Medication management and sex and gender aspects/Expert

Medication management

The starting point for medication management as a statutory pharmaceutical task is medication analysis. In this multifaceted analysis, medication-related problems are identified and individual measures are discussed with the doctor and the patient. This analysis is followed by continuous support of the patient in order to continuously follow up on the agreed measures and their results and to adjust them if necessary.

This concept has been applied for instance in Germany under the term "pharmaceutical care" in numerous studies with different chronic diseases. The proportion of female patients was mostly higher than that of male patients, which is explained by demographics and the generally higher frequency of female pharmacy visits. The consultation time for participating men was slightly higher, but did not reach statistical significance.

Supply aspects

Age- and sex/gender related analyses of drug consumption by health insurance companies consistently showed that the treatment rate and the drug prescription rate are higher among women. When looking at the groups of prescribed drugs, differences can be seen, for example, in psychotropic drugs (F>M), drugs for obstructive respiratory diseases (F>M) or lipid-lowering drugs (F>M).

Due to the higher prescription rate, significantly more drug-drug interactions have been observed in women under 79 years of age than in men. Women are more concerned about their health and go to the doctor more often and earlier than men. [1].

Especially due to the increasing complexity of pharmacotherapeutic treatment, the sex/gender aspect has been analysed in many sub-areas on the way to individualised therapy, but usually still too little attention is paid to it (see Table 1).

Table 1. Area of medicine and sex differences and related impact

Area of medicine	Sex differences	Impact	Lit.
Anaesthesia	Local anaesthetics (e.g. bupivacaine, ropivacaine)	Dosage differences	72,73,74
Dermatology	Melanoma	Aggressiveness, therapy (additional) benefits Skin protection measures	75
Infectiology	Pathogens (including MRS)	Management (AM selection, UAWs) ABS strategies	76
Cardiology	Heart attack signs Cardiovascular risk factors QTc time prolongation	Education Training, life style, treatment effectiveness Monitoring	74,77,78

Neurology	Epilepsy Multiple sclerosis Dementia/Alzheimer's disease Parkinson's disease Stroke	Therapy and side-effect management	79
Oncology	Cancer susceptibility Coping with the disease Therapy expectations Therapy effects (outcome) Tolerability (side effects)	Therapy and side-effect management	80, 90
Orthopaedics	Bone/muscle mass Cartilage mass (arthrosis	Osteoporosis, fracture risk Sarcopenia Pharmacogenic risks Prevention strategies Endoprosthetics	81, 82, 83
Pneumology	Lung volume Asthma COPD	Effect of noxious agents (smoking) Device selection Training participation	84,85
Psychiatry	Lifetime prevalence (e.g. depression, schizophrenia, pain disorders, addiction)	Therapy selection, side effects	86

Pharmacological aspects

When considering pharmacological differences, the evidence for sex/gender related aspects is greatest in the area of pharmacokinetics. The main focus is on aspects of metabolization and elimination via enzymatic processes such as cytochrome P450 (CYP) enzymes and efflux transporters such as P-*glycoprotein* (P-*gp*).[2]

The extent of the many pharmacokinetic differences between the sexes as summarised in Table 2 is mostly small (< 20 %). It becomes clinically significant when the difference exceeds 20 %. An analysis of 69 new drugs (FDA approval 09/2007 to 08/2010) showed that 73% had no sex-specific differences. Pharmacokinetic differences of less than 20 % existed in 8 % and of more than 20 % in 20 %. However, a sex-specific dose adjustment was not necessary for the drugs studied.[3]

With the diverse drug interactions, many different starting points but also questions in medication management can be derived from the respective sex/gender risk (see Table 3 and 4).

In recent years, pharmacodynamic differences have been analysed, for example in cardiovascular therapies (anticoagulation, beta-blockers, calcium channel blockers, statin therapy), pain therapy and oncology.[3,89,90]

Table 2. Pharmacokinetic parameters and impact of age and sex. M = male, F = female

Parameter	Effect of ageing	sex differences

Absorption	↓gastric secretion ↑stomach pH ↓gastrointestinal motility ↓gastrointestinal blood flow ↓AM transporter (P-gp)	Stomach pH (F: 2.59; M: 1.92) Gastric emptying speed (M > F) Oral bioavailability (F > M) Positive food effect (F > M) ADH enzyme activity (M > F)
Distribution	↓Body water ↓Muscle mass ↓Albumin ↑Body fat	Volume of distribution: lipophilic AM (F > M) hydrophilic AM (M > F) muscle mass (M > F) free drug concentration (AM-specific)
Metabolisation	↓Enzyme induction ↓Hepatic blood flow ↓ CYP activity	M: higher activity CYP 1A2, 2B6, 2D6, 2E1, thiopurine methyltransferase F: higher activity CYP 3A4
Elimination	↓ GFR ↓ Renal blood flow	Renal clearance (M > F)

