Danish Pharmacovigilance Update Year 3 #4
19 April 2012

Split and crushed tablets containing finasteride may pose a risk for pregnant and fertile women

Finasteride is a 5-α-reductase inhibitor with two different indications depending on strength.

Finasteride 1 mg (Propecia® and others) is approved for the treatment of hair loss in men, while finasteride 5 mg (Propecia® and others) is approved for the treatment of prostatic hypertrophy.

The Danish Health and Medicines Authority has received reports from pharmacies pointing out that finasteride 5 mg is sometimes prescribed in a daily dosage of 1/4 or 1/5 tablet.

Patients should be aware that tablets containing finasteride are unscored, and that the tablets are film-coated to prevent contact with the active ingredient during normal handling, provided the tablets are not crushed or broken.

Potential risk of abnormalities in male foetuses

Handling split or crushed tablets involves a risk of finasteride absorption through the skin. If pregnant women are exposed to this, there is a potential risk of malformations in male foetuses.

Also, during clinical studies, small amounts of finasteride have been recovered from the sperm in subjects receiving finasteride 5 mg/day. It is not known whether a mother's contact with sperm from a patient in treatment with finasteride may result in adverse reactions in a male foetus. When the patient's sexual partner is or might be pregnant, the patient should make every effort to ensure that his partner does not get into contact with his sperm.

Guidelines for the handling of finasteride 5 mg and 1 mg are outlined in the approved summaries of product characteristics for medicines containing finasteride.

Risk of overdose of intravenous paracetamol (Perfalgan®)

Danish Pharmacovigilance Update, April 2010, described cases of overdose of intravenous paracetamol (Perfalgan®) in infants. The overdosing was due to confusion between mg and ml, which led to accidental administration of a dose 10 times higher than prescribed. Since then, two deaths due to overdose in underweight adult patients (<50 kg) have been reported.

No deaths have been reported in Denmark.

Based on this, the European Pharmacovigilance Working Party, PhVWP, has decided to issue a DHPC (Direct Healthcare Professional Communication) letter in order to draw attention to this risk of overdose in underweight adults.

The dosing table below clearly states the maximum dose in mg/kg and the corresponding volume in ml for the different weight classes. Furthermore, the table includes a row with guidelines on doses and volumes for underweight adults with additional risk factors for liver toxicity.

Dosing Table for Perfalgan® 10 mg/ml

Patient weight	Dose per administration	Volume per administration	Maximum volume per administration based on the upper weight limit for the group (ml)*	Maximum daily dose
≤10 kg	7.5 mg/kg	0.75 ml/kg	7.5 ml	30 mg/kg
> 10 kg to ≤ 33 kg	15 mg/kg	1.5 ml/kg	49.5 ml	60 mg/kg, but not above 2 g
> 33 kg to ≤ 50 kg	15 mg/kg	1.5 ml/kg	75 ml	60 mg/kg, but not above 3 g
> 50 kg with additional risk factors for liver toxicity	1 g	100 ml	100 ml	3 g
> 50 kg and no additional risk factors for liver toxicity	1 g	100 ml	100 ml	4 g

*Patients with a lower body weight need a smaller volume. The minimum interval between each administration must be at least 4 hours. The minimum interval between each administration in patients with severe renal impairment must be at least 6 hours. The maximum number of daily doses is limited to 4.

Indication for Perfalgan®
Short-term treatment of moderate pain, especially following surgery, and short-term treatment of fever. Intravenous administration is clinically indicated when there is an urgent need to treat pain, temperature elevation, or when other routes of administration are not possible.

A European survey shows that during the period December 2003 to December 2009, 22 cases of overdose of i.v. paracetamol in infants were reported (including 19 in Europe). In all cases, the overdose was due to accidental administration of a dose 10 times higher than prescribed. Additionally, two deaths due to overdose in underweight adult patients (<50 kg) have been reported.

For further information, please read the *PhVWP monthly report from March 2012*.

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Proton-pump inhibitors and the risk of bone fracture

Based on several relatively new pharmacoepidemiological studies, the European Pharmacovigilance Working Party, PhVWP, reviewed data from clinical trials and observational studies investigating the risk of fracture with use of proton-pump inhibitors (PPIs), see references 1-13.

The PhVWP concluded that use of PPIs, especially in high doses and over a longer period of time (> 1 year) is associated with a modestly increased risk of hip, wrist or spine fractures, particularly in the elderly or in patients with other known risk factors.

