TABU

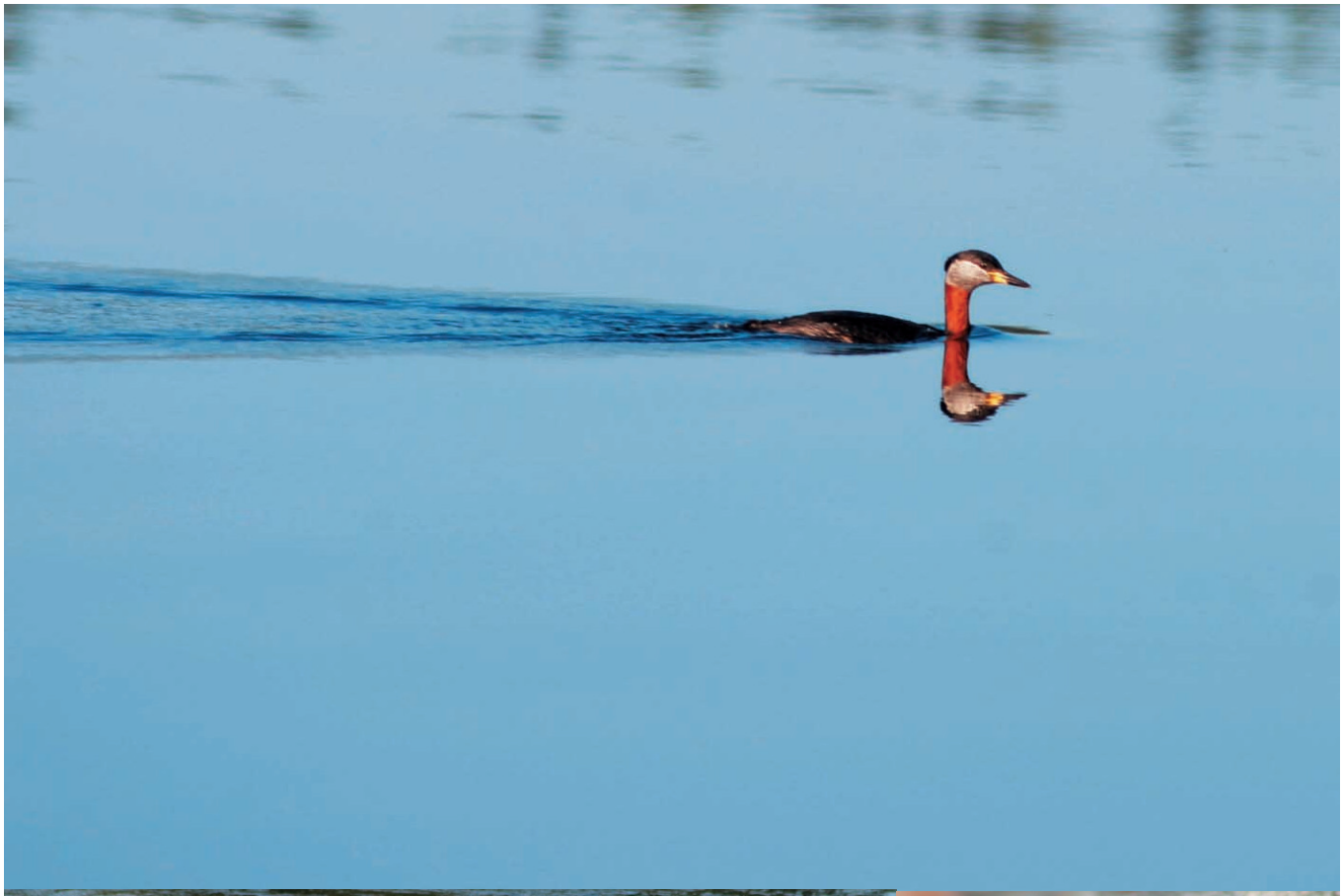
Lääkeinformaatiota Lääkelaitokselta

Läkemedelsinformation från
Läkemedelsverket, Finland

Drug information from the National
Agency for Medicines, Finland

4 | 2006

eu2006.fi



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The development of biological medicinal products: innovations and regulation

Biological, especially biotechnology-derived medicinal products, have enjoyed very high success during recent years. Several rare diseases have, for the first time, been managed with effective therapies, and significant progress has been made in the treatment of many common diseases. The development of gene and cell therapies and tissue engineering products has reached the stage where therapeutic breakthroughs are to be expected in the next few years.

The development and introduction into use of therapies based on new mechanisms of action and technologies are always associated with uncertainties. The drug regulatory authorities are continuously struggling to find a balance between the application of the most recent achievements in science and technology and ensuring the safety of patients. Excessive boldness may eventually cause safety problems, but then again excessive cautiousness and an urge towards self-protection will slow down development and delay the introduction of new therapies.

The European Medicines Agency (EMEA) and its Committee for Medical Products for Human Use (CHMP) are in the forefront of regulation of the recent biotechnology-derived medicinal products. The authorities are making an effort to keep up with ongoing developments in science and technology. The experts of EMEA and CHMP, in collaboration with the pharmaceutical companies and scientific organisations, are at present examining ways to facilitate the introduction of new innovative medicinal products on to the market (Innovation and Drug Development in Europe, "Innovation Think Tank"). As set out by its strategy, NAM has been active in this and other development programmes focusing on the development and regulation of biological medicinal products. The experts of NAM have become resolutely engaged in solving current topics in their area, such as similar biological medicinal products, nanoparticles activated in the cells, and the use of autologous cells for various therapeutic purposes.

