

2.2003

L Ä Ä K E I N F O R M A A T I O T A L Ä Ä K E L A I T O K S E L T A  
LÄKEMEDELSINFORMATION FRÅN LÄKEMEDELSVERKET, FINLAND | DRUG INFORMATION FROM THE NATIONAL AGENCY FOR MEDICINES, FINLAND

*Lääkepoliittinen keskustelu käyntiin 3 Hankalan potilaan lääkehoito 4 Atooppisen ekseeman uudet immuunomodulatiiviset hoidot: takrolimuusi ja pimekrolimuusi 8 Tadalafiili 10 Olopatadiini 11 Bupropioni 12 Haittavai-  
kusrekisteriin tehdyt ilmoitukset 14 Anakinran ja eta-*



## 2.2003

11. vuosikerta  
11 årgången  
11th Annual volume

### S a m m a n d r a g

#### Ledare

- Hannes Wahlroos ..... 30 Läkemedelspolitisk diskussion kom i gång  
Pekka Tuomola ..... 31 Läkemedelsbehandling av en besvärlig patient

#### Biverkningar

- Marja-Leena Nurminen | Leena Sommarberg .. 34 Anmälningar till biverkningsregistret år 2002  
Jussi Holmalahti ..... 37 Vad avslöjar förpackningen om läkemedlet?

#### Medicintekniska produkter

- Harri Sievänen ..... 39 Defibrillator och risksituationer

### S u m m a r y

#### Editorial

- Hannes Wahlroos ..... 41 Public discussion of pharmaceutical policy starts up

#### ADR News

- Marja-Leena Nurminen | Leena Sommarberg .. 42 Adverse drug reactions reported to the Finnish ADR Register in 2002

- Jussi Holmalahti ..... 45 What does the drug package reveal of its contents?

#### Drug use

- Ulla Myllykangas | Ulla Närhi |  
Jaana Martikainen ..... 47 The use of antipsychotics and the national social insurance reimbursements in Finland 1995–2001

#### Medical devices

- Harri Sievänen ..... 51 Defibrillators and adverse incidents

53 Lääkelaitoksen päätöksiä

**Hannes Wahlroos**

DIRECTOR GENERAL

National Agency for Medicines

## Public discussion of pharmaceutical policy starts up

Public discussion of pharmaceutical policy has finally begun in Finland. The Ministry of Social Affairs and Health arranged a hearing on the subject on 14 March 2003. Nearly 20 years had passed since the previous discussion, which arose during the drafting of the Medicines Act. An even longer period – more than 30 years – has lapsed since pharmaceutical matters were discussed at committee level by the Pajula Committees I and II. It is high time that political decision-makers review the tenability of the medicine policy in a changed Finland and world.

Most of the time, the first pharmaceutical policy issue raised by the media is pharmacy-related. This is understandable, as the consumer and patient encounter medicines primarily and repeatedly at the pharmacy. Easy availability and safety of medicines are felt to be essential, basic points of departure. In a broader view, and especially when assessing health policy, other questions rise in priority. For this reason, pharmaceutical policy is a necessary means for placing issues into an order of importance.

In my opinion, it is clear that the greatest challenge to pharmaceutical policy in the coming years will concern the funding of pharmacotherapy, and the related pertinent issue of sensible prescribing and use of medicines. When resources are limited, their rational use is emphasised. It is a question of priorities, as discussed widely in health care in general. What pharmaceutical and medical therapies are used, who is treated, how is the treatment funded, what is a fair and socially acceptable level of excess, and how can the impartial availability of medicines be assured? These are the questions that our pharmaceutical policy should address.

In a proposal drawn up by officials of the Ministry of Social Affairs and Health, the possibility of changing to a reimbursement based on cost and insurance policies was presented. This would increase the transparency of the medicines reimbursement system. The level of reimbursements in Finland should correspond to the prac-

tices of those EU member states comparable to our country.

Finland can act independently to maintain medicines safety and ensure the availability of medicines, but much is reliant on the European operating environment. Safety of medicines can be maintained, if the authorities and health care professionals understand it to be a top priority for medicines control, research, manufacture, prescribing, distribution and usage. Neglecting any one of these components will endanger the whole system.

The significance of the pharmaceutical industry within the so-called health cluster should be taken into consideration under pharmaceutical policy. The effects of the pharmaceutical industry, as reflected on basic and clinical research, and on changes in treatment regimes, are aspects of a comprehensive health and pharmaceutical policy.

A sparsely populated country poses extra challenges to the supply of health services of a high professional standard and their easy accessibility. In Finnish pharmaceutical services, this matter has been competitively dealt with compared to other countries. Any medicine has always been found on pharmacy shelves, and in recent years this has been supplemented with an information service. This extensive service does, however, come with a price, and in Finland this price has been translated to the pharmacy fee. For pharmaceutical policy purposes, it should be contemplated whether a well-run, professional basic service could be achieved without the price-raising effect of the pharmacy fee.

When reforming pharmaceutical policy, one should dare to challenge former truths. Similarly, one should have the courage to admit if some matters, even after consideration, still stand on firm ground. Changes for the sake of change are not desirable. The known problems of health care services in Finland result in caution in the assessment of new directions in pharmaceutical policy.

# Summary

**Marja-Leena Nurminen**

SENIOR MEDICAL OFFICER

**Leena Sommarberg**

RESEARCHER

Safety&Drug Information  
National Agency for Medicines

## Adverse drug reactions reported to the Finnish ADR Register in 2002

In 2002, the ADR Register of the National Agency for Medicines received a total of 805 reports on suspected adverse drug reactions (ADRs), about half of which were serious. There were ten or more reports on 19 different medicinal substances (Table). The substances at the top of the list were by and large the same as in the previous year. Many of the drugs were recently launched. Generally, a greater number of reports of new drugs is received than of old familiar drugs. The attached list cannot be used for the comparative evaluation of the safety of the drugs as there is a considerable variation in the number of users: a drug used frequently may be associated with a greater number of reports than a less frequently used one despite equal incidence of the adverse reaction.