Increased risk of fractures in women receiving treatment with PPIs

The majority of the trials and studies reviewed, but not all, showed an increased risk of fractures in women receiving treatment with PPIs. The size of the risk varied between the trials and studies. Also, there was a difference in adjustments in the trials and studies as regards other possible risk factors.

In general, the risk of fractures of all types was 10-40% higher in women receiving treatment with PPIs compared with women who had not used PPIs.

Patients at risk of osteoporosis should be treated according to applicable clinical guidelines to ensure an adequate intake of vitamin D and calcium.

The product information for proton-pump inhibitors will be updated with the information regarding the risk of bone fracture.

For further information, please read the *PhVWP monthly report from March 2012*.

References

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11. *Kwok CS et. al. Meta-analysis: risk of fractures with acid-suppressing medication. Bone. 2011; 48: 768-776.*
12. *Eom CS et. al. Use of acid-suppressive drugs and risk of fracture: a meta-analysis of observational studies. Ann Fam Med. 2011; 9: 257-267.*
13. *Khalili H et. al. Use of proton pump inhibitors and risk of hip fracture in relation to dietary and lifestyle factors: a prospective cohort study. BMJ. 2012 Jan 30;344:e372.*

Premature detachment of the placenta (abruptio placentae) and Zymelin®

The Danish Health and Medicines Authority has received an adverse reaction report concerning a woman in an advanced state of pregnancy (week 36 + 1) who had abruptio placentae. The foetus died in utero. The woman stated that she of her own accord, throughout the pregnancy, had taken two sprays of xylometazoline at least five times a day, using approximately two bottles (1 mg/ml) a week.

According to the adverse reaction report, the woman most likely did not have hypertension. Also, the report made no mention of other systemic adverse reactions. The adverse reaction report does not state whether the woman was taking any other medicines.

The Danish Health and Medicines Authority has received no other reports of premature detachment of the placenta for products with the active ingredients oxymetazoline* and xylometazoline. The summary of product characteristics for this product states that it should not be used in pregnant women due to its potential systemic vasoconstrictor effect.

It cannot be ruled out nor confirmed that Zymelin® may have contributed to the premature detachment of this woman's placenta.

Indication for xylometazoline
Treatment of rhinitis and sinusitis. Use for more than 10 consecutive days is not recommended, since frequent and long-term use may lead to swelling of the mucous membrane of the nose and hypersecretion due to increased sensibility in the cells ('rebound effect').

*Deregistered in Denmark.

Animal data on SSRIs and reduced sperm quality

Based on published studies (see references 1,2), the European Pharmacovigilance Working Party, PhVWP, reviewed the available data on the effect of selective serotonin receptor inhibitors (SSRIs) on sperm quality and assessed whether treatment with SSRIs may impact male fertility in humans.

In this connection, animal data showed impairment of sperm quality with all SSRIs, except for sertraline, in doses higher than those normally recommended for humans. Furthermore, there are case reports describing a negative effect of certain SSRIs on the sperm quality in humans – an effect which is reversible if the treatment is discontinued. The effect on fertility is unknown.

The product information for SSRIs will be updated with the new information

PhVWP concluded their review, recommending to update summaries of product characteristics and package leaflets of all SSRI products authorised in the EU which contain citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine or sertraline. In future, the product information, according to data available for each active ingredient respectively – must contain information stating that animal data showed impairment of sperm quality with SSRIs, that the effect on the sperm quality in humans is reversible and that impaired male fertility in humans has so far not been observed.

For further information, please read the *PhVWP monthly report from March 2012*.

References

1 *Tanrikut C, Schlegel PN. Antidepressant-associated changes in semen parameters. Urology. 2007; 69: 185.e5-7.*

2 *Safarinejad MR. Sperm DNA damage and semen quality impairment after treatment with selective serotonin reuptake inhibitors detected using semen analysis and sperm chromatin structure assay. J Urol. 2008; 180: 2124-2128.*

New contraindications and warnings for the use of Protelos® in the treatment of postmenopausal osteoporosis

Protelos® (strontium ranelate) will now be contraindicated in patients with current or previous venous thromboembolism, as well as in temporarily or permanently immobilised patients. Also, the warning regarding serious allergic skin reactions will be updated.

