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Hannes Wahlroos
Professor, Director General
National Agency for Medicines

Editorial

Medicines marketing, image and medicalisation

The pharmaceutical industry is described as an innovative and marketing-intensive sector. This is certainly true. It is also claimed that the more insignificant the innovation, the more significant and image-making should the marketing aim to be if the intention is to sell medicinal products. This statement, like many others, is based on experience.

One also gets an impression as if 'nothing in the world ever changes'. In the Editorial[1] I wrote for this journal 14 years ago I expressed my wish that the pharmaceutical industry would rid itself of overstatements as a consequence of regulations in the EC Directive issued a year earlier. The pharmaceutical industry had at the time reformed its own internal rules regarding regulation and these have been amended several times since then. From the perspective of the National Agency for Medicines I had been – perhaps naively – expecting that there would be no need to shift the emphasis of drug regulation on to the monitoring of drug marketing. The review by Tiina Kostiainen and Erkki Palva of the cases of regulation within drug marketing is a reflection of a need for regulation which cannot be ignored.

Despite a certain increase in clarity of the rules and the environment of the operation, for example in the contacts between the pharmaceutical industry, doctors and pharmacists, the problems have moved elsewhere. Suddenly it seems that the primary aim of the pharmaceutical industry is to get 'under the skin' of the consumer in the marketing of prescription drugs as well. With disease- and symptomoriented communications along with good intentions, consumers are drawn towards the pharmaceutical companies' websites and doctors' appointments; the message being that there is a drug for almost any symptom. Impressions about the everyday need for drugs in normal life are part of the medicalisation of society. It may be that the bestknown example of this is that of the drugs for erection disorders. There are even others.

I think the development described above may have several reasons. Competition in the pharmaceutical sector has become tougher, which at the company level usually means cost trimming and/or increased shrewdness in marketing. Even a quick gain by way of increased sales may tempt the marketing manager despite the blows necessarily to be suffered later in the form of rectification measures or fines applicable internally in the sector.

Another reason is in my view associated with the management culture and *Corporate Governance* of pharmaceutical firms, i.e. good management practice. In "the good old days", i.e. when Finland still had a number of important Finnish pharmaceutical industry firms, an honour held in high esteem by company managing directors, other managers and owners was not to get trapped into drug marketing which was against the rules, regulations and good manners. The situation today, unfortunately, appears to be such that the main emphasis of enterprise in many of the drug companies operating in Finland nowadays lies on drug marketing tricks. The drugs distributed have, in most cases, been researched, developed and manufactured abroad.

The third reason may be associated with the phenomenon of *empowerment* prevailing in health care, which means that patients and consumers become fully empowered in matters relating to themselves. Marketing professionals have obviously realised that it is also worth focussing marketing efforts on fully empowered potential patients, who are themselves expected to influence the decisions about their treatment. According to a recently published dissertation, the patients often have a big influence on decisions about prescribing. Patient participation is common especially in relation to such diseases as have been to the forefront in the media and advertising.

Whatever the reason may be, advertising of prescription medicines to the public is prohibited. Presentations and marketing of medicinal products which focus on doctors – within the framework of the legislation – constitute a task with ample challenge for all pharmaceutical companies.

1. Wahlroos H: Lääkemarkkinointi uusille urille. TABU 2.1993, 3.

Pekka Lahdenne
Senior Lecturer, Head of Department
HUS, Hospital District of Helsinki and Uusimaa
Hospital for Children and Adolescents
e-mail:pekka.lahdenne@hus.fi

Visa Honkanen
Senior Lecturer, Paediatric Rheumatologist
Medical Director
UCB Pharma Oy Finland
e-mail:visa.honkanen@fimnet.fi

Medical treatment of childhood arthritis

Between 150 and 200 children develop juvenile rheumatoid arthritis (nowadays formally called juvenile idiopathic arthritis) in Finland every year. Consequently, there are about 5,000 affected sufferers in the country, of whom perhaps 1,500 are under 16 years of age. Huge leaps forward have taken place in the treatment. The target at present is to offer the possibility of normal growth, development and functional abilities to every child affected by the disease. Medication with methotrexate, local treatment of the affected joints and physiotherapy still remain the cornerstones of the management. Tumour necrosis factor inhibitors have constituted a crucial reform in the treatment of the most difficult cases. We commence this paper by first discussing the various treatment lines and then moving on to the special properties of the various drugs.

In juvenile rheumatoid arthritis a persistent inflammation develops on the synovial membrane. In the long term the inflammation will damage the cartilage and eventually the bone. The process of the inflammation of the synovial membrane is similar to that in rheumatoid arthritis suffered by adults. With regard to the cartilage, the situation for children is both better and worse than that of adults: a child's cartilage is more easily restored, while damage to cartilage during a period of growth has an increased tendency to lead to incorrect postures. Juvenile rheumatoid arthritis (juvenile idiopathic arthritis) is nowadays divided into seven groups (Table).

Despite its being an uncommon disease, juvenile rheumatoid arthritis has, due to the long duration of the condition, serious implications for our national health. As many as 19% of the children who acquired the disease as late as the 1970s were never able to enter into working life, and the rest of the children often suffered permanently reduced functional ability.

Treatment lines

Nowadays the aim of treatment of juvenile rheumatoid arthritis is to obtain remission. This means invisibility of active arthritis, lack of symptoms, and normal growth of the child. Common sense should nonetheless prevail. Occasional slight pain in the interphalangeal joint is not a valid reason for increasing the medical treatment.

The basic measures for the treatment of juvenile rheumatoid arthritis in Finland have for a couple of decades consisted of methotrexate and local glucocorticoid injections, including an anti-inflammatory analgesic as necessary. In fact, many of the diseases associated with 1–4 joints are well managed by local treatments alone (1). However, if there is a need for frequent local repeated treatments (more often than half-yearly) or the response is inadequate, a small dose of methotrexate is given as an adjunct to treatment. With decades of experience it is found to be safe and well tolerated. However, if a single joint causes persistent discomfort to the patient, an operative debridement of the synovial membrane may be considered. There is nevertheless very small need for this nowadays. Hospital in Helsinki for children and adolescents, responsible for the treatment of about 400 patients with juvenile rheumatoid arthritis, only performs two to three such operations every year.

In a disease involving more than four joints, polyarthritis, treatment with methotrexate is usually introduced immediately. If problems of tolerance emerge, either azathioprine, sulphasalazine or leflunomide may be tried, whereas if their efficacy is not adequate, there are two alternative approaches: 1) a combination of several antirheumatic agents may be used, or 2) the dose of methotrexate is increased, and oral administration may be replaced by subcutaneous administration as necessary. The latter alternative is more frequently used in children, because the intake of several drugs by mouth is often experienced as uncomfortable and difficult by both the child and the family. If this does not give a desired result either, the use of biological agents should be considered.

Systemic juvenile rheumatoid arthritis with generalized symptoms still remains a difficult disease. Fortunately, the disease will remain permanent in only about half of those who have contracted it. Arthritis is the long-term manifestation of the disease in the majority of patients, but a small proportion of them exhibit recurring general symptoms,

Table 1. Types of juvenile idiopathic arthritis, JIA

1. Systemic juvenile arthritis (M08.2)
Affects 10% of all children.
The initial symptoms include high fever flaring up 1-2 times a day, rash while the fever is rising, and often pericarditis.
Polyarthritis, as the condition persists.

2. Oligo-articular/pauciarticular JIA (M08.4)
a) Affects 40-45% of the patients. A typical patient is a girl at the age of playing.
The condition affects 1-4 joints.
General symptoms are rare.
Pauciarticular JIA is often associated with chronic uveitis, which can affect the sight if left untreated.
b) The spreading form of the condition: a fifth joint becomes inflamed more than 6 months after the onset of the condition.

3. Juvenile polyarthritis (seronegative) (M08.3)
Affects 20% of the patients.
The fifth joint becomes affected within less than 6 months from the onset of the condition.
The condition is general in both girls and boys. Due to the large synovial membrane mass, the condition is often associated with general symptoms, such as tiredness, and occasionally also feverishness.
The condition may be associated with chronic uveitis.

4. Polyarthritis with a positive rheumatoid factor (M08.0)
Affects less than 10% of the rheumatoid arthritis patients.
A typical patient is a teenage girl.
The disease behaves similarly to the corresponding disease in adults (-> rheumatoid arthritis) at large, i.e. the risk of erosions is high.

5. Juvenile arthritis in psoriaris (M09.0, L40.5)
Affects 10% of the patients.
The clinical picture is generally mild. Skin symptoms are often minor.
The condition is often characterised by oedema involving the whole digit, i.e. dactylitis.