The majority of ADR reports in 2002 concerned an anti-inflammatory analgesic nimesulide (48 reports). Liver reactions were the cause of nearly all the reports. Due to serious liver reactions, nimesulide tablets and dose granules were suspended from the Finnish drug market in March 2002. Due to the safety concerns, a referral on nimesulide, in accordance with EU Directive, was initiated by the Committee for Proprietary Medicinal Products (CPMP). This review leads eventually to a Commission decision which will be common to all EU countries. Marketing authorisation for nime-

sulide is approved in ten EU countries (Belgium, Spain, Ireland, Italy, Austria, Greece, Luxembourg, Portugal, France and Finland). In addition to Finland, the marketing of nimesulide is suspended in Spain due to its adverse liver reactions.

A total of 45 suspected adverse reactions were reported during the use of COX 2-selective anti-inflammatory analgesics, rofecoxib and celecoxib (26 on rofecoxib and 19 on celecoxib). A large proportion of the reports on rofecoxib (10) were of oedema, weight gain and/or ele-

vated serum creatinine concentration. Hepatitis was reported in two patients receiving rofecoxib; nimesulide was also suspected in one of these patients and esomeprazole in the other. The majority of adverse reactions associated with celecoxib therapy were various allergic symptoms and rashes (11 cases). Oedema, weight gain or elevated creatinine concentration was reported in three patients on celecoxib therapy. Caution should be exercised in the use of coxibs, for instance, in patients with cardiac insufficiency or hyper-

### Medicinal substances most frequently reported to the ADR Register of the National Agency for Medicines in 2002

<i>medicinal substance</i>	<i>number of reports</i>
<i>nimesulide (Nimed)</i>	48
<i>clozapin (Leponex, Froidir)</i>	44
<i>rofecoxib (Vioxx, Vioxxakut)</i>	26
<i>iopromide (Ultravist)</i>	23
<i>atorvastatin (Lipitor)</i>	20
<i>terbinafine (Lamisil)</i>	19
<i>levofloxacin (Tavanic)</i>	19
<i>celecoxib (Celebra)</i>	19
<i>esomeprazole (Nexium)</i>	18
<i>sulfasalazine (Salazopyrin, Salazopyrin EN)</i>	16
<i>risperidone (Risperdal)</i>	16
<i>infliximab (Remicade)</i>	15
<i>simvastatin (several preparations incl. Corolin, Lipcut, Zocor)</i>	14
<i>oxcarbazepine (Apydan, Trileptal)</i>	14
<i>leflunomide (Arava)</i>	13
<i>quetiapine (Seroquel)</i>	13
<i>nitrofurantoin (Nitrofur-C)</i>	10
<i>paclitaxel (Taxol)</i>	10
<i>carbamazepine (several preparations incl. Tegretol, Neurotol)</i>	10



tension because the inhibition of renal prostaglandin synthesis may reduce renal function and cause accumulation of fluid.

As in previous years, the most frequently reported antirheumatics were infliximab (15) and leflunomide (13). Infliximab is a monoclonal antibody which inhibits the biological activity of tumour necrosis factor alfa (TNF- $\alpha$ ). In addition to severe, active rheumatoid arthritis, it is also used in the treatment of Crohn's disease, for example, when the response to other therapies has been inadequate. Last year, a serious infection was reported in six patients who had received infliximab; two of the patients had pulmonary tuberculosis. Infliximab was suspected to be associated with the development of malignancy in two patients (ovarian cancer, lymphoma). Infliximab is known to increase susceptibility to infections due to its immunosuppressive effect and is consequently contraindicated in patients with tuberculosis or other severe infection. Patients should also be carefully monitored prior to the treatment, during the treatment and for six months after the treatment to exclude tuberculosis and other infections. At present it is unknown if exposure to infliximab can increase the incidence of malignant diseases.

Three cases of granulocytopenia and two cases of elevated liver enzymes were reported in association with the use of leflunomide. Leflunomide may also cause serious liver reactions and consequently the S-ALAT level should be determined prior to leflunomide therapy. S-ALAT level should also be regularly monitored during treatment.

Adverse effects on the blood count also require regular monitoring by laboratory tests (see Summary of Product Characteristics). Concomitant therapy with other hepatotoxic or haematotoxic medicinal substances (e.g. methotrexate) is not recommended as the risk of these serious reactions may be increased.

Among old antirheumatics, the largest number of reports received was on sulfasalazine (16). The adverse reaction reported in the majority of the cases was granulocytopenia or agranulocytosis. Two patients were reported as having elevated liver enzymes, and one had hepatitis. To avoid these well known adverse reactions, the blood count (leucocytes and differential count) and liver function should be determined at the beginning of treatment and every second week during the first three months of treatment. During the following three months the analyses are carried out at four weeks' intervals, and the blood count and liver function are thereafter determined at three months' intervals. In addition to the treatment of rheumatoid arthritis, sulfasalazine is also used in the medical treatment of inflammatory intestinal diseases.

Among drugs used in psychiatric disorders, the majority of reports were received on the second generation antipsychotics, clozapine (44), risperidone (16) and quetiapine (13).

The majority of reports concerning clozapine were cases of granulocytopenia or agranulocytosis. The blood count is altered in one percent of patients on clozapine therapy, and the leucocyte count should therefore be carried out prior to treatment and regularly during med-

ication. One of the patients on clozapine therapy was reported as having cardiomyopathy. The patient was concomitantly receiving olanzapine, which was also suspected drug in this reaction. The patient recovered when these drugs were withdrawn and the patient received medical treatment for cardiac insufficiency. Due to the risks associated with the use of clozapine, its Summary of Product Characteristics has recently been updated and harmonised in the EU. Its previous therapeutic indications included patients with schizophrenia who do not respond to conventional neuroleptic agents or do not tolerate them. A mention of the new generation antipsychotics has now been included in the therapeutic indications. A special warning of agranulocytosis and myocarditis has been framed in and placed at the beginning of the product information. Paralytic ileus and the concurrent use of drugs known to have a high risk of causing agranulocytosis, for example, have been included among the contraindications.