These complicated issues typically relate to new spheres of science and technology of which the drug regulatory authorities have no previous experience, or to areas which fall in between the different regulatory sectors (e.g. combinations of medicines and medical devices). In those sectors of influence within the EU in which it has chosen to be a part, NAM relies heavily on its national networks of experts. The assignments of expertise within NAM provide an opportunity for university and hospital experts to familiarise themselves with the technical and clinical applications of top-level research before they become public. For NAM, this opens up an opportunity to get a balanced overall view of the complicated and novel innovations.

Drug development is able to be tracked down easily from its very first stages up to the evaluation of the application for marketing authorisation. The risk management of new therapies can be developed by making use of and combining various health care registers. In Finland, for example, it is possible to carry out extensive epidemiological studies into the effects of modern vaccines. Well organised post-marketing safety surveillance benefit both the patients and the drug developers, allowing safe introduction into use of new biotechnological medicinal products.

The pharmaceutical industry which develops biological medicinal products is in the forefront of innovations along the route staked out by primary research. The risks, both financial and those relating to drug safety, are high. Successful outcomes naturally lead to success stories about medical therapies and hence to continued investments in research by drug companies. NAM offers the companies the best possible scientific and administrative advice in support of the success stories, without haggling over safety.

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To err is human

A survey of dispensing errors made by pharmacies in Finland

Drug treatment has an aim the dispense the correct drug in the correct dose to the correct patient via the correct route of administration and at the correct time.

The viewpoint traditionally taken in health care is that errors will not occur and must not occur. The confidence in the health care staff's faultless operation has been high. Nevertheless, the fact that there are deficiencies in the safety and quality of health care is gradually coming to be understood.

In the United States discussion about patient safety was triggered by a report by the Institute of Medicine (IOM), 'To err is human' (IOM 2000). According to the report, an estimate of 44,000–98,000 patients die and over a million suffer injuries every year as a result of a treatment error. Of these deaths, 7,000 have been associated with medication errors. Finland has participated in the work of experts in the Council of Europe with the aim of formulating recommendations in order to improve the safety of patients and their medication.

A medication error is defined as an event associated with a drug therapy which can lead to a risk and which may be caused by something that has been done, or been ignored, or by safety measures that failed. A medical error can occur at any stage of the drug therapy and treatment, and at anytime between the prescribing and dispensing and the administration and follow-up (National Coordinating Council of Medicat-ion Errors and Prevention, NCC MERP 1998). A dispensing error is considered to have occurred when the strength, dosage, pharmaceutical form or a dosage of a medicinal product dispensed by a pharmacy differs from that prescribed by the doctor. A dispensing error has also occurred if the drug dispensed is outdated, supplied with inadequate or incorrect instructions and labelling, or if the drug is manufactured, packed or stored incorrectly before dispensing from the pharmacy.

The survey was carried out by sending a questionnaire to all private main pharmacies in Finland (n=599) in March 2005. The questionnaire was completed by over a half (n=340) of private main pharmacies in Finland (response percentage 57%).

Prevalence of dispensing errors

The pharmacies were requested to state the number and type or evaluation of any dispensing errors recorded in 2004 (Savikko 2006). Of those completing the questionnaire, 66% reported the dispensing errors recorded and 31% gave their evaluation of them. The pharmacies had recorded a total of 1,955 dispensing errors, (8.7 errors per pharmacy) during 2004. The estimated numbers of dispensing errors were also close to the published numbers, an average estimate of 8.4 errors per pharmacy. The frequency of errors from prescriptions was one per 6,000 prescriptions. According to the pharmacies, not all errors are recorded and some pharmacies do not record them at all. The most common dispensing errors consisted of incorrect strengths, packet sizes and pharmaceutical forms.

Causes and prevention of dispensing errors

Dispensing errors are caused by factors associated with the working environment, the nature and actions of pharmacists, the prescriptions, the drugs and the patients. The most common individual causes were considered to be shortage of time, ambiguous or inaccurate prescriptions, carelessness on the part of the pharmacist, and similarities between packages. Ambiguous and inaccurate prescriptions were the result of obscure handwriting, obscure notes including e.g. abbreviations and renewals, and inaccurate notes, for instance regarding computerised prescriptions or therapeutic indications.

The survey participants considered that the dispensing errors from prescriptions could mostly be prevented by carefulness, concentration, accuracy and attentiveness on the part of the staff at all stages of the process, calm and undisturbed working environment, wider introduction of computerised prescriptions, adequate numbers of staff, and discussing the dispensing errors that have occurred with the staff.

Handling of dispensing errors

The majority of the survey participants (59%) had written instructions for the handling of dispensing errors. Most of the participants (89%) said their pharmacy would always reimburse the client for any error, and the rest (11%) also said they would nearly always do so. Dispensing errors are always or nearly always recorded by 76% of the pharmacies in the survey. The recording was almost as often made anonymously. Dispensing error cases are

more often discussed with the individual involved rather than jointly with the staff.

