Epidemiology

An estimation of patients at potential risk for drug-induced sexual dysfunction using pharmacy dispensing data

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Abstract

Background and Objectives: Adverse drug reactions on sexual functioning (sADRs) may seriously decrease a person’s quality of life. A multitude of diseases and drugs are known risk factors for sexual dysfunction. To inform patients better about these potential effects, more insight is needed on the estimated number of patients at high risk for sADRs and their characteristics.

Methods: This cross-sectional study estimated the number of patients in the Netherlands who were dispensed drugs with a potential very high risk (>10%) or high risk (1–10%) for sADRs as registered in the Summary of Product Characteristics, the official drug information text in Europe.

Results: In April 2019, 2.06% of the inhabitants of the Netherlands received drugs with >10% risk for sADRs and 7.76% with 1–10% risk. The majority of these patients had at least one additional risk factor for decreased sexual function such as high age or depression. Almost half of the patients were identified with two or more morbidities influencing sexual functioning. Paroxetine, sertraline and spironolactone were the most dispensed drugs with a potential >10% risk for sADRs. One-third of their first dispenses were not followed by a second dispense, with a higher risk of discontinuation for a decreasing number of morbidities.

Conclusion: About 1 in 11 inhabitants of the Netherlands was dispensed a drug with a potential high risk for sADRs, often with other risk factors for sexual complaints. Further research is needed whether these users actually experience sADRs, to understand its impact on multimorbid patients and to provide alternatives if needed.

Key words: Adverse drug reaction, drug database, evidence-based practice, patient-centred care, pharmacoepidemiology, sexual dysfunction.

Introduction

Sexual functioning is considered an important factor for quality of life, also for individuals with medical conditions and those who are older (1–4). The burden of sexual dysfunction can be as high as the burden of a disease, as expressed by patients with schizophrenia (5). In addition, patients with depression acknowledged low adherence to drug treatment because they associated it with sexual complaints (6). Assuming that the drug efficacy is more important than potential sexual adverse drug reactions (sADRs) may not correspond with patients’ considerations, as shown by a recent citizen petition...
that requested a serious warning for sADRs on the product labels of SSRIs and SNRIs (7). Thus, the possible impact of sADRs should be taken seriously by healthcare providers in the choice for treatment.

Patients can experience sexual complaints from various drug groups. In Europe, 346 drugs were registered with sADRs according to the Summary of Product Characteristics (SmPC) (8). SmPC-texts provide reliable drug information to healthcare professionals mainly based on registration trials. More than 10% of the trial participants had reported sADRs for 16 drugs, and 1–10% of the participants for 82 drugs. These potential risks may be different in clinical practice. Firstly, the validity and completeness of the reporting numbers might be influenced by the methods used in registration trials to gather information on non-serious ADRs such as sADRs (9). Bonierbale et al. exemplified this when they determined the prevalence of sexual dysfunction under 4557 depressed patients; 35% of the subjects reported sexual dysfunction spontaneously, whereas the prevalence doubled to 69% when a physician directly questioned the patient (10). Secondly, both patients and healthcare providers might not recognize sexual complaints as sADRs or feel a barrier to discuss sexual dysfunction (11–15). Lastly, the user of the drug may have medical conditions that hamper sexual functioning (16). This impedes to identify a drug as the cause of sexual dysfunction. In registration trials, sexual problems may be easier relatable to the drug treatment than in other clinical studies with generally more diverse and multimorbid patients. This is a reason to focus on registered sADRs when identifying potential risks of drugs to decrease sexual functioning.

The complex relations between sexual functioning, medical condition and treatment have not yet been untangled. In comparison, the risks of isolated morbidities on sexual dysfunction are already widely described (16). With the growing number of multimorbid persons, more insight is needed on the possible interactions between medical conditions, drug treatment and sexual function. As a first step to understand the influence of drug treatment, this study aimed to estimate the number of patients in the Netherlands that use drugs with a potential high risk for sADRs according to their SmPC leaflet.

**Methods**

**Design**

This cross-sectional study identified user numbers of drugs with a potential high risk for sADRs with pharmacy dispensing data from community-dwelling patients, a method that has been applied before (17,18).