Granulocytopenia associated with the use of quetiapine was reported in four patients. Other adverse reactions included neuroleptic malignant syndrome in three patients on quetiapine therapy. The syndrome is characterised by fever, severe muscular stiffness, elevated concentration of creatinine phosphokinase and myoglobinuria caused by muscular damage, electrolyte imbalance, hepatic and renal dysfunction and reduced level of consciousness. If symptoms of neuroleptic malignant syndrome appear, the medication causing the syndrome should be

interrupted and the patient treated with, for example, bromocriptine or dantrolene. Medication with antipsychotics can be re-introduced after 2–4 weeks using an antipsychotic of some group other than that of the drug causing the symptoms.

The majority of the adverse reactions caused by risperidone were hormonal reactions (hyperprolactinaemia, menstrual irregularities and secretion of milk). Risperidone blocks dopamine receptors and may by this mechanism increase prolactin concentration. The old conventional antipsychotics also have a similar characteristic, but it is less significant with the newer, second generation antipsychotics. If the adverse reactions which have developed as a result of the elevated concentration of prolactin are significant, it may be beneficial to decrease the dose or replace the antipsychotic with another substance which has only a minor effect on the serum prolactin or lacks the effect. Extrapyramidal symptoms were reported in two patients and neuroleptic malignant syndrome in one patient receiving risperidone.

The majority of reports received on cholesterol-synthesis-inhibiting statins last year were about the use of atorvastatin (20 reports) and simvastatin (14 reports). The most typical adverse reaction associated with the use of atorvastatin was muscular pains and/or increased concentration of creatinine phosphokinase (11 reports). Elevated liver enzyme levels were reported in five patients. Muscular symptoms associated with the use of simvastatin were reported in seven patients, with the diagnosis of rhabdomyolysis in one patient. The

patient was given concurrent clarithromycin which inhibits the cytochrome P450 3A4 enzyme and increases the risk of muscular injuries when used concurrently with statins which are metabolised by the enzyme (atorvastatin, lovastatin, simvastatin).

The majority of reports of adverse reactions caused by antibacterials were on levofloxacin (19 reports) of the fluoroquinolone group. Most of these reports (16) related to adverse effects on the Achilles tendon (tendinitis and rupture of tendon). Nearly all the patients were over 70 years of age and a large number of them were concurrently receiving a systemic corticosteroid which increases the risk of rupture of the tendon. If tendinitis is suspected, the use of fluoroquinolones should be terminated immediately.

A total of ten reports were received last year of the adverse reaction to nitrofurantoin which is used in the treatment of urinary tract infections. The reason for the reporting in six cases was serious pulmonary reaction (pulmonary infiltrate or fibrosis), two patients were also reported as having dyspnoea. Nitrofurantoin was used as long-term therapy in four of the patients, whereas the rest of the patients were treated for acute infection. Due to the risk of serious pulmonary reactions, all respiratory symptoms such as cough and dyspnoea in patients on nitrofurantoin should receive special attention.

Among antifungals, the majority of the reports of adverse effects were associated with the use of terbinafine tablets (19 reports). The most common reactions included various

skin reactions (9). Liver reactions were also reported (two elevated liver enzymes and one cholestatic hepatitis).

The majority of reports concerning antiepileptics were on the use of oxcarbazepine (14) and carbamazepine (10). Two of the cases of oxcarbazepine involved oedema and two hyponatraemia. The rest of the reports were on single adverse reactions. During carbamazepine therapy, various skin reactions (5) and elevated liver enzymes (2) were reported.

The majority of reports of adverse reactions caused by drugs for gastrointestinal disorders were associated with the use of esomeprazole, the new proton pump inhibitor (18 reports). The most common reactions were urticaria and skin rash. In two patients, the medication was suspected to be associated with hepatitis. In both cases, involvement of another drug was also suspected (azitromycin, rofecoxib).

Iopromide is a low-osmolar, iodine-containing contrast medium used in angiography, urography and contrast enhancement in computerised tomography. A total of 23 adverse reactions were reported to the National Agency for Medicines in 2002, the majority of which involved allergic reactions (urticaria, anaphylaxis). Special care should be exercised in the use of the preparation in patients with hypersensitivity to iodine. Hypersensitivity reactions are more common in patients prone to allergies. Prior to the contrast media administration, antihistamines and/or corticosteroids can be used for prophylaxis of allergic reactions.

# Summary

Jussi Holmalahti

D. Sc. (Pharm.)

Marketing Authorisations

National Agency for Medicines

## What does the drug package reveal of its contents?

Despite its small size the drug package contains plenty of information for the user of the drug. There is information found on the packaging itself and in the leaflet inside the package.

The information on the outer package ensures that the correct drug is supplied. The Patient Information Leaflet (PIL) in the package contains information concerning the indications, the dosage, and the adverse effects. All these details should be based on the approved Summary Product Characteristics (SPC) of the drug. The primary responsibility for the correctness of the information and for its being understood lies with the marketing authorisation holder and the manufacturer. The authorities assess the factual contents of the information at the processing stage of the marketing authorisation.

### Summary of Product Characteristics

The SPC is a drug description designed on the basis of research results and aimed at medical prescribers and other health care professionals. The aim is to give adequate and up-to-date information about the drug and thereby ensure successful treatment. The SPC approved in association with the marketing authorisation approval process is an essential part of the marketing authorisation and should form the basis of all the information given concerning the drug and its marketing. After approval the SPC may not be changed without the consent of the authorities.

### Patient Information Leaflet

The marketing authorisation holder draws up a legible and comprehensible Patient Information Leaflet, based on the SPC and intended for the user of the drug. Naturally the text of the SPC intended for drug prescribers is not such as is appropriate for patients. The PIL follows the normative headings given by the authorities and an established order of presentation. The PIL contains headings taken from questions frequently asked by patients, and the replies are presented in clear language. Typical questions are, for example, What does the drug contain?, What is the effect of the drug? etc.

As an aid in the design of the PIL, a legibility study can be used, by which it is possible to assess the clarity of the information given in the PIL, the sequence of the details presented, and the actual presentation.