Most of the survey participants emphasised the importance of recording the errors and discussing the case jointly with the staff. According to the survey participants, this would make it easier to follow the possible causes of the errors and to discuss openly ways to reduce errors. Suggested ways of handling the errors included principally a rectification of the error and reimbursing the customer, as well as written instructions for handling of the dispensing errors.

Conclusion

Pharmacies make an effort to take a systematic approach to the handling of dispensing errors. This is seen, for example, in the written instructions available in pharmacies and in the reporting practices adopted for errors. In a large number of pharmacies any errors that have occurred are recorded and are discussed later jointly by the staff. The frequency and common practice of recording errors could nevertheless be improved to achieve a more complete picture of the errors and near misses that have occurred. The weakness of self-reporting is, in fact, under-reporting of dispensing errors (Ashcroft et al. 2006). A prerequisite for reporting errors is being able to detect them, and prevention requires identification and recognition of the errors. Reporting is made easier by an open working community with a tendency to discuss rather than victimise. Self-reporting has been seen to be a cost-effective method for following up dispensing errors, and the only method suitable for continuous use (Chua et al. 2003).

Previous surveys have indicated pharmaceutical advice as playing a part in the detection and prevention of errors in dispensing (Abood 1996). As a last resort, pharmaceutical advice ensures that the correct drug is dispensed to the correct customer. According to one survey, as many as 83% of dispensing errors can be detected and adjusted as a result of pharmaceutical advice before the wrong medicine reaches the customer (Ukens 1997).

Pharmacies are also carefully preparing themselves to use a national reporting system of dispensing errors. Reporting systems are in use in, for example, the USA, UK and Denmark.

The experience of pharmacists is that the dispensing errors are mostly due to the nature of the individual rather than the operation of the entire working community. Emphasis among the causes and preventive factors for the errors was laid on the individual's character, such as carefulness and ability to concentrate. There are two different approaches that can be taken to errors committed by humans; one of them concentrates on the individual and the other on the system (Reason 2000). The approach concentrating on the system emphasises the organisation and the circumstances in which the individual works (DH 2000). This approach takes into account the fact that humans make mistakes and errors are possible. They are seen as results rather than causes, while their origin lies in the system rather than in the individual.

The collaboration between pharmacies and prescribers could be further improved. Pharmacies should avoid excessive interpretation of prescriptions in ambiguous cases and contact the doctor to check prescriptions and to ensure patient safety.

The customer was also considered to play an error-promoting role, with a hurried or unusual behaviour and a large number of prescriptions. Creating undisturbed and calm conditions for mechanical checking of drug dispensing was seen as a solution.

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Medication error inquiries in the Poison Information Centre

The Poison Information Centre receives 40,000 telephone inquiries every year, 30,000 of which concern acute poisoning in humans. An average of 200 of these telephone inquiries relate to medication errors that have occurred in health care.

A survey was carried out of the telephone inquiries received by the Poison Information Centre between June 2000 and December 2005 in which the cause was either a medication error or a suspected medication error in humans. The use of an incorrect drug, dose or route of administration by a health care professional was considered a medication error.

Findings

There were a total of 150,036 inquiries about acute poisoning during the survey period, 852 (0.6 %) of which were about medication errors. Fifty percent of those in whom medication error had occurred were women and 37% were men. The sex was not reported in 12% of the cases and 1% of the inquiries concerned more than one patient. There were three main types of errors (Figure).

The majority of the medication errors reported occurred in the medication of children under 10 years of age and the elderly between 80 and 89 years of age. The youngest patient was one day old and the oldest 99 years of age. The majority of calls were from the Province of Southern Finland (56%). The location where the medication error had taken place was usually registered when the call was made from a health care unit. It was nevertheless not known in many cases, because the patient had already been moved to a health centre or hospital, and contact was made from there.

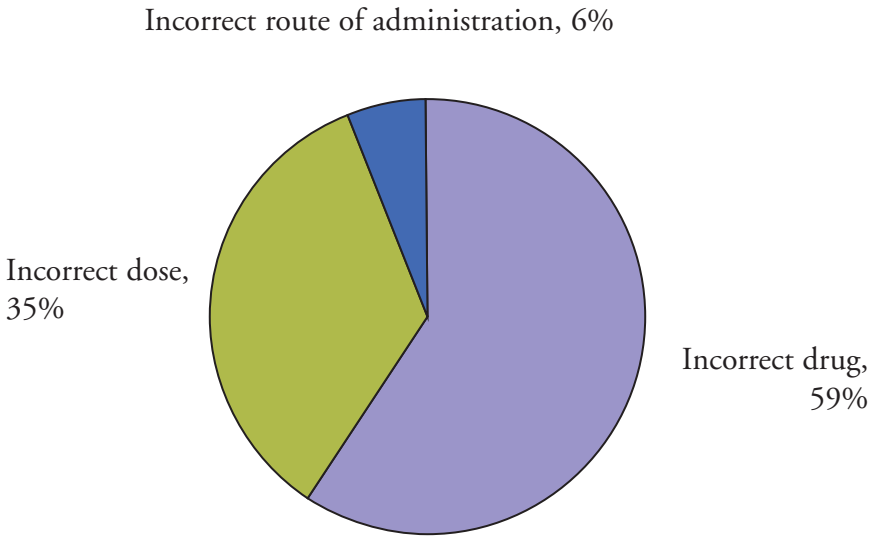
The medication error was usually detected quickly, and calls to the Poison Information Centre regarding severity and necessary measures were made rather soon after the incident. A total of 562 (66%) of the inquiries were received within less than one hour from the incident. Incorrect doses were repeatedly administered to 61 patients (7%). Every year the number of inquiries has peaked in the summer months and in December, when the number of permanent staff is lower and the number of temporary replacements higher than usual.