**Source of drug dispensing data**

In the Netherlands, the Foundation for Pharmaceutical Statistics collects drug dispensing data from ~95% of community pharmacies (19). Within these pharmacies, dispensing data are aggregated on patient level. For each patient, information on the year of birth and sex are accessible. Drugs are specified by the Anatomic, Chemical, Therapeutic (ATC) classification system (20), drug formulation and number of units dispensed. Additional information is available on the dispensing date, the specialism of the prescriber (e.g. General Practitioner (GP)) and the prescribed daily dose, as registered in the computerized pharmacy system. No information is collected on diagnoses.

**Inclusion of community pharmacies**

To assess repeat dispensing of first prescriptions, community pharmacies were eligible that had supplied a complete data history of 14 months. Conventionally, first dispensing are defined as a dispensing without a previous dispensing within the prior 12 months and a notification for a first dispensing fee as registered in the community pharmacy (21). In the Netherlands, first dispensing for drugs with separate entities for daily use generally covers a period of 14 days. This enables pharmacists to evaluate patients’ experiences, reconsider treatment choices with prescribers and avoid medication waste. Thus, to establish whether a dispensing in the observation month was a first dispensing and whether it was followed by a second dispensing during the remaining days in the observation month or subsequent month, a history of 12 months prior, and 1 month after the observation month was needed. Correspondingly, pharmacies with complete data from March 2018 to May 2019 were included.

**Patient selection**

From eligible community pharmacies, those patients were selected who used at least one drug with a high risk for sADRs during the observation month. In previous research, 16 drugs with a potential >10% (very high) risk and 82 drugs with 1–10% (high) risk as registered in the SmPC were collected and adopted for this study (8). For spironolactone and cyproterone, the registered risk for sADRs was lower for females (1–10%) than males (>10%). Thus, user numbers for these drugs were counted as >10% risk for sADRs for males and 1–10% risk for females.

**Data collection**

**Data aggregation on patient level**

Data of community pharmacies was collected on patient level. Patients were followed for dispensings from different community pharmacies, which contributed to the validity of the results. A trusted third party aggregated different patient codes for one patient who visited multiple pharmacies, to one anonymous identification number for each patient.

**Observation period**

An observation period of 1 month was chosen because 1 month was considered as a reasonable time period to assume that dispensed drugs available within this period were used concomitantly. April 2019 was the most recent month at start of data collection. Additionally, the month April was likely to resemble

### Key Messages

- In the Netherlands, 1 in 11 persons are at risk for sexual adverse drug reactions (sADRs).
- Additional risk factors such as age, comorbidity and co-medication are common.
- One-third of first dispenses of drugs with very high risk were discontinued.
- Physicians and pharmacists should be alert for sADRs.
usual patterns for chronic drug use and was not likely to be influenced by different dispensing behaviors due to holidays or end of year drug storage.

Periods of drug use
Drug use during the observation month could result from dispensing during the observation month and from earlier dispensing, if according to the amount of dispensed units and the prescribed daily dose, the amount of the earlier dispensing included use during the observation month (21). If the prescribed daily dose was not registered in the pharmacy system (circa 6% of dispenses), the period of use was standardized to 1 day. For each patient, multiple high-risk drugs with a period of use during the observation month were calculated as in concomitant use.

Selection of morbidities
Morbidities that might decrease sexual function were identified for each patient. As the dispensing database did not include information on diagnosis, comorbidities were estimated by corresponding drug use. Morbidities that might decrease sexual function according to literature (16) and could be identified by specific drug use were the following: depression (ATC code: N06A), diabetes (A10), lower urinary tract symptoms (G04BD), cardiovascular diseases (C02, C03, C07, C08, C09 and C10), epilepsy (N03), hypothyroidism (H03AA) and COPD or asthma (R03). Patients were labelled for morbidity if they received at least three dispensing of a relevant drug during the last 12 months of data available. Two of the possible morbidities are also the main indication of very high-risk (>10%) drugs: three drugs are antidepressants and one is used in treatment for cardiovascular diseases.

Drug discontinuation
Of the drugs with >10% risk for sADRs, only paroxetine, sertraline, clomipramine and spironolactone are generally used daily, for a longer period of time and eligible for a first dispensing of 14 days. Therefore, only for these drugs discontinuation rates were calculated. First dispenses were considered discontinued, if there was no follow-up dispensing until the end of the post-measurement month, May 2019.

Data analysis
Patient numbers were calculated for drug use with a potential >1% risk for sADRs in the observation month together with information on age, sex, first dispensing of >10% risk drugs, concomitant use of drugs with >1% risk for sADRs and morbidities as described above.