A good PIL has a clear, simple and short structure comprehensible to the user. The user is generally only interested in the type of information, which will give a clear answer to the question of what he or she should do and what is to be expected. Clear instructions for use and on how to deal with emergencies are essential. The text of the PIL should avoid unnecessary general information, which may submerge any message essential for the use of the drug. Positive instructions and active language targeted directly at the patient are preferred.

The presentation is of great importance from the point of view of readability and comprehensibility. The text should be of sufficiently

large type and easily readable. Different colours and text sizes may be used for distinguishing purposes. Clear listings of adverse effects, for example, improve the understanding of the message. The following is a list of some general observations associated with readability:

- *It is recommended that the headings be emphasised with different colours*
- *Numbering of the main headings will help the reader to follow the text of the PIL; this is especially important when the PIL is double-sided or folded*
- *The main headings should be placed on the left, not centered*
- *The text size of the main headings should be a minimum of 13 points*
- *The less important information (the marketing authorisation holder and manufacturer, addresses) may be written in smaller style*
- *Bulletins should be used instead of lists of texts.*

### Test of readability of the PIL

The EU drug legislation requires that the Patient Information Leaflets should be clear and comprehensible. The current guidelines also mention a readability test, which is to be carried out among the PIL users, and which will allow the comprehensibility and clarity of the PILs to be studied. The *Guideline on the readability of the label and package leaflet of medicinal product for human use* was approved in 1998. The guideline recommends the use of a readability test developed in Aus-

tralia to be used in the assessment of clarity and comprehensibility of PILs. If other methods than the EU model are used in the design of the PIL, the testing of readability is entirely the responsibility of the marketing authorisation holder.

For several years there has been particular attention paid to association of the readability testing with the centralised procedure of marketing authorisation approval processes. The PILs of a number of drug products have been put through the readability test in accordance with the EU guideline. These tests have permitted better understanding of the problems associated with PILs.

The readability is tested with questions, some of which directly concern the factual content of the PIL. A typical question could be, for example: *Imagine that you are allergic to penicillin, could you in that case use penicillin?* Some of the questions are aimed at testing the general structure of the PIL (e.g. the ease or difficulty of finding required information) and could typically be: *What are the disadvantages of the Patient Information Leaflet, and how could it be improved?* The time allowed for the test is naturally limited. The readability test can be carried out in two stages, which will provide an opportunity to find out whether the improvements made on the PIL have had any effect on the readability.

There are complexities involved in the readability test. The test methods are not yet quite established, and the testing of the reliability of the various methods is inadequate. The question is: *Are we testing the readability of the Patient Information Leaflets or the comprehensibility of the list of questions?*

In accordance with the EU guideline, the various languages are divided into three groups, and one language of each group is required for the testing of readability:

- A French, Italian, Portuguese and Spanish
- B Dutch, English, German
- C Danish, Finnish, Greek and Swedish

Some of the languages, especially those in group C, are not related to each other, which makes it doubtful whether any conclusions can be

drawn from the results. A review of the analysed tests shows that there have seldom been any important differences between the results from different countries, which is why the testing of various language versions should be expanded.

## Conclusion

The content and quality of information supplied with the drug products are one of the more specifically defined areas associated with the products for sale. The size of drug packages is rather small; inserting adequate labelling which would satisfy everybody on the outer package is consequently impossible. Including all information essential for the choice of OTC drugs in the Patient Information Leaflet is, of course, difficult. In the selection of services the pharmacies offer they should therefore focus on whether it is possible for the patients to familiarise themselves with the information leaflet. The PILs in Finnish and in Swedish for drugs marketed in Finland can be obtained from the website of the National Agency for Medicines under the heading *Lääkeinformaatio* ([www.nam.fi](http://www.nam.fi)).

Patient Information Leaflets are sources of information which complement the package labelling. The readability testing of PILs is an important stage in the process of refining the texts contained in the SPCs to make them comprehensible to the users. Readability testing of PILs is not legally required by the authorities, but the tests may improve the PILs. The responsibility of PILs lies distinctly with the marketing authorisation holder, whereas the correctness of the factual contents is checked by the authorities. From the patient's viewpoint, the implementation of readability testing could be a step towards improved drug information.

## Information given in the drug packaging

- *The name of the drug product consists of a trade name, strength and dosage form of drug. The name should be unambiguous, in order to enable it to be distinguished from other drug products and from items of the same group of products.*
- *The package should also contain the name of the medicinal substance, and, in some cases, the complete declaration of the drug. All excipients used are detailed in the PIL. The quantities of excipients are only given in special cases. The colorants used in the drug products are approved for use in food products. The codes of colorants are given on the outer packaging.*
- *Instructions for use, indications and usual dosage intended for the patient are only given on the outer packaging of OTC drugs. The usual dosage and indications of prescription drugs are given in the PILs. The PIL will also include a reminder of the fact that the doctor may have prescribed the drug with different dosages or different therapeutic indications.*
- *The package will always include instructions for storage of the drug, according to which the quality of the product will remain unimpaired until the expiry date marked on the package. The outer and inner packaging will also include a batch number, which will restrict any possible complication that may arise from a particular production batch.*
- *The package will also include details of the name and address of the marketing authorisation holder, which will help the patient to obtain further information about the drug.*



**Ulla Myllykangas**  
M Sc. (PHARM.)  
Matinkylä Pharmacy

**Ulla Närhi**  
PH D (PHARM)  
Safety & Drug Information  
National Agency for Medicines

**Jaana Martikainen**  
Lic.Sc. (PHARM.)  
Research Department, Social Insurance Institution  
Dept of Social Pharmacy, University of Kuopio

## Summary

# The use of antipsychotics and the national social insurance reimbursements in Finland 1995–2001

Antipsychotics are mainly used for the treatment of symptoms of schizophrenia, but also of delusional psychosis or personality disorder, severe depression or other affective syndrome, or for the prevention of recurrence of symptoms. Antipsychotics are also used for the treatment of, for example, psychic disorders of the elderly and mentally retarded, e.g. anxiety, delusion and confusion, and for the alleviation of psychotic symptoms associated with the use of intoxicants (1).

