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Läkemedelsinformation från Läkemedelsverket, Finland

Drug information from the National Agency for Medicines, Finland

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Editorial

The impact of written information about medicinal products is limited

The big issue on the mind of the producer and supplier of information about medicinal products is whether the information reaches its target and what impact does it have? This is a relevant question irrespective of whether the recipient of the information is a health care professional or a consumer who needs the product. The basic starting point in Europe is for the pharmaceutical industry to produce written summaries of product characteristics (for health care professionals) and patient information leaflets (for patients) concerning their medicinal products, followed by approval from the regulatory authorities. There is, however, limited knowledge about the effectiveness of these or of any other written information.

Newly published information about the relevance and impact of written drug information to the patient is now available, based on the evaluation of extensive research data and on patients' own views.[1] The main observation made by British researchers was that most people do not appreciate the written information they receive about medicinal products. There appears to be a gap of some magnitude between the written information and the information actually valued and experienced as something useful by patients. Patients prefer information tailored to their own needs and revealing both benefits and harmful effects of treatments with pharmaceuticals. Information about harmful effects of medicinal products are still considered very important and they ought to be based on numerical assessments rather than on verbal risk evaluations.

Even though the significance of the quality and readability of the written information is emphasised by researchers, preference is predominantly given to the verbal information delivered by health care professionals. Written information about medicines should not replace a discussion with a professional.

It is well known that Finns have great faith in the written word. The results of the study made in the UK can therefore hardly be generalised as such to the situation in Finland. It is a different matter whether texts are understood in the way they are intended to be understood even though they were in fact believed.

In April the European Commission published a draft report[2] in which, among other things, the practices of different countries are reviewed with regard to the provision of information to patients about diseases and their medication. Based on the final report the Commission will consider any proposals for a strategy for future information about medicines. New models of operation may have to be considered with the Internet as a channel for information and the role of the pharmaceutical industry associated with it.

Information about medicinal products is to an increasing degree searched for on the Internet, and the significance of the Internet in the acquisition of this information is likely to increase.[3] Reliable information should also be available on the Internet for the consumer. Whose task is it to satisfy this need – is it that of the authorities, the public health care organisations, the professional bodies and the scientific community, or of the pharmaceutical industry? Or should we just rely on it, that consumers are capable of evaluating critically any information about medicinal products published on the Internet? Drawing the line in pharmaceutical marketing is nevertheless clear. Advertising of prescription drugs to the public is prohibited, and if the consumer bodies in Finland were asked, a preference for also preserving it in future would prevail.[4] Moreover, nowhere in Europe is there any declared support for the advertising of prescription medicines to the public.

If a new role be proposed for or recommended to the pharmaceutical industry, involving the provision of drug information about diseases and prescription drugs also to consumers, the challenges involved are great. In that case, the responsibility for supplying information about medicinal products would be shifted towards the pharmaceutical industry.

Whether we are ready for this in Europe remains to be seen. It is not only a question of producing and providing the information as such, but also one of the interaction between the consumer and the pharmaceutical industry in general.

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The medicines treatment of tuberculosis, a challenge for the patient and the health care staff

Tuberculosis (TB) is the most fatal infectious disease after AIDS in the world. Drug resistant strains are, for example, a problem in Russia and the Baltic countries.

The epidemiological situation in Finland is good, but as the disease is becoming rarer it is posing ever-increasing challenges. The number of new cases in 2006 was for the first time below 300, while the prevalence was 5.6 per 100,000 inhabitants. Consequently, health care centre personnel in Finland do not necessarily even see a patient with tuberculosis every year. We should bear in mind the possibility of tuberculosis, however, when patients attending the appointment belong to a risk group (e.g. the elderly, intoxicant abusers, immigrants from countries with high prevalence of TB and close contacts with TB patients) and present with symptoms. Early suspicion of a disease and directing the patient for examinations and therapy are essential for preventing the spread of the disease.

The treatment of elderly patients with multiple diseases and of abusers has become a particular challenge. According to a Finnish study investigating the final outcome of treatment in tuberculosis, there are great variations in the combinations of drugs used and the duration of the courses of treatment (1). The final outcome of treatment has been good, according to the WHO criteria, in 65% of the study subjects suffering from pulmonary tuberculosis confirmed by cultivation (according to microbiological criteria, the disease was healed and the treatment was concluded while the clinical response was good) (2). The knowledge and skills for treatment possessed by the care staff, together with immigration movement from countries of high prevalence, are decisive for keeping the present epidemiological situation in control in the future. A book on the National tuberculosis treatment programme was published last year by the Ministry of Social Affairs and Health in Finland (3).

Principles of medications

Tuberculosis is a reportable contagious disease, with free treatment for patients. The treatment principles for tuberculosis differ from those for other microbial diseases. A build-up of resistance to the few basic drugs develops relatively rapidly and a combination of drugs ought therefore always to be used in the treatment of any disease caused by *Mycobacterium tuberculosis*. In addition, the treatment should last for months. There are five primary drugs for the treatment of tuberculosis: isoniazide (INH), rifampicin (RIF), pyrazinamide (PZA), ethambutol (EMB) and streptomycin (SM).

Mycobacteria enter the cells, and their destruction consequently also requires effective cell-mediated immunity. The lipid wall of the tuberculosis bacterium is an effective protection against immune defence and antimicrobial drugs. The thick bacterial wall containing mycolic acids also protects against the cytolytic effects of phagocytes. The bacterium is also capable of synthetisizing enzymes able to degrade drugs (4). The primary drugs are bactericidal, except for ethambutol. Their mechanisms of action differ from one to another, in that isoniazide is able to quickly destroy actively dividing bacteria, and rifampicin is at its best against mycobacteria which reproduce in stages. Isoniazide and rifampicin together form the basis of the treatment; their combination should always be used during the entire course of treatment, unless restricted by adverse reactions.

The standard duration of treatment is six months (Table 1). The treatment is initiated by an intensive stage lasting for 2 months, during which pyrazinamide is also used adjunctively with isoniazide and rifampicin. In situations where there is cause to suspect drug-resistant tuberculosis, or where the disease has recurred, all five primary drugs should be used concomitantly.

Table 1. *Primary drug treatment and intensified treatment in tuberculosis*

Treatment of tuberculosis	*Initial treatment*	*Follow-up treatment*	*Duration of treatment*
Primary treatment	*INH, RIF and PZA 2 months*	*INH and RIF 4 months*	*6 months*[1]
Intensified treatment	*INH, RIF, PZA, EMB ± SM*[2] *2 months*	*RIF and EMB 10 months*	*12 months*[3]
	INH, RIF, PZA, EMB and SM 2 months and INH, RIF, PZA and EMB 1 months	*INH, RIF and EMB 5 months*	*8 months*[4]

INH isoniazide, RIF rifampicin, PZA pyrazinamide, EMB ethambutol, SM streptomycin

[1] *In skeletal and miliary tuberculosis the total duration of treatment is 6–9 months and in meningitis 12 months*

[2] *Suspected resistance to INH or INH and SM*

[3] *Resistance to INH or INH and SM confirmed*

[4] *Disease recurred*

The total duration of treatment is then prolonged, even up to 12 months. Adding one drug at a time to an ineffective combination of drugs is malpractice and may rapidly lead to the development of resistance.

