

Lääketietoa Lääkelaitokselta



Läkemedelsinformation från Läkemedelsverket, Finland

Drug information from the National Agency for Medicines, Finland

■ På svenska | Översättning Mats Forsskåhl

Ledare	24	EU-tåget rullar <i>Hannes Wahlroos</i>
	25	Läkemedelsterapi mot ADHD och biverkningar <i>Arja Voutilainen</i>
Om biverkningar	30	Biverkningsanmälningar gjorda av apotekspersonal <i>Tiina Karonen Leena Sommarberg Marja Forsell</i>
Växtbaserade läkemedel	33	Monografier över växtbaserade läkemedel – vad handlar det om? <i>Sari Koski</i>
Medicintekniska produkter	36 36	System för risksituationer i anknytning till utrustning En ny publikation
Läkemedel för djur	37	Användarsäkerheten hos läkemedel för djur <i>Tita-Maria Muhonen</i>

Läs TABU också vid Läkemedelsverkets web-sidor
<http://www.nam.fi/svenska/publikationer/tabu/index.html>

■ In English | Translation Mervi Moisander

Editorial	40	The EU train keeps on going <i>Hannes Wahlroos</i>
	41	ADHD medication and adverse drug reaction <i>Arja Voutilainen</i>
ADR News	46	ADRs reported by pharmacists in Finland <i>Tiina Karonen Leena Sommarberg Marja Forsell</i>

Read TABU also on the web
<http://www.nam.fi/english/publications/tabu/index.html>

The EU train keeps on going

The European Union is often blamed for its secretive and undemocratic policy preparation process, with lobbyists heavily influencing future developments. The drafting process for EU pharmaceutical policies is in an open phase at the moment, however, and active players have already had an opportunity to influence matters.

The European Commission is preparing a communication on the future of pharmaceuticals for human use in Europe. The Commission consultation paper, with questions, was published for comments from all stakeholder groups last autumn. A total of 104 contributions were received, which are published on the Commission website¹. A summary of the contributions will also be published shortly, following which a communication by the Commission to the European Parliament and the Council of the European Union can still be expected in the course of this year. Once these reactions have been received, it is reasonable to expect legislative proposals from the Commission that will define EU pharmaceutical policies far into the next decade. The preparation of policies is a process that will extend over several years.

The challenges surrounding future EU pharmaceutical policies this time include the globalisation of the sector, ensuring the smooth running of the internal market in a widening Europe, and advances in science and technology. The key issues include six themes, the new ones being the prevention of counterfeit medicines and the promotion of transparency and harmonisation with regard to pricing and reimbursement practices.

Familiarity with the contributions is recommended to anyone who would like to know and learn about the differences in emphasis among the interests of stakeholders and even Member States in EU pharmaceutical policies. Even though Finland did not make use of its opportunity to have an influence last autumn (a majority of the Member States did not submit a contribution), it would be wise for those involved in the future policy making processes to familiarise themselves even at this stage with the factors that are of importance to the most active opinion formers.

The most unconditional support appears to be

for the fight against counterfeit medicines. Attempts to liberalise pharmaceutical sales and distribution will certainly be scrutinised in this respect.

The contributions made by European pharmaceutical industry organisations are thorough, but in terms of their content they are incoherently split according to the interests of each industry group. The self-medication sector focuses on achieving less stringent regulation. The innovative pharmaceutical industry places emphasis on, for example, protecting innovations, the national features of pricing and reimbursement practices, and on preventing supranational evaluations of medicines with regard to their relative efficacy. The generic pharmaceutical industry would like to increase the use of generic medicines in Europe. The contributions contain plenty of useful information about the pharmaceutical markets in Europe.

Contributions were also received from the European doctors', pharmacists', wholesalers' and consumers' associations and the well-known British Medical Association (BMA). The viewpoints of the pharmaceutical industry are taken yet further in these contributions. Attention is also drawn to the fact that health-care professionals and consumers take a very critical view of the role of the pharmaceutical industry as the distributor of pharmaceutical information to consumers.