Based on a review of all available data on the effect and safety of Protelos®, the European Medicines Agency's Committee for Medicinal Products for Human Use, CHMP, concluded that the risk of venous thromboembolism is higher in patients with a history of venous thromboembolism, as well as in temporarily or permanently immobilised patients. The risk of venous thromboembolism is also higher in patients over 80 years of age being treated with Protelos®.

Additionally, CHMP finds that the incidence rate of serious allergic skin reactions – DRESS syndrome (Drug Rash with Eosinophilia and Systemic Symptoms), Stevens-Johnson syndrome and toxic epidermal necrolysis – is low when treating with Protelos®. But immediate discontinuation of the treatment is the key to managing these conditions successfully, and therefore patients should know about the early symptoms.

Doctors should inform about symptoms of serious allergic skin reactions

It is important that patients are informed about the risk and symptoms of serious allergic skin reactions, including that they often occur after 3-6 weeks of treatment and start with skin rash, fever, blisters or mucosal lesions, and swollen lymph glands.

In patients experiencing such symptoms the treatment should be discontinued immediately. Treatment should not be re-started in patients who have experienced serious allergic skin reactions.

For further information, please read *EMA's press release*

Danish adverse reaction reports related to Protelos®

In 2011, approx. 1900 persons in Denmark redeemed a prescription for Protelos® at least once, of which well over 600 were over 80 years of age.

The Danish Health and Medicines Authority has received a total of 31 reports of suspected adverse reactions in patients treated with Protelos®, including six serious adverse reactions. Four of these six serious reports are related to venous thromboembolism in women aged 80-95 years. The remaining two serious reports are related to a case of angiooedema and a case of drug interaction. Furthermore, there are seven cases of skin rash among the non-serious reports.

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Mesalazine (Asacol®, Pentasa®) for the treatment of ulcerative colitis, Crohn's disease and renal impairment

In February 2012, the Danish Health and Medicines Authority received an adverse reaction report concerning a patient with ulcerative colitis who developed chronic interstitial nephritis during treatment with the product Asacol®. The patient was diagnosed with ulcerative colitis in 1997 and was treated with an unspecified product up until 2007. In the period 2007-2010, the patient was treated with Asacol®. In 2010, serum creatinine levels were elevated, and later a renal biopsy showed that the patient had developed interstitial nephritis. The product was discontinued.

Five reports concerning patients who developed interstitial nephritis

The Danish Health and Medicines Authority has received a total of 17 reports relating to patients who developed renal impairment in association with taking mesalazine. Five of these reports are cases of interstitial nephritis. None of the patients had a renal disease before start-up of treatment with mesalazine.

The summary of product characteristics for mesalazine recommends to take blood samples, before start-up and during treatment with mesalazine, to determine differential count, ALT and AST, serum creatinine, and to perform a urine dipstick test. As a guideline, blood and urine tests 14 days after start-up are recommended, followed by an additional two or three tests at an interval of four weeks. If the test results are within the normal range, follow-up tests should be carried out every three months. If additional symptoms appear, blood and urine should be tested immediately.

Mesalazine should not be used in patients with renal impairment

Medicines containing mesalazine (Asacol®, Pentasa®) should not be used in patients with renal impairment. Mesalazine-induced nephrotoxicity should be suspected in patients developing renal impairment during treatment. Concomitant use of other known nephrotoxic products, such as NSAIDs and azathioprine, may increase the risk of renal impairment.

Strengthened warning against the risk associated with over-rapid increase in serum sodium in patients treated with tolvaptan (Samsca®)

Treatment with tolvaptan (Samsca®) increases serum sodium and is indicated in adult patients with hyponatraemia secondary to the syndrome of inappropriate antidiuretic hormone secretion (SIADH).

Based on reports of neurological sequelae in patients treated with tolvaptan where the correction of serum sodium exceeded the recommended rate, the product information for tolvaptan has been updated with strengthened information on the risk associated with over-rapid increase in serum sodium and how to minimise this risk.