If the suspected cause of the disease is a multi-drug resistant (MDR) or an extensively drug resistant (XDR) strain, gene testing for rifampicin and isoniazide resistance on the patient's sputum sample should be requested from the laboratory for mycobacterial testing at the National Public Health Institute in Finland. Drug treatment should be planned individually, based on the patient's background data and the drug sensitivity data for the possible source of the infection. In these patients the treatment will last for about two years. More details about the treatment of drug resistant tuberculosis is available at: *http://whqlibdoc.who.int/publications/2006/9241546956_eng.pdf*.

Five primary drugs

Isoniazide is a synthetic medicinal substance inhibiting the bacterial wall mycolic acid metabolism. It is orally well absorbed and an adequate plasma concentration is achieved within a couple of hours, as well as equivalent levels in the pleural and spinal cord fluids. The drug causes peripheral neuritis in some people, and patients ought therefore always also to take vitamin B_6. Rifampicin is a semi-synthetic rifamycin derivative, which was introduced into general use at the end of the 1960s. Its effect is bactericidal. Rifampicin is orally quickly absorbed. Its distribution in the body is uniform with adequate concentrations also achieved in tissue and infection fluids, as well as tuberculous cavities. Its peak blood concentration is attained within about three hours of administration. Isoniazide and rifampicin may also be administered intravenously.

Pyrazinamide is a synthetic drug which becomes active within the body and is at its best inside the cells and in an acid environment. It has an effect only on the bacillus *Mycobacterium tuberculosis* and is a bactericidal medicine, which effectively rids the tissue of bacteria, and is therefore important at the intensive stage of the treatment. Its oral absorption is efficient and it is evenly distributed in the body. Ethambutol is a bacteriostatic medicinal substance, which is well absorbed from the gastrointestinal canal, evenly distributed in the body, and penetrates the blood-brain barrier when inflammation requires this. It is mainly excreted unchanged in the urine. The patients with renal insufficiency (creatinine clearance < 30 ml/min) should take ethambutol 3 times in week.

Streptomycin in the form of the aminoglycoside administrates intramuscularly. It has a bactericidal effect on mycobacteria, but the effect is low. It may quickly lead to mycobacterial resistance (within 1–2 months) if it is used without the support of any other effective TB medication. Streptomycin has a low blood-brain barrier penetration. It is chiefly excreted in the urine, and therefore, when the renal function is deteriorating the dose is reduced to the level of 12 to 15 mg/kg and the dose interval is increased. The doses for the primary drugs are shown in Table 2.

Steroid treatment as adjunct to tuberculosis medication?

Adequate proof of the advantage of steroid treatment has been obtained primarily in the treatment of tubercular meningitis and pericarditis. Steroid treatment in these patient groups reduces the risk of death and may decrease symptoms and complications. Steroid treatment may be beneficial if the patient has severe tissue damage induced by tuberculosis, such as advanced pulmonary tuberculosis and malnutrition including excessive pleural fluid accumulation which is not cleared by aspiration. Corticosteroids may also be used in the treatment of the rare IRIS reaction (*immune reconstitution inflammatory syndrome*, i.e. a paradoxical increase

Table 2. *The primary tuberculosis drug doses in adults*

Drug	mg/kg/day (maximum)	Daily dose	mg/kg x 3 / week (maximum)
Isoniazide INH	5 (300 mg)	300 mg	15 (900 mg)
Rifampicin RIF	10 (600 mg)	450 mg <50 kg 600 mg >50 kg	10 (600 mg)
Pyrazinamide PZA	20–30 (2,000 mg)	1000 mg <55 kg 1,500 mg 55–75 kg 2,000 mg >75 kg	35–40 (3,000 mg)
Ethambutol EMB	15–25 (1,600 mg)	800 mg <55 kg 1,200 mg 55-75 kg 1,600 mg >75 kg	25–30 (2,400 mg)
Streptomycin SM	15 (1,000 mg)	750-1,000 mg	15 [1] (1,000 mg)

[1] *The dosage x 5–7/week during the intensive period (usually 2 months), and as the treatment continues, the dosage x 3 / week*

in symptoms and findings during therapy while the immunological defence capacity is recovering) and of serious drug-induced hypersensitivity reactions.

Monitoring of treatment is the responsibility of specialised care

The treatment of a contagious patient (with a positive-staining slide of the sputum) is initiated in an isolation room. The isolation treatment of a patient with drug sensitive tuberculosis should be continued for at least 2 weeks, after which the patient is discharged from hospital, and the first control appointment is arranged at an outpatient clinic a month after the start of treatment. Follow-up appointments are continued thereafter at 1 to 2 months intervals. It is recommended that the introduction of treatment in a tuberculosis patient with a negative-staining sputum test should take place in an inpatient ward when the patient is elderly, suffering from multiple diseases or using several other drugs; this makes the monitoring of the patient's condition easier insofar as any adverse reactions are concerned. During inpatient care the drug treatments are explained to the patient and his or her compliance is assessed.

Outpatient control appointments are aimed at monitoring the patient's clinical condition and for any adverse drug reactions, while the efficacy of treatment is assessed with the help of pulmonary X-rays, sputum samples and blood tests. It is recommended that laboratory tests (ALT, Bil, blood cell count and CRP and ESR if they were elevated at the start of the treatment) are carried out at 2 weeks' intervals during the first month, followed by lab tests at 2 and 4 months after the start of treatment unless the liver enzyme values are significantly elevated. A pulmonary X-ray will be performed after 2 months of treatment and at the end of treatment. TB bacterial staining and cultivation of the sputum samples will be examined 2 to 5 weeks after the initiation and at the end of the treatment. If sputum is no longer being produced by the patient, this will be mentioned in the concluding evaluation. During ethambutol medication, in order to exclude optic neuritis, undergoing a monthly visual check and a colour vision examination should not be neglected.

Table 3. *Recommendations for measures in case of liver reaction due to tuberculosis medication*

Liver enzyme value from the upper limit of normal value	Condition of patient	Continuation of tuberculosis medication (isoniazide, rifampicin, pyrazinamide)	Follow-up of laboratory values
ALT value < 3-fold	Symptomfree Symptoms[1]	Tuberculosis medication is continued Tuberculosis medication is continued	ALT once in 2 weeks until value is normal ALT and Bil x 1 / week[2]
ALT value ≥ 3-fold	Symptomfree Symptoms[3]	Tuberculosis medication is continued Tuberculosis medication is interrupted	ALT and Bil x 1 / week[2] ALT and Bil x 1–2 / week Medication is continued if values are normal and patient is symptomfree
ALT value ≥ 5-fold or bilirubin level is increasing	Symptomfree or with symptoms	Tuberculosis medication is interrupted	ALT and Bil x 1–2 / week Medication is continued if values are normal and patient is symptomfree

[1] *Lack of appetite, mild nausea or abdominal pain*
[2] *If bilirubin is elevated, medication should be interrupted*
[3] *Nausea, abdominal pain, vomiting, fever, jaundice or unexplained impairment of general condition*

Table 4. *Recommendation for reintroducing tuberculosis medication after an interruption due to adverse reactions*