Member States in which the pharmaceutical industry is a significant industry sector did not miss out on their opportunity to have an influence. In their contributions, the harmonisation of pharmaceutical pricing and reimbursement practices and evaluation of the relative efficacy of medicines are generally presented as important issues. The issues as a whole are nevertheless considered to fall within the competence of the Member States.

According to an old truth about exerting influence on EU issues, it is considered that the best results are achieved by comprehensively exerting influence at the initial stage of preparations. This method has already been adopted by many.

¹ <http://ec.europa.eu/enterprise/pharmaceuticals/pharmacommunication/pubconsult.htm>

Arja Voutilainen

Paediatric Neurologist

HUS, Hospital District of Helsinki and Uusimaa

Hospital for Children and Adolescent

ADHD medication and adverse drug reactions

Attention-deficit/hyperactivity disorder (ADHD) is a common disorder which restricts the functional ability; its key symptoms consist of inability to concentrate, hyperactivity and impulsiveness. ADHD is one of the most important developmental disorders, both with regard to frequency and prognosis. The prevalence of ADHD in international and Finnish studies is 4–8%. Especially in association with behavioural disorders and without appropriate treatment it may significantly increase the risk of mental disorders, intoxicant abuse and criminality.

In the autumn of 2007 the National Current Care recommendation was issued for the treatment of ADHD in children and adolescents (1). The recommendation of the expert group set up by the Finnish Child Psychiatry Association, the Finnish Child Neurology Society and the Finnish Medical Society Duodecim is that primarily non-medical care should be used in ADHD in children under school age and in ADHD in school age children with mild symptoms. For severe symptoms medication should be added if adequate benefit is not attained with other forms of treatment. Medication should be tried if the symptoms of ADHD cause significant disadvantage in some particular area of life, for example in family life, in school, or in relationships with friends. In severe problems the medical treatment combined with psychosocial therapies can be introduced right away following consultation and the setting of guidelines.

Medical treatment

The medical treatment of ADHD is evidence-based. The efficacy of

methylphenidate, dextroamphetamine and atomoxetine has been proven in several controlled trials with respect to symptoms of attention deficit, hyperactivity and impulsiveness.

The first stimulant therapies in Finland were introduced in the 1960's at HYKS Paediatric Out-patient Clinic for the treatment of severe cases of MBD. The longest history of medical treatment for ADHD is found in Norway, where last year about one per cent of the under 16-year-olds were receiving medical treatment. This was three times more than in Finland. The use of medication is still growing in Norway at the rate of 10% per year (2), and the same applies to North America, where already five per cent of the underaged population are receiving medical treatment for their ADHD.

Medical treatment for children's ADHD has increased rapidly in Finland also. The total number of paediatric patients in 1999 was 274. In 2005, a total of 4,343 patients received methylphenidate or amphetamine therapy; 2,748 of whom were under the age of 17. In 2005 stimulants were received by a to-

tal of 4,703 persons, 175 of whom received atomoxetine and 185 modafinil. In the age group most frequently on the medication, the 7 to 14-year-olds, stimulants were given (mostly as long-acting methylphenidate) on average to slightly fewer than 1 in 200 children in the year 2005, i.e. fewer than one in ten paediatric ADHD patients (3).

Among the stimulants, there is no distinct difference in the efficacy and adverse effects between short- and long-acting preparations. Compliance is generally better with a drug that is taken once a day, and the risk of a stimulant's ending up in the wrong hands is smaller than that for a short-acting preparation. Commonly known adverse reactions including loss of appetite, sleep disturbances, headache and abdominal pain; light-headedness and tiredness are possible. A stimulant may sometimes trigger symptoms of tic or epileptic seizures in those prone to them. When such reactions occur, it is usually enough just to replace the drug with one that is more beneficial in terms of duration of action or to adjust the quantity or time of administration of the

dose. Aids used for falling asleep including medication with melatonin can be considered. It is seldom necessary to withdraw medication altogether, and even then it is recommended that another active agent be tried, similarly to a situation in which an adequate response is not achieved.