6. Arthritis in children over 6 years of age, accompanied by inflammation in the attachment area of tendons and bones (enthesitis) or inflammation of the spinal column or sacral bone joints (M08.4, M08.1)
Affects 10% of the patients.
A typical patient is a teenage boy with spondyloarthropathy (M08.1); if it is arthritis affecting a couple of joints with enthesitis, it would occasionally be called seronegative enthesoarthritis (SEA) syndrome. The condition may be associated with both symptomatic acute episodes of uveitis and asymptomatic chronic uveitis.

7. Other unspecified juvenile arthritis (M08.9)

Inflammatory bowel disease may also be associated with arthritis. Children mainly exhibit two types: 1) pauciarticular juvenile arthritis, which may be associated with dactylitis. The symptoms vary according to the severity of the bowel disease, 2) a condition similar to that of ankylosing spondylitis, which does not follow the development of the bowel disease and may continue to be present in ulcerative colitis once the inflamed intestine is excised.

such as rash, pericarditis and fever. The only effective treatment at the beginning of the disease is high-dose systemic glucocorticoid therapy, the dose of which is subsequently reduced as soon as possible once the patient has become fever-free and the pericarditis has been resolved.

Once the general symptoms are managed, the arthritis is treated in the same way as other forms of the disease.

In children and adolescents, seronegative enthesoarthritis causes inflammation in the attachment area of the tendons to the bones, i.e. enthesitis, which is often painful. This is difficult to treat with local injections and there is often a poor response to antirheumatic agents. Long-term use of anti-inflammatory analgesics, which is otherwise rare in juvenile rheumatoid arthritis nowadays, is sometimes necessary in these patients.

Disease-modifying anti-rheumatic drugs (DMARDS)

The most commonly used drug in both adult type and juvenile rheumatoid arthritis is **methotrexate**. Its effect in arthritis is based rather more on its anti-inflammatory properties than on folic acid inhibition. The initial dose in children is 15 mg/m^2 orally per week. The dose may be increased up to 30 mg/m^2 per week as necessary. In general, doses in excess of 20 mg/m^2 should preferably be given as subcutaneous injections, because the absorption of large doses by mouth is variable. The most common undesirable effect is nausea following administration of the drug. In some people the treatment causes painful ulcers, known as aphthae, in the mouth. This is nevertheless rare if the patient's supportive treatment consists of folic acid. Elevation of liver enzyme parameters is relatively common. This is often the result of a concomitant virus infection present. Liver parameters are monitored as required at 2 to 8 week intervals. As the enzyme levels rise the dose of the drug is decreased and an interval is interposed in the medication. There is no evidence that methotrexate would have caused permanent liver damage in a juvenile rheumatoid arthritis patient. According to an Italian study, methotrexate achieves an adequate response in about 80% of polyarthritis patients, i.e. the central parameters indicating the disease are corrected in at least 50% of the patients (2).

Leflunomide is a dihydro-orotate dehydrogenase inhibitor. A particular target for its effect is the T cells. It is a drug developed for the treatment of rheumatoid arthritis. The dose is 20 mg orally at intervals of 1–3 days depending on the weight of the patient. For the treatment of juvenile rheumatoid arthritis leflunomide is as effective as methotrexate (3). Its adverse effect profile is

very close to that of metho-trexate. Since it is clearly more expensive than methotrexate and the experience of follow-up is not as long term, it is not a primary drug.

Sulphasalazine is used mainly in school-age children and as an adjunct in combination therapies. Its effect is comparable to that of methotrexate at least in adults, but it is not as well tolerated in children as methotrexate is (4). Twice daily administration is also occasionally experienced as a difficulty. In addition to stomach complaints the drug may also cause rash, reduced cell counts and elevated liver enzymes.

The dose of **azathioprine** is 2–3 mg/kg orally per day. It is not as effective as methotrexate. It does not usually cause stomach complaints. In patients with hereditary 5-thiopurine methyl transferase deficiency, azathioprine may cause a deep and prolonged cell deficiency. Azathioprine is always a secondary drug of choice.

Hydroxychloroquine has been used in the treatment of rheumatoid arthritis for a long time. Its exact mechanism of action is unknown. The dose is 5–6 mg/kg/day. The drug is well tolerated. Undesirable effects include mild stomach upsets, rash and, occasionally, sleep disturbances. The effect of the drug is clearly less potent compared with other antirheumatics. It is mainly used an adjunct to combination treatments and occasionally for the maintenance of remission of a locally treated disease.

Bioligical substances

There are three biological agents used in the treatment of juvenile rheumatoid arthritis. They inhibit the effect of tumour necrosis factor (TNF). **Etanercept** binds the free factor in the tissue. **Infliximab** and **adalimumab** are TNF antibodies. Infliximab is chimaeric, i.e. the binding section originates from a mouse and the major part of the stem is of human origin. The drug is administered intravenously at 4 to 8 week intervals. The most common problems include various infusion reactions varying from rash and a tickly throat to anaphylaxis. Adalimumab is a TNF antibody constructed from human protein and administered as subcutaneous injections at 2-week intervals. In some patients the injection causes a painful lump. Etanercept is a soluble TNF-binding protein. It is administered subcutaneously twice weekly. The drug is usually well tolerated.

In the Finnish patient material, there were no great variations observed in the effect of infliximab and etanercept in paediatric patients (5). In adults, adalimumab has been found as effective as these. The issue is being studied in paediatric patients. All biological agents increase somewhat the risk of patients contracting inflammations. So far, no clear relationship has been shown between malignant tumours and drugs which reduce the effect of TNF. There are, nevertheless, some reports of malignant lymphatic tissue tumours manifested in adolescents during infliximab therapy (6). Knowledge about these issues is increasing along with reports of long-term follow-up registers.

Anakinra is an interleukin-1 antagonist. It is administered daily subcutaneously. Its effect in arthritis is less than that of TNF drugs. There are nevertheless indications of the fact that anakinra may work well in some generalized autoimmune diseases, such as NOMID (*neonatal onset multisystem inflammatory disease*) and possibly in juvenile rheumatoid arthritis with generalized symptoms.

It is important to achieve proper management of juvenile rheumatoid arthritis without delay. This does not mean, however, that expensive biological agents would be the first choice, but rather that treatment should be initiated with methotrexate and local therapies. If the use of a biological agent is necessary, the continuation of these costly therapies is likely to be a bigger economic problem – since the patient would in fact cope without them – than an early introduction of the therapy. When a biological therapy is started it is recommended that the patient be told that it is a drug which is aimed at controlling the disease, and that the aim is to manage with conventional therapies thereafter.

The treatment of juvenile rheumatoid arthritis has been revolutionised during the last 10 years. In the past, it was necessary to prepare the family with a juvenile rheumatoid arthritis sufferer to accept the idea of continuous illness and possible reduction in functional abilities, whereas nowadays the argument always is that the child can be assured of normal development, good quality childhood and a normal work capacity.

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Tiina Kostiainen
Senior Pharmaceutical Officer
National Agency for Medicines

Erkki Palva
Professor
National Agency for Medicines

A year of pharmaceutical marketing – 2006

To ensure the appropriateness of advertising and sales promotion of medicinal products the National Agency for Medicines in Finland has the task to enforce the compliance with the legislation, the Medicines Act and Decree. The contents of pharmaceutical marketing are governed in detail by the Act and the Decree which stipulate the type of information the marketing of medicinal products may offer and the type of material prohibited for use in that context. The purpose of the statutes is to promote the correct and safe use of medicinal products.

In 2006, a total of 38 cases involved with the marketing of medicinal products were brought forword. About half of the cases processed were brought to the attention of NAM through complaints by other companies. Complaints about drug marketing have also been made by individuals. The processing of some of the cases have been initiated by the NAM.

It usually takes several months to process and conclude an issue of marketing of a medicinal product. The company involved always has an opportunity to express its views on the matter under discussion. In the majority of cases, adjustments in the company's marketing will be made and issues settled with the pharmaceutical companies by good mutual agreement. Decisions to ban continuing or renewing unlawful marketing, are as a rule made when there is disagreement on the issue between the regulatory authority and the company in question, or if the decision to ban is otherwise considered necessary owing to the nature of the issue.

Two decisions to ban advertising

As a result of two cases concerning marketing of a medicinal product, NAM made a decision, enforced by a default fine, to ban the company's marketing (Table). In the advertising of a medicinal product, Eeze spray gel, produced by Antula Healthcare Ab, it was maintained that there were no adverse effects associated with the use of the product. In the advertising targeted at the general public the product was placed in a more advantageous position compared with other products, an action which is prohibited by the Medicines Decree. Eeze spray gel is a locally used anti-inflammatory analgesic containing diclofenac. The marketing ban concerning a drug called Lipitor marketed by Pfizer Oy was the result of a letter, targeted at physicians, which referred to a published study while omitting the mention of a detail essential to drug safety. The therapeutic indication for atorvastatin-containing Lipitor is prevention of cardiovascular events in patients considered to be at a high risk of having a cardiovascular event for the first time. NAM considered that the marketing of Lipitor did not comply fully with the therapeutic indication approved for the product. Pfizer Ltd was required to deliver a correction of its marketing material.