Antipsychotics can be divided into two main groups: conventional and second-generation antipsychotics (Table 1). The division is based on the various mechanisms of action of the drugs. The main antipsychotic effect of the conventional antipsychotics is based on the

dopamine-2-receptor blockade, especially in the mesolimbic and mesocortical area of the brain. The more primary blockade by second-generation antipsychotics is targeted at the dopamine receptors of the limbic area and the receptors 5-HT<sub>2A</sub> and 5-HT<sub>2C</sub> among the serotonin-receptors (2).

Conventional antipsychotics diminish the positive symptoms of psychosis in particular, including hallucinations, delusions and psychomotor anxiety. On the other hand second-generation antipsychotics may alleviate especially the negative symptoms of psychosis, e.g. emotional withdrawal. They cause fewer adverse reactions than conventional antipsychotics and treatment compliance can therefore be expected to be better. The use of sec-

ond-generation antipsychotics is nevertheless restricted by their high price (3).

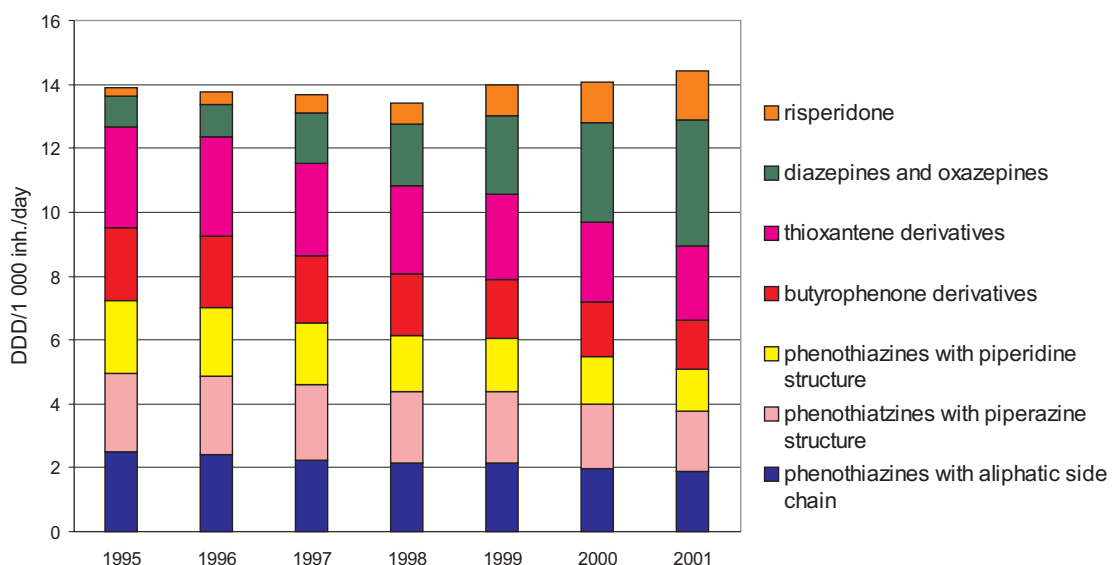
### Total consumption

The following is a review of the consumption of antipsychotics as detailed in the wholesalers' drug sales register maintained by the National Agency for Medicines in Finland. The antipsychotics referred to here are drugs of the ATC Code N05A, except for lithium.

The total consumption of antipsychotics has not changed significantly during 1995–2001. The choice of drug has changed, however, over the years. The consumption of conventional antipsychotics has diminished and that of second-generation drugs increased (Fig. 1). In

**Fig. 1. Total consumption of anti-psychotics calculated as daily doses per 1,000 inhabitants per day during 1995–2001.**

Source: National Agency for Medicines.



**Table 1. Antipsychotics divided into groups with their ATC Codes. Medicinal substances on the market in Finland in 1995–2001 have been included.**

**CONVENTIONAL ANTIPSYCHOTICS**

**No5AA Phenothiazines with aliphatic side chain**

- No5AA01 chlorpromazine
- No5AA02 levomepromazine
- No5AA03 promazine

**No5AB Phenothiazines with piperazine structure**

- No5AB01 dixyrazine
- No5AB02 fluphenazine
- No5AB03 perphenazine
- No5AB04 prochlorperazine
- No5AB08 thioproperazine\* (1999)

**No5AC Phenothiazines with piperidine structure**

- No5AC01 periciazine
- No5AC02 thioridazine
- No5AC04 pipothiazine\* (1997)

**No5AD Butyrophenone derivatives**

- No5AD01 haloperidol
- No5AD03 melperone

**No5AE Indole derivatives**

- No5AE02 molindone\* (1998)
- No5AE03 sertindole

**No5AF Thioxanthene derivatives**

- No5AF01 flupentixol
- No5AF03 chlorprothixene
- No5AF04 thiothixene\* (1995)
- No5AF05 zuclopenthixol

**No5AG Diphenyl butylpiperidine derivatives**

- No5AG02 pimozide\* (1995)

**SECOND-GENERATION ANTIPSYCHOTICS**

**No5AH Diazepines and oxazepines**

- No5AH02 clozapine
- No5AH03 olanzapine
- No5AH04 quetiapine

**No5AL Benzamides**

- No5AL01 sulpiride

**No51AX Other antipsychotics**

- No5AX08 risperidone

Source: Finnish Statistics on Medicines 1995–2001

\* Marketing authorisation cancelled in the year indicated in brackets

1995, the consumption of second-generation antipsychotics came to 10.3% and that of the conventional variety to 89.7% of the total consumption of antipsychotics (4). In 2001, the corresponding figures were 38.8% and 61.2% (4). The consumption of conventional antipsychotics still remains above half of the total consumption. Second-generation antipsychotics can nevertheless be considered primary drugs for patients who suffer from schizophrenic psychosis for the first time, or patients who suffer from adverse reactions from conventional antipsychotics and whose response to treatment with these is poor (1).