To estimate the proportion of drug users with a potential high risk for sADR, patient numbers were first extrapolated to the amount of all 1996 community pharmacies in the Netherlands (2019) and then divided by the population number for April, 2019 from the Statistics Netherlands’ database (22).

Multivariate logistic regression was performed to identify risk factors for discontinuation of paroxetine, sertraline, clomipramine and spironolactone after first dispenses. The following variables were included as potential risk factors: age, sex, comorbidity and co-medication with 1–10% or >10% risk for sADR. Analysis was performed with IBM Corp SPSS statistics, Chicago, IL, USA, version 26.

Ethical approval of the study protocol
The board of the Dutch Foundation of Pharmaceutical Statistics approved the use of their data for this research. Data from pharmacies and patients were coded and anonymized before analyses. Use of observational data in descriptive retrospective studies in the Netherlands is not considered as an interventional trial according to Directive 2001/20/EC and Dutch legislation (23). Therefore, the study protocol did not need approval by a medical ethic committee.

Results
Data were available from 1782 (91%) community pharmacies in the Netherlands. During the month of April 2019, drugs with very high (>10%) risk for sADRs were dispensed to 318 821 patients and drugs with a high risk (1–10%) for sADRs to 1 198 754 patients (see Table 1). About 1.7% of users was <18 years old. When extrapolating to all 1996 community pharmacies in the Netherlands (19), there were 1 614 934 users of drugs with >1% risk for sADRs. Compared with a population number of 17 306 978, the user numbers of drugs with >10% and 1–10% risk correspond with 2.06% and 7.76% of the inhabitants of the Netherlands, respectively (22).

Table 1. Population in the Netherlands at risk to endure reduced sexual functioning from a sADR in April, 2019

| Users (%) of NL | FD (%) | Age (µ) | Female (%) | Proportions with morbidity known to affect sexual functioning as identified by specific drug use (%) | DM | DP | CV | LUTS | EP | HT | AS/CO | ≥2 mor |
|----------------|--------|---------|------------|--------------------------------|----|----|------|-------|----|----|-------|-------|
| Drugs with >10% risk for sADR | 318 821 (2.06%) | 3.2 | 58.3 (SD = 17) | 52.2 | 12.4 | 66.6 | 48.0 | 2.1 | 5.9 | 6.1 | 11.3 | 43.9 |
| Drugs with 1–10% risk for sADR | 1 198 754 (7.76%) | NA | 58.7 (SD = 19) | 55.8 | 12.6 | 41.4 | 50.6 | 2.5 | 10.2 | 6.0 | 11.4 | 38.3 |
| Drugs with >1% risk for sADR | 1 441 790 (9.33%) | NA | 58.5 (SD = 19) | 55.6 |

AS/CO, Asthma or COPD; CV, cardiovascular diseases; DM, diabetes mellitus; DP, depression; LUTS, lower urinary tract symptoms; EP, epilepsy; FD, first dispense; HT, hypothyroidism; NA, not available; NL, The Netherlands; ≥2 mor, proportion of users with two or more morbidities.

*These numbers were generated with data from 1782 community pharmacies in the Netherlands (91% of all community pharmacies in the Netherlands).

Percentages of the population of the Netherlands were calculated by extrapolation to all community pharmacies in the Netherlands and divided by a population number of 17 306 978 (April 2019) from the Statistics Netherlands’ database.
Patients that received a drug with >10% risk for sADRs had a mean age of 58.3 years and 52.2% were female. More than half of these patients were treated for depression (66.6%) or cardiovascular diseases (48.0%). Almost half were treated for more than one medical condition (43.9%). Without the users of spironolactone 37.8% of the patients were treated for cardiovascular diseases. Similarly 14.8% of the patients were treated for depression when adjusted for the antidepressants registered with >10% risk for sADRs. About a quarter of drug users with a potential >10% risk for sADRs was dispensed another drug with at least a >1% potential risk for sADRs during the observation month: 23.8% for an additional drug with high risk and 2.23% for an additional drug with a very high risk for sADRs. The users of two or more drugs with >10% risk for sADRs most often combined olanzapine with sertraline (22.7% of the combinations) or paroxetine (18.9%), see Table 2.