It was not until the turn of the century that atomoxetine, a specific noradrenaline re-uptake inhibitor, was developed to treat ADHD. New adverse reactions have consequently emerged in recent years, when the use of the drug has been growing. The usual adverse reactions caused by atomoxetine are, especially at the start of treatment, loss of appetite, gastrointestinal symptoms and tiredness. The symptoms of tic are not aggravated by atomoxetine and it is not associated with the risk of abuse. It may, however, trigger seizures in epileptics. Liver toxicity may also occur as a very rare side effect. The treatment should be discontinued if jaundice occurs or if laboratory results show evidence of liver dysfunction, and treatment should not be reintroduced. Atomoxetine may increase an aggressive or suicidal tendency. Prolongation of the QT interval has also been reported.

Effect on growth

The therapy is at the beginning often associated with a loss of weight which may later revert to normal. Despite several studies it has remained unclear how stimulant therapies affect growth. One review included 21 studies on children's growth development during or after therapy with methylphenidate or dextroamphetamine (4). In nine studies a statistically significant reduction in growth rate was found, whereas no effect was found in twelve other studies. In two studies the

growth rate was found to increase after discontinuation of therapy. Researchers estimated the probable reduction in growth rate during stimulant therapy to be as much as 1 cm a year. Even though the reduction in growth rate during stimulant therapy is generally considered insignificant in comparison with the benefits of the therapy, the growth rate should be regularly monitored during both stimulant and atomoxetine therapy. This is important especially in infants, in dwarfism and during the administration of high doses of stimulants.

Long-term medication

The benefits of ADHD drugs not diminished as the therapy is prolonged. About a third of patients introduced to this therapy use it for more than two years, and over 15% for longer than five years (5). The longest controlled trials have lasted for less than two years and follow-up studies for three to five years, so knowledge of the benefits and risks of long-term use is scarce. Performance during therapy and life quality have been shown to improve with therapy, but permanent change in the control of behaviour or in learning have not been proven.

The lack of long-term monitoring has raised concern about possible adverse effects on chronic treatment. While the treatment became more popular and the use among adults increased suspicion arose, especially in North-America, of possible severe harmful cardiovascular effects of ADHD drugs. Information about the common occurrence of psychic reactions in trials involving the use of long-acting methylphenidate caused concern about the psychiatric harmful effects of ADHD drug therapy. As a result,

the FDA was even considering attaching a warning about cardiovascular and psychiatric risks (*black box warning*) on the ADHD drug packages. Following careful discussion it was, however, abandoned, but advice was given that information about possible cardiovascular and psychiatric risks should be added on the drug packages.

Adverse cardiovascular reactions caused by ADHD drugs

The majority of ADHD drugs are sympathomimetics with a stimulant effect also on the cardiovascular system. A high pulse rate and hypertension are common. The changes are nevertheless mild, mostly transient, dose-dependent and clinically of minor relevance compared with the benefits of the therapy. The pulse rate and blood pressure should nevertheless be monitored during treatment.

The FDA has commissioned a survey of the cases of sudden death during ADHD therapy (short-acting and long-acting amphetamine, dextroamphetamine, methylphenidate and atomoxetine) during the period of 1.1.1992 to 28.2.2005 reported to the adverse drug reaction register (6). The analysis includes all those deaths which were not caused by an overdose of medication, abuse of medication, or by any other specific reason or medication. The quantity of drugs used was assessed on the basis of prescriptions and numbers dispensed by pharmacies, divided into two groups: the under 18-year-olds and the over 18-year-olds.

The number of sudden deaths reported in the under 18-year-olds during amphetamine therapy was 14 in total (0.3/100,000 patient years), 13 of which were associated with the use of long-

term amphetamine–dextroamphetamine therapy. The age of the patients varied from seven to 16 years, the duration of therapy from one day to eight years. In three fatal cases several drugs had been used. In six cases a cardiovascular structural defect was found in autopsy. The cases resulted in the banning of the preparation of amphetamine–dextroamphetamine in Canada in February 2005 until additional reports were submitted, and the drug was subsequently reintroduced on to the market in August the same year. The instructions for use include a warning about the use in cardiac patients, and a warning was also added about abuse which can cause a sudden death.