Adverse reaction	*1. reintroduction*[1]	*2. reintroduction*[1]	*3. reintroduction*[1]
Skin or fever reaction	*One drug at a time at intervals of 2–3 days, normal doses* *Use of reaction-inducing drug is discontinued and replaced by another drug.*	*One drug at a time*[2] *at intervals of 2–3 days, normal doses* *Use of reaction-inducing drug is discontinued and replaced by another drug.*	*One drug at a time*[2] *at intervals of 2–3 days, normal doses* *Use of reaction-inducing drug is discontinued and replaced by another drug.*
Elevation of ALT or bilirubin value	*All drugs at the same time, normal doses.*	*One drug at a time*[2] *at intervals of 5 days, normal doses.*[3]	*Concomitant introduction of INH + EMB, normal doses. Thereafter, introduction of RMP and PZA with dose increments at intervals of 5 days.*[3] *Use of reaction-inducing drug is discontinued and replaced by an other drug.*

[1] *Treatment may be continued once symptoms have been alleviated and laboratory values restored to normal.*
[2] *Introduction of treatment with a drug which is most likely to cause a reaction.*
[3] *ALT and Bil x 2 / week at reintroduction.*

Adverse drug reactions — what measures to take?

A relatively large proportion of the patients treated, 5 to 33%, suffer adverse drug reactions from tuberculosis drugs, mostly exhibited during the first months of treatment (5). Elevation of hepatic enzyme values is common and the values may be reduced during ongoing treatment. Monitoring of the laboratory results is adequate at this stage. If more distinct elevation of the values and/or serious symptoms occur, the treatment should be discontinued (Table 3) (3,5). At this point other causes for disrupting the liver function should be reviewed (virus hepatitis, alcohol, biliary duct disorder, other drugs with liver toxicity).

Isoniazide and rifampicin still remain the most important tuberculosis drugs. Their efficacy and adequate duration of treatment have been the subject of several studies. The aim is to continue the use of these drugs unless serious adverse reactions occur. Depending on the situation, medications are initiated individually increasing the dose as necessary (Table 4).

A reminder of interactions

Potential interactions should always be checked when tuberculosis drugs are introduced, as well as when a new drug is prescribed to treat another disease in a patient on tuberculosis therapy. Rifampicin induces many cytochrome P-450 system isoenzymes and accelerates the elimination of drugs metabolised via this system. This results, for example, in reduced efficacy of warfarin, antidiabetic agents and diazepam, which often makes it necessary to increase the therapeutic dose of these drugs. During rifampicin therapy it is usually necessary to double the dose of steroids to maintain their efficacy. Female patients should be informed about the reduced efficacy of estrogen products and advised to change their method of contraception. Equally, on discontinuation of rifampicin therapy (inducing effect continues for about 2 weeks), the therapeutic doses of the drugs above should be reduced back to their appropriate level. Isoniazide inhibits the cytochrome P-450 system isoenzymes, and the efficacy of carbamazepine, for example, may increase and follow-up of the drug concentration during treatment may be necessary.

Right to supervised care

We are dealing with a long period of treatment with several drugs, all of which have their own adverse effects. Irregular intake of drugs and occasionally omitting some drug will increase the risk for development of drug resistance significantly. The patient will consequently need constant support and motivation in order to comply with a very demanding therapy. The therapy should be supervised if it appears that the patient is unable to cope alone with the treatment. Patient groups in need of supervised therapy include the elderly, individuals with memory problems, drug and alcohol abusers, the socially deprived, immigrants and individuals with mental problems.

The treatment is carried out in outpatient care. Traditionally, the carer's responsibilities include monitoring of adverse drug reactions and also making sure that the patient takes the dose prescribed, but overall support to the patient during the treatment is the most important thing. The patient's life style, cultural background and language ought to be considered. The patient decides every day whether to take the medication, and the use of intoxicants and/or homelessness may

Table 5. *Medication and duration of treatment if adverse reactions prevent the use of any primary drug*

Drug omitted	*Initial treatment*	*Follow-up treatment*	*Duration of treatment*
PZA	*INH, RIF, EMB 2 months*	*INH, RIF 7 months*	*9 months*
RIF	*INH, PZA, EMB 2 months*	*INH, EMB 10–16 months*	*12–18 months*
INH	*RIF, PZA, EMB 2 months*	*RIF, EMB 10 months*	*12 months*

INH = isoniazide, RIF = rifampicin, PZA = pyrazinamide, EMB = ethambutol

pose another challenge in the management of treatment. It is important for the carer or any other person supervising the treatment that sufficient time should be devoted to these responsibilities and that a network of co-operation should be created with those involved in specialised nursing care, and that clear instructions for solving problem situations should be agreed upon.

Caution required on discontinuation of treatment

When the physician decides to discontinue the patient's treatment, he makes sure that the duration of the patient's medication has been adequately long (Tables 1 and 5). Any treatment intervals will be deducted from the total duration of treatment. If any of the three primary drugs (isoniazide, rifampicin, pyrazinamide) has been withdrawn due to adverse reactions, the duration of the treatment is prolonged correspondingly in accordance with Table 5. If after two months of treatment sputum culture still remains positive and cavities or other changes have been found in abundance on pulmonary X-ray at the initial stage, then the duration of treatment should be prolonged up to 9 months.

Follow-up monitoring is usually not necessary if, in the main, no complications have occurred during the treatment. Monitoring at half-yearly intervals for 6 months to 2 years is recommended if an abundance of changes remain on pulmonary X-ray, or if the patient's lifestyle is such that a new infection is possible.

Monitoring the end result

In accordance with the criteria recommended by the WHO, the end result of treatment of tuberculosis can be divided into seven different categories (healed, treatment completed, unsuccessful treatment, patient died, interrupted treatment, patient transferred, treatment continues) (2). The end result is assessed at the latest a year after initiation of treatment. The end result first achieved is recorded. Several European countries already have in use a monitoring system of end results. Its introduction is also planned in Finland as part of the recording system for National infectious disease register. The monitoring allows comparison of end results in tuberculosis treatment internationally, while important data are obtained for national development purposes.

New drugs and methods of administration?

New drugs and drug combinations for the treatment of tuberculosis are constantly being studied and developed. A significant step forward in pharmacotherapy is expected within the next decade. The aims include a shorter duration of treatment and less frequent dosages in order to improve treatment compliance, and development of drugs with an effect on treatment-resistant *Mycobacterium tuberculosis* strains. New methods of administration such as inhalation are also under development. Various immunotherapies such as interferon-gamma inhalation and TNF blockers have been tried, with no breakthrough so far.

In conclusion

At its best, the treatment of tuberculosis consists of interesting team work, in which the attending physician carries an important responsibility to initiate and maintain progress. The best end result is achieved when both the patient and the care personnel are committed to the treatment and monitoring.

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Special challenges involved with regard to medicinal products appropriate for children

Many studies have shown that paediatric pharmaceutical therapies lack adequate research data respecting their efficacy, safety and quality. The number of different pharmaceutical formulations suitable for the various age groups of children is also inadequate. In the EU, about half the medicinal products used in children do not have a marketing authorisation for paediatric use. This is a problem with both new and old medicinal products, both in developed countries and elsewhere. Globally the shortcoming in paediatric medicinal products is especially acute with respect to pharmaceutical formulations which tolerate transport and storage in a warm and humid atmosphere.