In Table 3, patient characteristics that may contribute to decreased sexual functioning are shown for each drug with >10% risk for sADRs. Of these, paroxetine, sertraline and spironolactone were dispensed most. The majority of paroxetine users was female (69.1%), with a mean age of 58.8 years, and almost half of the paroxetine users was also treated for cardiovascular disease (43.2%). Users of spironolactone were older (mean 71.2 years) and a quarter concomitantly used drugs with 1–10% risk for sADRs. Moreover, one in four patients who received spironolactone was labelled for diabetes comorbidity. Half of the users of paroxetine and spironolactone were identified with more than one medical condition associated with sexual complaints, of which 14.2% of the paroxetine users and 18.7% of the paroxetine users for two or more additional medical conditions besides cardiovascular diseases or depression.

During the observation month, 3.2% of drug users with very high risk for sADRs received a first dispensing. The proportion of first users was highest for lynestrenol (67.5%). First dispenses of the antidepressants, lynestrenol and terazosin were mainly prescribed by GPs. About 36.2% of the patients with a first dispense for antidepressants and 29.9% of first-time spironolactone users did not receive a second dispense. Logistic regression showed an increased risk for discontinuation for a decreasing number of comorbidities (Table 4). The risk to discontinue an antidepressant was decreased by a higher number of concomitant drugs in use with high risk for sADRs.

### Discussion

In this cross-sectional study, almost 10% of the population in the Netherlands received drugs with a (very) high risk for sADRs. This equals on an average per pharmacy, 179 users of drugs with >10% risk for sADRs and 673 users with 1–10% risk for sADRs. Per pharmacy, five to six patients started with a drug with >10% risk for sADRs in 1 month. Additional risk factors for decreased sexual function were common. For example, one of every three users of antidepressants was treated for cardiovascular disease. Since antidepressants have rated sADRs as ‘difficult to live with’ (6), prescribers and pharmacists should be more alert for sADRs in almost 1 in 10 of their patients, often on top of other risk factors for decreased sexual functioning.

To our knowledge, this is the first study that estimated the number of persons at potential risk to experience sexual complaints as an adverse drug event. Morbidity affecting sexual functioning were present in 4 of 10 users of drugs with >1% risk for sADRs. Moreover, we found that one in three first dispenses of paroxetine, sertraline, clomipramine and spironolactone were not continued. Earlier, Holvast et al. showed that, with pharmacy dispensing data in the Netherlands, 10% of antidepressant users (ATC: N06A) discontinued therapy within a comparable period (the first four weeks) (24). Also based on pharmacy dispensing data, Alfan et al. reported that 18% of diabetes patients in the North of the Netherlands stopped their cardiovascular drug treatment (ATC: C03, C07, C08 and C09) within the first year (25).

Compared with both studies, our analysis was more specific, focusing on spironolactone and antidepressants that are registered with >10% risk for sADRs. Compared with the longer observation period of Alfan et al., our discontinuation rates after first dispense were already considerably higher. Reasons for these high rates should be further explored.

Unexpectedly, in our study more morbidity decreased the risk for treatment cessation. For the antidepressants, additional drug use with 1–10% risk for sADRs also contributed to a lower risk of stopping. Similarly, Holvast et al. reported that antidepressants users were less likely to stop treatment with increasing numbers of drugs (24). Possibly, patients who already suffer from medical conditions were more willing or accustomed to taking chronic medication and thus less likely to stop. Also, if decreased sexual function was already present due to another disease or treatment, additional sADRs might be considered less important.

In comparison, Appa et al. showed a linear relationship between the number of morbidities and low sexual desire [OR 1.10 (CI 1.03–1.18)] in 1997 women over 40 years old (26). In their study population, 72% had two or more chronic morbidities. For each additional morbidity, the risk of reporting sexual problems such as difficulty with arousal, lubrication, orgasm or pain during intercourse increased with 10–16% (26). Thus, future research should clarify to what extent the experience of sADRs depends on comorbidities and
concomitant drug use and if the linear relationship found by Appa et al. also applies for the number of high-risk drugs or a combination of medical risk factors. With the assumption that more medical risk factors such as smoking, physical activity, or mental or cultural factors such as arthritis or end-stage renal disease are likely to contribute to patients experiencing decreased sexual functioning, but cannot be identified from drug dispensing. This also applies for diabetes, hypertension and depression do not always require drug indication for eight anti-diabetic drugs, two anti-epileptic drugs and nine drugs targeting cardiovascular diseases, but the influence on the proportions detected was regarded as limited. Moreover, medical conditions such as arthritis or end-stage renal disease are likely to contribute to patients experiencing decreased sexual functioning, but cannot be identified from drug dispensing. This also applies for risk factors such as smoking, physical activity, or mental or cultural characteristics.