Doctors should pay attention to the following:

- Increases in serum sodium which are too rapid can be harmful and cause osmotic demyelination, resulting in dysarthria, mutism, dysphagia, lethargy, affective changes, spastic tetraplegia, seizures, coma, or death.
- Close monitoring of serum sodium during tolvaptan treatment is recommended – especially in patients with very low serum sodium (<120 mmol/l) – when starting treatment or in patients at high risk of demyelination syndromes, e.g. patients with hypoxia, alcoholism, or malnutrition.
- Sodium correction that exceeds 6 mmol/l during the first 6 hours of administration or 8 mmol/l during the first 6-12 hours may be too rapid. In such patients, close monitoring of serum sodium and administration of hypotonic fluid is recommended.
- If the increase in serum sodium is too rapid (i.e. exceeds 12 mmol/l in 24 hours, or 18 mmol/l in 48 hours) tolvaptan treatment should be discontinued or stopped and followed by administration of hypotonic fluid.
- Co-administration of tolvaptan with medicines with a high sodium content or with other treatments for hyponatraemia is not recommended, since there is a greater risk of a rapid serum sodium correction during the first 1-2 days of the treatment due to potential additive effects.

A DHPC (Direct Healthcare Professional Communication) letter regarding the risk of too rapid increase in serum sodium in association with the use of tolvaptan was issued to relevant doctors in March.

At the earliest possible opportunity, the product information for Samsca® will be updated with the information above.

Risk of potential leaks with 5 l Physioneal Clear-Flex bags for patients on dialysis

Ten cases of leaking bags of peritoneal dialysis fluid have been reported in Denmark. The bags in question are 5 l bags of the type Physioneal Clear-Flex. The bags are used worldwide for patients on dialysis, and several countries have received reports of leaking bags.

DHPC (Direct Healthcare Professional Communication) letters have been issued to all hospitals and hospital pharmacies.

Patients and hospital staff must check the bags thoroughly
It is important that patients and hospital staff check the bags thoroughly prior to every dialysis session – as described in the patient information provided with the bags.

Pay special attention when opening the bag, as this is exactly the situation where a tear may occur.

Healthcare professionals and patients are encouraged to report leaks to the Danish Health and Medicines Authority
It is important that identified problems are reported as described in the patient information – by patients themselves or by hospital staff.

There have been no reports of an increased number of infections associated with the use of the dialysis bags.

For further information, please read the *DHPC (in Danish)*.

Annual pharmacovigilance report 2011

The Danish Health and Medicines Authority's annual pharmacovigilance report offers an insight into some of the pharmacovigilance work performed by the Authority (the former Danish Medicines Agency) in 2011. The work in 2011 was characterised by five major activities in particular:

- The initial phase for implementing the new EU legislation on pharmacovigilance
- The establishment of most of our new IT system on the handling of adverse drug reaction reports and analyses
- Adoption and initiation of a new action plan for pharmacovigilance for 2011-2013
- Evaluation of an information campaign targeted at hospital doctors and launch of an information campaign targeted at municipal nursing staff.
- Establishment of cooperation agreements with Aalborg Hospital Science and Innovation Center, Aalborg Hospital, North Denmark Region and the National Institute for Health Data and Disease Control (SSI).

You can read the entire *Annual pharmacovigilance report 2011*.

Continued strong focus on making more people report adverse reactions

The number of adverse reaction reports in 2011 was more or less identical with that for 2010, but there are, however, indications that things are moving in the right direction. The number of adverse reaction reports from the hospitals, for example, shows an increasing trend (see pages 12-16).

To further call attention to the importance of reporting adverse reactions, the Danish Health and Medicines Authority (the former Danish Medicines Agency) launched a nationwide campaign at the end of November 2011 targeted at nursing staff in all Danish municipalities. We will continue these efforts in 2012.

You can read more about the development in the number of adverse reaction reports from 2009 to 2011 in the annual report (see page 5) and about the campaign "Respond to adverse reactions – an information effort towards healthcare professionals in the care sector" (see page 20).

Focus areas in 2011 – amongst others treatment of pregnant women with antidepressants

In 2011, another main focus area for the Danish Health and Medicines Authority (the former Danish Medicines Agency) was antidepressants of the SSRI type, in particular in relation to a potential risk to the foetus and child when the medicine is used for treatment of pregnant women. The background for this was the significant increase in the consumption of antidepressants, especially of the SSRI type, witnessed in recent years. This increase in consumption also applies to pregnant women undergoing treatment, which has given cause for concern.