The industry has taken care to develop some of the pharmaceutical formulations for children at pre-school age and older, but there are very few innovations designed for the medication of newborn and premature infants, and knowledge about these particular pharmaceutical formulations is scarce.

The problem with paediatric medicinal products is recognised in the USA and the EU where legislative measures have been taken to promote development and research in the area. EU Paediatric Medicinal Products Regulation came into force on 26.1.2007 with the aim of improving the health of children by increasing the quantity of medicinal products intended for paediatric use and of expanding the selection of products meeting their needs. The Regulation requires that when applying for a marketing authorisation the pharmaceutical companies should also show the results of drug trials carried out in children, including development work relating to pharmaceutical formulations meeting the needs of various age groups.

While the Regulation is being enforced, the need for research into pharmaceutical formulations tailored for children will grow. New approaches are, in fact, needed in order to solve the problems of paediatric medication. One example would be to develop further a pharmaceutical formulation for a medicine with poor solubility in water in order to make its administration to children easy and accurate. Ensuring the stability of medicinal products in liquid form and taste masking their possible bad taste would be other examples of where development is needed.

The problems start with raw materials

The impurities of raw materials used in the medicinal products may in fact be a problem in their development for paediatric use. For example, even if residues of impurities, e.g. solvents such as toluene were within recognised limits and not posing any danger to adults, they may actually be harmful to children. Medicinal substances may possibly also contain impurities such as residues of the parent substance which are harmless to adults, but are extremely harmful to newborn and premature infants.

Excipients as such may pose a problem. Owing to their poor solubility, bad taste or poor compressibility of drug substance, medicinal products often need excipients with special properties making handling easier. It may, however, happen that these excipients have toxic or other properties harmful especially to newborn and premature infants. Examples include sweeteners such as fructose, saccharose or saccharine and glucose syrups, inappropriate for patients with diabetes or fructose intolerance and associated with a risk of causing osmotic diarrhoea similar to that with sorbitol in small children. Preservatives are another risky group of excipients, including benzyl alcohol, which in sodium chloride solution caused 10 deaths worldwide in 1982. Benzoic acid and its salts may cause jaundice in the newborn.

Parabens may disturb bilirubin binding and cause allergies. The number of medicinal substances with poor solubility in water is growing, and consequently the use of various co-solvents and surface active substances is also growing. Even ethanol in surprisingly high volumes is contained in medicinal products for paediatric use. Propylene glycol, for example, is not recommended for use in children under 4 years of age due to its harmful CNS effects in large amounts in the newborn. Surfactants such as poly-

oxyethylated castor oil may cause anaphylactic shock. Fatal cases have been associated with the intravenous use of polysorbates in the underweight newborn. Overall, the number of safe excipients is relatively small, and this makes careful planning necessary in their choice and in the choice of their distributors with regard to product development in the industry and the pharmacies.

Innovative pharmaceutical formulations for children

Reforms in the legislation in the USA have led to an increase in the development of pharmaceutical formulations for children for the purpose of clinical studies and to their introduction on to the market. Most of the medicinal products introduced on to the market are, however, intended for children of pre-school age or older and for adolescents. Small technology companies have emerged offering various solutions to paediatric pharmaceutical therapies. An example of innovative solutions of this type is that of a clarithromycin straw by the German company Grünenthal allowing the medicinal granules to be packed in a straw and thereby improving the ease of use for the small patient when the granules can be sucked in in combination with a favourite drink. Fentanyl, a lollipop in its pharmaceutical form, or as technically known an integrated oromucosal applicator, is already also in use for pain relief in Finland. For the treatment of older children, intraoral pharmaceutical forms are used, such as polymer membranes soluble in the mouth, or soluble tablets. An innovation by the Danish company Egalet, consisting of a medicinal substance already dispensed in a spoon, has reached its conceptual stage. Nearly all of the above innovations are intended for children of pre-school age and older, who are commercially more profitable targets for pharmaceutical development. There are fewer innovative solutions available for the medication of newborn and premature infants.

Difficulty in taste masking

The bad taste of a medicinal substance in the oral pharmaceutical formulations such as solutions, suspensions and forms soluble in the mouth is often a problem for children. The taste of the product should not be too bitter, gritty or irritating. Masking the taste with a flavour constitutes a challenging exercise, as the medicinal substance may sometimes be bitter to the extent that even in small amounts it evokes a vomiting reflex. If, in addition to a bad taste, the substance also has a bad smell, trying to make it pleasant to use is a real challenge. A salty taste in a substance is easier to cover with flavours than a bitter taste. The physiology of a taste also makes the covering of it difficult. One would need to succeed in covering both the initial stages of the taste (the first 10 to 20 seconds) and the after-taste (1 to 10 minutes). This is rarely successfully done with only one flavour. There are also cultural differences in taste preferences; berry flavours such as cherry are popular in some countries, whereas sweet vanilla and tutti-frutti are desired flavours in others.

Another solution, but one often more costly, is to coat the medicinal substance with a polymer film which will not become soluble until it reaches the acid pH of the stomach. In that case, it should be possible to divide the substance into solid units: minitablets, granules or pellets, which can be coated without any problem. A frequent challenge in the coating is that it should cover the products as well as possible. Even a small crack in the film may cause the medicinal substance to become soluble in the oral fluids.

Improving dosage

Children in hospitals and outpatient care are in practice given a lot of medicinal products which have not been registered for paediatric use, or an appropriate medicinal product is not available on the Finnish market. The products are often manufactured *ex tempore* from the adult products into metered dose powders, capsules or suspensions, and this may cause problems both in the shelf-life of the product in a liquid form and in the dosage. The unsuitable dosage alternative is halving a non-scored tablet which may result in a situation where a child receives anything between 50 and 150 % of the intended dose. From the point of view of dosing, liquid preparations, solutions and suspensions are usually better as to their flexibility and accuracy. All medicinal substances cannot, however, be made into liquid preparations because of the difficulty of storage. Then we have to concentrate on novel innovations such as granules, pellets and other small solid pharmaceutical formulation with flexible but accurate administration.

An optimal medicinal product for paediatric use comprises excipients appropriate for children: it tastes good and can be readily administered orally, making the individual dosage easy. The absolute requirement is that the chemical and microbiological shelf-life of the product should be good in all climate zones of the world. The pharmaceutical formulation should also be cost-effective to manufacture. To solve the above challenges by economically viable means is a real problem for the pharmaceutical industry and a challenge offering scope for many new innovations both in companies and at universities.

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Adverse drug reactions in children

Our review covers adverse drug reactions (ADRs) caused by conventional drugs in children. Vaccines are excluded from the review. The ADR register of NAM has since 1973 received a total of 1,203 reports of adverse effects discovered in children, 0 to 15 years of age. The number of reports in this age group annually has varied between 24 and 69 since the start of the 1990s (Fig. 1). The proportion of serious ADRs over this timespan has varied between 18% and 63% of the reports.

In the review we have included the reports where the age of the child involved in the ADR incident is included. The majority of the reports are on the smallest children, the 1 to 2-year-olds (Fig. 2). The majority of the ADRs involving this age group have been caused by anti-infectives for systemic use, and this probably reflects the use of antibiotics in that age group. Reported reactions in boys (53%) slightly exceeded those in girls (47%).

