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Hannes Wahlroos  
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*Editorial*

## Thank you for your feedback – TABU will be further developed

During the past 12 years the journal TABU has consolidated its status as a producer and publisher of drug information in Finland. The mention of the journal in the most recent reader survey of several publications and other alternatives as the most common influential factor in the choice of prescription may also be considered an achievement. The survey results were introduced in the issue 2/2005 of TABU. Reader surveys provide valuable feedback helpful in the development of the journal.

TABU has a circulation 40,000 copies issued six times a year with annual costs totalling less than 300,000 Euros. The price of a single copy delivered to the reader is 1.2 Euros. The distribution effort easily encompasses pharmaceutical professionals in all fields. The journal is also delivered to some interest groups abroad.

The times, needs and publishing techniques are developing, and TABU wants to move with the times. Practical features should be promoted, which is a tough assignment for a publication originating from the realm of the authorities. This is where the extensive network of experts of the National Agency for Medicines is expected to be of help. The intention is to obtain articles with greater emphasis on the day-to-day practice relative to NAM's chosen areas of focus within the EU: biological and paediatric medicines.

According to reader feedback, the themes mostly preferred included new drugs, drug interactions and adverse

drug reactions. These themes will therefore not be discontinued, but instead be further developed.

The most visible changes in the contents of TABU will be seen in the October issue of the journal. Reporting on the usual details of marketing authorisations and cancellations, pharmacy and other authorisations will be discontinued and will in future be published on the website of NAM. The veterinary drugs section will also get its own new and a more specific feature in the journal. These drugs will in future be discussed especially from the viewpoint of veterinary drug control. The changes will contribute to making the contents of the journal reflect the interests of the readership better.

An electronic published version of TABU is intended to be improved on the website of NAM. This will make it possible to integrate the new and interesting topic in the journal called 'marketing' into NAM's normal communications on the web. The transformation will take effect at the beginning of next year.

Information available in the media, scientific journals, the Internet and websites is far beyond what anybody is able to digest. TABU has attained a high status in Finland as a supplier of information relative to drug control and objective data. The reliability of the published information and the expertise of the authors are also of importance for the success of the journal in future.

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## Dispensaries\* in Finland

The National Agency for Medicines in collaboration with the Faculty of Pharmacy of the University of Helsinki has carried out a study on dispensaries in Finland in order to survey their present status and development needs. The results showed an average dispensary to be a unit maintained by a municipality or a joint municipal authority and to operate in a health care centre. The authorisation of an average dispensary has been approved prior to the coming into force of the Medicines Act. The manager of a dispensary is usually a Bachelor of Pharmacy and there is no other staff.

There is demand and need for ward pharmacy in health care. The staff of dispensaries find ward pharmacy interesting and important. Due to the scarcity of manpower and working time, the operations are focused on logistics and the maintenance of the stocks of medicines.

The history of hospital pharmacy in its present form in Finland is relatively short compared with e.g. the history of outpatient pharmacies. In 1934, the Women's Hospital was the first among Finnish hospitals to employ a pharmacist. Prior to 1949, hospitals purchased their medicines from private pharmacies. Following the reform of pharmaceutical legislations, hospitals had the right to acquire medicines also from pharmaceutical wholesalers. The legislative reforms and growing numbers of hospitals increased the number of pharmaceutical staff in hospitals. The acquisition, storage, preparation and distribution of medicines became the normal practice of hospitals.

### Background

The study material consisted of the replies received in response to the sur-

vey sent by NAM in 2004 to all dispensary managers.

In the study special emphasis was placed on the operations and developmental needs of Finnish dispensaries. The starting point for the study was, that if the aim is to develop the public pharmaceutical services, the present state of Finnish hospital and health centre pharmacy should initially be approached as a whole. It is, for example, difficult to develop ward pharmacy and multidisciplinary collaboration until the present state is adequately known.

### Results

At the beginning of 2004, there were 183 dispensaries in operation in Finland. The number has decreased rather significantly in recent years, the number of dispensaries being 308 in 1990. The most important reasons for the decrease in the number of dispensaries include the mergers of small pharmaceutical service units into hospital pharmacies and the shortage of pharmacists, with the resultant need to close down and cease the operation of dispensaries.

The majority, 156 (85%), of the dispensaries were municipal. Most of them operated within primary health care, i.e. they were linked with health care centres.