Most of the inquiries concerning marketing processed during 2006 involved the marketing of OTC drugs to the public. A typical error concerned marketing material which contained a deviation from the information in the Summary of Product Characteris-

Company	*Product/issue*	*Decision*
Antula Healthcare Ab	*Eeze spray gel / TV-advertising and marketing material supplied to pharmacies*	*Marketing prohibition, a default fine of EUR 200 000. NAM prohibited Antula Healthcare Ab from marketing a product with information deviating from the Summary of Product Characteristics or material which is prohibited in accordance with Section 25 b of the Medicines Decree.*
Pfizer Ltd	*Lipitor / Leaflet sent to doctors with reference to the results of the SPARCL Study.*	*Marketing prohibition, a default fine of EUR 2 million. Correction of marketing. NAM prohibited Pfizer Oy from marketing a product using material which deviates from the approved Summary of Product Characteristics, or which omits mentioning a relevant point regarding the medical significance of the product, or refers to clinical trials in a way that gives an incorrect impression of the final conclusion, extent or importance of the trial.*

tics (SPC). The Medicines Act and Decree stipulate that all the information given in marketing material should comply exactly with the information in the approved SPC. Another typical defect in the cases processed concerned the presentation of information required in pharmaceutical marketing, such as the therapeutic indication and the advice for the patient to read the package information leaflet. Attention has also been drawn to the fact that these details essential for the correct and safe use of the product should in the advertising be presented clearly enough for the consumer to take notice of them.

Disease awareness information increases

According to a definition in the Medicines Decree, information on human health and diseases are not considered pharmaceutical advertising. Material which aims to promote the sale, use or prescription of a medicinal product is considered marketing. Marketing of prescription drugs to the general public is prohibited.

NAM has had its attention drawn to the increased interest of pharmaceutical companies in promoting the use of prescription drugs by disseminating disease awareness information targeted at the general public. NAM expressed its concern in the letter sent to pharmaceutical companies at the end of last year. NAM will this year increasingly concentrate on the enforcement of compliance with the prohibition concerning consumer marketing of prescription drugs.

A significant proportion of the individual marketing regulation issues processed in 2006 were also concerned with prescription drug marketing directed at consumers with the aid of medicinal product leaflets or disease awareness information.

Pharmacies must comply in their pharmaceutical marketing with the medicines legislation, and pharmacies are responsible for the marketing material they produce. Three of the cases processed last year were concerned with marketing material produced by pharmacies to promote the sale of OTC drugs.

Marketing directed at pharmacy pharmaceutical staff, both OTC and prescription drug advertising, should contain all the information required in advertising targeted at individuals authorised to prescribe or dispense drugs. In the distribution of information and advertising material produced by pharmaceutical companies to pharmacy clients it should be borne in mind that the requirements concerning advertising vary depending on whether it is targeted at the general public or individuals authorised to prescribe and dispense drugs. For example, information on prescription drugs intended as instructions for use for patients may be interpreted as pharmaceutical marketing if they are used for marketing purposes.

Advertising of nicotine products has been moderate

Since the beginning of February 2006, the sale of nicotine products has been released to the daily grocery shops and other stores selling tobacco after having been available as pharmacy-only products. Bearing in mind that most of these new entrepreneurs in pharmaceutical marketing may not be familiar with the requirements regarding marketing laid down by the medicines legislation, NAM sent out a letter at the time of the legislative reform as a reminder of the rules applicable to marketing. NAM has been made aware of only a single case of a failure by daily grocery store to comply with the medicines legislation associated with the marketing of nicotine products.

In addition to the OTC products intended to be used in nicotine replacement therapy, registrated traditional herbal medicinal products and some herbal medicinal products with marketing authorisation can also be sold elsewhere than the pharmacy. Since there is no pharmaceutical drug information available at the point of sale to assist in the choice and use of the medicinal product, in particular, disclosure of information associated with the correct and safe use of the product is of the utmost importance. Last year NAM intervened twice in the marketing of herbal medicinal products.

Recommendations for quality criteria for sales promotion of medicines

Recommendations for quality criteria for sales promotion of medicinal products were published by NAM in the previous issue of TABU. The compliance with these recommendations will be monitored at sales promotion events. The reason for producing the quality criteria was not based on any known or suspected inappropriateness in sales promotion of medicinal products. The criteria are intended as a reminder to pharmaceutical companies and professionals taking part in sales promotion events of the nature of these, which is (in accordance with their definition) the marketing of medicinal products. It is also emphasised that, in addition to complying with individual sections of the Medicines Act and Decree, it is relevant to focus on the purpose of the legislation governing pharmaceutical marketing – namely, the objective of correct and safe use of medicines.

Annikka Kalliokoski
Senior Medical Officer
National Agency for Medicines

Leena Sommarberg
Reseacher
National Agency for Medicines

Adverse reactions in Finland 2006

In 2006 a total of 1,045 reports concerning medicinal substances (other than vaccines) were received by the *National Adverse Drug Reaction* database in Finland. Of the reports, 617 concerned serious adverse reactions and the number of mortalities suspected to have resulted from medical treatment was 28. The total number of reports was for the first time in the 2000s less than that in the previous year; in 2005 the reports totalled 1,131.

Of the reports received from health care professionals, 20% were in electronic form, i.e. reports filled in and forwarded on line through the Internet.

In 2006 reports were received on 362 medicinal substances, most of which only attracted a couple of reports: 237 medicinal substances were reported on twice or even less frequently. The Table includes the medicinal substances, which were the subjects of 10 or more reports. The majority of these also figured among the medicinal substances most frequently reported on in the list of 2005. Newcomers in the list include 2 iodine-containing contrast media, iopromide and iobitridol, and the other drugs include duloxetine, fluvastatin, local anaesthetic containing adrenaline and artecaine, olanzapine, sulphasalazine and aripiprazole.

The Table is by no means a list of the most dangerous drugs, and the safety of the medicinal substances cannot be compared with one another on the basis of the number of reports submitted. The number of drug users varies greatly, and there may be more reports received on the ones that are used frequently than on those that are used only infrequently. NAM also advises that, for example, any adverse reaction suspected of being associated with the use of a drug which has been available on the market for less than two years, i.e. the use of a recently introduced drug, should be reported. This is likely to result in a greater number of reports being submitted on new drugs in comparison with old and well-known drugs. Other factors may also affect the frequency of reporting, e.g. adverse reactions reported in the media or otherwise prominently discussed may be reported on more comprehensively than other adverse reactions.

When sporadic adverse reactions mostly reported on are examined (excluding vaccines) skin reactions are those most common: urticaria was the subject of 69 and other various types of rashes of 59 reports. The more severe skin reactions were significantly less frequent, e.g. *erythema multiforme* was reported six times, epidermal necrolysis also six times and the Stevens-Johnson syndrome two times. Other common adverse reactions included for example nausea and vomiting (60 reports) and fever (31 reports).

Medicinal substances most frequently reported on in 2006

	No
iomeprol	38
clozapine	28
etonogestrel + ethinylestradiol	20
levofloxacin	20
zoledronic acid	19
pregabalin	19
drospirenone + ethinylestradiol	18
duloxetine	18
fluvastatin	16
etoricoxib	15
rosuvastatin	15
terbinafine	15
adalimumab	14
quetiapine	14
simvastatin	14
etanercept	13
infliximab	13
adrenaline + articaine	12
bevacizumab	12
capecitabine	12
iobromide	12
lamotrigine	12
bupropion	11
olanzapine	11
aripiprazole	10
iobitridol	10
risperidone	10
sulphasalazine	10
venlafaxine	10