Table 3. Drug interactions and sex associated risk

Targets of drug interactions		**drug-drug**	**drug-disease**	**drug-alcohol**	**drug-food**	**drug-herbs**	**drug-smoking**
pharma-kokinetic	Liberation	X			X		
	Absorption	X			X	X	
	Distribution	X					
	Metabolisation	X		X	X	X	X
	Elimination	X					
pharmacodynamic		X	X	X		X	X
Sex associated risk		F > M	F > M	M > F	F > M	F > M	M < F

Table 4. Medication management – sex related differences

Polypharmacy (> 5 medicines)	Women > Men
PIM quota	Women > Men
Side effect rate	Women > Men
Fall risks/frequency	Women > Men
Self-medication	Women > Men
Complementary medicines	Women > Men
Drug abuse	Women > Men
Oral bioavailability	Women > Men
Smoking	Women > Men
Alcohol consumption	Women < Men
Adherence with	
Chronic medication	Women < Men
Antihypertensive therapy	Women < Men

Antiosteoporotic therapy	Women > Men
Antiretroviral therapy	Women < Men
Eye drops	Women > Men
Oral cytostatic drugs (tyrosine kinase inhibitors, immunomodulatory agents)	Women = Men
Statins	Women < Men

Oncological aspects

Sex and gender differences in oncology can be seen, among other things, in cancer susceptibility, disease management, therapy expectations, therapy effects (outcome) and the tolerability of therapy (side effects).[5-9] The high proportion of complementary medicines used by women in particular can in turn lead to a higher risk of drug therapy safety.[10,11]

In the field of pharmacodynamics, the different sensitivity of pain receptors between the sexes are important in oncology, as well as mutation analyses (e.g. BRAF mutations in lung cancer, sometimes more in women), which require targeted therapy and thus certain drugs (BRAF and MEK inhibitors), and certain side effects are then expected to be more frequent in women (e.g. on the skin and eye).[12,13]

Higher rates of **side effects** in women are explained by pharmacokinetic differences. The dependence of sex on drug blood levels (AUC and/or Cmax) can be deduced from clinical trials for the newer oncologics and supportive drugs. However, these are usually not clinically relevant (e.g. AUC for nilotinib 17 percent and aprepitant 14 percent).[14]. Probably the best known example of higher side effects (severity >3) in women is the analysis for 5-fluororacil with significantly more stomatitis, leucopenias and diarrhoea.[15]

Of increasing interest are the activities of efflux transport systems (expression, genetic polymorphisms) and pharmacokinetic drug interactions, which on the one hand are compound-specific and on the other hand can show haematological side effects/toxicities.[16,17] Blood level monitoring (TDM) is currently uncommon for most TKIs and is only useful for special questions.[16]

Among the efflux transport systems, this is primarily the p-glycoprotein (ABC family). The reduction of the hepatic p-glycoprotein in women (2.4-fold) leads to a lower elimination of numerous cytostatic drugs (vinca alkaloids, docetaxel, doxorubicin, etoposide) and thus more side effects (myelosuppression, gastrointestinal toxicity).[18]

There are also relevant sex differences for some monoclonal antibodies. With the antibody bevacizumab, women have a 17 to 26 percent lower intrinsic clearance and consequently more side effects (hypertension, constipation, abdominal pain). Low clearance is also seen with cetuximab (25 %), rituximab (37 %) and ofatumumab (14 - 25 %).[19] In B-cell lymphoma, a sex-specific dose increase in men of rituximab (men 500mg/m2, women 375 mg/m2) in a phase II study resulted in an equalisation of outcomes between the sexes.[20]

Therapy-related side effects with the respective sex related risk are summarised in Table 5 for advanced tumours.[21,22] Tumour lysis syndrome as an oncological emergency occurs more in male cancer patients with cytotoxic therapy. The risk of hyperuricaemia itself is gender-dependent, especially before menopause (M>F) and then levels off postmenopausally (M=F).