Cases of sudden death in the under 18-year-olds during methylphenidate therapy numbered 11 (0.2/100,000 patient years). Seven of these occurred during short-acting and four during long-acting methylphenidate therapy with a dose variation of 18–60 mg/day. The patients were 9 to 15 years of age and had been using the medication for a period of two months to ten years. Five children had at least had one other medication in use, one even five medications. Six children showed cardiovascular abnormality on autopsy. Not a single fatal case appeared to be associated with methylphenidate either alone or directly.

Three sudden deaths in the under 18-year-olds during atomoxetine therapy were reported (0.5/100,000 patient years). The age of the patients varied between 2.5 years and 12 years, the period of use of the drug from six weeks to four months. There was no evidence of cardiovascular abnormalities in any of them. The youngest one was reported as having also been on another therapy, the concentration of

which was found on autopsy to be toxic.

Studies show that the risk of sudden death in all 1- to 20-year-olds is 1.3 to 4.6 deaths per 100,000 lifeyears. The number of sudden deaths reported during the use of ADHD drugs has been smaller than that which would be expected based on the general risk of sudden death in children and adolescents. There are no data on the assessed general mortal-

a paediatric cardiologist.

In healthy children the drugs are not considered to cause any special cardiovascular risk. Before trying the drugs it is nevertheless advisable to check the involvement of any cardiac symptoms, such as attacks of syncope and unconsciousness, palpitations, chest pain, hobbies involving heavy physical activity which increase the pulse rate, the use of other sympathomimetics and a



ity among children and adolescents with heart failure. Furthermore, nor is there any certain information about the proportion of severe adverse reactions that are reported to the adverse reaction register. Estimations have been proposed suggesting that only 1 to 10 percent of severe adverse reactions are reported to the FDA (7).

Children with a structural heart defect, cardiomyopathy or arrhythmia may be at increased risk of adverse cardiac reactions or of sudden death. The cardiovascular state of these children should be closely monitored during any ADHD therapies, and the Finnish current treatment recommendations do not advise ADHD therapy without cooperation with

family history of sudden death, cardiac death and arrhythmia. There is no need for cardiac examination (ECG, echography, consultation with a cardiologist) if the patient's heart is healthy and symptom-free and the clinical status is normal (growth data, cardiac auscultation, pulse rate and blood pressure) and no risk factors are detected in the patient's history.

The possibility of harmful cardiovascular effects has been discussed in the NEJM of 6.4.2006 (7–9). The Journal of Pediatrics has published a paper discussing the actions the doctor should take in this issue (10). A retrospective study was published recently in which cardiac deaths did not occur during stimulant

therapy (42,612 years) in the 55,384 ADHD patients of the age of 3 to 20 years (124,932 lifeyears). During the years of stimulant use, the number of cardiac symptoms resulting in hospitalisation was equal to that among those with previous use of stimulants (35,671 years) and those with no previous use of stimulants (46,649 years). The number of patients needing emergency care for some cardiac symptom, syncope, dysrhythmia, tachycardia or palpitations, or blood pressure was 1,091. The use of a stimulant was associated with a 20% higher risk for emergency appointments compared with the non-stimulant users (5).

Adverse psychiatric reactions

The FDA carried out a review of the adverse psychic reactions caused by ADHD drugs and observed in clinical trials and adverse reaction follow-ups between 1.1.2000 and 30.6.2005.

The randomised controlled clinical trials (RCT) consisted of a total of 425 placebo years in 3,990 patients. The ADHD drugs that were studied had in the RCTs 770 (N = 4,846) patient years and in the open label studies 8001 (N = 13,712) patient years. Many clinical trials were of a short duration and a proportion of them had patients enrolled who were known to benefit from the drug, which will limit the relevance of the clinical trials in the evaluation of drug safety. The samples were small, durations of treatment short, events few, and the reliability of the adverse reaction reports (about remaining unchanged, classification of the adverse reactions) could not be confirmed during the ongoing trials.