Contrast media

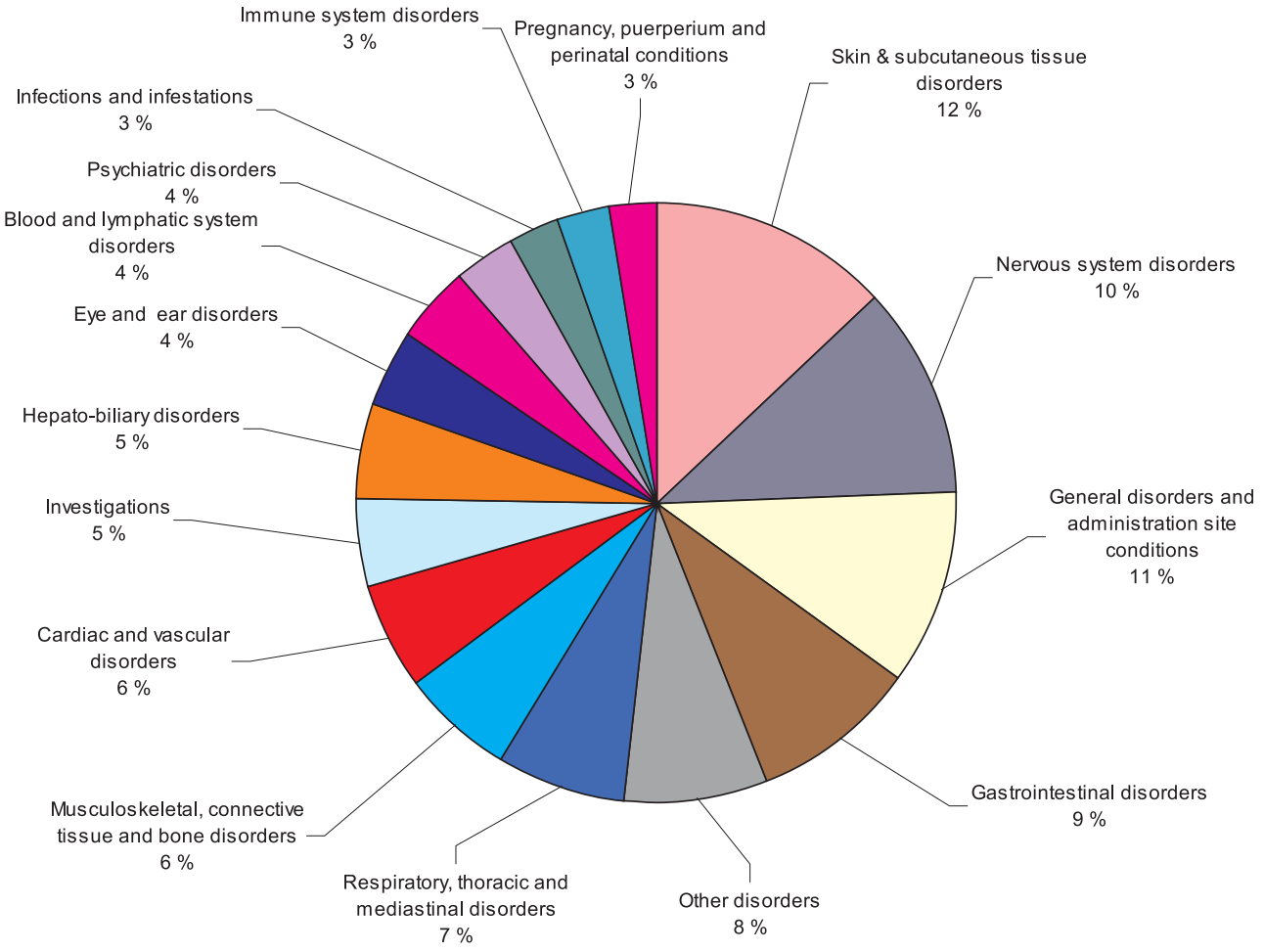
Reports received on iodine-containing contrast media totalled 66, mostly on iomeprol (38), iopromide (12) and iobitridol (10). Forty-one of the reports were submitted from the same area reflecting local reporting activity. Of all the reports, 26 were assessed as serious, even though it cannot be confirmed with certainty whether the criteria of seriousness were in fact fulfilled in every report, since the patient was often transferred from the X-ray department elsewhere for follow-up monitoring and treatment. The most frequently reported symptoms of adverse reactions included urticaria (37) and

other skin symptoms (12), such as flushing and nausea or vomiting (12). There were also reports made of more severe symptoms, such as anaphylactic reaction or shock (5).

Antipsychotics, antidepressants and bupropione

A total of 78 reports were received on antipsychotics (ATC N05A). Clozapine has over many years figured at the top of the list of medicinal substances most frequently reported on with 28 reports being received in 2006. Fifteen of these were concerned with various degrees of leucocyte deficiencies, three with pulmonary embolus and one with deep vein thrombosis. Quetiapine was reported on 14 times, the most common adverse reactions including elevation of liver enzymes (4) and malignant neuroleptic syndrome (3). Eleven reports were received on olanzapine, and risperidone and aripiprazole each received 10 reports. Tremor associated with the use of aripiprazole was reported twice, but apart from that no isolated adverse reactions which would have generated several reports emerged with the use of these drugs.

Antidepressants (N06A) were reported on a total of 59 times. The highest number of reports (18) received concerned a fairly recent serotonin and noradrenaline re-uptake inhibitor, duloxetine, with the additional therapeutic indication of female stress incontinence in addition to the treatment of depression. In 13 of the reports some type of adverse effect targeted at the central nervous system or mental state was mentioned, such as vertigo, headache, muscular tics, spasms, speech disorder, agitation and confusion; one report concerning withdrawal symptoms was also received. Gastrointestinal effects were reported four times. Ven-



Reported adverse drug reactions according to SOCs in 2006.

lafaxine among antidepressants with its 10 reports retained its position on the list of 10 drugs most reported on. The only adverse reactions reported more often than once were withdrawal symptoms (3) and hypertension (2). There were 11 reports received on bupropione, six of which described a rash. The rest of the adverse reactions were isolated (including confusion, vertigo, spasms and headache).

Contraceptives

Twenty reports were received on the etonogestrel and ethinylestradiol vaginal ring. Of the isolated adverse reactions that most commonly reported was unwanted pregnancy (12 cases, one of which was of a blighted ovum). Pulmonary embolus was mentioned in two reports, both deep vein thrombosis and sinus thrombosis was reported once.

Contraceptive pills were reported on 36 times, most commonly (18 reports) concerning a product containing drospirenone and ethinylestradiol. Seven of these dealt with pulmonary embolus (in addition a deep vein thrombosis was reported 3 times) and six were about unwanted pregnancy. Nine reports were received on the levonorgestrel IUD, six of which concerned pregnancy (one in the fallopian tube). The norelgestromin and ethinylestradiol contraceptive patch was reported on 9 times (6 being cases of unwanted pregnancy).

Statins

A total of 54 reports were received on statins, most commonly on fluvastatin (16), rosuvastatin (15) and simvastatin (14). The reports were mainly concerned with adverse effects on muscles, such as myalgia and elevation of creatinine kinase (22), and one of them mentioned rhabdomyolysis. The second most commonly reported reaction was elevated liver enzymes (15). There were four reports of pancreatitis, two of which involved users of rosuvastatin and two of fluvastatin; one of the latter of which also involved atorvastatin as the suspected causative drug.

Selective immunosuppressants, cytostatics and monoclonal antibodies

A total of 51 reports were received on selective immunosuppressants (L04AA), most commonly on adalimumab (14), five of these involved skin reactions; and tuberculosis was reported four times. Etanercept attracted 13 reports, three of which concerned malignant tumours, three were about infections, two mentioned psoriasis and one tuberculosis. Reports on infliximab (total of 13 reports) involved infection four times, melanoma twice, but no cases of tuberculosis were reported. The rest of the reports described isolated adverse reactions.

Capecitabine, a cytostatic, attracted 12 reports, two of which were about deep vein thrombosis. In addition, aortic thrombosis and pulmonary embolus were both reported once. Sudden death was a reaction reported three times, one of the cases also involved coronary artery disease, and one report concerned ventricular fibrillation. There were 21 reports relating to monoclonal antibodies, 12 of which were about bevacizumab, an angiogenesis inhibitor used for cancer treatment. Three of the reports on bevacizumab described aortic thrombosis, myocardial infarction was reported once, and so were cerebral infarct, sinus thrombosis and undefined thrombosis.

Pregabalin and lamotrigine

There have now been 19 reports received on pregabalin which had in 2005 reached the list of most frequently reported medicinal substances. Nine of these reports described various central nervous system and mental reactions. Peripheral oedema was reported twice, and so was rash. The rest concerned isolated adverse reactions. Lamotrigine received 12 reports, nine of which concerned various types of rashes.

Antimicrobials

The antimicrobials most frequently reported on were, as usual, fluoroquinolones. They attracted 33 reports, 22 of which concerned Achilles tendinitis or rupture. Levofloxacin topped the list of fluoroquinolones with its 20 reports (17 on Achilles tendinitis or rupture). Antifungal agent terbinafine was the subject of 15 reports, eight of which concerned loss of or change in taste perception. Four reports were received about skin reactions, among them one concerning *erhythema multiforme*, and pancreatitis was reported once.

Other drugs

Bisphosponates were reported on 23 times, 18 of which concerned zoledronic acid and osteonecrosis of jaw.

There were 17 reports on coxibs, 15 of which concerned etoricoxib. Five reports mentioned an adverse cardiovascular reaction (2 myocardial infarctions). Perforated gastric ulcer and renal insufficiency were both reported once.

A local anaesthetic containing adrenaline and articaine used in association with dental procedures, attracted a total of 12 reports, 7 in succession of which were received from the same source. The most common symptoms included palpitations, nausea, vertigo and hypoesthesia. Anaphylactic reaction was reported once.

Ten reports were received on sulphasalazine. Leucocyte deficiency and skin reaction were both reported three times.