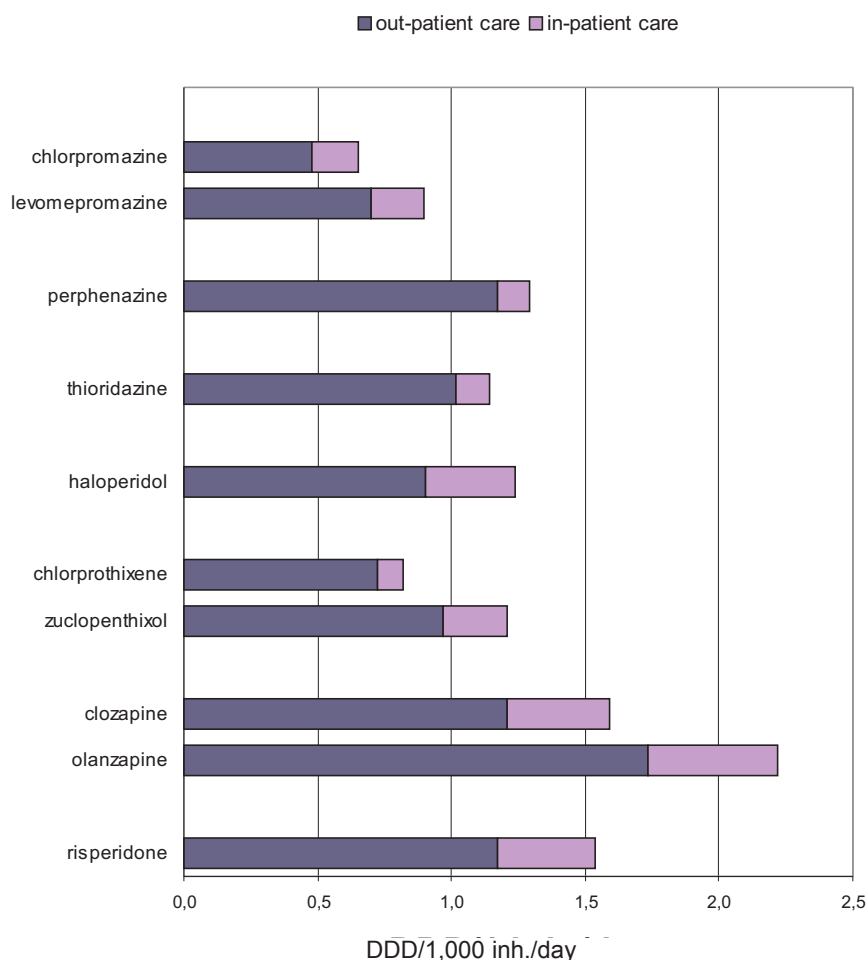
Phenothiazines were the most used antipsychotics in 1995, whereas in 2001, those most used were the second-generation antipsychotics, diazepines and oxazepines. Of these, the most used were olanzapine (2.22 DDD/1,000 inh/day), clozapine (1.59 DDD/1,000 inh/day) and risperidone (1.54 DDD/1,000 inh/day). The most commonly used

conventional antipsychotics in 2001 were perphenazine (1.29 DDD/1,000 inh/day), haloperidol (1.24 DDD/1,000 inh/day) and zuclopenthixol (1.21 DDD/1,000 inh/day) (4).

Out-patient use of antipsychotics is increasing. In 1995, the proportion consumed in out-patient care was 75% and in 2001 it had already reached 80%. The cause for the development is the reduction of beds in institutional care and the transfer of patients to out-patient care (5).

Olanzapine and clozapine were the antipsychotics most used in out-patient care in 2001 (Fig. 2). In in-patient use up until 1999, clozapine was the mostly used antipsychotic, followed by olanzapine. Out-patient use of olanzapine grew by 31% and in-patient use by 14% in 2001 compared with the previous year. The rapid increase in out-patient consumption is likely to have been caused by the fact that olanzapine fell into the category of special refund in the national health insurance scheme in the year 2000.

**Fig. 2. Consumption of the most used antipsychotics (DDD/1, 000 inh/day) in out- and in-patient care 2001. Source: National Agency for Medicines**



**Table 2. National health insurance refunds received for antipsychotics during 1995 and 2001. Includes only drugs for which over 1,000 patients/year have received refunds.** Source: Social Insurance Institution, prescription register

	1995		2001		
	No. of recipients of refunds	Proportion (%) of special refund recipients of all refund recipients	No. of recipients of refunds	Proportion (%) of special refund recipients of all refund recipients	Change (%) in the No. of recipients of refunds
<b>CONVENTIONAL ANTIPSYCHOTICS</b>	109 127	44	90 562	46	-17
<i>Phenothiazines with aliphatic side chain</i>	28 275	53	23 171	56	-18
<i>chlorpromazine</i>	7 519	80	4 906	84	-35
<i>levomepromazine</i>	21 899	46	18 946	50	-13
<i>Phenothiazines with piperazine structure</i>	41 051	38	31 817	39	-22
<i>dixyrazine</i>	3 589	14	3 298	12	-8
<i>fluphenazine</i>	3 976	30	2 188	31	-45
<i>perphenazine</i>	21 495	64	17 798	63	-17
<i>prochlorperazine</i>	12 389	3	8 830	3	-29
<i>Phenothiazines with piperidine structure</i>	22 592	69	14 686	74	-35
<i>periciazine</i>	3 876	37	2 418	44	-38
<i>thioridazine</i>	18 722	76	12 410	80	-34
<i>Butyrophenone derivatives</i>	22 357	37	19 488	34	-13
<i>haloperidol</i>	13 617	48	11 420	44	-16
<i>melperone</i>	9 547	22	8 533	19	-11
<i>Thioxanthene derivatives</i>	21 892	64	18 107	68	-17
<i>flupentixol</i>	6 159	34	4 012	37	-35
<i>chlorprothixene</i>	10 841	72	9 748	71	-10
<i>zuclopenthixol</i>	6 062	86	5 180	91	-15
<b>SECOND-GENERATION ANTI-PSYCHOTICS</b>	11 009	58	38 606	59	+251
<i>Diazepines and oxazepines</i>	2 367	97	16 138	71	+582
<i>clozapine</i>	2 367	97	5 501	97	+132
<i>olanzapine</i>	-	-	10 163	62	-
<i>quetiapine</i>	-	-	1 163	-	-
<i>Benzamides</i>	7 075	39	3 874	40	-45
<i>sulpiride</i>	7 075	39	3 874	40	-45
<i>Other antipsychotics</i>	1 815	83	20 731	53	+1 042
<i>risperidone</i>	1 815	83	20 731	53	+1 042
<b>All</b>	115 322	44	116 137	48	+1