Incorrect drug

A total of 507 calls concerned the administration of an incorrect medication, where it was usually a question of administering a drug to the wrong patient.

The majority of cases of an incorrect drug having been administered occurred in nursing homes or responsible care units for the elderly, for the mentally retarded and for dementia patients. The largest age group was the 80- to 89-year-olds, who made up 19% (94 patients) of the total.

The majority of the inquiries were about drugs with a central nervous system effect (61%), drugs with an effect on the cardiovascular system (15%), and drugs with an effect on the alimentary tract and the metabolism (6%). The most common medicinal substances concerned included carbamazepine, sodium valproate, clozapine, risperidone and lorazepam. Sixty-seven percent of the calls concerned medication errors involving 1–3 drugs at the



Types of medication errors (n=855)

same time; in 33% of the cases the number of drugs erroneously used was between 4 and 13.

Incorrect dose

Enquiries were made in 299 calls about the administration of an incorrect dose or a dose with an incorrect strength. The majority of these also occurred in nursing homes or responsible care units for the elderly, for the mentally retarded and for dementia patients.

The incorrect dosages administered were mostly to patients under 10 years of age (24%), usually in hospital, at the pharmacy, or in association with vaccination. There were 8 newborns, all of whom were incorrectly dosed in hospital. Five of these infants had received an overdose which was 10 times the required dose.

The groups of therapy most frequently enquired about included drugs with a CNS effect (71%), systemic anti-infectives (19%), and cardiovascular drugs (17%). The most common drugs included vaccines, sodium valproate, carbamazepine, paracetamol and lamotrigine. Almost 80% of the inquiries concerned incorrect dosage of one medicinal substance.

Incorrect route of administration

Forty-nine of the calls concerned cases where an incorrect route of administration had been used. The calls were usually made from hospitals, with the majority of them concerning adults. The largest age groups were the 80- to 89-year-olds (11 calls out of 49) and under 10-year-olds (8 calls out of 49).

The groups of drugs about which queries were most frequently raised included systemic anti-infectives (30%), drugs with a CNS effect (22%) and drugs used to treat respiratory diseases (8%). In most cases the drug had been inadvertently administered via the intravascular (38%), oral (10%) or intramuscular route (8%). The most common incorrect routes of administration included the intravascular administration of drugs intended for intramuscular or oral administration.

Inquiries concerning pharmacies

Seventeen (2%) of the 852 calls in total were cases where a prescription error was suspected of having occurred in the pharmacy. The ages of the patients varied between 6 months and 90 years: the under 16-year-olds numbered 11, the 16- to 75-year-olds 3, and the over 75-year-olds 2 (in one case, the age was unknown). Calls were received from the public (10), the pharmacy (6) and the physician (1).

The patient instructions supplied with the drugs included 7 cases of incorrect dosage instructions, and an incorrect strength of the drug was supplied by the pharmacy on 10 occasions. In one case medicine was dispensed incorrectly in the drug dispenser, and in the other case both incorrect strength and dosage instructions were supplied. The majority of inquiries made were about antimicrobials, cough medicine and antihistamines.

Even though errors of this type can in the worst scenario have severe consequences, the medicines about which queries were made were nevertheless in a large number of cases fairly risk-free. The Poison Information Centre recommended follow-up at home for 15 patients, and two patients were considered to need treatment by a physician.

Symptoms and treatment

Of the total of 852 patients in the survey 77% were symptom-free at the time of the call, probably owing to the fact that the call was made not long after the erroneous administration and before any symptoms had developed. No information is available about the symptoms the patients possibly manifested later and the treatment they may have required. The longer the time that had passed since the incident, the higher the number of inquiries concerning patients with symptoms. About 75% of the patients could remain in follow-up treatment at home, and 25% were recommended for treatment at a health centre or hospitalisation.

Conclusions

The statistics of the Poison Information Centre include telephone inquiries spontaneously received about cases of medication error or poisoning.

The majority of inquiries received by the Centre concerning erroneous medication relate to a normal dose of medicine being given to the wrong patient. The error usually occurs in a nursing home for the elderly to a patient with several primary diseases and on several drug therapies. Even if it is a drug dose intended for a patient, it may in another patient cause unexpectedly strong symptoms and even be fatal.

When an accident occurs it is important to act immediately and establish whether the situation requires any treatment measures. Information about risks involved with medicines and their dispensing should also be increased, especially among staff working in in-patient wards, nursing homes or responsible units.