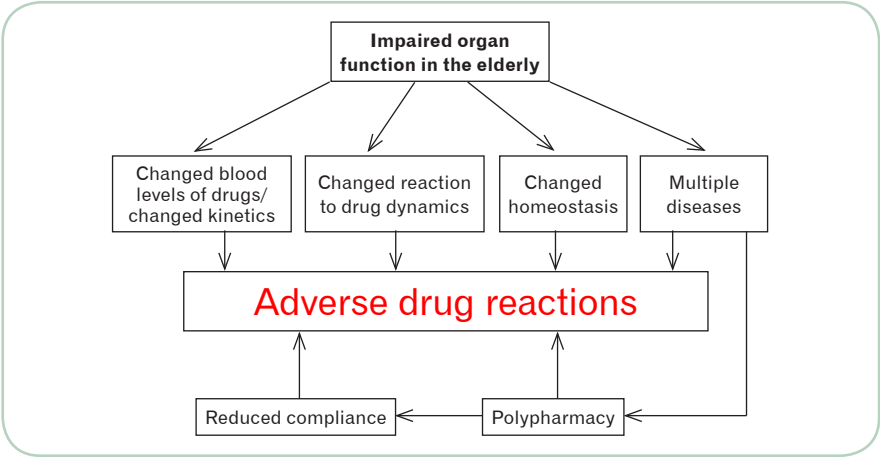
Read more about this and the other focus areas on pages 23-28 in the annual report.

Focus on medical treatment of elderly people

Elderly people are a vulnerable group with impaired organ function who have many different diseases, and they are often polymedicated. (Figure 1). In connection with EMA's (the European Medicines Agency) focused attention over the next couple of years on medicines used in the elderly (EMA's Geriatric Medicines Strategy) and the designation of 2012 as the European Year on Active Ageing and Intergenerational Solidarity, the Danish Health and Medicines Authority asked Jens-Ulrik Rosholm, Consultant, PhD, Clinical Lecturer, Department of Geriatrics, Odense University Hospital, to prepare an article with a particular focus on adverse reactions in the elderly.

You can read the article below:

Figure 1.
Factors contributing to adverse drug reactions in the elderly



Medical Treatment of Elderly People

By Jens-Ulrik Rosholm, Consultant, PhD, Clinical Lecturer, Department of Geriatrics, Odense University Hospital, Sdr. Boulevard 29, DK-5000 Odense C, Denmark, jens-ulrik.rosholm@ouh.regionsyddanmark.dk

Physiology

With age, renal and hepatic functions are reduced, which is of particular importance in relation to drug metabolism in the body. The age-related reduction in renal function must give rise to increased attention when using drugs that are fully or partially renally eliminated. In the elderly, assessing the renal function based on s-creatinine is an unsafe method due to the decreasing muscle mass. A better measure of the actual renal function is eGFR (estimated Glomerular Filtration Rate).

In addition, a certain age-related, physiological reduction in the hepatic drug elimination takes place (decreased liver mass and blood flow) including, inter alia, reduced first-pass metabolism (see reference 1). A reduction that may have an impact in the most fragile, poorly nourished patients in relation to, e.g., dosage of paracetamol (2).

Pharmacodynamic changes in the elderly are poorly described (3) and generally very complex to investigate. Increased sensitivity to the effects of drugs in the elderly, however, is well-described for benzodiazepines, psychotropics, opoids, and warfarin, but the patophysiological basis has not been established (4).

Consequences of adverse reactions

Numerous studies have documented that adverse reactions have many consequences for elderly people:

- In 1992, Hallas et al. showed that 13.3% of the acute admissions of patients to a geriatric department were drug-related (5). For medical departments the number was 8.4% (6). Later, foreign studies found similar numbers (7).
- The consequences of adverse reactions lead to many emergency room visits, among others fall-related visits (8).
- In a Swedish study of 2007 (9), an expert panel found that 3.1% of a number of random deaths were drug-related.