Radhakrishnan Rajaratnam
Senior Medical Officer
National Agency for Medicines

Marja Forsell
Pharmacovigilance Officer
National Agency for Medicines

Biological response modifiers in rheumatoid arthritis: a view on their adverse drug reactions

In Finland infliximab and other biological drugs have been used since 1999 in the treatment of rheumatoid arthritis. According to the national sales statistics, the consumption of infliximab in 2006 was 0.31, etanercept 0.22, adalimumab 0.19 and of anakinra 0.01 DDD/1,000 inhabitants/day. Safety data of these new drugs were limited before their authorisation, but have been accumulating continuously. 186 reports including 265 ADRs were reported to the Finnish Adverse Drug Reaction database until 15.3.2007. Infections and general disorders and administration site reactions are the most frequently reported adverse reactions.

Rheumatoid arthritis (RA) is a chronic, inflammatory condition causing systemic illness and swelling, pain, and destruction of the joints. Treatment of RA aims to control pain and inflammation, reduce joint destruction and disability, and maintain or improve physical function and quality of life. The current therapies include symptomatic relief with nonsteroidal anti-inflammatory drugs or simple analgesics and treatment with disease-modifying antirheumatic drugs (DMARDs) to inhibit joint destruction. Glucocorticoids and other antirheumatic drugs are also used to treat RA.

Although DMARDs are considered to be first line therapy for all newly diagnosed cases of RA, the treatment options of RA have expanded to include biological DMARDs. Biological response modifiers are targeted against the cytokines believed to be important in the mediation of inflammation (tumour necrosis factor, TNF) and joint destruction (interleukin-1) in arthritic joints. Infliximab, etanercept, and adalimumab inhibit TNF-alpha, where as anakinra is a recombinant inhibitor of interleukin-1. In addition, rituximab, a chimeric anti-CD20 monoclonal antibody is also indicated for the treatment of RA.

Table 1. Most frequently reported adverse drug reactions (ADRs) associated with the use biological substances in rheumatic diseases according to System organ classification (SOC)

Drug	Number of patients	Number of ADRs	Number of serious ADRs	System organ classification (SOC) term	Number of ADRs
Infliximab	100	139	72 *	Infections and infestations	14
				Neoplasm benign and malignant	9
				Skin and subcutaneous tissue disorders	9
Etanercept	47	70	28	Infections and Infestations	12
				General disorders and administration site condition	8
				Nervous system disorders	8
				Skin and subcutaneous tissue disorders	8
Adalimumab	32	45	24	Infections and Infestations	8
				General disorders and administration site condition	5
				General disorders and administration site condition	5
Anakinra	4	6	3	different SOCs	
Rituximab**	3	5	3	different SOCs	
Total	186	265	130		

* Including 5 fatal cases
** ADRs in RA patients.

Biological agents may cause a variety of adverse effects. Safety data of these new drugs were limited before their authorisation, but have been accumulating continuously from clinical trials as well as from postmarketing surveillance (1). 186 ADR reports were retrieved from the *Finnish Adverse Drug Reaction* database with a cut off date of 15.3.2007 (Table 1).

Table 2. Injection site - and infusion reactions

	Infliximab	Etanercept	Adalimumab	Anakinra	Rituximab
Allergic reaction and rash	12	3	1		
Anaphylactoid reaction	4	2			
Anaphylactic reaction and shock	2+2				1
Injection site reaction		3		1	

Table 3. Infections

	Infliximab	Etanercept	Adalimumab	Anakinra	Rituximab
Pneumonia	2		1		
Pneumocystis carini pneumonia	2				
(Pulmonary infiltration)	2		1	1	
(Pericarditis)	2	1			
(Pleuritis)	1				
Arthritis bacterial/ septic	2	2			
Encephalitis herpes	1				
Cytomegalovirus infection	2				
Herpes zoster	1				
Varicella zoster			1		
Infection	2	1			
Infection TBC	10	2	8		
Sepsis	1	2			
Erysipelas		1	1		
Infection mycobacterium avium			1		

Injection site and infusion reactions

Injection or infusion reactions are the most common adverse effect of biological agents. 12% of reported ADRs to the NAM were injection site and infusion reactions (Table 2). Injection site reactions associated with subcutaneously administered drugs (adalimumab, etanercept and anakinra) consist of erythema and induration limited to the injection site. These reactions are mild and require no specific therapy other than symptomatic relief by antihistamine or corticosteroid.

Infusion reactions including anaphylactic reactions are the most common adverse effect associated with intravenous infliximab and rituximab administration. These reactions are transient and can be treated by decreasing infusion rate and, if needed, by antihistamine or intravenous corticosteroid. Prior to rituximab infusion, patients should receive methylprednisolone to decrease the acute infusion reactions.

Infections

Although the risk of infection is increased in the rheumatic diseases, an additional risk of serious infections has been reported in some clinical trials with anti-TNF therapy. Postmarketing surveillance and meta-analysis have also suggested an enhanced risk of infections in patients treated with TNF-antagonists in RA (1, 2). Also the risk of serious infections has been shown to be increased in patients treated concurrently with anakinra and etanercept.

Recently published results from the *British Society for Rheumatology Biologics Register* indicated that in patients with active RA, anti-TNF therapy was associated with increased risk of skin and soft tissue infection but not with overall serious infection compared with DMARD treatment after adjustment for baseline risk.

TNF alpha is a key component of host defence against *Mycobacterium tuberculosis*, especially in the formation of granulomas. Inhibition of TNF appears to increase the risk of M. tuberculosis and other agents causing granulomatous diseases, such as listeriosis and histoplasmosis. Most of the TBC cases occured within a relatively short time after the exposure to the drugs, implicating reactivation of the latent disease rather than newly acquired primary disease by the biological agents. EMEA made a public statement on infliximab in 2000 after reviewing 28 cases of infection TBC associated with infliximab therapy. In general, pre-treatment screening of patients for latent tuberculosis and greater vigilance for bacterial and opportunistic infections are recommended in patients treated with anti TNF agents. Patients requiring surgery should

Table 4. Malignancies

	Infliximab	Etanercept	Adalimumab	Anakinra	Rituximab
Breast neoplasm malignant		1	1		
Carcinoma hepatocellular	1				
Lymphoma	1				
Melanoma	1	1			
Meningioma	1				
Acute/chronic myeloid leukaemia	2				
Ovarian cancer	1	1			
Pancreas cancer	1				
Prostate cancer		1			

Table 5. Hematologic adverse effects

Granulocytopenia			1		
Leucopenia	2				
Neutropenia	1	1			
Thrombocytopenia	1				
Pancytopenia		1	1		

Table 6. Hepatic adverse effects

	Infliximab	Etanercept	Adalimumab	Anakinra	Rituximab
Hepatitis	2		1		
Hepatic enzymes increased	7	1			
Liver fatty	1				

be closely monitored for infections.

In the database of NAM there were 20 cases of infection TBC associated with the biological agents. Latency varied in these cases from one to 27 months. Other majority of the main reactions related to infection are summarised in the Table 3.

Malignancies

Safety concerns on a possible increased risk of cancer, particularly hematologic malignancies, have emerged recently, although evidence is conflicting. In clinical trials, increased incidence of lymphoma and non-melanoma skin cancers have been reported in patients treated with TNF inhibitors. On the other hand, the incidence of other types of malignancies in patients treated with TNF antagonist was found to be similar to or lower than that observed in the general population (3). A recent study indicated that users of biologic agents are unlikely to have a substantial increase in the risk of hematologic malignancies and solid tumors as compared with methotrexate users (4). Given the complexity of duration and severity of disease and the relatively short duration of experience with biological agents, it has not been established whether these agents modify the risk of malignancies. However, caution should be exercised when considering anti-TNF therapy for patients with a history of malignancy, or when considering continuing treatment in patients who develop a malignancy. A signal for increased incidence of smoking related malignancies with infliximab exposure was detected in 2005 by EMEA in patients with moderate to severe chronic obstructive pulmonary disease and heavy smoking history. The SPC for infliximab was updated accordingly. All the malignancies reported to NAM associated with TNF antagonists are listed in Table 4.

Congestive heart failure

Higher incidences of hospitalisation and mortality for worsening heart failure were seen in patients treated with infliximab, especially during use of high doses. Worsening of heart failure has also been reported in patients treated with adalimumab and etanercept. Infliximab and adalimumab are contraindicated in patients with moderate or severe heart failure. In the NAM database, only one case was identified for heart failure in patients using biological drugs. In this case infliximab aggravated heart failure.

Hematological effects

Hemotologic adverse events including clinically significant cytopenia have been infrequently reported with biological agents (Table 5). Cases with pancytopenia and aplastic anaemia, some with fatal outcome have been reported rarely in patients with RA treated with etanercept. If blood dyscrasias are confirmed the therapy should be discontinued.