During placebo therapy no manic or psychotic symptoms occurred. During active ADHD

therapy in RCTs the different drugs triggered 0 to 2.8 cases of psychosis or mania per 100 patient years. In open label studies psychotic or manic symptoms were exhibited to an equal extent with long-acting methylphenidate, atomoxetine, modafinil and amphetamine-dextroamphetamine in 0.2–0.3% of patients.

During placebo therapy in all RCTs 0.9 cases of suicidal tendency occurred per 100 patient years. During atomoxetine therapy in RCTs suicidal tendency occurred in 1.5 cases and in open label studies in 0.9 cases per 100 patient years. According to the pharmaceutical company Eli Lilly's own studies, the occurrence of suicidality in association with atomoxetine therapy was significantly higher (0.4% of the patients, $p < 0.01$) in comparison with the placebo therapy; no suicides actually occurred.

Aggressiveness occurred during placebo therapy in 7.1 cases per 100 patient years. Aggression decreased during modafinil therapy. According to the Marketing authorisation holder Eli Lilly's own analysis, aggressiveness occurred in clinical trials in 1.6% of patients on atomoxetine therapy (N = 1,308), in 1.1% on placebo therapy (N = 806) and in 0.8% on methylphenidate therapy (N = 472).

There were many post-marketing reports of adverse reactions including cases of psychosis, mania, suicidal tendency and aggressiveness, they were mostly mild or transient. There are also several case reports of psychotic symptoms.

An analysis of the adverse reactions did not reveal risk factors which would predict psychic adverse reactions. New instructions on the package for use by both the patient and the doctor are under way. In addition to the warning about aggravation of a previ-

ous psychosis or mania, the risk of these even in other patients should be cautioned about. The medication can cause visual, sensory and hearing hallucinations. The package of atomoxetine already contains warnings about suicidal tendencies. Children should be monitored during the treatment in case of adverse psychiatric reactions, and parents should be advised to contact a doctor if the child's behaviour changes unexpectedly during treatment. Several of the harmful psychiatric reactions caused by the drug disappear spontaneously within a couple of days when the administration is stopped, which is what should be done, temporarily at least. Aggression can be part of ADHD, which can be alleviated by the drug. If new aggression or severe exacerbation occurs, the therapy should be discontinued. In addition to the FDA website (11, 12) guidelines are also provided in a paper published in American Journal of Psychiatry (13).

Medication for children and adolescents with ADHD

Medication can be introduced by a paediatrician or a paediatric neurologist, paediatric or adolescent psychiatrist or other doctor well familiar with the psychic and physical development of children/adolescents. The family and the child/adolescent should receive adequate information about the medication and its aims. The medical therapy should be consistent, the follow-up should be systematic and, especially at the start of the therapy, adequately concise. Follow-up treatment can also be taken care of by a primary healthcare doctor.

In the choice of drugs consideration should be given to the occurrence of symptoms in various situations and at various times of

the day, as well as to other possible concurrent problems. Before prescribing the drug the prescriber should gain familiarity with current drug-specific instructions in respect of contraindications and adverse reactions.

The choice of drug is dependent on any concurrent illnesses (other psychic symptoms, symptoms of tic, Tourette's syndrome, epilepsy, sleep disturbances), history of adverse reactions, treatment compliance, risk of abuse, the wishes of the child/adolescent or family, and the price. Upon introduction of the therapy, it will be decided which changes of symptoms and functions should be monitored. The therapy should always be introduced at a low dose. The stimulant dose is then increased, for example weekly, while the response and any adverse reactions are concomitantly monitored. When adjusting the dose a weekly contact should also be maintained with those responsible for the treatment, and the decision about continued therapy should be made at an appointment visit within two to three months. The therapy should aim at achieving adequate efficacy without causing any significant adverse reactions.

ADHD medication should be consistent and, as with all other medical therapies, monitoring should be systematic. Compliance can be improved by securing the continuance of the therapy, for example by monitoring at 3–6 monthly intervals. Its efficacy and any adverse reactions, as well as symptoms of concomitant illnesses, should be monitored; these are assessed by means of questionnaires and regular clinical tests and interviews. The overall situation and the need for continued medical therapy are again assessed during follow-up.