A total of 246 Bachelors and Masters of Pharmacy were employed in dispensaries. Of these, 179 were managers of dispensaries and 67 consisted of other pharmaceutical staff. Other, non-pharmaceutical, staff at the dispensaries totalled 149.

In 163 dispensaries (over 89% of the dispensaries) the manager was a Bachelor of Pharmacy, 16 dispensaries were managed by a Master of Pharmacy and four were managed by a nurse.

The number of pharmacy staff in addition to the manager varied in between zero and four. In most cases the manager of a dispensary worked alone without other staff.

Fifty-six of the dispensaries (31%) were, at least to some degree, involved in the preparation of pharmaceutical products in 2003. The number of batches prepared varied from one to 1,445 with the arithmetical mean being 209 and the median 109. The preparation of pharmaceuticals requiring an aseptic space was occurring in 22 dispensaries (12%). Only 55% of these (12) had premises incorporating a laminar flow cabinet and a changing room with an airlock for the production of pharmaceutical products.

Dispensaries were responsible for pharmaceutical services incorporating an average of 192 beds, ranging in number between 7 and 1,013. The number of pharmaceutical staff per one hundred beds was on average 0.7, i.e. one pharmacist was responsible for a pharmaceutical service consisting on average of 139 beds.

Ward pharmacy and its development into a multidisciplinary collaboration were considered as the most important development needs. The lack of resources was seen as the biggest obstacle to development. However, there is a strong vision among dispensary managers to move to more patient-oriented services. The change requires the recognition of the benefit of ward pharmacy, courage to break professional barriers and an improvement in the employment situation. In addition, more education in the field of clinical pharmacy is needed.

\*) *Dispensary means a small hospital pharmacy unit*

## Adverse drug reactions reported in 2004 by symptom groups in Finland

ADR reporting is a rather recent phenomenon: it wasn't until the beginning of the 1960s that authorities in Europe as well as elsewhere, prompted by the thalidomide catastrophe, started to search for methods which would enable the early detection of unexpected adverse reactions. This is of course in part impossible, since a rare reaction will not be detected until the drug is in wide use, irrespective of how well the drug is studied before its introduction. Searching for an international scapegoat associated with the drugs called coxibs, for example, is therefore pointless. It is not a question of the inadequate safety measures or failed advance monitoring systems of any particular company or authority, but simply of the fact that some rare and slowly emerging adverse reactions do not occur until after sufficiently extensive and long-term exposure to the drug.

The number of ADR reports last year in Finland amounted to 1,118. It should be borne in mind, nevertheless, that one report often contains several adverse symptoms (and perhaps even drugs), and therefore the total number of ADRs is distinctly higher than the number of reports.

### Adverse reactions of the skin

The most commonly reported reactions are those of the skin (216 in all) (figure). They are divided into several subcategories, the largest one of which is *epidermal and dermal conditions*. This includes a number of ADRs very different from each other, e.g. rashes, exacerbation of psoriasis, skin irritation and photosensitivity. The total number of reports received was 123. These reports also include effects

of the coxibs (16 in all) and statins (13 in all). This is probably a result of the frequency of their use. This group also includes one case of Stevens-Johnson syndrome exhibited in a celecoxib user, and this has also been the target of attention in the assessments and bulletins of the FDA and EMEA.

The same main category (skin) of ADRs above includes urticaria, which featured in 70 reports. The largest group of 24 reports consisted of iodine-containing contrast media, a group which always attracts a great number of reports. Other smaller groups that stick out especially are hyposensitisation preparations, and bupropione, and valdecoxib.

### Adverse reactions of the nervous system

The second largest group of reports was that of the nervous system (177 reactions in all). The group as a category is rather heterogeneous, including e.g. headache, cerebral infarct, convulsions or taste disturbances. Attention is drawn to a couple of points: 59 of these reports belong to the ATC main code N, *Nervous system*. Other groups consist of statins and coxibs, but the reactions reported are a mixture, the likely explanation being their wide use.