Aspects of supportive therapy

Side-effect management can also increase sex-associated risks, such as QTc prolongation in women taking SSRIs and with AM combinations for nausea/vomiting (setrone). In the context of treatment with analgesics (diclofenac, COX-II inhibitors), benzodiazepines and proton pump inhibitors, no sex-associated treatment successes are known.[23]

Following the guidelines of the FDA from 2013, women should only receive half the maximum daily dose of zolpidem (Z analogues) for sleep problems, regardless of age, due to pharmacokinetic differences (distribution: water-fat ratio).[24] In March 2014, the Pharmacovigilance Risk Assessment Committee (PRAC) does not follow this gender-based dosing, but includes the increased risk of morning driving impairment in the product information, advises the lowest dose and limits the zolpidem dose to 5 mg in the elderly (> 65 years).[25] The lower risk in men is partly due to testosterone, which increases the enzymatic activity of the degrading cytochrome CYP 3A4.

Vitamin D(3) is becoming increasingly important in numerous cancers, also as a therapeutic adjuvant (e.g. multiple myeloma, breast cancer, colorectal cancer) and has a stronger immunomodulatory effect in women. Numerous active agents reduce the vitamin D blood level, including taxanes, cyclophosphamide and aromatase inhibitors.[26] Overall, only about 40 percent in the German general population have sufficient vitamin D levels.[27] Even though the studies and determinations are difficult to compare, women are more likely than men to have a sufficient vitamin D level (proportion of 25-OH-cholecalciferol > 25 nmol/l).[28]

After stem cell transplantation (SCT), the risk of bone fractures is significantly increased - eightfold in women and seven to ninefold in men. Pharmacogenic risks from high-dose steroids and altered calcium and vitamin D metabolism increase the long-term risk of fractures. Therefore, bone density should be determined before and six months after SCT.[29]

Table 5. Sex differences in therapy side effects (Advanced tumours)

Depression	Women > Men
Dysphagia	Women < Men
Dyspnoea	Women < Men
Fatigue	Women > Men
Taste changes	Women > Men
Weight loss > 10 %	Women < Men
Sleep problems	Women > Men
Pain	Women > Men
Dry mouth, mucositis	Women > Men
Nausea, vomiting, diarrhoea	Women > Men

Medication management in oncology

The longer gastrointestinal passage time in women can be an advantage in the case of intoxication, as the example of imatinib overdose shows [30], but it can also be a disadvantage due to higher plasma levels and interaction risks (drug-food) due to longer residence time in the stomach. This has consequences for the optimal intake of lapatinib - at least 60 min before a meal (also applies to erlotinib and for nilotinib even 2 h) and influences adherence [31,32]

The vast majority of postmenopausal patients have a vitamin 25(OH)D level below <30 ng/ml (78-88%) when starting therapy with aromatase inhibitors. Increasing the level (target: ≥ 40 ng/ml) can reduce musculoskeletal pain with aromatase inhibitors (OR: 0.12, CI 0.03 - 0.40).[33]

The cardiotoxicity of the anthracyclines (doxorubicin, epirubicin) and some TKIs, the oto- and nephrotoxicity of cisplatin and the neurotoxicity of ifosphamide is more pronounced in women. [34,35] Corticosteroids such as prednisolone have a shorter half-life in women. The concern for steroid side effects is greater in women, which in turn affects adherence.[36]

Antihistamines as well as setrons are more likely to cause severe cardiac side effects (arrhythmias) in women. [23] Men are more likely to show hypersensitivity reactions with rituximab.[19] Under

androgen suppression in prostate cancer, the risk of QT interval prolongation and those with concomitant QT interval-prolonging therapy or drugs that can cause torsade de pointes is increased and a benefit/risk assessment should be performed before starting therapy.[37,38,39]

Evidence-based information, for example in the form of events or written material, is necessary for the use of complementary medicines.[10] The sex aspect should also be the focus, not only for breast cancer and gynaecological tumours.

Adherence differences

Many known factors influence adherence, which can be divided into 5 types of factors: patient-related factors (such as age, sex), disease-related factors, therapy-related factors, social/economic factors and care-related factors. [32, 40] Due to the increasing oralisation of cancer therapy, the question of sex differences in adherence also arises here.[32] Suboptimal adherence to oral tyrosine kinase inhibitors (TKIs) is a key element in daily management, for example in CML therapy.[41] Recent studies have shown that TKIs and other "cytoralia" (capecitabine, temozolomide, immunomodulatory agents: lenalidomide, thalidomide) no sex-dependent adherence.[42,43,44] The focus of physicians and pharmacists should be on poorer adherence, especially with cyclical dose regimens.[42] Adherence is also greater when taken with food.[32]

An analysis of adherence in patients with metastatic cancers (breast cancer, prostate cancer) showed no sex-associated differences after 12 months of initial treatment with bisphosphonates.[45] In practice, numerous side effects, with the exception of gastrointestinal and infusion-related effects, usually occur much later and should always be the focus of the pharmacy with this group of active agents.