In some patients the need for therapy continues until adult age, in others the therapy can be discontinued as symptoms are alleviated and new skills learned. Studies have shown that the therapy continues for more than two years in on average a third of the patients. When discontinuation is considered in a balanced situation, an interval with no medication may for example be introduced, and the extent of the symptoms and disability experienced by the patient at home, in school and in other situations (based on questionnaires and clinical reviews) are assessed. Medical therapy can be discontinued when the symptoms no longer constitute a significant disability. The continuation of other forms of treatment is generally advised.

In the planning of medical therapy any possible risks should also always be considered: there should be awareness of their existence, and their significance should be compared with the benefits of the medical therapy. Treatment of ADHD offers clear evidence of benefits, and in addition to the decrease in the actual symptoms, reduced abuse and reduced risk of accidents can for example be distinguished. The current treatment recommendations are there to assist the clinician in the planning and carrying out of the overall treatments. New forms of drugs are being developed and introduced. The possibility of abuse is reduced as drugs which the FDA has already approved such as the methylphenidate transdermal system (MTS) and lisdexamfetamine, which is a precursor of dextroamphetamine and bio-degradable in the intestines, are introduced on to the market.

Literature

1. Lasten ja nuorten aktiivisuuden ja tarkkaavuuden häiriön (ADHD) hoito Käypä hoito -suositus (in Finnish) Duodecim 2007;123(24):3042–58.
2. Wannag Ebba, 32nd Nordic Neuro-Pediatric Congress June 8th, 2007.
3. Lundström B, Voutilainen A, Sou-rander A. Keskushermostostimulanttien käyttö Suomessa (in Finnish). Suom Lääkäri. 2006; 49–50:5184–5189.
4. Poulton A. Growth on stimulant medication; clarifying the confusion: a review. Arch Dis Child 2005;90:801–6.
5. Winterstein AG, Gerhard T, Shuster J ym. Cardiac safety of central nervous system stimulants in children and adolescents with attention-deficit/hyperactivity disorder. Pediatrics 2007;120; e1494–e1501.
6. http://www.fda.gov/ohrms/dockets/ac/06/briefing/2006-4210b_17_01_safetyreview.pdf
7. Nissen SE. ADHD drugs and cardiovascular risk. N Engl J Med 2006;354: 1445–1448.
8. Anders and Sharfstein. (Comment). N Engl J Med 2006;354:1445–1448.
9. Rappley et al. (Comment) N Engl J Med 2006;354:1445–1448.
10. Wilens TE. Stimulants and sudden death: what is a physician to do? Pediatrics 2006;118:1215–1219.
11. http://www.fda.gov/ohrms/dockets/ac/06/briefing/2006-4210b_10_01_Mosholder.pdf
12. http://www.fda.gov/ohrms/dockets/ac/06/briefing/2006-4210b_11_01_AdverseEvents.pdf
13. Ross R. Psychotic and manic-like symptoms during treatment of attention deficit hyperactivity disorder. Am J Psychiatry 2006;163:1149–1152.

Tiina Karonen
Senior Medical Officer
National Agency for Medicines

Leena Sommarberg
Researcher
National Agency for Medicines

Marja Forsell
Pharmacovigilance Co-ordinator
National Agency for Medicines

ADRs reported by pharmacists in Finland

Adverse drug reactions (ADR) have also been reported by drug dispensers, i.e. pharmacists since 2005 as stipulated in the pharmaceutical legislation reformed that year. Prior to this, the guidance only applied to drug prescribers: doctors and dentists. Sporadic reports had nevertheless been received from pharmacists even before the legislative reform. In this paper we discuss the ADR reports submitted by them to National Agency for Medicines (NAM) between 2002 and 2007 in Finland. A total of 141 reports were received from pharmacies during that period (Table 1). The 57 of these cases was classified as serious. No reports of any fatal cases were received. Adverse reactions caused by vaccines are excluded from this review.