Among the various drug groups the highest number of reports have been received on anti-infectives for systemic use (612 in total), drugs affecting the nervous system (254) and drugs affecting the respiratory system (103). The reports, divided into drug groups, are shown in the Table.

Among the anti-infectives for systemic use, the drugs most fre-

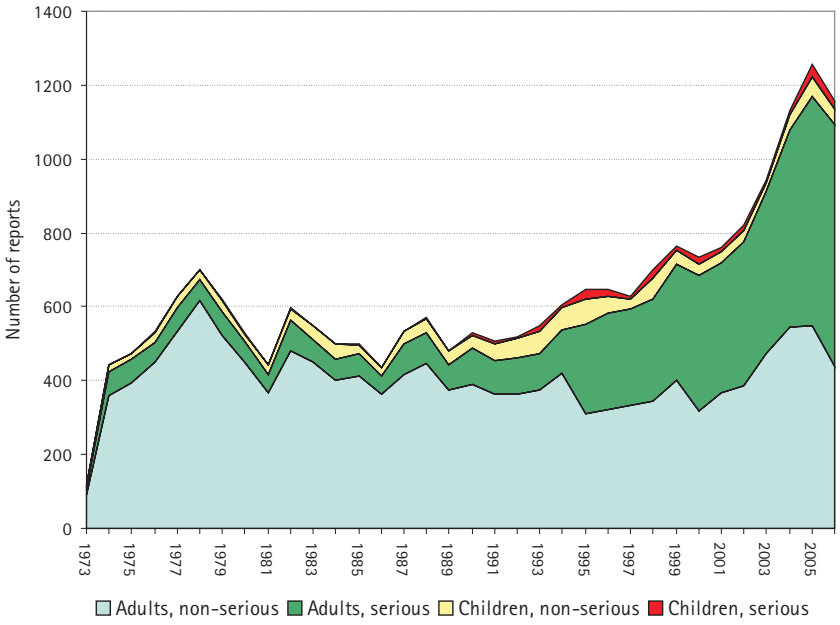

Fig. 1. *All ADR reports 1973–2006.*

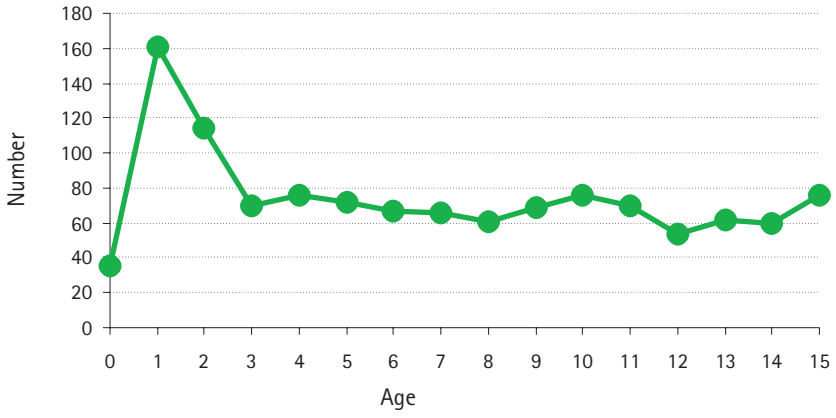

Fig. 2. *ADR reports in children age of 0–15 years*

quently reported on included cefaclor (137 reports), amoxicillin (133), sulfamethoxazole-trimethoprim combination (54) and penicillin V (51). Skin was the target of 120 reactions caused by cefaclor, and the reaction almost without exception was urticaria with associated joint symptoms. Serum sickness was the actual diagnosis in 10 cases.

Of the reports on amoxicillin, 107 described various rashes, generally the ADR consisted of only rash or urticaria, while occasionally other symptoms were reported such as fever or arthritis. Serum sickness was mentioned in three and erythema multiforme in two reports. Bowel symptoms were a subject of 20 reports, 15 of which involved as the adverse reaction melaena or some other bowel haemorrhage, and the others included pseudomembranous enterocolitis / *Clostridium difficile* (3), colitis (1) and diarrhoea (1). The ADRs of penicillin V were similar to those of amoxicillin, but reports of actual serum sickness totalled 11.

Forty-four of the ADRs caused by sulfamethoxazole-trimethoprim included various rashes, the diagnosis in five cases being the Stevens-Johnson syndrome. Nine reports described a reduction in the leukocyte level. The majority (22) of reports concerning sulfadiazine-trimethoprime (27 in total) described various harmful skin effects; there were 4 reports each of epidermal necrolysis and of the Stevens-Johnson syndrome.

The largest group of medicinal substances affecting the nervous system consisted of antiepileptics. There were 40 reports on carbamazepine, 36 on oxcarbazepine, 22 on valproic acid and 15 on vigabatrin. Twenty-nine of the reports on carbamazepine involved skin symptoms, and hepatic reactions and leukocyte level reduction were each reported on four occasions. Following the 18 skin reactions caused by oxcarbazepine the most frequently reported adverse reaction alone was 4 from hyponatraemia. The most frequently reported ADRs caused by valproic acid were the 7 targeted at the liver and those by vigabatrine the 10 targeted at the visual field.

A total of 24 reports were received on various local anaesthetics, most frequently on combination therapies containing either lidocaine or articaine (7 reports on each). The ADRs mainly consisted of various hypersensitivity reactions and nausea.

In the group of drugs used for respiratory system diseases the one that stood out was montelukast, with 16 reports received. Nine of these described adverse effects on the central nervous system and the psyche (agitation, muscle stiffness, aggressive reaction, sleep disturbances including nightmares and night terror attacks, headache). There were 2 reports on skin reactions, and other isolated adverse reactions included vomiting, nosebleed, dyspnoea associated with urticaria, QT interval prolongation and elevated liver enzyme values.

The above-mentioned central nervous system and psychic symptoms were of the kind mentioned in the SPC of Singulair. These adverse drug reactions may in fact be significant; for example, there was one case of **a 7-year-old boy** who was afraid of going to school due to his panic attacks. A week after discontinuation of the medication, the child was symptomfree.

Figure 3 shows all the reports according to the system organ class of the most significant ADR. The majority of the reports (46%) described adverse skin effects, followed by effects on the alimentary tract (11%), general adverse reactions (6%), effects on the nervous system (5%) and the immune system (5%). General adverse reactions also included local reactions associated with the method of administration, fever and various types of oedema and effects on the immune system, including various allergic reactions, such as anaphylaxis and serum sickness.