Hepatic reactions

A review of occurrence of hepatic adverse effects in clinical trials and post marketing data revealed that rare cases of jaundice and non-infectous hepatitis are associated with biological agents. Sporadic cases of liver failure resulting in liver transplantation or death have occurred. Reactivation of hepatitis B occurred in patients receiving infliximab who were carriers of this virus. 12 hepatic adverse effects have been reported to the NAM registry (Table 6).

Drug induced lupus erythematosus and vasculitis

Approximately half of infliximab-treated patients in clinical trials who were antinuclear antibody (ANA) negative at baseline developed a positive ANA during the trial. Clinical signs consistent with a lupus-like syndrome have developed rarely. In the NAM registry, two LE rash cases, one with infliximab and the other with adalimumab were identified. One case with antinuclear factor test positive was reported in a patient receiving infliximab. Three cases of vasculitis were reported in 2 patients with infliximab and in one patient with adalimumab.

Neurological adverse effects

TNF-alpha inhibitors have been associated with rare cases of clinical symptoms and or radiographic evidence of demyelinating diseases suggestive of multiple sclerosis or optic neuritis. A careful risk benefit evaluation is recommended when prescribing these drugs to patients with pre existing demyelinating disases. In the NAM registry, one case of demyelination was identified in a patient treated with etanercept.

Skin reactions

The published data collected over a 5-year period from the National Register of Biological treatment in Finland (ROB-FIN) indicated that 35 % of the reported 308 reactions were skin reactions (5). In the NAM registry, one serious urticaria case associated with infliximab and 9 non serious rash reactions, of which 6 with etanercept, 1 with infliximab and 2 with adalimumab were identified.

Conclusions

Although biological medicines for rheumatic diseases have now been on the Finnish market for more than 7 years, the full spectrum of their safety risk has not yet to be fully elucidated.

After their authorisation several new safety concerns have arisen, involving mycobacterial and opportunistic infections, cytopenias, lymphoma, drug-induced lupus, demyelinating diseases, congestive heart failure and hepatotoxicity. Regarding these safety issues, EMEA has drawn attention to precautionary measures and, accordingly, prescribing and patient information for these drugs have been amended to include these new safety data in SPCs.

NAM has received 186 reports including 265 ADRs associated with these biological medicines in the treatment of RA. Most of reported cases have classified as serious.

Some of ADR cases remain unreported. To further analyse their impact on patient safety, widespread post-marketing pharmacovigilance and monitoring of these biological agents is necessary. The clinician must weigh the therapeutic benefits of these drugs against adverse effects. Patients should be evaluated carefully for the risk of adverse effects by regular clinical assessments.

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Anna Koski-Pirilä
PhD, Senior Researcher
Planning for Pharmaceutical Policies
National Agency for Medicines

The elderly and the consumption of antipsychotics

An increasing proportion of psycholeptics is used outside inpatient facilities: in 2005, 83% of antipsychotic and 93% of antidepressant drugs were consumed in outpatient care in Finland [1]. The use of psycholeptics in outpatient care was commonest in the oldest age groups: reimbursable antidepressants were most often purchased by 85–94-year-olds (12% of men and 17% of women) [2] and reimbursable antipsychotics by 90-year-olds and older (8.6% of women and 7.2% of men), followed by 80–89-year-olds (6.5% of women and 5.3% of men) [3]. The use of anti-dementia drugs is also commonest among the elderly [4] and has rapidly increased: both the consumption of anti-dementia drugs and the number of entitlements to refunds has shown a 10-fold increase from 1999 to 2005 [1, 5].

The use of psycholeptics in the elderly has been investigated in several Finnish studies, but a more accurate picture is warranted on the home-dwelling elderly, whose primary illness has not consisted of a severe mental disorder. This survey was undertaken to give a comprehensive picture of the outpatient use of antipsychotics and antidepressants in the over 74-year-olds. Use of anti-dementia drugs was incorporated in the study, because in earlier surveys the use of psycholeptics has differed between the dementia sufferers and those without dementia [6, 7]. Data from the special refund register were used to exclude from the survey persons with mental handicap, severe psychosis or other severe mental disorders.

Methods

The subject data were collected from the files of the Finnish Social Insurance Institution. The prescription register was used to identify individuals who had in 2005 been refunded for antipsychotics (N05A), antidepressants (N06A, N06C) or anti-dementia drugs (N06D). A 50% sample of the individuals was taken. The drug purchase details on their psych-oleptics purchases in 2005 were extracted from the prescription register. Their entitlement to special refunds on psycholeptic and anti-dementia drugs was checked in the refund register.

In this survey, psycholeptics refer to antipsychotics (ATC class N05A), anxiolytics (N05B), hypnotics and sedatives (N05C), antidepressants (N06A) and psycholeptics and psychoanaleptics in combination (N06C). However, drugs having main indications other than psychosis (lithium, prochlorperazine and dixyrazine) were omitted from the survey of antipsychotics (N05A). Users of class N06C drugs alone were few and consequently excluded from the survey.

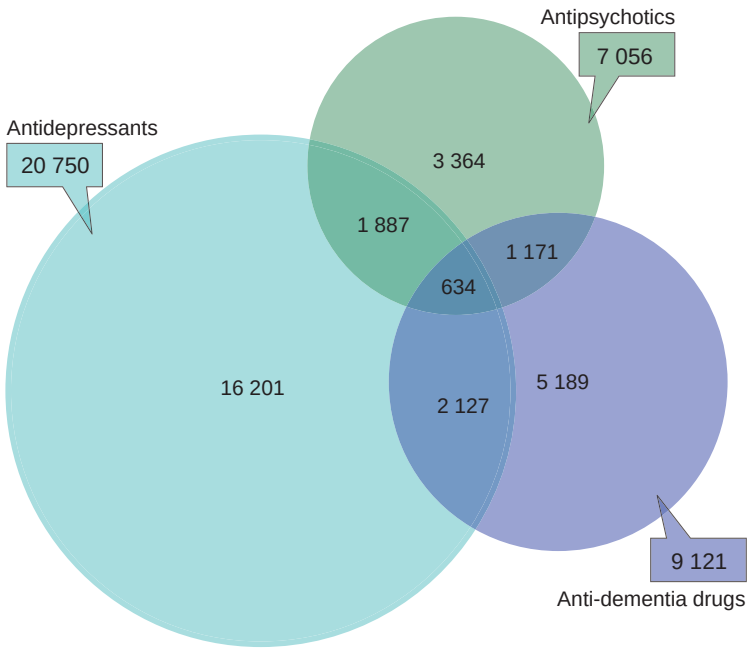
The survey data did not cover the entire outpatient consumption, because the reimbursement system does not include all psycholeptic products, strengths and package sizes. The drug consumption covered by the survey data was therefore compared with the drug sale statistics from NAM. The survey data covered on average over 90% of the outpatient consumption of antipsychotics and antidepressants and about 86% of the antidementia drug consumption. The outpatient consumption of anxiolytics (N05B) was covered by about 47% and hypnotics and sedatives (N05C) by 33%. However, midazolam and triazolam were not refunded and thus not included at all.

From the sample described above, only those elderly persons who did not in 2005 or earlier have a special refund entitlement for psycholeptics were eligible for this survey. The final survey data therefore covered 72% of the elderly antipsychotics users and 92% of the antidepressants users. Of the reimbursed antipsychotic and antidepressant consumption by the elderly, the survey data covered 51% and 90%, respectively. The final data included 30,474 individuals split up into sub-groups for each drug group (Figure).

Results and conclusion

The survey data suggest that of the entire elderly population in Finland in 2005 about 4% used antipsychotics, about 11% used antidepressants and about 5% used anti-dementia drugs, with basic refund entitlement. It is conspicuous that as much as half

Over 74-year-old users of psycholeptics and anti-dementia drugs without special refund status (a 50% sample in 2005).



of the reimbursed antipsychotic consumption in the elderly was covered by basic refund entitlement. Special refund entitlement requires severe and long-term illness. In the case of antipsychotics, the most common special refund entitlement 112 requires severe psychosis or other severe mental capacity disorder. Therefore it is presumed that half of the reimbursed antipsychotic consumption in the elderly is used for the treatment of less pronounced and more short-term symptoms.

Some of the elderly have in the course of the study year bought psycholeptics of many different drug groups (Figure), which, owing to the length of the survey period, does not necessarily mean their concomitant use. These psycholeptics consumer groups without special refund entitlement included elderly women more often than men, which was also the case in relation to the entire elderly population studied as 5-year age groups. The use of the above drug groups became more common in both sexes with increasing age; the use of antidepressants and anti-dementia drugs was most common in the group of 85–90-year-olds, and the use of antipsychotics in the group of 90–94-year-olds in both sexes.

Elderly women using antipsychotics also used antidepressant medication more often than men. About half of the elderly using antipsychotics or antidepressants also used anxiolytics or hypnotics. Moreover, women using antipsychotics had purchased anxiolytics or hypnotics more often if they were on anti-dementia therapy. Elderly persons using antidepressants were twice as often also using anxiolytics, hypnotics or antipsychotics if they were on anti-dementia therapy.

