapies though this is predominately limited to chiropractic, naturopathic, osteopathic and registered practitioners of traditional Chinese medicine. Medicare (publicly funded healthcare) will cover the cost of acupuncture if it is part of a doctors' consultation.

Final thoughts

In spite of the regulatory efforts of a number of countries, the safety of the products used by consumers cannot be guaranteed. Domestically produced products may be relatively well regulated. However, internet sales and private import of these products have changed the whole landscape. It is now so easy to obtain products from ill-defined sources that in many cases the efforts of local regulation are significantly compromised. In addition the international discrepancies in regulation contribute to consumer confusion.

Major issues continue to be associated with the use of complementary medicines. These include public perception that natural products are inherently safe. With the increased use of a wide range of complementary medicines it is possible that previously unrecognised or delayed toxicity may emerge and it is certain that there will be increasing numbers of interactions between complementary and conventional medicines.

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Renewed website offers new services www.nam.fi

Namweb search – up-to-date information on drugs

The search facility for medicinal products is a free service available to all. It can be used for searching information both on human and veterinary medicinal products with marketing authorisation. The service also provides information of availability on the market.

The various links will open up summaries of product characteristics (SPC) and package information leaflets (PIL) and synonyme medicinal products in accordance with their ATC code. The search facility can also be used for looking up information on medicinal products recommended not to be used when driving, and on medicines associated with prescription or distribution restrictions.

In addition to information covering approximately 6,400 products with marketing authorisation, about 5,500 whose marketing authorisations have been withdrawn are also included. The information is updated daily. The search facility is also available in English (http://namweb.nam.fi/namweb/do/haku/view?locale=en).

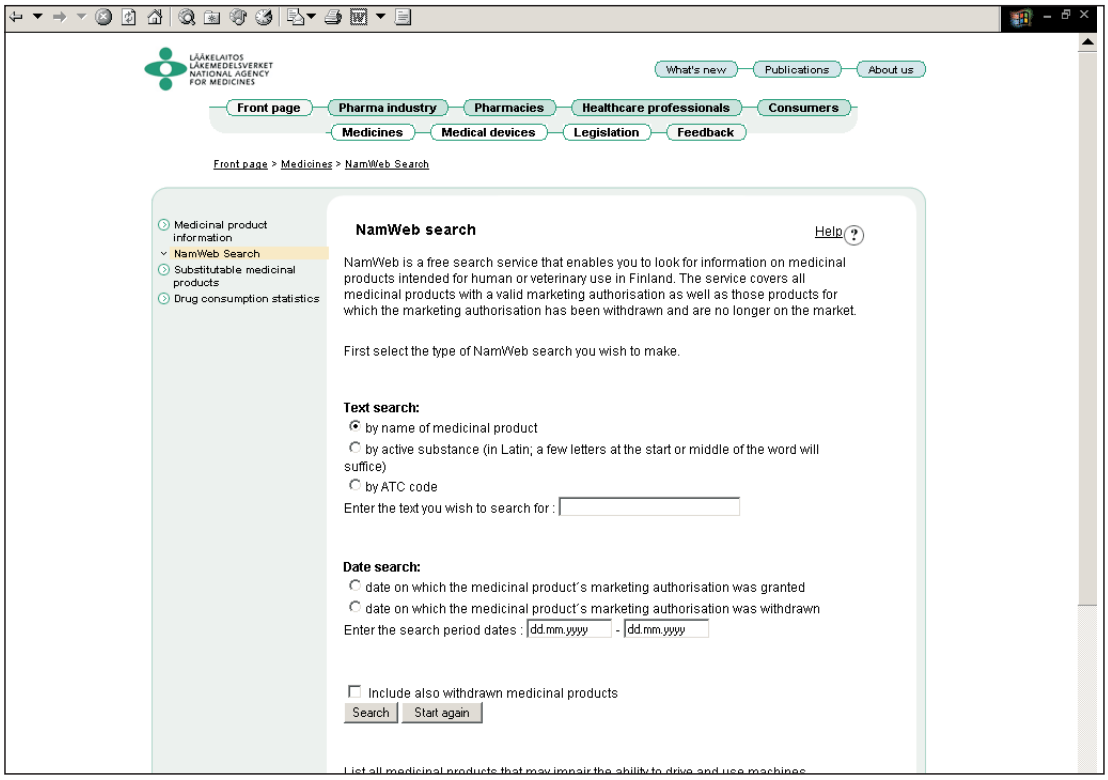
New structure and layout with news items for each target group

The pharmaceutical industry, pharmacies, healthcare professionals and users of medicines will find that the contents of the website and news of particular interest to them are targeted individually for each group. New features of interest to the pharmaceutical industry include issues on biological medicinal products and medical treatment of children, and new features intended for the consumers include traveller's medicines.

Topics of current interest include news and press releases issued. The opening screen always contains the ten most recently published topics, and more news items of current interest may also be found by using the search facility provided for each target group.

In addition to the sections for each target group, the website contains sections for information on medicines, legislation, medical devices, and publications and information about the operations of the Agency. You may also order publications, give feedback and inform the Agency about your new contact details by using the feedback form provided.

Katja Lindgren-Äimänen



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