Reports of adverse drug reactions in children since 1973 lined up by drug groups	*Number of reports*
Anti-infectives for systemic use	*612*
Drugs affecting the nervous system	*254*
Drugs affecting the respiratory system	*103*
Drugs affecting the alimentary tract and metabolism	*75*
Antineoplastic and immunomodulating agents	*26*
Other drugs	*25*
Drugs affecting the musculoskeletal system	*18*
Dermatologicals	*17*
Drugs affecting the genito urinary system and sex hormones	*17*
Systemic hormonal preparations (excl. sex hormones and insulins)	*16*
Drugs affecting the blood and blood-forming organs	*12*
Drugs affecting the sensory organs	*12*
Antiparasitic products, insecticides and repellants	*9*
Drugs affecting the cardiovascular system	*7*

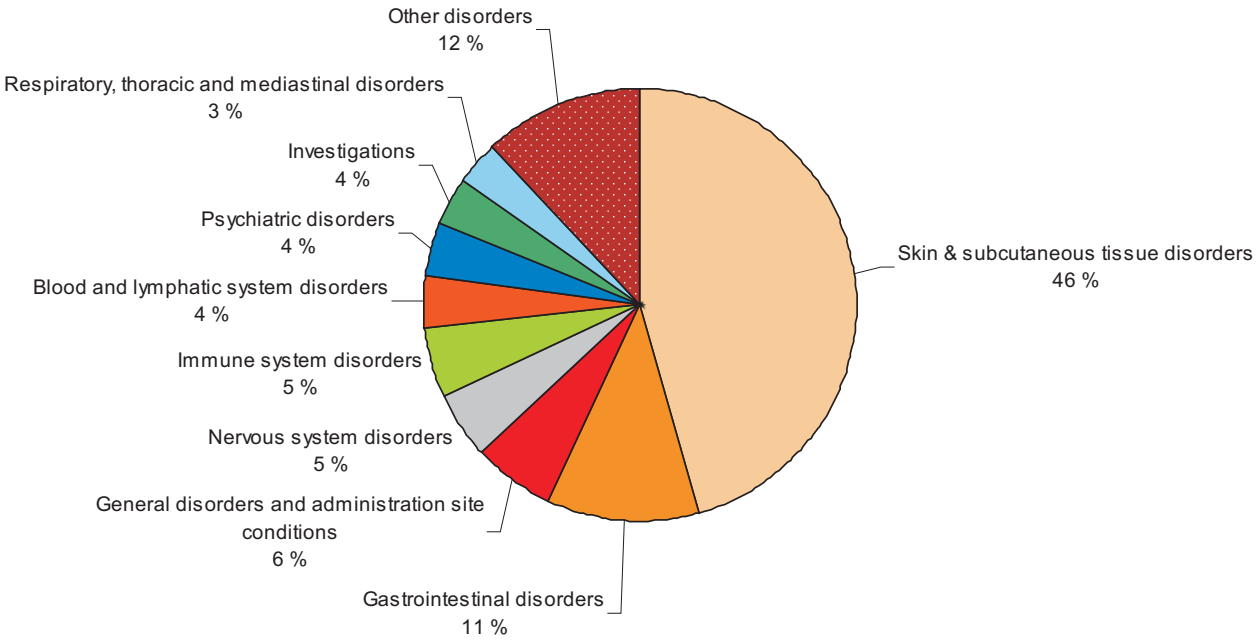

Fig. 3. *Reported adverse drug reactions according to SOCs .*

The spectrum of adverse reactions in children starts with problems associated with neonates' drug exposure during pregnancy and ends up with reactions emerging at the threshold of adulthood, which could be associated, for example, with the use of isotretinoin or contraceptives.

Paediatric case reports

Due to a panic disorder a female had been using essitalopram throughout her pregnancy. Her **newborn baby** was initially sleepy and did not eat well, but ultimately recovered from the symptoms. Symptoms in the newborn exposed to SSRI drugs during the final stages of pregnancy can be varied (including irritability, seizures, tremor, difficulties in breathing) and are the results of either the serotonergic effects of the drug or withdrawal symptoms associated with the discontinuation of the medication.

A 3-year-old girl was started on cetirizine therapy for allergic symptoms of the eye with a daily dose 5 mg. The following day the girl started to stutter. The therapy was discontinued and the child recovered. No such symptom occurred with the use of loratadine. In connection with the use of cetirizine, this is the only report of its kind in the ADR Register.

A 4-year-old boy was in intensive care due to tracheal surgery, and the sedatives used included oxicone and midazolam. About a week after surgery tropisetron 2 mg was administered intravenously for nausea. A couple of hours afterwards the child became restless and suffered from involuntary movements of the hands, which could well be interpreted as extrapyramidal symptoms. As the symptoms were prolonged, suspicion rose about the unusual metabolism of tropisetron. Tropisetron is metabolised via the CYP2D6 enzyme, which in this child had slow metabolic action, a condition found in 5 to 10% of whites. The symptoms were alleviated by biperiden therapy, and once this had been gradually withdrawn the child was totally symptom-free.

A 5-year-old girl weighing 18 kg and suffering from rheumatoid arthritis was given scopolamine eye drops for the treatment of iritis (inflammation of the iris); the drops had been administered twice. The girl started swaying while walking and she fell; after which the girl became over-excited, did not sleep for 36 hours, played and talked constantly and had hallucinations. She was also sweating and suffering from tachycardia. Following discontinuation of her medication, the girl recovered from the symptoms, which were of a type which could have been caused by scopolamine.

A 6-year-old girl experienced (unspecified) extrapyramidal symptoms and an oculogyric crisis (involuntary turning of the eye balls, usually upwards) 2 days after the introduction of metoclopramide therapy (30 mg/day). She recovered once the medication was discontinued. Extrapyramidal symptoms are known adverse reactions associated with metoclopramide dopamine antagonism. Dystonic reactions such as oculogyric crisis, torticollis and

trismus, occur in children in particular and may even develop following the first single dose.

A 7-year-old boy was admitted to hospital due to vomiting and shifting levels of consciousness (*motor movements similar to those of a drunkard, with rolling eyes, unclear speech, need to be supported on arrival to hospital, opened eyes when prompted, did not speak*). A computer tomography of the head and a cerebrospinal fluid examination did not reveal anything abnormal, but serum ammonia and aminotransferase levels were clearly elevated. Two days afterwards mild unspecific changes were detected on electroencephalography (EEG). In follow-up, ammonia and aminotransferase values started on a downward trend and consciousness returned to normal. It became clear that during the week prior to admission to hospital the child had been receiving acetylsalicylic acid for three days due to a virus infection. He was diagnosed as suffering from Reye's syndrome, a severe disease of unknown aetiology which causes damage to the brain and liver. It is a rare disease, manifested predominantly in children. Reye's syndrome has been linked with the use of acetylsalicylic acid during infections, which is why some other preparation should be chosen for fever therapy in children and adolescents.

A 10-year-old girl received a five-day course of treatment with sulfadiazine-trimethoprim. On the second day after discontinuation of the medication, a toxic epidermal necrolysis (extensive scaling of the skin) developed. There were no more details available about treatments, and the child had not yet recovered at the time of reporting (12 days after the emergence of the symptoms). A toxic epidermal necrolysis may as a rare ADR be associated with both sulphonamides and trimethoprim and is life-threatening similarly to an extensive burn, because the patient is exposed to disturbances in the fluid balance and temperature control as well as to severe infections.

A 12-year-old boy had received citalopram 20 mg daily for about three months, when a rash of the erythema fixum type developed in the little finger. The change in the skin disappeared after discontinuation of the medication, and there is no knowledge about re-exposure. Erythema fixum (fixed drug eruption) is always caused by a drug, e.g. doxycycline, a sulphonamide or carbamazepine. With re-exposure a change in the skin always appears on the same spot as before and heals within a couple of days, followed by a pigmentation left in the skin. In addition to the "old" spots, a drug re-exposure may expand the skin syndrome. Consequently, the patient should not be re-exposed to the causative agent once the diagnosis is confirmed.