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Factbox 1:
Drugs that should give rise to increased attention in relation to adverse reactions

Drug	Source/Reference			Comment
	Data from DHMA (Fig. 2)	Var. statements (see text)	Empiricism/ Geriatric journals	
Antithrombotics/ due to an admittedly AC therapy		+	+	Anticoagulant therapy (AC therapy) modest risk of intracranial bleeding caused by head traumas associated with falls, but also a general risk of bleeding due to poor compliance and trouble handling the treatment correctly
NSAIDs	+	+	+	NSAIDs due to increased risk of gastrointestinal bleeding, among other things
Immunosuppressants		+	+	Prednisolone: Osteoporosis, diabetes, hypertension etc. This drug is generally causing many adverse reactions
Antidiabetics	+		+	Hypoglycaemia Note! Metformin in case of renal impairment
Psychotropics	+	+	+	May not only lead to reduced cognitive function, particularly benzodiazepines, but also to an increased risk of falls
Anticholinergics			+	Use as antispasmodics as well as for treating overactive bladder conditions - may lead to confusion
Antihypertensives and other blood pressure lowering medicines			+	Orthostatic hypotension
Digoxin			+	Cardiac arrhythmia, general condition affected
Antibacterials		+		
Thiazides			+	Hyponatraemia Note! Thiazide 'hidden' in various combination products.
Thyroid therapy	+			Nausea and various others according to reports

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In all of these studies – except for Reference 9 – the elderly were more at risk than younger people.

Which drugs?
When deciding which drugs to focus on in relation to adverse reactions, the question arises whether to look into drugs most frequently causing adverse events, or drugs causing the most serious adverse reactions.

In publications on adverse reactions and their consequences (3,5,6,7), the most frequently mentioned drugs are:

- Antirheumatics and analgesics
- Cardiotropics
- Insulin
- Antithrombotics
- Oral antidiabetics
- Psychotropics (sedatives and hypnotics, antidepressants, and benzodiazepines)
- Antineoplastics

Practically all of these drugs are also included in the Danish Health and Medicines Authority's list of drugs involved in serious adverse events (from the report of drugs involved in serious adverse events, Reference 10).

These drugs are commonly used in the elderly, and often there are no relevant alternatives with fewer adverse reactions. So the way forward is not to stop the use of these drugs, but to draw increased attention to the patient when using them.

This increased attention applies, among other things, to monitoring and thus to dosage, as several of the above-mentioned studies showed that lack of dosage adjustment for, inter alia, insulin, anticoagulant therapy or digoxin caused the adverse reaction. Based on the above, extra attention is recommended when using the drugs included in Factbox 1, which is supplemented by the further, general recommendations/warnings in geriatric journals.

Reports to the Danish Health and Medicines Authority (the former Danish Medicines Agency) in 2010
In 2010, the patients were aged 70 or over when the adverse reaction occurred, in 516 of a total of 3817 reports received by the Danish Health and Medicines Authority (the former Danish Medicines Agency). For around 84% of the reports, it was possible to extract the age of the patient at the time when the adverse reaction occurred. Each report may include several adverse reactions.
A total of 1255 adverse reactions were reported relating to elderly people over 70 years of age.

For the 70-79-year olds, a total of 353 reports (852 adverse reactions) were received, and for the group over 80 years of age, the number was 163 (403 adverse reactions). More than one drug may be suspected for a single adverse reaction. Thus, for the first age group, 904 drugs are suspected for 852 adverse reactions, and for the group over 80 years of age, 431 drugs are suspected for 403 adverse reactions.