Among those using anti-dementia drugs, 50% of men and 40% of women had not acquired other reimbursable drugs in the ATC classes N05 and N06. An average of 30% had used antidepressants, the proportion of women (34%) being higher than that of men (23%). About 20% had used antipsychotics and 32% had used anxiolytics or hypnotics with basic entitlement to a refund.

Drugs most commonly used

Among the elderly using antipsychotics without entitlement to a special refund, 39% used risperidone, 28% quetiapine, 11% melperone and 10% haloperidol. Haloperidol, owing to its having few anticholinergic effects, and melperone, owing to its having few extrapyramidal adverse effects have been recommended for the elderly among the conventional antipsychotics [8].

The most commonly used antidepressant without entitlement to a special refund was citalopram, which had been prescribed to 43% of the elderly who were on antidepressant therapy. Mirtazapine was the second (24%) and escitalopram the third most commonly used (16%). The next most commonly used antidepressants were the tricyclic amitriptyline and doxepin, even though tricyclic antidepressants should be avoided in the elderly owing to their anticholinergic effects [9]. However, amitriptyline in particular is also used for the treatment of chronic, especially neuropathic pain, albeit in smaller doses than in antidepressant use.

Risperidone was relatively more common among antipsychotics used by those elderly who were on anti-dementia therapy (48%) versus those who were not (36%). This complies with the recommendations, as risperidone is the only antipsychotic having the therapeutic indication of treatment of severe behavioural disorders associated with dementia (with certain restrictions) [10]. Citalopram was relatively more common among antidepressants used by those who were on anti-dementia therapy (52%) versus those who were not (43%). This was also in line with recommendations, as

serotonin re-uptake inhibitors are the primary choice in the treatment of depression in dementia patients [10]. As anti-dementia drugs should not generally be used concomitantly with potent anticholinergics [10], compliance with recommendations was also brought about in the situation where the proportion of perphenazine and levomepromazine among the antipsychotics and the proportion of amitriptyline and doxepin among the antidepressants used by elderly anti-dementia drug users were smaller when compared with other elderly persons.

Drugs with a long half-life

The frequency of use of anxiolytics, hypnotics and sedatives was not studied extensively due to scanty prescription data. Special attention was, however, drawn to the use of benzodiazepines with long-term effect (diazepam, chlordiazepoxide, nitrazepam), since benzodiazepines with a long half-life should not, as a rule, be used in the elderly owing to the risk of long-term sedative and cumulative effects [11].

Among the elderly in these survey data, 5% of the antidepressant users, 4% of the antipsychotic users and 2% of the anti-dementia drug users had also used benzodiazepines with a long-term effect entitling them to a basic refund. In reality, the use of benzodiazepines with a long-term effect can be assumed to be more prevalent, because the data only covered just over a third (36%) of their consumption in outpatient care.

Fluoxetine, a serotonin re-uptake inhibitor with a long half-life, should also be avoided in the elderly [11]. In this sample, 919 (4%) of the elderly on an antidepressant therapy entitling them to a basic refund had used fluoxetine. Consequently, in the whole country almost 2,000 elderly patients, i.e. about half a percent of the elderly population, were using fluoxetine. However, its use in the elderly appears to have diminished since 1999, when, calculated on the basis of annual purchases, fluoxetine used to be the second commonest antidepressant among the elderly [12].

Conclusions

In 2005, about half the reimbursed antipsychotic use and 90% of the reimbursed antidepressant use in the elderly were acquired without special refund entitlement. It most likely indicates their use in the treatment of other than severe and long-term mental disorders. Moreover, some psycholeptic use contrary to the recommendations occurred among the elderly in the survey data. The psycholeptic medication among the elderly on anti-dementia drug therapy differed slightly from that among the rest of the elderly in the direction of the recommendations.

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Tinna Voipio
Researcher
National Agency for Medicines

Pirkko Paakkari
Chief Medical Officer
National Agency for Medicines

Drug sales growth at a standstill

The drug wholesale value in 2006 amounted to 1.7 billion euros in Finland, which is about half a percent less than in 2005. The pharmacy sale value decreased (by 3%). There was a further increase in the sales to hospitals (7%).

Cuts in the drug wholesale prices, generic substitution, price competition and the Medicines Act reform at the beginning of 2006 have had a negative influence on drug sales value. For example, the consumption of simvastatin increased by almost 40%, but its sales value dropped by 20%. The consumption of ramipril increased by 10%, but the sales in wholesale prices were 60% lower than the previous year.

The largest groups

Drugs with an effect on the nervous system (N) remained the largest drug group by sales. The second largest group by sales was that of antineoplastics and immunomodulating drugs (L). The largest group according to the doses used daily, drugs used for the cardiovascular system (C), was the third largest group according to its sales figures (Figure 1).

The list of the ten most commonly used drugs showed hardly any changes in comparison with the previous year. Ibuprofen was moved from second place to fifth following simvastatin, ramipril and furosemide, each of which were moved one stage upwards (Table 1).

Atorvastatin at wholesale prices kept its position as the best sold drug even though its sales decreased by 20% and its consumption by 11% (Table 2).

Table 1. The 10 medicinal substances most commonly used in 2006

ATC Code			EUR million	Change in %	DDD/1,000 inh/day	Change in %
B01AC06	acetylsalicylic acid	antithrombotic prophylactic	7,8	-16,7 %	83,76	-20,6 %
C10AA01	simvastatin	cholesterol-lowering drug	7,4	-19,9 %	56,33	39,2 %
C09AA05	ramipril	drug for cardiac disorders	3,1	-59,6 %	43,56	10,1 %
C03CA01	furosemide	drug for cardiac disorders	4,6	-1,8 %	34,86	4,0 %
M01AE01	ibuprofen	anti-inflammatory analgesic	16,2	-35,5 %	32,89	-19,7 %
C10AA05	atorvastatin	cholesterol-lowering drug	33,5	-19,5 %	29,22	-11,0 %
N05CF01	zopiclone	hypnotic and sedative	4,3	-15,4 %	26,82	-0,5 %
C09AA02	enalapril	drug for cardiac disorders	2,1	-11,1 %	25,71	-3,8 %
C08CA01	amlodipine	drug for cardiac disorders	9,3	-52,6 %	24,40	3,2 %
C07AB07	bisoprolol	drug for cardiac disorders	7,5	2,2 %	24,24	6,7 %

Table 2. 10 medicinal substances most commonly sold at wholesale prices in 2006

ATC Code			EUR million	Change in %	DDD/1,000 inh/day	Change in %
C10AA05	atorvastatin	cholesterol-lowering drug	33,5	-19,5 %	29,22	-11,0 %
N05AH03	olanzapine	antipsychotic	33,1	8,2 %	4,90	13,1 %
R03AK06	salmeterol och fluticasone	anti-asthmatic	25,4	-0,5 %	8,23	6,2 %
J01DC02	cefuroxime	anti-microbial	24,4	36,5 %	0,59	7,4 %
N07BA01	nicotine	nicotine replacement therapy	21,5	23,0 %	6,37	19,6 %
N05AH04	quetiapine	antipsychotic	20,4	15,9	2,59	23,7 %
N05AX08	risperidone	antipsychotic	19,5	7,8 %	2,46	9,9 %
A02BC05	esomeprazole	drug for acid related disorders	18,8	-0,6 %	9,70	23,9 %
L04AA11	etanercept	antirheumatic	16,8	22,0 %	0,22	28,4 %
M01AE01	ibuprofen	anti-inflammatory analgesic	16,2	-35,5 %	32,89	-19,7 %

Since October 2006 refund for atorvastatin has been granted only when the prescription contained a doctor's specification about a lipid metabolism disorder difficult to manage. Amlodipine, which was dropped from the list of ten best sold drugs, had occupied the fifth place the previous year. A new antirheumatic agent, etanercept, was included in the list, with a consumption of only 0.2 DDD/1,000 inhabitants/day.

The most commonly used drug was acetylsalicylic acid indicated for prevention of arterial thrombosis with a consumption rate of 84 DDD/1,000 inhabitants/day. Consequently about 8% of the population was using this drug. The consumption was 17% lower compared with the year 2005. Some of the drop in the sales value is explained by the stipulation in the Medicines Act reform at the beginning of 2006 of a ban on targeted reduced prices. At the end of 2005 pharmacies filled their stocks by buying popular products, the sales of which were lower than usual at the beginning of the year (Figure 2). A similar apparent drop in the annual consumption owing to stockpiling is also seen in the case of ibuprofen with reduced consumption by 20%.

The total sales of OTC drugs remained 18% lower compared with the previous year. This is also explained to a large extent by the considerable stockpiling that had taken place at the end of that previous year.

Nicotine products

Since the beginning of February 2006 nicotine products have also been allowed to be sold from retail shops, petrol stations and kiosks. The sale of the products requires authorisation obtainable from the municipality. Pharmacies received 70% of the nicotine products wholesale and about 30% was sold direct to retailers, kiosks and petrol stations.