A 14-year-old boy, who, following a 4-month course of olanzapine (dose increased gradually up to the level of 20 mg daily), was diagnosed as having a slightly elevated level of serum alanine aminotransferase. An ultrasound examination of the upper abdomen was carried out, the finding of which fitted in well with a fatty liver. During olanzapine therapy the patient had gained weight by about 40 kg. Weight gain is a common adverse reaction associated with olanzapine and it may be associated with the development of a fatty liver as was the case with this patient. Olanzapine may also for other reasons cause elevation of aminotransferases.

A 15-year-old boy with cancer was initially treated with intravenous metronidazol 1 g about midday, followed by clindamycin 600 mg about three hours afterwards. The boy developed an antabus type of reaction (palpitations, hypotension, cold sweat, pallor) during the clindamycin infusion, which was thought to have been caused by the combination of benzyl alcohol, contained in the clindamycin preparation, and metronidazole. The boy was given intravenously promethazine which relieved the reaction.

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Own observation of an adverse reaction

Delirium in an adolescent patient with the use of cephalexin

A 16-year-old boy was admitted to the central hospital emergency unit on a referral from a doctor at a health care centre, the cause being tiredness and forgetfulness. The patient did not have any history of psychiatric illnesses or of intoxicants abuse as far as we know. Earlier in the same year he had been examined at the paediatric ward for reduced growth rate and delayed puberty. At the age of 12 he had been examined in the paediatric neurology unit for delayed development and learning difficulties. Owing to borderline mental retardation he had attended comprehensive school in the special needs teaching unit. At the age of 14 he had fallen on his bicycle with a resultant fracture of the right temporal bone and evidently also a minor left-sided subarachnoid haemorrhage.

A week before admission to the emergency clinic the patient had started a course of cephalexin at a dose of 750 mg twice daily for the treatment of a nail fringe inflammation. According to the description by the parents, following the introduction of the medication the patient had become weary and forgetful, and tended to stare and look vacant. In many situations, impairment of the patient's immediate memory became evident. He had, for example, lost his goods and suspected others of having stolen them. Furthermore, he had not slept well for some time. For the 24 hours prior to admission to hospital he was described as having been tired, confused and disorientated.

When interviewed at the emergency clinic the patient did not say much and hardly had any eye contact. He delayed replying to many questions and on occasion it appeared as if he had not heard the question at all, but stared in front of him deep in his own thoughts. The boy maintained that sounds (e.g. the TV) disturbed him, but he denied having any hallucinations. He also said he had recently wanted mostly to be alone and to ruminate over his own affairs, and that there were things 'you should not talk to anybody about'. Mild motor restlessness and tearfulness also emerged during the interview.

The patient had no symptoms of infections. A somatic examination and laboratory tests did not reveal any cause explaining the delirium. B-Hb was on the low side: 130, B leucocytes 7.4, plasma potassium 4.1, plasma sodium 141, CRP < 1, plasma glucose 5.4, intoxicants screening of the urine was negative. EEG was normal.

Owing to suspected psychosis it was decided to admit the patient to the adolescent psychiatric ward for a more close assessment of his condition, and the cephalexin therapy was discontinued. The boy quickly started to feel better on the ward to the extent that all symptoms indicative of delirium or psychosis disappeared within two days. He was still monitored on the ward for a couple of days, was discharged thereafter and was immediately able to start his studies at a vocational school. During the 7-month follow-up period the patient's condition has remained good.

Conclusion

Cephalosporins are widely used for the treatment of various types of infections and are usually well tolerated as a medication. It appears, however, that they may in some patients cause significant central nervous system effects. The probable factors which could have exposed the patient I have described to CNS effects of medicines include a young age, delayed neurological development and a history of a skull-brain injury (1). Korn et al. (2) have presented study results showing that even a relatively mild head injury may impair the blood-brain barrier function even for years, which is likely to facilitate the penetration of medicinal substances into the brain tissue.

In the literature, at least two previous descriptions of states of delirium during cephalexin therapy in adult patients can be found (3, 4) and also several observations of a similar type associated with the use of other cephalosporins (5). In the ADR database in Finland, in addition to my patient's case, there are nineteen reports made of cephalosporins psychiatric and nervous disorders (Kari Salmela, National Agency for Medicines).

See literature on page 48.

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Use of antipsychotics in outpatient care in 2005

According to a recent survey (1), the lifetime prevalence of all psychotic disorders in the Finns is 3.5%, and the most common disorder is schizophrenia. The treatment of psychotic disorders includes both conventional and more recently introduced antipsychotics. Second-generation antipsychotics have become more generally used during the last decade: only about a fifth of the total consumption of antipsychotics in 1998 were of the second-generation, whereas in 2005 they already accounted for two-thirds of the consumption. The costs of antipsychotics have more than tripled over the same time span. As the consumption measured in drug doses has increased in this period by only about 20%, the main cause for the increase in costs is the higher cost of the new drugs (2).

Reimbursements to cover the cost of antipsychotics consist of both basic and special refunds. In 2005 the patient only paid five euros per purchase transaction for drugs covered by a higher special refund entitlement, but the special refund entitlement for antipsychotics (code 112) was reserved for patients with a severe psychosis or other severe mental health disorders.

The proportion of the antipsychotics consumed in outpatient care has grown steadily and reached 83% in 2005 (3, 4). In the same year the Social Insurance Institution (SII) paid out refunds for antipsychotics (N05A) to 116,634 patients in total, 63,166 (54%) of whom were entitled to a special refund.

This study surveyed the use of antipsychotics in outpatient care as well as at the distribution of use and cost by age, sex, mother tongue and domicile in 2005. Subjects with special refund entitlement of antipsychotics were distinguished from those who had purchased antipsychotics without special refund entitlement.

Subject data and methods

The subject data were picked from the prescription records and the database of special refund entitlement of SII and the statistics produced by Statistics Finland as described earlier (5). From the original sample, i.e. a 50% sample of subjects using antipsychotics in 2005, those subjects were selected who had been refunded for the cost of their drugs in ATC group N05A.

Subjects were excluded from this study if they had no other purchases of the N05A group drugs than lithium, prochlorperazine or dixyrazine, if their special refund entitlement 112 was valid only part of or before the year 2005, or if they had special refund entitlements associated with delayed mental development, neuralgia or epilepsy. The final subject material consisted of 47,503 individuals, of whom 27,756 (58%) had a valid special refund entitlement 112 throughout the year. The rest of the subjects, 19,747 (42%) had never been a holder of special refund entitlement 112. Of the total antipsychotics consumed among the subjects, 90% was covered by a special refund.

Results

Women made up 54% of those using antipsychotics with a special refund entitlement, but the majority of the under 55-year-olds were men. The average age of men was 48 years (the same figure being the median), and of women 54 years (idem). Judged by this subject material, the proportion of those using antipsychotics with a special refund entitlement in 2005 was highest among men of ages 45 to 59 (2.0% of the age group) and among women of 50 to 69 (2.4% of the age group).