Reports on cerebral infarcts or haemorrhages numbered 14; contraceptive preparations containing ethinylestradiol were suspected in four cases, and drugs with an effect on blood coagulation in three. Cases of convulsions numbered 11, of which as many as 7 involved mirtazapine, which includes a mention of convulsions in its SPC. Headache was reported associated with a variety of drugs in 18 reports, and disturbances of the sense

of smell caused by a mixture of drugs were reported 5 times. Various forms of lack of sensation were reported in 18 cases, and vertigo was suffered by 16 users of a mixture of drugs. Twelve reports involved taste disturbances, of which 7 of those affected were on terbinafine, of which this reaction is typical.

### 'General' adverse reactions

The third largest group is a category defined as *general disorders and application site conditions*, part of the MedDRA coding system, and contains a mixture of ADRs. A total of 173 reports were classified as falling into this group. Reactions associated with the method of administration (27 in all) understandably consist of various rashes, burning sensations and lumps at the site of injection or e.g. of a medicinal plaster, such as those in the three reports on fentanyl plaster. Fever was mentioned 46 times and various cases of oedema were mentioned in 32 reports (oral and pharyngeal oedema are not included in this category).

Oedema was only reported in the use of etoricoxib 5 times and celecoxib 3 times. The SPCs of both these drugs include a mention of this adverse reaction.

Death was reported in 24 cases; four of the reports stated the adverse reaction as a contributory factor in the death, and the rest claimed that it had caused the death. The cases were isolated, except for three haemorrhaging ulcers, in two of which the reporting doctor considered the patient to have died of the reaction, and in one of which the adverse reaction was considered a contributory factor. In all the cases of ulcer, the medication used was

a coxib either alone or in combination with other (anti-inflammatory analgesic) agents.

### Gastrointestinal and hepatic reactions

A total of 118 reports of gastrointestinal adverse reactions were notified. This group contains quite a mixture of ADRs. Some type of unspecific symptom was referred to in 70 of the reports: nausea, abdominal pain, flatulence, vomiting or diarrhoea. Various contrast media appear in this group (13 reports), in which nausea is probably more likely to be associated with reactions of allergic nature rather than with gastrointestinal complaints. Coxibs also figure in the reports on gastrointestinal reactions, with 17 reports. The interesting point is that 5 of these reports were about a bleeding abdominal or duodenal ulcer. The suspected medication in one case was two different coxibs and acetylsalicylic acid. According to present knowledge, the concomitant use of acetylsalicylic acid and coxibs is indeed detrimental to the stomach. Seven cases of pancreatitis were reported, in four of which the suspected drug was simvastatin. The only other prominent symptom group was that of three cases of gingival hyperplasia, with amlodipine being the suspected cause.

Adverse reactions of the liver figure as a main category of their own. The number of reports received was 35. Elevations of liver values are recorded in a different main category, i.e. studies, which is slightly illogical. There were 46 cases reported. Statins figure in the liver complaints (22 times in total in the above groups), which is logical as the liver is their target of effect. A couple of coxibs also appear,

and this may be due to their common use.