The majority of the reports were on antimicrobials (12 in total), antiinflammatory analgesics (10), antiasthmatics (10) and antiepileptics and statins, six of each. The reports involved mostly a variety of different symptoms such as headache, dizziness, nausea and skin disorders. The major single adverse reaction reported was a rash (Table 2). As a rule, over half of the reported reactions were expected ADRs, in other words, they are already mentioned in the undesirable adverse effects section of SPC of the particular drug. No reports were received on the more recent drugs that had been on the market for less than two years.

Medical devices

Pharmacists submitted 16 reports associated with the function of medical devices and ADRs that had occurred in association with their use. The use of adrenaline auto-injector had evoked four reports of cases where the injector did not function normally. In these reports were also described the lack of efficacy, delayed therapeutic response and allergic reactions.

Four reports were received on insulin pens and pumps and six on asthma inhalators. Reports on malfunctions of insulin administration devices also referred to alterations of blood sugar levels, hyperglycaemia, hypoglycaemia and, in one case, unconsciousness associated with low blood sugar. Correspondingly, together with malfunctions of inhalators, ADRs such as exacerbations of asthmatic symptoms, lack of efficacy, dyspnoea, as well as headache, palpitations and oral or respiratory tract irritation were reported. Most of such problems are probably caused by incorrect use of the mechanical device, poor instructions for its use or poor guidance given. Table 3 contains detailed individual cases pertaining to these ADR reports.

Postcoital contraception preparations

Postcoital contraception preparations were released to the OTC sale (over-the-counter) in 2002 in

Table 1. ADR reports submitted by pharmacies each year.

<u>Year</u>	<u>Number</u>
2002	2
2003	0
2004	1
2005	9*
2006	59
2007	70

* A new Medicines Act came into force on 7.11.2005.

Table 2. The most frequently reported ADR terms. Singel case report may relate to more than one reaction.

<u>ADR</u>	<u>Number</u>
Rash	15
Lack of drug effect	11
Device failure	10
Headache	9
Erythema	7
Dizziness	6
Pruritus	6
Nausea	6
Dyspnoea	5
Cramps legs	5
Oedema legs and hands	5
Pharmaceutical product complaint	5

Table 3. *Examples of cases associated with ADR reports on medical devices.*

<u>Patient and drug</u>	<u>Adverse drug reaction</u>
1) 83-year old male Durogesic prolonged released patch	<i>An analgesic patch was twice applied to the patient, with a one day interval because it had become detached . The patient's pain became worse, and he was consequently admitted to a hospital. About a week after the event, while still in hospital, the patient noticed that the patch had again become detached and it was found in the bed. A nurse had attached the patch which had become detached. The marketing authorisation holder carried out investigations due to a suspected product defect. Nothing out of the ordinary, however, was found in the batch of drugs.</i>
2) 4-year-old female Epipen auto-injector	<i>While prick tests were being carried out the patient suffered an anaphylactic reaction. The Epipen auto-injector was placed ready for use, but it was not until after force had been applied at the third attempt that this was successful. The child returned to full consciousness. The child sat in a chair thereafter and attempts were made to administer adrenaline without success. The girl was placed in supine position, and by applying enormous force Epipen was successfully activated. The child was admitted to hospital.</i>
3) 36-year-old male Epipen auto-injector	<i>The patient was unable to activate Epipen auto-injector as required for an allergic reaction. His level of consciousness started to drop and his girl friend decided to drive him to the hospital. On the way to hospital the patient's level of consciousness dropped further, and he had for example difficulties in identifying traffic signs. Once in hospital he received appropriate treatment for an allergic reaction (including intravenous fluid balance correction and cortisone). He spent the night in hospital and made a full recovery.</i>
4) 40-year-old female Epipen auto-injector	<i>It was not until on the fourth attempt that the patient was able to activate Epipen auto-injector in response to an allergic reaction. In previous similar situations she had always succeeded on the first attempt. She recovered from breathing problems immediately when she managed to inject the adrenaline into herself.</i>
5) Female, age unknown Imigran nasal spray	<i>According to the patient, when pressure was applied the spray was too quickly exhausted after which the drug had no effect at all. She had used the same drug for years. The specific medicinal spray was sent for an examination to the marketing authorisation holder, but no explanation to support the patient's description was found. Therefore, it could be a case of incorrect use.</i>
6) Female, age unknown Novorapid injection	<i>For her insulin pump, the patient bought 4 x 10 ml Novorapid injections from the pharmacy. No problems emerged with the first two vials. On the third day she noticed, however, that there were problems with the efficacy of the insulin. She replaced the container, but her condition did not improve. Then she took a third vial of Novorapid injection from the fridge but it had no effect. She was taken in for first aid treatment due to high blood sugar concentrations (measured by herself: 33 mmol/l). At the first aid unit insulin was administered and her state returned to normal. The insulins were sent to the marketing authorisation holder, but no defects were found. The insulin had not been exposed to sunlight and it had not been frozen.</i>
7) 64-year old female Seretide diskus inhalation powder	<i>The patient noticed that her asthma inhaler did not function well and she felt that the drug was ineffective. The inhaler was sent to the marketing authorisation holder, but no defects were found.</i>
8) Male, age unknown Seretide diskus inhalation powder	<i>A non-smoking patient complained that his asthmatic symptoms were getting worse when there were ten doses left. The same had happened already three times before (all of the doses had the same batch number). The patient had suffered from asthma for years. All of the four powder inhalers were sent to the marketing authorisation holder, but no defects were detected.</i>