Of those using antipsychotics with a basic refund entitlement 56% were women; while in the age groups below 75 years the majority were men. The average age of the men was 55 years (median of 56 years), and that of the women 64 years (median of 70 years). Judged by this subject material, the proportion of those using antipsychotics with only basic refunds in 2005 was highest in the age group of 90 to 94 years in both men (6.7% of the age group) and women (7.1% of the age group).

Drug use

Of those entitled to a special refund, 31% had during the year of the survey used only conventional antipsychotics, 49% had used only new-generation drugs, and 20% had used both. The more recent the entitlement to a special refund, the higher the proportion of users of the new-generation drugs.

During the year of the survey, among those using antipsychotics without special refund entitlement, 43% had used only conventional antipsychotics, 52% had used only new-generation drugs, and 5% had used both.

The majority of the middle-aged subjects had used only conventional antipsychotics, whereas the majority of under 35-year-olds and the over 74-year-olds had used only the more recent antipsychotics.

Fifty-one percent of adolescents and working age adults (the 15- to 64-year-olds) entitled to special refunds had been using only new-generation antipsychotics as were 43% of adolescents and working age adults without special refund entitlement. Conventional antipsychotics alone were used by 27% of those with a special refund entitlement and 51% of those who received only basic refunds. The differences between the sexes in this age group were not statistically significant.

The antipsychotics most commonly used by those entitled to special refunds included olanzapine, risperidone and quetiapine. Antipsychotic-users with a basic refund entitlement were most frequently using risperidone, quetiapine and levomepromazine. Olanzapine, perphenazine, levomepromazine, clozapine, chlorprothixene, thioridazine, zuclopenthixol and chlorpromazine had been used by a greater number of those with entitlement to a special refund than those with entitlement to a basic refund; risperidone, quetiapine, haloperidol and melperone were more commonly used by those receiving only basic refunds rather than those with special refund entitlement.

Those entitled to special refunds had during the year used on average about 1.5 antipsychotics, and those receiving only basic refunds on average about 1.1, irrespective of sex. Among those with a special refund entitlement, 63% (61% of men, 65% of women) had during the year received refunds for only one antipsychotic, 90% for two at the most. Of those not entitled to special refunds, 90% had received refunds for one antipsychotic alone.

Tabell. *Average costs of antipsychotics by the subjects in the survey material in 2005.*

	Those with special refund entitlement		*Those with basic refund entitlement*	
	Cost (€) and refund percentage	*Excess paid by the patient (€)*	*Cost (€) and refund percentage*	*Excess paid by the patient (€)*
Those having used only conventional antipsychotics				
Men	*186 (91%)*	*18*	*47 (39%)*	*29*
Women	*145 (89%)*	*17*	*42 (39%)*	*25*
Those having used only new-generation antipsychotics				
Men	*1 743 (98%)*	*33*	*374 (60%)*	*149*
Women	*1 501 (98%)*	*30*	*352 (61%)*	*137*
Those having used both conventional and new-generation antipsychotics				
Men	*2 176 (98%)*	*42*	*627 (66%)*	*217*
Women	*1 858 (98%)*	*40*	*493 (65%)*	*171*

Drug costs

In this subject material, 93% of the costs of the antipsychotics were incurred by the new-generation drugs. There were great individual variations in the annual costs of these drugs, depending on the refund group, sex and the type of drug used (Table). The average costs of antipsychotics used by men were without exception slightly higher compared with those used by women. The costs of antipsychotics used by those entitled to a special refund were on average 5 to 6 times higher compared with those without special refund entitlement.

Compared with those who had used conventional antipsychotics alone, the drug costs for those who had used only new-generation antipsychotics were on average 8 to 10-fold as high, and the costs for those having used both types of drugs were 12 to 13-fold.

Discussion

The growth and qualitative change of antipsychotics consumption may partly be explained by the wider spectrum of effect and improved tolerability of the new-generation drugs compared with the conventional ones. The conventional antipsychotics are nevertheless cost-effective and do have an effect on positive symptoms. Perphenazine especially has been successfully used in the treatment of schizophrenia in the more recent control studies (6, 7). Nevertheless, conventional antipsychotics have many adverse effects, and the so-called high-dose neuroleptics (chlorpromazine, chlorprothixene, levomepromazine, promazine and thioridazine), in particular, have had serious, even fatal toxic effects. The reduced use of conventional antipsychotics is actually also evident in the fact that deaths caused by antipsychotics intoxication have been halved between the years 2000 and 2004 (8, 9).

Another factor to explain the increased total consumption of antipsychotics is the steady increase in the numbers of special refund entitlement during the entire first half of the 2000s; that is, compared with the year 2000, in 2005 there were 16% more holders of the entitlement 112. This increase is partly due to the aging of the population, since the proportion of the over 55-year-olds grew by 14% (from 26% to 30%) over the same period, while the proportion of those entitled to a special refund for antipsychotics is growing with age; in 2005, 2.9% of the over 55-year-olds were holders of entitlement 112, as were 1.2% of the under 55-year-olds (10).

This survey indicates that those using antipsychotics without special refund entitlement are on average older than those with a special refund entitlement; in 2005, over a third of those using antipsychotics without special refund entitlement were 75 years of age and older. The use of psychotropics among the elderly without special refund entitlement has been discussed in detail in a separate review (5).

With regard to the refund group and the first year of entitlement to a special refund, distinct differences were seen in both the use of the first and second-generation antipsychotics and the use of individual medicinal substances. The number of users of conventional antipsychotics alone was higher among those receiving only basic refunds (43%) compared with those with a special refund entitlement (31%). This may be partly explained by the fact that, without the entitlement to a special refund, the drug costs born by the patient are multiplied many times over as a conventional drug is replaced by a new-generation drug, whereas to a holder of a special refund entitlement the annual excess in euros actually has little relevance (Table).

In the Finnish Current Care guidelines for schizophrenia (11), reference is made to the key importance of avoiding adverse reactions in the pharmaceutical treatment of psychoses. The relevance of this is emphasised in the treatment of the elderly, in particular (12). Over 60% of the elderly who had used antipsychotics without special refund entitlement had in fact only used the new-generation antipsychotics. However, the proportion of those using the new-generation antipsychotics alone was highest among the under 25-year-olds. It is in fact considered that the second-generation antipsychotics have made it possible to start the treatment of psychotic disorders in young patients earlier than before (12).

According to the Current Care guidelines (11), the use of the more recent antipsychotics in the treatment of first-episode psychoses is justified by the lower number of neurological adverse effects and a broader spectrum of effect, even though conventional antipsychotics are also still appropriate in the treatment of first-episode psychoses and in particular for such patients who have earlier benefited from these drugs. In this subject material, the longer the duration of the disease, the more common was the use of conventional antipsychotics by the patient. It appears that the recommendation for using antipsychotics as a monotherapy is also well adhered to (11), since in 2005 three quarters of the subjects had received refunds relating to one antipsychotic agent only.

Despite the high cost of the new generation antipsychotics, pharmaceutical therapy only accounts for a small proportion of the costs incurred to the society by psychotic disorders, while other direct (institutional care, outpatient rehabilitation) and indirect (lost productivity, disability pensions) costs make up the major part (13). To counterbalance the rise in the costs of drugs, consideration should be given to the progress introduced by the new medicinal substances and pharmaceutical forms in the treatment of psychotic disorders.

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