## Reimbursements for anti- psychotics

A review of out-patient consumption of antipsychotics can also be obtained from the drug reimbursement record of the national social insurance scheme. Antipsychotics may be included in the special refund category for patients with severe psychosis or other severe mental disorders, and also for the mentally retarded patients with anxiety disorders. Patients using the drugs with other disorders are entitled to a basic refund. The number of patients entitled to a special refund is slightly lower than that of patients receiving basic refunds. In 2001, an average of 48% of patients on antipsychotics received special refunds for at least one of the antipsychotics they used (Table 2). The quantity of drugs used by those entitled to special refunds (calculated in DDDs) is nevertheless larger than that used by those entitled to basic refunds only, the likely cause for this being that those entitled to special refunds use their drugs in larger quantities and more continuously, or for longer periods, than other users of antipsychotics (6).

The change in the choice of drugs seen in the consumption statistics is also reflected in the drug reimbursement statistics. In 1995, a total of 109,000 persons were entitled to refunds on conventional antipsychotics, whereas in 2001 the figure had dropped to 90,000. The drop in the numbers of patients receiving refunds is shown most explicitly in the group of patients using phenothiazines. The number of patients receiving second-generation antipsychotics increased from

11,000 to 38,600 during the same period. In 2001, based on the number of users who had received refunds, it is clear that the refunds were mostly given for risperidone: refunds were received by nearly 21,000 persons. The most frequently used conventional antipsychotics were levomepromazine (refunds received by 19,000 people) and perphenazine (refunds received by 18,000 people).

A review of the proportion of patients having received special refunds also shows that some channelling has occurred in the prescription of second-generation antipsychotics. Since soon after their introduction on to the market, clozapine and risperidone have been prescribed mainly for patients who were entitled to a special refund for their antipsychotic drugs. Risperidone has since also been prescribed to other patients.

## Costs

Even though the total consumption of antipsychotics has hardly increased, their costs have increased rapidly during the past seven years. The national health insurance statistics show an increase from EUR 135 to EUR 364 in the average annual costs per patient at the same time. The increase in the costs is the result of increased use of more expensive second-generation antipsychotics, but the transfer of psychotic patients to out-patient care has also increased the costs of drugs slightly. The highest wholesale costs in 2001 resulted from the use of olanzapine (EUR 16.2 million) and risperidone (EUR 9.5 million) (4).

## Conclusion

The use of conventional antipsychotics has been replaced increasingly by that of second-generation antipsychotics in both the out- and in-patient treatment of psychosis. The increasing use of second-generation antipsychotics in out-patient treatment is partly the result of the superior tolerability of these drugs and also partly due to their inclusion in the special refund category in the national health insurance scheme. This development has multiplied the costs of antipsychotics during 1995–2001.

## Literature

1. Koponen H, Lönnqvist J. Psykoosilääkkeet. Kapseli 29, Toim. Lääkelaitos ja Kela, Uusi Kivipaino, Tampere 2001
2. Syvälahti E, Hietala J. Psykoosien hoitoon tarkoitettut lääkeaineet. Kirjassa: Farmakologia ja toksikologia, ss 363-374, 6. painos. Toim. Koulu M, Tuomisto J, Gummerus Oy Kirjapaino, Jyväskylä 2001
3. Leinonen E. Uudet ja vanhat neuroleptit. Suomen Lääkärilehti 1999;16:2131-2134
4. Finnish Statistics of Medicines 1995-2001. NAM and SII, Helsinki
5. Pirinen O, Närhi U. Changes in the consumption of antipsychotics. TABU 2001;6: 37-39.
6. Myllykangas U. Psykoosilääkkeiden kulutus ja sairausvakuutuskorvaukset Suomessa vuosina 1995-2001. Pro gradu-tutkielma. Helsingin yliopisto, 2002



# Summary

**Harri Sievänen**

Sc.D., DOCENT, SENIOR OFFICER

Medical Devices Department

National Agency for Medicines

## Defibrillators and adverse incidents

A defibrillator is a device used during ambulance transports, first aid and intensive care. Its purpose is to eliminate life-threatening cardiac arrhythmia and to restore the heart's normal pumping activity by applying a powerful direct-current electric shock to the patient's chest. Defibrillation immediately following a cardiac arrest results in a patient survival rate as high as 80%, and a third of the patients survive even after 'out-of-hospital' defibrillation. The general condition of the patient and the duration of the cardiac arrest prior to commencing the (basic) resuscitation will affect the survival.

Conventional manual defibrillators have been in therapeutic use for decades. The proportion of automated external defibrillators (AED) among all devices in use has increased significantly, especially during the last decade. The patient's physiological functions are monitored and analysed by the device which can also, as necessary, advise the user with display and voice prompts on the method and timing of the treatment. Defibrillators intended for use by health care professionals are semi-automated, which allows the user to make important decisions pertaining to the treatment himself/herself. Automated, compact devices easy to use are also found on the market; they are appropriate for defibrillation carried out by non-medical personnel also practised in Finland.

### **The manufacturer and the user are both responsible for the performance of the device**

Medical devices should be designed and manufactured so as not to jeopardise the health and safety of the

patient or the user when used in accordance with their purpose. The manufacturer should therefore aim at identifying all apparent hazards associated with the properties, performance and use of the device, and minimising any consequential risks, as early as at the stage of designing and manufacturing. Risks associated with use should be clearly stated in the instructions for use and in the labelling of the device.