Figure 1. Drug sales in Finland according to ATC code in 2006 (total in wholesale prices

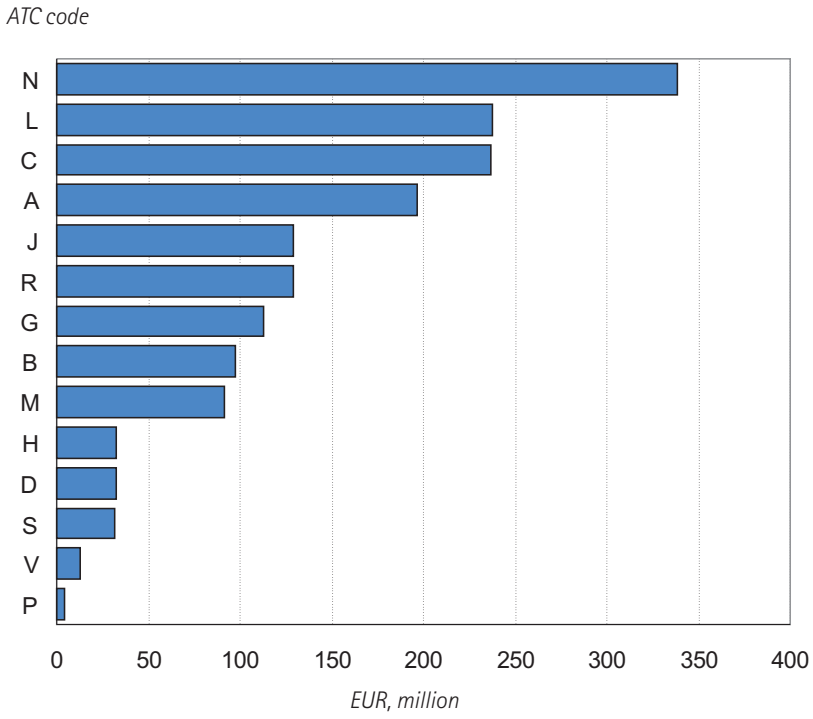
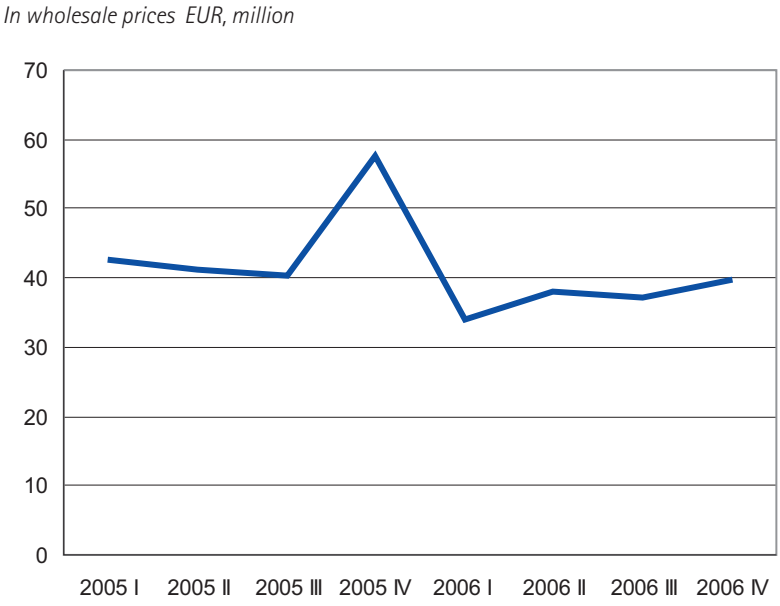


Figure 2. Sale of OTC drugs in Finland quarterly in years 2005–2006.



TEO provides guidelines and supervision

The National Authority for Medicolegal Affairs in Finland, TEO, promotes the quality of services and the use of legal safeguards in social and health care.

TEO has frequently been called the health care licensing and supervisory authority. We do indeed grant various licences. As regards professional practice, we legalised and granted licences for over 6,000 health care professionals last year alone. We also granted to health care professionals over 7,000 rights to use certain titles. The health care professionals register, Terhikki, contains the records of more than 330,000 professionals. The responsibilities of TEO go beyond the registering of professionals. The register continuously receives requests for various certificates, intended for job applications, for example, as well as requests for details of the blameless conduct of health care professionals. A lot of work for TEO is generated by health care professionals arriving from outside the EU countries and aiming to work in Finland, because qualifications obtained by them need to be compared with qualifications required in our country, and the likelihood of their being able/allowed to work as physicians in Finland is examined.

We also issue other types of authorisations. Authorisation to abort a pregnancy must in certain cases be applied for from TEO. These authorisations are discussed by a board specialising in issues of abortion and sterilisation, with meetings every Tuesday and Thursday. Last year we issued a total of 889 authorisations to abort a pregnancy. Sterilisation authorisations almost belong to history nowadays, but isolated cases are still authorised from time to time.

An Act on fertility treatment will come into force in September. According to the Act, giving treatment and storing spermatozoa and ova, as well as embryos are subject to licence. The records of these are also maintained and licences granted by TEO.

What about the supervision?

Since its inception TEO has issued guidelines about, and supervised the work of, individual health care professionals, mainly by way of complaints and various reports. The complaints are made by the patients themselves or their relatives. TEO will deal with them when they concern suspected errors of treatment resulting in mortality or severe injury. Other complaints are dealt with by the Provincial State Offices. Last year TEO handled 267 complaints. Reports on health care professionals are made, for example, by pharmacies, employers, legal courts or the police. For example, a pharmacy may report that a certain physician prescribes rather high amounts of CNS drugs, and TEO would consequently investigate the appropriateness of the doctor's actions. Or it may be the case that an employer suspects the work ability of a doctor or a nurse owing to e.g. illness or alcohol abuse; these are also issues examined at TEO. Last year a total of 660 complaints, reports and requests for statements relating to the supervision of health care professionals were received by TEO. Ten years earlier less than half as many were received, under 300.

While TEO supervises health care professionals it also at the same time gives them guidelines. Each case of supervision is thoroughly investigated together with experts, and the professionals involved and possibly also their superiors receive as necessary a notification which will, for example, focus on the discrepancies of their work and place emphasis on the correct way of working. Solutions to complaints are annually collected into a short summary which is published and sent to the rank and file health care workers and it is hoped that it will serve as a form of precaution for health care units in their work.

The faulty or reprehensible work or action of a health care professional is not always his or her fault alone. The circum-

stances may be influenced, for example, by poorly designed performance practices at a hospital, which, combined with work overload, expose the professional to making errors. It is in these circumstances rather unfair that individual employees alone be at the receiving end of complaints.

This situation was changed in September last year, when the provision of guidelines and supervision were extended to cover health care units as well. TEO was also made responsible for coordinating and harmonising the health care guidelines given and supervision provided by social services and health departments of the Provincial State Offices. The aim is that people in the various parts of Finland should receive equal treatment and that complaints about treatment should be processed following uniform principles in every province.

In accordance with its extended job description, TEO will in future attach increased importance to prophylactic work and the provision of guidelines, which will improve the safety and quality of health care and diminish inappropriate actions and thereby hopefully also the volume of complaints and other appeals.

The focus areas in guidelines and supervision chosen by us for this year include e.g. making sure that treatment guarantees work, together with medical treatment, harmonisation of the management of licences in private health care, and elderly care. We work in close collaboration with the Provincial State Offices and make quarterly joint inspections, also in public, of the results of our efforts.

TEO is also an authority which grants state subsidies. Last year we granted a total of almost EUR 900,000 in subsidies to hospital districts for forensic psychiatric examinations of children and adolescents associated with preliminary criminal investigations. These concerned forensic psychiatric examinations of adolescents under the age of 16 and children, where requested by courts or prosecuting authorities in cases where sexual abuse or assault.

But let's go back to that to which I was referring to at the beginning, statements of mental state of health and withdrawals of rights to practise a profession. Last year we issued over 130 statements of mental state of health to the courts. In compliance with our job description as extended in October we also made assessments of the danger posed by offenders who, having been sentenced to serve an entire term and who, after having served 5/6 of it, have applied for a release on parole. We restricted or withdrew the right to practise professionally of 24 health care professionals. We also focused our attention on 43 cases, issued a notice in 26 cases and a written warning to four professionals.

When I moved from the Communications Department of the Ministry of Social Affairs and Health a couple of months ago to become an Information Officer at TEO, people wondered why I left a hectic observation post and chose to join TEO. I was even offered a police badge and a gun as a working tool in this supervisory police office. I can assure you that I have arrived in a dynamic, growing office with challenges in the ever-varying field of health care and probably in the future also in the field of social care, and these are challenges which are not by any means small.

Tarja Tamminen
Information Officer
TEO