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My observation of an adverse drug reaction

Telithromycin and photodermatitis

My patient is a 54-year-old office worker, with asthma as her primary disease since 1987. For the treatment of her asthma the patient has for years used Seretide 25/250 mg 2 x 2, theophylline prolonged-release tablet 200 mg in the evening, tiotropium inhalation powder 18 microg 1 x 1 and, as necessary, salbutamol inhalation 100 microg. On diagnosing asthma in 1995, prick tests showed positive reactions to epithelia from cats and guinea pigs. The patient had suffered from atopic dermatitis in childhood.

During her working life the patient suffered from recurrent bronchitis and sinusitis, which were often treated with courses of antibiotics. These usually included doxicycline and cefalexin, a few times also azithromycin and once roxithromycin and a course of cefuroxime. In November 1998, after a course of azithromycin, the patient experienced a short-term facial rash of the urticaria type. The course was given during a dark season. But a course of azithromycin given later on did not cause a rash.

A 7-day course of telithromycin for the treatment of bronchitis was started at the beginning of April. On the second day of the course, an itching, erythematous, small papular rash developed on the light-exposed areas of the face, neck and upper chest, and the back of the metacarpal area and the arms. The itch was intense, even disturbing night-time sleep. The patient continued using telithromycin for a period of 5 days. She did not use other medicines, except for her anti-asthmatic agents.

I met my patient at the beginning of May and prescribed hydrocortisone-17-butyrate cream, saline baths and cetirizine 10 mg 1 x 1 for the treatment of the rash. A week later the patient told me that the rash had abated, there was no itching or redness, but that some scaling remained.

Certain cosmetic preparations have caused irritation of the skin, but no epicutaneus tests have been carried out. From then on, the patient only used the basic ointments which usually did not cause a problem.

Since 1973, the adverse drug reaction register of NAM in Finland has received 107 reports of photosensitivity cases. There are no further reports associated with the use of telithromycin; and azithromycin, one of the antibiotics of the macrolide group, has been reported on twice. Azithromycin is the only macrolide, the SPC of which mentions photosensitivity as an adverse reaction (albeit rare).

The majority of reports on photosensitivity have concerned products containing a thiazide diuretic (14 reports) and tetracyclines (13 reports, 7 of which were on doxicycline). Products containing ketoprofen have been reported on 8 times in total (7 of which concerned the topical preparation), and piroxicam 6 times (all of them concerning the oral preparation). Preparations containing sulpha have been reported on 6 times (on 4 of which the trimethoprim combination product was concerned), and amiodarone has been reported on 4 times. These reports serve as a good account of the spectrum of drugs known to cause photosensitivity.

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Adverse reactions due to antidepressants

From 1998 to 2005 the adverse reaction register of NAM in Finland received a total of 396 reports of adverse reactions associated with antidepressants. Of these, 268 concerned women and 126 men. Two reports did not mention the sex. The Figure represents the number of reports categorised into age groups.

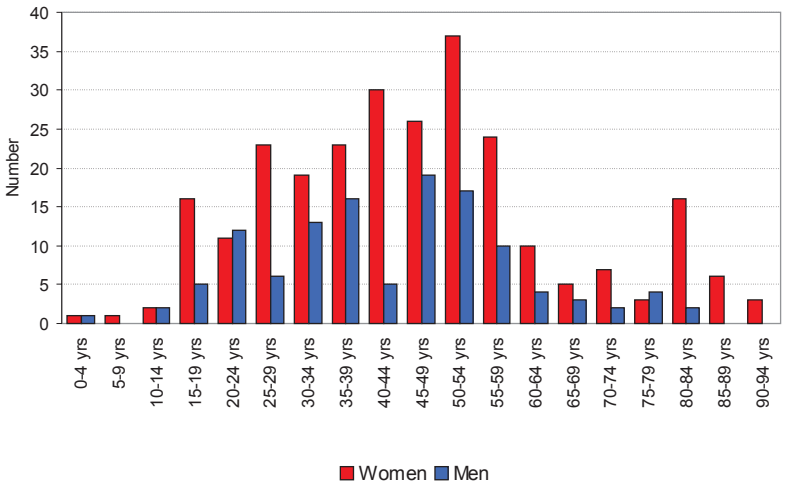
The number of reports according to the category of the active ingredient are presented in the Table. The report may involve more than one suspected drug, and therefore the number of suspected drugs is higher than that of the reports. Equally, one report may include one or more symptoms.

A total of 170 reports were received on the selective serotonin re-uptake inhibitors (SSRIs), the majority of which were on sertraline (51), citalopram (44) and paroxetine (27). About a third of the cases related to various adverse reactions involving the nervous system (including headache, dizziness, tics, seizures, dysaesthesia, sleep disturbances, hallucinations, confusion). Adverse reactions relating to the skin and the digestive organs (nausea, abdominal pain, diarrhoea) and oedema were also common. Intentional overdose was reported on 8 cases. Serotonin syndrome was mentioned in four reports, two of which were in association with an interaction and one with an overdose. There were also 11 reports about withdrawal symptoms.