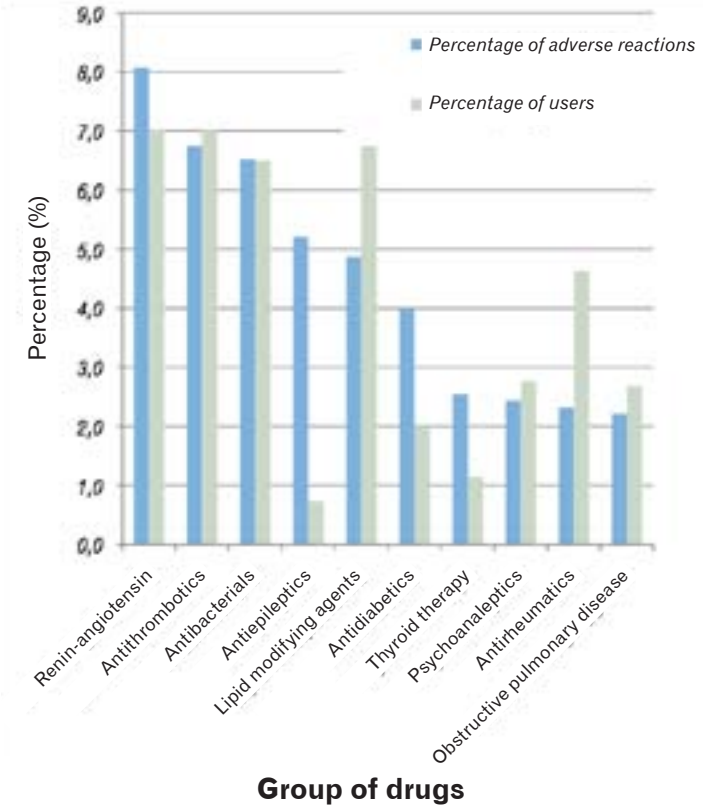

Figure 2a:
Percentage of all adverse reactions reported vs. percentage of users (2,322,717) for the 10 most frequently reported drugs with a min. sale of 90% in the primary care sector, persons aged 70-79 years (Denmark 2010).

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268 of the reports are classified as serious, i.e., they involved hospitalisation or prolonged hospitalisation, caused disability, were life-threatening, or the patient died. The 176 serious reports concern the 70-79 year-old age group, and the remaining 92 concern the age group over 80 years.

For the 70-79 year-old age group, the four organ classes most frequently involved in reports of adverse reactions are general symptoms and problems at the application site (e.g., malaise and fatigue), gastrointestinal disorders (e.g., nausea and diarrhoea), skin symptoms (e.g., itching and rash), and symptoms from the nervous system (e.g., dizziness and the nervous system).

For the age group over 80 years, the two most frequent organ classes also include general symptoms and gastrointestinal symptoms, while the third most frequent for this group is eye symptoms (e.g., decreased visual acuity and eye pain). These adverse reactions were mainly reported in association with ophthalmologicals (ATC S01). Also for this age group, symptoms from the nervous system are in the fourth place.

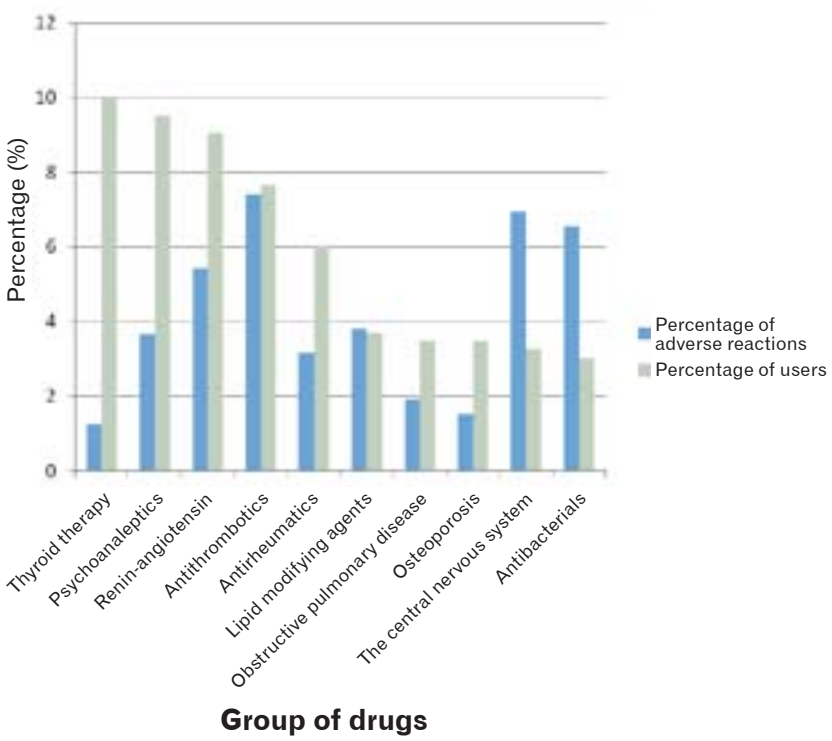

Figure 2b:
Percentage of all adverse reactions reported vs. percentage of users (1,593,002) for the 10 most frequently reported drugs with a min. sale of 90% in the primary care sector, persons aged ≥80 years (Denmark 2010).

When looking at adverse reactions reported to the Danish Health and Medicines Authority (the former Danish Medicines Agency) by product group for these age groups (Figures 2a and 2b), in the 70-79 year-old age group it can be seen that for the product groups antiepileptics, antidiabetics and thyroid agents there were disproportionately large numbers of adverse reactions reported as compared to the sales, whereas for patients ≥80 years the same applies for thyroid agents, psychoanaleptics, renin-angiotensin agents, and antirheumatics.