Table 4. ADR reports received from pharmacies, involving patients who had become pregnant despite the use according to instructions of a postcoital contraception product

Adverse drug reaction

- 1) **24-year old female** took a postcoital contraception pill (750 micrograms) within less than two days following intercourse and an other pill within about 3 days of it. When her period did not start as usual, she carried out a pregnancy test which was positive. The pregnancy was confirmed on ultrasound examination and was not terminated.
- 2) **27-year old female** took a postcoital contraception pill (750 micrograms) within 10 and 22 hours from unprotected intercourse. A pregnancy test a month later proved positive. The report was made one and a half months following the use of the pill and up until then termination of pregnancy had not been planned.
- 3) **30-year old female** took a postcoital contraception pill (1.5 milligrams) 32 hours following unprotected intercourse. Following administration of the drug the patient had no diarrhoea or vomiting. About a month after the use of the postcoital contraception product the patient carried out a pregnancy test twice, both tests being positive. Nothing is known regarding continuation of the pregnancy.
- 4) **38-year old female** took a postcoital contraception pill (1.5 milligrams) within about a day following intercourse. Despite this, she became pregnant. The patients underwent an abortion.

Finland. This is also evident in the drug consumption, as their use initially doubled and has since stabilised to reflect the level of use in 2003.

A total of five unintended pregnancies associated with the use of a postcoital contraception preparation have been reported to NAM. Four of these reports were received from pharmacies between 2002 and 2007 (Table 4), in other words only one report has been received from elsewhere than pharmacies. Evaluating by the descriptions received, postcoital contraception was carried out appropriately.

In conclusion

The number of ADRs submitted by pharmacies during the review period between 2002 and 2007 is small and does not as such enable us to draw accurate conclusions or especially make any kind of

safety comparisons between different medicinal substances. For example, in 2006 a total of 1,045 reports were received on ADRs, 59 of which, i.e. less than 6% were submitted by pharmacists. The reports submitted by them do nevertheless reflect the role of pharmacy as an important point of contact and source of information to the client especially with regard to OTC medicines such as postcoital contraception preparations and antiinflammatory analgesics. Moreover, in the case of malfunction of the medical device the patient's natural contact is the pharmacy that dispensed the drug with the device, and that is where the report of a possible malfunction or ADR will be reported.

NAM wishes to thank all those healthcare professionals who have submitted ADR reports. It is important to report any suspected ADRs, since especially rare ADRs and interactions

may not emerge until the drug is widely used and the treatment covers various patient groups. Busy pharmacists should also remember to advise their clients to discuss ADRs with their own doctors as necessary; the doctor may then also submit an ADR report. Suspected ADRs should be reported especially when the reaction is serious, it is a suspected interaction, unexpected adverse reaction, or in the case of a more recent drug that has been on the market for not more than two years, or where according to the person submitting the report the frequency of the reaction appears to have increased.