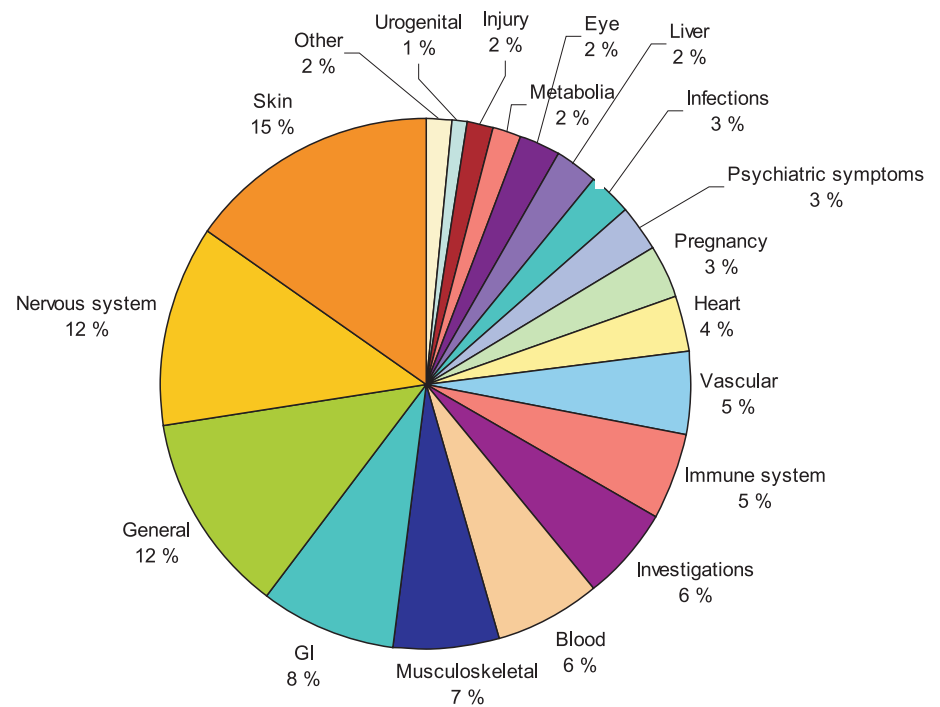
### Musculoskeletal disorders

This category included 93 reports. The biggest group was formed by statins with 30 reports of muscular pain. Rosuvastatin stands out in this group with its 19 reports. Cases of Achilles tendinitis or associated pain total 19, all of them concerning fluoroquinolones. Fourteen of the cases are typically associated with levofloxacin. The MedDRA classification performs an act here: Achilles tendon ruptures are recorded in the category of *injuries*. There were 11 of them with levofloxacin as the suspected culprit. Six reports concerned back pain, the cause

of which was suspected to have been verteporfine with the therapeutic indication of occult subfoveal choroidal neovascularisation and with back pain mentioned as a common reaction in its SPC.

### Blood

The number of ADRs associated with blood were 88, of which 53 concerned cases of agranulocytosis, granulocytopenia or leukopenia. The drug suspected to have caused the ADRs was most often clozapine, (19 reports + 1 report on eosinophilia). In addition to a group of eight psychiatric drugs, one that stands out with its 4 reports is sulphasalazine.



ADR reports received in 2004 by symptom groups

### Immune system disorders

In practice, all of the reported ADRs in this group were about various allergic conditions: a combination of only a couple of annoying symptoms at its mildest, but a life-threatening anaphylaxis at its worst. Various allergic symptoms were reported 74 times, the biggest suspected group of drugs being iodine-containing contrast media (15) and a couple of other contrast media (5). The second largest distinct group is made up of coxibs (9 cases in total), probably reflecting the common use and novelty of the drug. Use of hyposensitisation drugs have caused four cases of allergic reactions.

### Vascular disorders

Various of these, perhaps more like a mixture of vascular effects, were reported in 71 cases, the biggest groups made up of cases of bruising, hyper- or hypotension, blushing/congestion, a couple of case of vasculitis and also 4 cases of thrombophlebitis. It is very difficult to discern any special pattern in the group, but milnacipran stands out with its three reports in the group of cases of hypertension. The adverse reaction is mentioned in the SPC.

### Cardiac disorders

Adverse cardiac reactions were reported 50 times. Thirty of them concerned various cases of arrhythmia, for example, either as a symptom on its own, or together with other cardiac symptoms. The only group standing out is that of coxibs, of which there are 5 reports. Myocardial infarction was the reason for reporting on three occasions, and cardiac arrest on two. The two last-mentioned cases involved anaphylaxis

associated with the administration of a contrast medium. The reactions overall of this group, except for arrhythmia, were often isolated cases. It is certain also that frequently a background murmur would be detected, since various palpitations are probably very common in the population.

### Pregnancy

In the case of contraceptives, not only adverse reactions are monitored but also pregnancies, and then it is a question of lack of efficacy rather than an adverse reaction. The total number of pregnancies reported was 44, which is a small number considering the wide use of contraceptives. About 200,000 Finnish females use systemic hormonal contraception. The more recent medicinal preparations and administrations are among those most frequently reported on. This is perhaps rather a reflection of the general trend in ADR reporting: the more recent drugs are more actively reported on, which is of course desirable.

### Psychiatric symptoms

There were 42 reports on psychiatric symptoms. It is difficult to detect any special pattern in the material, the reports referred, for example, to hallucinations, depression, insomnia, nightmares and anxiety. Various psychiatric drugs are prominent among the drugs, especially bupropione, conspicuous with its five reports, used on this occasion in patients who are trying to stop smoking.