However, it should be noted that the reports received by the Authority are spontaneous. Therefore, inevitably, adverse reactions are under-reported. Furthermore, certain reservations were made. Please see the text under 2a and 2b.

How can the number of adverse reactions and their consequences be reduced or totally avoided? (Factbox 2)

A central element in the medical treatment of elderly people is the concern for medication errors or adverse reactions. In the elderly, many variables may affect the risk thereof.

A good geriatric principle is 'start low – go slow', i.e., start with a small dose and use slower titration.

If the patient experiences unexpected symptoms, it is important to constantly consider whether the patient's condition may be due to adverse reactions – i.e., to continue to focus attention on whether the patient is in fact receiving the right medicine.

Before initiating a medical treatment, doctors should assess the likelihood of future adverse reactions in the patient due to this treatment, if the treat-

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Factbox 2:
How to reduce the incidence of adverse reactions in elderly people:

- Base assessment of the patient not only on age, but also on the functional level (impaired organ function)
- Get an overview of the patient's medication
- Consider whether the patient's symptoms could be an adverse reaction
- Before initiating a treatment, assess whether adverse reactions may occur – if so, consider alternatives (other medicines – no medicine)
- Follow the dosage principle: start low – go slow
- Remember that adverse reactions may also occur after many years of treatment
- Use tools to review medicines used by elderly people
- And most important: Are the medicines and the patient a good match?

ment should be initiated anyway, or whether there are better alternatives.

The first step in these considerations will be to gain an overview of the patient's situation and not just base the treatment on the patient's age. Is the patient a small, fragile, multimorbid, multimedicated elderly lady with reduced organ functions, or is the patient an elderly - but not aged – quite healthy gentleman with full functionality? Although they may be of similar age, the fragile lady should be treated differently than the robust gentleman (1).

The next step is to get an overview of the patient's medication. Information from medical records, epicrises, records from the patient's family doctor, the patient's list(s) of medicines etc., will need to be combined. Also, Medicin-it.dk/Sundhed.dk may be very helpful, as these websites contain information (in Danish) about the prescription medicines redeemed at a pharmacy by the patient (you will need a digital signature). During the course of 2012, hopefully, the 'Shared Medication Record (Fælles Medicin Kort)' will be fully rolled out (11).

Using the above information, the third step is to review the list of medicines, considering the indication product by product in relation to adverse reactions, interactions, dose etc. (12). As the elderly are often polymedicated, the Danish Drug Interaction Database is a useful tool for studying interactions. It is accessed via www.interaktionsdatabasen.dk and describes approx. 2,500 interactions between different types of medicines.

Normally, adverse reactions are expected to occur in association with start of treatment, and, also, the temporal correlation is one of the strongest types of evidence to suggest that actual symptoms are caused by an adverse reaction, especially if the symptom is a well-described adverse reaction for the product in question. However, it may be difficult for an elderly person with dementia to provide valid information about the temporal correlation, and at the same time many of the common adverse reactions (nausea, fatigue, dizziness etc.) are identical to general complaints from many elderly patients. Discontinuation of the suspected drug to see whether the symptom disappears, may be a prerequisite for the final clarification of the correlation.

Treatments that were well-tolerated for many years regularly start to cause problems because the patients change with age, and the risk of adverse reactions increases. One such example is patients who received digoxin for 20 years without problems, but now are overdosed due to the age-related renal impairment or acute dehydration. Also, patients who received thiazides without problems for many years, often develop hyponatraemia with no obvious cause other than the thiazide treatment – a hyponatraemia which is quickly corrected after discontinuation of the thiazide.

The actions outlined above may seem difficult, but, luckily, there are different helpful tools available. Several instructions (13) are available from the Institute for Rational Pharmacotherapy,

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among others. At international level, the Irish START/STOPP criteria provide the best tool for review of the medicines used by an elderly patient (14). This tool includes an organ-related list of medicines that should not be used in elderly people (STOPP), and medicines they should receive (START). Also, for both lists there are considerations related to indication and the patient's "condition", as to whether the suggestions should be implemented or not. The tool is fast and user-friendly.

Unfortunately, the criteria have not yet been adapted to Danish conditions. A new version is expected to be issued in 2012. This new version will be adapted to Danish conditions.

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