Aspects of musculo-skeletal diseases

Diseases of the musculo-skeletal system are among the most common chronic diseases in many countries and often require extensive care. For example, back pain, osteoporosis and rheumatoid arthritis affect women significantly more often (see Table 6). Men are primarily physiologically stronger built and thus have a better musculoskeletal starting position.[46]

Prevention strategies should focus more on known risk factors such as physical inactivity, smoking, diet and bone-damaging drugs. Awareness of risk factors is more pronounced in women than in men. This means that men in particular should also be included in the preventive options and that there should be a sex-specific orientation with regard to preventive measures. Health insurance companies have also recognised this necessity. The participation rates in behavioural preventive measures in the areas of weight reduction, healthy nutrition, stress management/relaxation and exercise are twice as high among women (20.1 %) as among men (10.9 %).[91]

Osteoporosis

The interaction of calcium and vitamin D is important for healthy bone metabolism and thus also for osteoporosis prevention. Sex-specific differences in the daily intake via diet as well as supplementation have been determined. According to the National Nutrition Survey II, more women (55%) than men (46%) fall below the recommendation for daily calcium intake (1000 mg). Women consume less vitamin D through their diet (2.2 µg/d vs. 2.9 µg/d) and are thus below the recommended intake. Women support more frequently through supplements.[47]

The effect of the vegan diet on bone health has also been discussed for some time. The vegan diet increases the fracture risk by about 30 percent compared to meat and fish eaters or vegetarians (EPIC-Oxford study). Also, 92 percent of vegans do not reach the recommended daily calcium intake of 1000 mg.[48] According to various surveys, more women than men are vegans.

The important regular review of patient medication for pharmacogenic risk drugs has been part of the S3 guideline on osteoporosis of the DVO for a very long time. Only in practice are there still some deficits here. In secondary osteoporosis, long-term use of corticosteroids is a risk factor for

fractures independent of gender.

Adherence is very low outside clinical trials, especially with oral therapy with bisphosphonates. In women, according to an Italian patient survey (n=2191, hip fractures), the treatment discontinuation rate is half lower (OR: 0.49; CI: 0.37-0.45).[49]

In the case of bisphosphonates, the risk of atypical femur fractures depends not only on the duration of therapy but also on sex. Women are significantly more at risk (RR = 3.1, CI: 1.1-8.4) than men due to lower morphological as well as biomechanical skeletal compensations.[50,51]

Rheumatoid arthritis

The lifetime prevalence of rheumatoid arthritis is sex-dependent with a higher age-dependent prevalence for women (e.g. 60-69 years: women 4.9% and men 2.9%).[52] The peak of new cases is between 55 and 64 years of age for women and 65-75 years of age for men.

There are sex-specific differences in the symptoms of the disease (pain) and in the course of the disease (remission). Women have a higher sensitivity to pain and a lower pain threshold. This has an impact on pain intensity and pain management (analgesics, corticoids). Functional capacity is also more impaired and drug treatment success is lower (type and duration of remission). Studies show higher MTX doses in women, but higher steroid doses in men.[53] In this context, the higher hepatic clearance of methylprednisolone in women (CYP 3A4 activity) should be noted. Nevertheless, women react more sensitively to glucocortiocides than men (receptor sensitivity). The focus of pharmacy should be on women's higher concern for steroid side effects, which minimises adherence.

In the context of treatment of rheumatoid arthritis with methotrexate, men take less folic acid.[54] An analysis of German health insurance data (2009-2013, N = 12,451) shows folic acid prescription in only 73 percent of MTX patients. Unfortunately, there was no sex dependent analysis. Overall, however, adherence to MTX does not seem to depend on sex.[55] The female sex shows higher MTX levels (AUC), which is explained by the lower clearance and the sex-specific carrier-mediated absorption so far.