Also most of the adverse reactions associated with the use of mirtazapine, venlafaxine and reboxetine involved the nervous system. Adverse reactions associated with the use of mirtazapine included seizures (12 reports) and restless legs (6 reports); others were e.g. dizziness, tremor and headache. Various adverse reactions associated with the skin were also reported, besides edema; a total of 12 reports were received on various degrees of leucopenia. Oral adverse reactions were reported on 12 times, four of which concerned stomatitis.

The most common nervous system adverse reaction associated with venlafaxine was dizziness. A total of 4 reports were received on the serotonin syndrome, and 5 on withdrawal symptoms. There were also 4 reports on the prolongation of the QT interval. Of the 15 reports on mianserin, 8 mentioned agranulocytosis/granulocytopenia.

There were a total of 21 adverse reactions involving 15–19-year-old adolescents (16 women and 5 men). The adverse reactions manifested in this age group were of the same type as those in older age groups. Intentional overdosing was reported on three occasions. Reports on complications involving the newborn totalled 7, all of them on the SSRI drugs. Some of the complications involving the newborn have been recorded in the mother's report. Symptoms in the newborn included, for example, somnolence, seizures, breathing and eating difficulties.



Adverse reactions due to antidepressants from 1998 to 2005

	Number of reports
Tricyclic antidepressants (e.g. amitriptyline)	7
Selective serotonin re-uptake inhibitors (SSRIs), total	170
sertraline	51
citalopram	44
paroxetine	27
fluoxetine	22
escitalopram	18
fluvoxamine	8
Others, total	227
mirtazapine	106
venlafaxine	53
reboxetine	20
milnacipran	15
mianserin	15
moclobemide	9
duloxetine	5
trazodone	4

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The use of antidepressants in young women has increased

The consumption of antidepressants took an upward turn in Finland and other Western countries at the end of the 1980s, i.e. after the introduction of group SSRI drugs with a new mechanism of action. According to the sales records of medicinal products of NAM in Finland, the consumption had increased seven-fold in 2005 compared with the year 1990. The Social Insurance Institution statistics for refunds show that 328,000 individuals, or 6.3% of the population, were reimbursed for these drugs last year. The proportion of women was 7.8% and of men 4.6%.

In 2005, a great regional variation in the use was seen (See map on page 18). The use was most common in Pohjois-Savo, where the proportion of the population using these drugs reached over 7%. The next largest proportions were found in Pohjois-Karjala and Varsinais-Suomi. The consumption was smallest in the hospital districts of Länsi-Pohja and Lappi, where it was about 5%. The highest figure for consumption in the health-care centre districts was found at Hyrynsalmi, 9.2%, while Heinävesi and Rautavaara also nearly reached the level of 9%.

Citalopram is the most commonly used

The antidepressant most commonly used in Finland ever since the first years of the 1990s has been citalopram. The number of people receiving a refund for it in 2005 was 99,000. Mirtazapine was the next most commonly used, with 64,000 people receiving a refund, and escitalopram came in third place with 49,000 recipients of a refund. Among the old antidepressants, amitriptyline was the most frequently used with 19,500 recipients of a refund, while 11,500 people had used doxepin. A proportion of the consumption of amitriptyline may have been for the treatment of chronic pain.

Prices reduced through generic substitution

The end of patent protection has introduced several important antidepressants into the generic substitution sector. This is shown in the strong decrease in their consumer specific costs (Fig. 1). Among the drugs

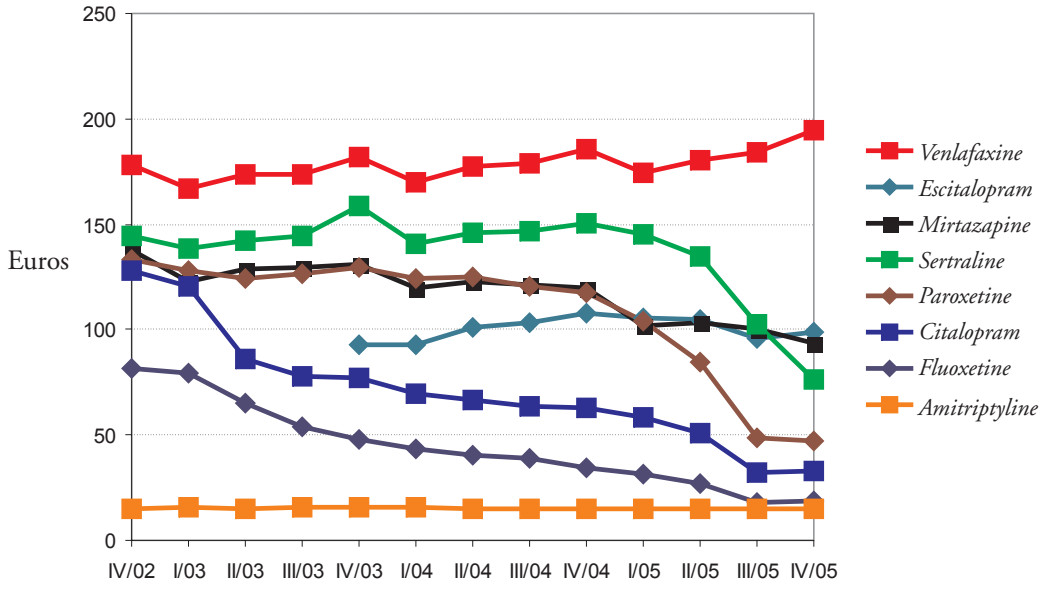

Fig. 1. The costs of antidepressants per user during three months between October 2002 – December 2005