Importantly, we relied on SmPC-information for the quantification of drug users with a potential high risk for sADRs. In clinical practice, also drugs that are not registered with high risk for sADRs were reported to decrease sexual functioning, e.g. beta-blockers (28). ADRs in the SmPC are reported during registration trials with generally more healthy and homogenous patients. Nevertheless, by evaluating only drugs registered with a high risk, a drug's potential evaluation only drugs registered with a high risk, a drug's potential

| Table 3 | Characteristics of users of drugs with very high risk for sexual adverse drug reactions (>10%) in the Netherlands in April, 2019 |
|---------|--------------------------------------------------------------------------------------------------|
| Age     | Female (%) | 1–10% dispenses (%) | Female dispenses (%) | Discharges of all other drugs (%) | Gender (%) |
| (µ)     | (%)        | (%)                  | (%)                | (%)                             |            |
| DM      | DP         | CV                  | LUTS               | EP                              | AS/CO      |
| 55.6    | 68.5       | 19.5                | 1.7 (63.5)         | 9.0                             | 94.9       |
| 58.8    | 69.0       | 15.5                | 1.0 (86.9)         | 9.5                             | 95.2       |
| 48.7    | 67.4       | 23.9                | 3.3 (52.5)         | 6.9                             | 93.8       |
| 58.7    | 68.3       | 29.2                | 1.3 (50.4)         | 12.5                            | 96.5       |
| 71.2    | –          | 27.7                | 3.4 (25.6)         | 30.0                            | 79.9       |
| 71.2    | –          | 27.7                | 3.4 (25.6)         | 30.0                            | 79.9       |
| 52.7    | 47.4       | 42.8                | 3.7 (27.8)         | 9.2                             | 46.6       |
| 52.7    | 47.4       | 42.8                | 3.7 (27.8)         | 9.2                             | 46.8       |
| 59.3    | 49.5       | 48.3                | 0.6 (0.0)          | 15.3                            | 50.5       |
| 61.9    | 34.8       | 25.2                | 7.1 (5.2)          | 8.9                             | 6.0        |
| 44.9    | 74.2       | 17.9                | 25.7 (81.9)        | 5.0                             | 9.9        |
| 37.5    | 99.2       | 11.9                | 67.5 (86.8)        | 2.9                             | 9.2        |
| 66.1    | –          | 35.9                | 5.8 (10.0)         | 11.5                            | 11.8       |
| 73.5    | 1.8        | 34.1                | 5.5 (17.0)         | 17.0                            | 9.7        |
| 73.7    | 1.2        | 34.6                | 5.7 (14.3)         | 17.1                            | 9.8        |
| 70.7    | 7.8        | 28.8                | 2.8 (77.8)         | 16.3                            | 8.7        |
| –       | –          | –                   | –                  | –                               | –          |

AS/CO, Asthma or COPD; CV, cardiovascular diseases; DM, diabetes mellitus; DP, depression; EP, epilepsy; FD, first dispense; GP, amount of first dispenses prescribed by a GP; HT, hypothyroidism; LUTS, lower urinary tract symptoms.

A morbidity is indicated with at least three dispensing of the corresponding drug class during 12 months. 
Total user number is lesser than the sum of the users of the separate drugs due to combined use of these drugs.
This drug is used as treatment for this morbidity and therefore approaches 100%.
Spironolactone and cyproterone are registered with >10% risk for sADRs for men and 1–10% risk for women. For this reason, female users of spironolactone and/or cyproterone were excluded for the analysis of the characteristics of spironolactone and cyproterone users.
Though not indicated for LUTS, silodosin is indicated for benign prostatic hyperplasia associated with LUTS.
Table 4. Influence of patient characteristics on discontinuation after first dispense of paroxetine, sertraline, clomipramine and spironolactone in the Netherlands (April 2019)

| Age | 1.01 (1.01 – 1.01) | 0.98 (0.98 – 0.99) |
| --- | --- | --- |
| Female sex | 0.99 (0.86–1.14) | NAa |
| Number of comorbiditiesb | 0.82 (0.73–0.92) | 0.79 (0.68–0.92) |
| Number of drugs with 1–10% risk for sADR | 0.81 (0.72–0.91) | 0.99 (0.83–1.18) |
| Number of other drugs with >10% risk for sADR | 0.72 (0.48–1.07) | 0.84 (0.44–1.62) |