Table 6. Sex associated differences in musculoskeletal disorders

Disease pattern/AMTS	Gender distribution	Note
Rheumatic diseases		
Arthrosis	F > M	Lifetime prevalence and risk
Fibromyalgia	F > M	
Ankylosing spondylitis	F > M	
Rheumatoide Arthritis	F > M	Testosterone has an anti-inflammatory effect
Gout	F < M	Oestrogens buffer uric acid levels
Osteoarthritis	F > M	Women have less cartilage mass
Bones/muscles		
Osteoporosis	F > M	Proportion of secondary osteoporosis: women (30%) < men (30 - 60%). Men have a higher bone mineral density
Fractures: spine, hip, distal radius	F > M	Men have "thicker" bones (cortical bone) and suffer a fracture on average 10 years later

Fractures: Midface	F < M	Different causes of fracture: Fall F:M (1:1.1) Rough offences F:M (1:12)
Mortality after osteoporotic fractures	M > F	
Sarcopenia	F > M	
Drug therapy		
Bisphosphonate side effects (atypical fractures, necrosis of the jaw)	F > M	Biomechanical capacity of the femur and limb geometry
Adherence with osteoporosis medication	F > M	

Aspects of pneumological diseases

Lung diseases are on the increase and are characterised by a decisive decrease in health-related quality of life. There are also sex differences in the frequency, impairment and severity of bronchial asthma, allergic rhinitis, bronchitis and chronic obstructive pulmonary disease (COPD).[56,57] Here again, anatomical aspects, hormones and other factors (comorbidities, smoking) play an important role in explaining the differences. The increasing lung cancer morbidity and mortality rates among women compared to the decrease among men reflect the sex-associated trends in smoking behaviour until around the turn of the millennium.[58]

In childhood asthma, more boys develop the disease up to 2 times more often than girls. This sex difference changes with increasing age. The hypersensitivity of the bronchial tract decreases in boys with age. Among adults, more women develop asthma than men.[59] The health-related quality of life in COPD is lower in women. This is already evident when looking at the sex differences in the severity of the disease symptoms (see Table 7). It is therefore not surprising that the drug effect in relation to the clinically relevant improvement in quality of life, for example in the disease-specific Saint George's Respiratory Questionnaire, is higher in women.

Table 7. COPD symptom reporting.[62]

Dyspnoea	F > M
Chronic cough	F > M
Sputum production	F < M
Depression	F > M
Anxiety	F > M
Fatigue	F > M

Therapeutic measures should focus more on the aspects of prevention and patient education in asthma, according to the Lung White Paper 2014. Regular and correct intake of medicines is also important in COPD. Adherence is determined by concerns about corticosteroid side effects. These fears are more pronounced in women.[36] Women are more prone to weight gain and bone loss (GIO).[60] Cigarette smoking has a higher "lung-destroying" effect in women as the main trigger for COPD. CYP 1A2 activity is lower in women, and thus oxidative stress from smoking metabolites is higher due to enzyme induction. Drug-smoking interactions with psychotropic drugs (clozapine, olanzapine) at the level of metabolisation (see Table 3) must be considered, especially during inpatient stays.[61]

The deposition of inhaled active substances is lower in women due to the narrower airways. This makes the correct inhalation process (head overstretched) particularly important.

The performance of the correct inhalation steps independent of the device is more sufficient in men (88 % vs. 77 %), as is the use of peak flow meters. Women hold their breath for a shorter time than men (< 10 seconds).[63,64] This aspect should be the focus of patient education, especially for the female gender. Men take up such training offers less often than women.

Outlook

The desire for sex-dependend evidence-based guidelines has existed for some time. In this way, health care can be tailored to the respective characteristics and needs of women and men and the quality of care can be improved.[65] This includes sex and gender-specific prevention strategies (e.g. use of preventive examinations). While initial progress is already noticeable in cardiology, it is lacking in many medical fields, including oncology.[66]

Differences were also found in the sex of physicians with regard to disease management, again in cardiology and oncology patients.[67,68] According to an analysis, female physicians treat patients in the hospital in a more guideline-compliant manner, with a more patient-oriented conversational style with longer style of conversation (more patient-oriented) and longer ward rounds.[69]

In order to optimally target the diagnosis and therapy of chronic diseases, it is important for personalised medicine to systematically take sex and gender into account. It is also important to link this with electronic prescription support in the practice as well as in the clinic (eAMTS) in order to come even closer to the goal of medication management according to an effective and tolerable therapy.[70]

Analyses on sex-associated adverse drug events and combinations shows the potential for further and certainly exciting AMTS assessments.[3,71]

External Links

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