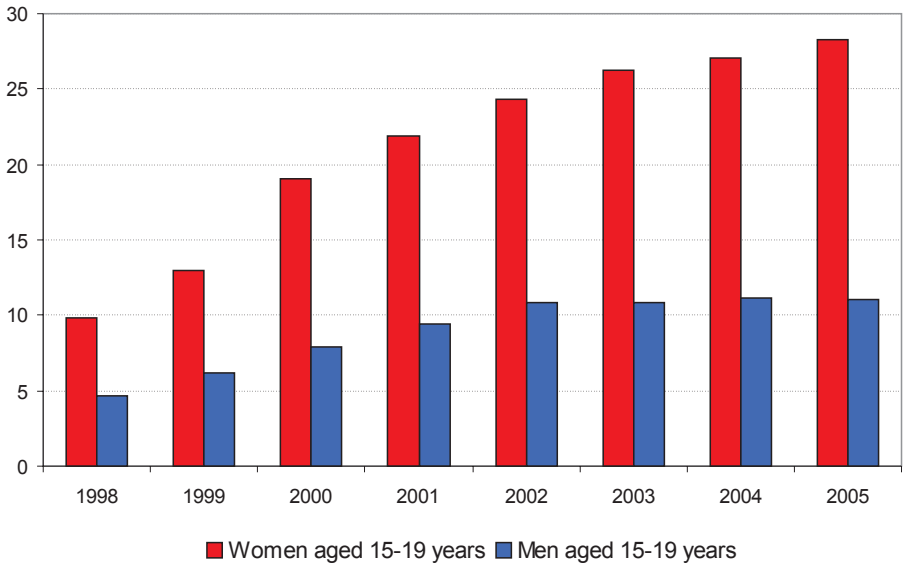

Fig. 2. The frequence of the use of antidepressants among 15–19 year old women and men in Finland 1998–2005

mostly used, only venlafaxin and escitalopram have retained a relatively stable cost level. Citalopram, paroxetine and fluoxetin in particular have been at the centre of tough price competition, and certraline was targeted by price competition during 2005. Mirtazapine is already also available as a number of generic products, and its average cost level has started on a downward trend. Calculated per consumer, the cost of the most commonly used antidepressant, citalopram, was less than a fifth of that of the most expensive one, venlafaxine.

As a result of the price competition, the cost of antidepressants in outpatient care has decreased in the last couple of years. In 2002, i.e. before the generic substitution, the total costs of this drug group amounted to 80 million euros, whereas the corresponding figure last year was 65 million.

The use is most frequent among the elderly, while adolescent use has been increasing

Last year the frequency of use varied greatly by age group. The consumption curves had two peaks, i.e. 50 to 59-year-old patients used these drugs more commonly than the next younger and older age groups. The second, and at the same time higher, peak was found among the over 85-year-olds. Among the female patients the frequency of use was 1.7 fold that of the 70 to 74-year-olds. On another study, the consumption was found to become frequent up until the age of about 90 years.

Special attention has recently been focused on the use of antidepressants by children and adolescents, because this is considered to be associated with self-destruction. From 1998 to 2005 the proportion of 15 to 19-year-old women receiving refunds for antidepressants has nearly trebled, and in men in that age group it has doubled (Fig. 2). Consumption in the groups younger than this has clearly been rarer, nor has it become generalised. The difference between the sexes in the frequency of use in 15 to 19-year-olds has been relatively wide for the whole period reviewed, and men have only now reached the level at which young women already were in 1998.

Review

The use of antidepressants has been under lively discussion for as long as two decades. Concern has been expressed about the rapid increase in their use, while it is also considered that prevanlence of depression has increased and a proportion of the depressed has been left without medical treatment. According to a Health 2000 study in Finland, about 7% of adults aged 30 years and over suffered from a severe state of depression. The proportion of antidepressant users in the population shown in the statistics is therefore of the same magnitude as the prevalence of severe depression. This, however, does not reveal whether there are any false positives among the users, or how many of those in need of treatment have been left without it. The number of elderly among the users in particular is essentially higher than the prevalence of severe depression in the group would necessitate.

The use of antidepressants has increased in recent years relatively rapidly among the 15 to 19-year-olds, and among women of the age group in particular. Reports of self-destruction associated with the use of antidepressants in this age group have been received recently to such a degree that warnings about it have been added in the patient information leaflets of several drugs. Careful monitoring of the effect of these warnings on the treatment practices during the current year is recommended.

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The use of antihypertensives in Finland in 2004

In 2004, 499,658 people with chronic hypertension, 194,369 with coronary artery disease and 64,135 with cardiac insufficiency were entitled to a special refund of the price of their medication. Some of these people enjoyed several entitlements to a refund (1).