### Infections

This group contains a batch (40 reports) of mixed but understandable

adverse reactions: the drug has (possibly) caused agranulocytosis followed by sepsis. There are a couple of cases concerning clindamycin, the use of which was found to have been associated with symptoms caused by *Clostridium difficile*, and in a couple of cases the suspected drug was found to be immunosuppressive either in topical or systemic use. In such cases the adverse reaction was, for example, herpetic rash or erysipelas.

### Other ADRs

Eye disorders (35) were reported on, including e.g. conjunctivitis, photophobia, and chromatopsia. The only group standing out here is five cases of blurred vision/visual disturbances typical of telithromycin (*rare* according to the SPC). Adverse reactions of the ear were reported on 10 times, with 3 cases of tinnitus and vertigo among them.

Metabolic ADRs were reported on 25 times. The cases of either hypo- or hyperglycaemia associated with insulin are distinguishable in the group, but also one associated with olanzapine and quetiapine (hyperglycaemia). Some cases of hyponatraemia were reported, and also of hyperkalaemia.

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## Own observation of an ADR

# Withdrawal symptoms following discontinuation of venlafaxine therapy

A 34-year-old inspector of motor vehicles came for an appointment in November 2003. In the event there were regular, weekly appointments continuing until the beginning of the summer 2005. The man was diagnosed at first as having symptoms of depression associated with decision making difficulties, continuous tiredness, difficulties of concentration and nightmares. The underlying background comprised a particularly difficult childhood and adolescence characterised by dejection and feelings of worthlessness. At no stage were there any signs of psychotic illness apparent in the patient.

Venlafaxine (Efexor depot) therapy was introduced at an early stage and given in doses of up to 150 mg x 1.

When the dose was halved in the beginning of August 2004 and then followed by discontinuation of the medication altogether, the patient reported a complex of symptoms: light-headedness, discomfort, vertigo, sensations resembling electric shock. The symptoms were difficult to manage insofar as the patient wanted to continue the therapy especially as symptoms of depression had also started recurring. It was decided to continue the therapy at a dose of 150 mg x 1.

The dose was again halved on 10.3.2005. The patient took the last medication on 11.4.2005, and on 13.4.2005 he started experiencing mild symptoms similar to those associated with the previous withdrawal. The

symptoms became worse: the patient experienced continuous sparks of light, confusion, vertigo over the whole area of the head, ocular tenderness inhibited eye movement, and it felt like having electricity in the head. At home he was unable to carry on with daily chores, and as a consequence, he was written off sick for a week. Sick leave due to depression had not been necessary earlier because of the high threshold the patient had for taking sick leave. As late as 2.5 weeks after the discontinuation of the therapy the patient experienced difficult symptoms, the most severe of which was the feeling of sparks of light in the head. The symptoms have gradually disappeared altogether, the therapy has been discontinued and the patient is back at work.

## Comment

The adverse reactions of antidepressants with an effect on the serotonin and noradrenaline re-uptake inhibition (SSRI/SNRI) have in recent times been the focus of special interest. An assessment was made in April 2005 by the CHMP of EMEA of the safety of use of SSRI/SNRI antidepressants in children and adolescents.

The United Kingdom's Medicine and Healthcare Products Regulatory Agency has recently reviewed safety of SSRI/SNRI products (<http://www.mhra.gov.uk/news/2004/SSRIfinal.pdf>). According to the review, withdrawal reactions occur with all SSRI/SNRIs, most commonly with paroxetine and venlafaxine. According to clinical studies, approximately 30% of patients will experience withdrawal reactions upon stopping venlafaxine treatment, and of these up to approximately 12% will be severe in nature. The most commonly reported withdrawal reactions were dizziness, headache, nausea and/or vomiting, sleep disturbances (including insomnia and abnormal dreams), diarrhoea, agitation, anxiety, sweating, tremor, paraesthesia, palpitations and emotional instability.

The kind of experiences similar to electric shock as described in this case study have seldom been reported as a withdrawal symptom of venlafaxine. In the database of adverse reactions maintained by NAM this report is the only one of its kind. Withdrawal symptoms on the whole have seldom been reported. In addition to the case above, a 39-year-old woman experienced upper abdominal pains and feeling of swelling for a week following the withdrawal of venlafaxine therapy. Withdrawal symptoms in a newborn as a result of mother's use of venlafaxine during pregnancy have also been reported once.

The SPC for Efexor mentions symptoms caused by withdrawal of therapy and includes instructions for a gradual withdrawal.

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