Results are shown as odds ratio (95% confidence interval), statistically significant results are printed in bold; Stop after FD, the proportion of users that discontinued drug treatment after receiving a first dispense of one of these drugs in April, 2019; NA, not available.

| | Antidepressants | Spironolactone |
| --- | --- | --- |
| Age | Stop after FD = 36.2% | Stop after FD = 29.9% |
| Female sex | 0.99 (0.83–1.18) | NAa |
| Number of comorbiditiesb | 0.82 (0.73–0.92) | 0.79 (0.68–0.92) |
| Number of drugs with 1–10% risk for sADR | 0.81 (0.72–0.91) | 0.99 (0.83–1.18) |
| Number of other drugs with >10% risk for sADR | 0.72 (0.48–1.07) | 0.84 (0.44–1.62) |

Conclusion
This study showed that 1 in 11 inhabitants of the Netherlands used drugs with a (very) high risk for sADRs according to their registration files. The majority of these patients had additional risk factors for sexual dysfunction such as high age, depression and comorbidities of other drugs with high risk for sADRs. One-third of patients with antidepressants or spironolactone did not continue their treatment with a second dispense. More research is needed on patients’ actual experience of sADRs and the consequences for their drug adherence and quality of life. In the meantime, physicians and pharmacists should be alert to patients experiencing sexual dysfunction, especially those with a high risk for sADRs.

Declaration
Funding: none.
Ethical approval: not necessary, see method.
Conflict of interest: none declared.

References
1. Flynn KE, Lin L, Bruner DW et al. Sexual satisfaction and the importance of sexual health to quality of life throughout the life course of U.S. adults. J Sex Med 2016; 13(11): 1642–50.
2. de Boer MK, Castelein S, Wiersma D, Schoevers RA, Kneptgering H. The facts about sexual (dis)function in schizophrenia: an overview of clinically relevant findings. Schizophr Bull 2015; 41(3): 674–86.
3. Merghati-Khoei E, Pirak A, Yazdikhasti M, Rezasoltani P. Sexuality and elderly with chronic diseases: a review of the existing literature. J Res Med Sci 2016; 21: 136.
4. Gott M, Hinchliff S. How important is sex in later life? The views of older people. Soc Sci Med 2003; 56(8): 1617–28.
5. Finn SE, Bailey JM, Schultz RT, Faber R. Subjective utility ratings of neuroleptics in treating schizophrenia. Psychol Med 1990; 20(4): 843–8.
6. Ashton AK, Jamerson BD, L. Weinstein W, Wagoner C. Antidepressant-related adverse effects impacting treatment compliance: results of a patient survey. Curr Ther Res Clin Exp 2003; 66(2): 96–106.
7. Healy D. Citizen petition: sexual side effects of SSRIs and SNRIs. Int J Risk Saf Med 2018; 29(3–4): 135–47.
8. Gordijn R, Teichert M, Nicolai MPJ, Elzevier HW, Ghuchelaar HJ. Adverse drug reactions on sexual functioning: a systematic overview. Drug Discov Today 2019; 24(3): 890–7.
9. Reichenpfader U, Gartlehner G, Morgan LC et al. Sexual dysfunction associated with second-generation antidepressants in patients with major depressive disorder: results from a systematic review with network meta-analysis. Drug Saf 2014; 37(1): 19–31.
25. Alfian SD, Denig P, Coelho A, Hak E. Pharmacy-based predictors of non-adherence, non-persistence and reinitiation of antihypertensive drugs among patients on oral diabetes drugs in the Netherlands. *PLoS One* 2019; 14(11): e0225390.

26. Appa AA, Creasman J, Brown JS et al. The impact of multimorbidity on sexual function in middle-aged and older women: beyond the single disease perspective. *J Sex Med* 2014; 11(11): 2744–55.

27. Kuipers E, Wensing M, De Smet PAGM, Teichert M. Considerations of prescribers and pharmacists for the use of non-selective β-blockers in asthma and COPD patients: an explorative study. *J Eval Clin Pract* 2018; 24(2): 396–402.

28. Nicolai MP, Liem SS, Both S et al. A review of the positive and negative effects of cardiovascular drugs on sexual function: a proposed table for use in clinical practice. *Neth Heart J* 2014; 22(1): 11–9.