The main group of drugs used in the treatment of hypertension includes diuretics, beta-blockers, calcium channel blockers, ACE inhibitors and angiotensin receptor antagonists, which all have an approximately equal hypotensive effect (2). A combination of two or more drugs is needed in over half of the patients to achieve the treatment target (3). Beta-blockers were the most commonly used antihypertensives (either alone or in combination) in the study by Rantanen et al. (4). The use of diuretics in Finland is too low in relation to the efficacy proven and the associated benefits (4, 5).

The consumption of antihypertensives has increased in all the Nordic countries during 1999–2003. Diuretics were the treatment of choice during this period in Denmark and Sweden more often than in the other Nordic countries. The use of beta-blockers was becoming more common in all the Nordic countries, but their consumption (DDD/1,000 inh./day) in Denmark was half that in Finland or Sweden. In relation to population, the consumption of combination products of ACE inhibitors and diuretics was highest in Finland, and the consumption of combination products of angiotensin receptor antagonists and diuretics highest in Norway (6).

The aim of the study was to establish which antihypertensives were in use, and how the consumption and costs of drugs were distributed in Finland with regard to income level, educational level, age, sex, mother tongue and employment status in 2004. Drug therapies were also reviewed from the viewpoint of the recommended treatment in hypertension and some associated diseases (2, 3).

The study was carried out as a register review based on the data of the Social Insurance Institution and the Statistical Finland. The study subjects were randomly chosen among people with special refund entitlement from the Social Insurance Institution for the drugs they used for chronic hypertension (205) and/or chronic coronary heart disease (206) and/or chronic cardiac insufficiency (201). Their prescription data were checked and all drugs classified as antihypertensives were included in the study irrespective of which of these three special refund entitlements the drugs were assigned to. The study included potassium (A12B), antihypertensives (C02), diuretics (C03), beta-blockers (C07), calcium channel blockers (C08), ACE inhibitors (C09A/C09B) and angiotensin receptor antagonists (C09C/C09D) (7).

Results

The subjects of the study were 335,879 individuals on antihypertensive therapy. The data were collected from 53% of those with special refund entitlement for antihypertensives, 59% of those with special refund entitlement for cardiac insufficiency and 31% for coronary heart disease during 2004.

The use of antihypertensives was relatively more common in women, in older people, in those of Finnish mother tongue, in those with a lower level of education, and in those living in eastern Finland and small municipalities, rather than in men, in younger people, in those of Swedish or other mother tongue, those with a higher level of education, or those living in either southern or south-western Finland and/or in large municipalities.

The most common antihypertensive therapies consisted of either a beta-blocker alone and/or a combination product containing it (19%), an ACE inhibitor alone and/or a combination product containing it (8%), a beta-blocker together with an ACE inhibitor and/or a combination product containing it (7%) and a beta-blocker together with a calcium channel blocker and/or a combination product containing it (7%). The use of ACE inhibitors in men under the age of 65 was slightly more common than the use of beta-blockers, whereas the situation in women was the reverse. The use of calcium channel blockers in men older than this was relatively more common, whereas in women the use of diuretics became more common with age.

The groups of antihypertensives most commonly used and number of users are presented in the Table. The subjects had an average of 2 antihypertensives in use during the year: 38% were using one, 33% two and 18% three antihypertensives.

The Finnish Treatment recommendations for hypertension were fairly well adhered to in respect of people suffering from coronary heart disease, cardiac insufficiency and diabetes. Of the patients who had asthma in addition to cardiovascukar disease 23% used beta-blockers and/or combination products containing them, whereas the percentage for all the study patients was 59%. One and a half percent of

The antihypertensives most commonly used and number of users

Antihypertensive and/or a combination product	*Number of users*
Beta-blocker	*197,000*
Diuretic	*171,000*
ACE inhibitor	*120,000*
Calcium channel blocker	*113,000*
Angiotensin receptor antagonist	*72,000*

the asthma patients were using a non-selective beta-blocker. According to the treatment recommendation, however, beta-blockers are usually contraindicated in asthma patients. In compelling circumstances (such as coronary heart disease), either as potent a beta-1-selective blocker as possible or a blocker with an additional beta-2-agonist effect may be used (2).

The cost of antihypertensives per person Finland in 2004 was on average EUR 301. The cost of drugs increased with age up to the age of 55–59 years, after which it diminished again. In relation to other socio-economic variables, there were no significant differences in the cost of drugs. The annual costs for individuals using one drug only were on average EUR 157, for those using two drugs EUR 313, and for those using three drugs EUR 430. The costs for antihypertensive drugs in diabetics were higher than in others, an average of EUR 366, owing to the stricter target level of blood pressure in diabetics and, consequently, the increased medication.

Conclusion

The use of antihypertensives corresponded fairly well with the treatment recommendations. Beta-blockers and diuretics and/or combinations containing them remained the most common antihypertensives. Over a half of the study subjects used more than one antihypertensive. Almost one in every four asthma patients used beta-blockers, which did not comply with the Finnish Treatment recommendations except under compelling circumstances (such as if the patient was suffering from a coronary heart disease). The prevalence of use differed by sex and age group.

The differences in drug costs between individuals were relatively speaking highest among those on one antihypertensive alone. The least expensive drugs were the diuretics and the most expensive ones the angiotensin receptor antagonists. When several drugs were used, the costs increased almost linearly with the number of drugs. The annual costs of antihypertensives for diabetics were higher than those for others.

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