As to the condition and operation of medical devices, it is the responsibility of the professional user to ensure that they are maintained at the level required by regulations during the entire period of use. Compliance with special conditions relating to their storage, use, maintenance and service is required, including instructions for the carrying out of these operations. It is important that users receive adequate training in the use of the devices and have knowledge of any risks associated with their use. Experience in using them should be maintained at all times and further training arranged as required. Important labelling information and details pertaining to the safety of the device, including appropriate instructions for use, should receive special attention at the time of purchase and should be made available on request. According to Finnish legislation, information pertaining to the safe use of devices should be provided in both Finnish and Swedish.

### **New defibrillators speak the correct language**

In the autumn of 2002, the National Agency for Medicines decided to carry out a review of the new models of defibrillators marketed in Finland at present. Compliance with

regulations relative to their instructions for use, display and voice messages, and the frequency of training arranged by the distributors of the manufacturers of the device, were reviewed. A questionnaire was sent out to 11 Finnish companies, which were assumed to market defibrillators at the time.

Six Finnish companies reported as marketers of defibrillators. The replies consisted of reports on 13 models of devices on the market at present, manufactured by six different manufacturers. Six of the models were claimed to be appropriate for use also by non-professionals in the automated external mode (AED).

Instructions for use and labelling, and information essential for the safety of use, were supplied in Finnish for 12 and in Swedish for nine devices. Ten devices had display and voice prompts in Finnish, and 9 devices in Swedish. The instructions for use of one device were only provided in English at the time of the questionnaire, but its Finnish version was being prepared.

All companies reported that they offered training in the use of the device at the time of supply and further training on request by the client. Only one distributor claimed to arrange regular training for the company's clients.

### **Only very few adverse incidents**

During 1995–2002 the National Agency for Medicines received a total of 32 reports of adverse incidents relative to defibrillators: Seventeen reports (from 13 users) were on Finnish incidents, five reports were submitted by manufacturers themselves on the corrective measures they had taken on their devices, and 10 were submitted by the authorities

reporting on measures taken by manufacturers. Seven of these reports on corrective measures did not concern Finland.

The reason for corrective measures in general was the increased frequency of defects detected in the electrical or mechanical components of certain models or batches of products, or problems that were detected in the operation of the software of the device.

Four of the Finnish incidents involved a fatal accident, six involved a serious incident, five involved a near-incident and two were in relation to ambiguities associated with the instructions for use or properties of monitoring. In relation to the large number of defibrillators in use and the critical use of the devices, the frequency of serious incidents is unexpectedly low; only 10 cases during the last eight years.

The number of serious incidents is very likely to be higher than the number reported to the National Agency for Medicines. Such an incident should always be reported when there is reason to believe that the performance or other properties of the device (including usability) have resulted in the development of an adverse event or a fatality, or when it did not have serious consequences at the time, but could have a serious consequence if recurred. The user should report any hazardous incidents to both the distributor or manufacturer and the authority. The reporting is essential because sharing the background information on hazardous incidents is the only way of helping others to avoid similar incidents and take appropriate measures should one occur. The intention is not to blame anybody, but to learn.

### **Contributory reasons for an adverse incident**

A serious incident may have been caused by a certain property of the device which, despite the manufacturer's necessary risk analysis, is not detected until the device is being properly used – perhaps not until years after it has been taken into use.

A case was reported last year in which, as part of their scheduled

maintenance operations, the technical service personnel in a hospital detected that all the defibrillators purchased in 1998 had faulty power supply units. Fortunately, nothing serious happened as the faults were detected before the devices were needed in an actual resuscitation. Faulty power supply units are well-known complications in defibrillators and they have occurred sporadically or, as in this case, they may have been associated with a certain production batch. Both of the two fatalities that occurred in 1996 took place in ambulances, when the electrodes were damaged due to difficulty in removing the protective plastic covers, and defibrillation was consequently unsuccessful. This particular model of electrode was subsequently withdrawn from the market and the durability of the new electrodes and the feasibility of the covers were improved. The importance of the correct handling of electrodes was also emphasised.

It is very important that the performance and operation of defibrillators as well as other medical devices be checked at health care units as part of their routine procedures. The personnel should be trained to detect malfunctions of the devices or signs or symptoms indicative of such malfunction.

Despite regular checks on the operation, normal wear and tear of medical devices during use or an individual defect may result in an unanticipated adverse event. In an incident which occurred in 2001, the cable between the defibrillator and the electrode was broken, preventing instant treatment of the patient. In another incident occurring in the same year, the ECG cable of the defibrillator was faulty, causing ventricular fibrillation in the patient as a result of the twisting cable and the unsynchronised defibrillator shock received from the device. In a third case, the contact between the cable and the electrode of a certain type was poor, resulting in a delay in the treatment. In all these cases, however, the patients were successfully resuscitated. A spare device and spare supplies important for the treatment (e.g. electrodes, cables, and fully charged batteries) should be readily available in order to manage unex-

pected situations and avoid fatal consequences.

Inadequate instructions for use, or inadequate skills of the user may also contribute to the development of a seriously hazardous incident. Use error can be considered to be the cause for only one of the Finnish cases. In this case, the alarm function of the defibrillator used in a monitoring situation had been switched off; ventricular fibrillation in the patient was fortunately detected in time and treated successfully. A fatal incident occurred in an ambulance in 1997 due to a battery being inadequately charged. As a result of the event the user changed the standard operating procedures of charging the batteries. The above case with the poor connection between cable and electrode also prompted the user to change the guidelines for the use of electrodes.

All the three serious incidents last year were associated with faulty operation, which was detected as the device was being used, and were not possible to repeat in test situations following the incident; consequently, the actual causes remained unclear. The underlying causes for these inexplicable faults in operation may well be associated with the increased complexity of the devices. The operation of the more recent models of defibrillators is, to an increasing degree, based on the computerised identification of physiological signals and associated conclusions.

Serious incidents are very infrequent at present. The near future will show whether the proneness to faulty operation and to defects will increase with the increasing variety of operations and automation. The professional skills of the user and his/her ability to use the device even in unexpected situations, and early detection of any associated complications, are nevertheless important for successful treatment. Maintenance of these skills should be continually emphasised.

### **Literature**

<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfMAUDE/search.CFM> (haku-sanat "defibrillator", "incident", "software" jne.).

**Translation Mervi Moisander**