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Perceived sensitivity to medicines: a study among chronic medicine users in Norway

--Manuscript Draft--

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Abstract:	Background Little is known about patients' Perceived Sensitivity to Medicines (PSM), "the belief that one is especially sensitive to the actions and side effects of medicines". Objective i) To explore the extent of and factors associated with high PSM in a Norwegian population of chronic medicine users; ii) to assess the psychometric characteristics of the PSM. Setting Community pharmacies in the Oslo area, Norway. Method A cross-sectional, questionnaire-based study was conducted between October 2015 and January 2016. Patients filling prescriptions for chronic disorders were recruited. Main outcome measure Perceived sensitivity to medicines. Results The study population included 214 patients (response rate 36.7%). In total 20.1% of the patients reported low, 61.7% moderate and 18.2% high perceived sensitivity to medicines. Factors positively associated with high PSM were female gender (Adjusted Odds Ratio (aOR) 5.33, 95% CI 1.52 to 18.72, $p < 0.001$) and having a non-native language (aOR 4.76, 95% CI 1.48 to 15.30, $p < 0.001$); lower educational level (aOR 0.43, 95% CI 0.17 to 1.07, $p < 0.001$) and using generic medicines (aOR 0.12, 95% CI 0.03 to 0.57, $p < 0.001$) were negatively associated with high PSM. There was no association between PSM and the number of prescription medicines taken. The Norwegian version of the PSM demonstrated good psychometric characteristics. Conclusion Almost one out of five patients in this study reported high sensitivity to medicines. Female gender, having a non-native language, lower educational level and using generic medicines were important factors related to PSM. Health care providers should be aware of the impact negative expectations about medicines can have on health behaviors and treatment outcomes, and seek to elicit and address patients' beliefs about their personal sensitivity to medicines. Implications on practice

	•The PSM scale could be easily administered in a community setting, and it can serve as a discussion tool to elicit and address negative treatment expectations. •Health care providers should be aware that many patients believe that they are particularly sensitive to the effects of medicines, and that this is related to treatment side effects and use of generic medicines. •Regulatory agencies and other stakeholders should take the nocebo effect into consideration when developing counselling guidelines on generic medicine use.
Response to Reviewers:	We thank the Editors and the Reviewers for the opportunity to revise our manuscript and for the valuable feedback provided. We have tried to address and implement in the revised manuscript all comments rose by the Reviewers. To facilitate readability, we have split some of the comments, and numbered them within each Reviewer. Our replies to each individual comment are provided below and numbered accordingly. EDITOR'S SPECIFIC COMMENTS: Comment 1: Key words- Key words not indicative enough, particulary 'generic medicine' please adapt. Reply 1: We have now indicated more indicative keywords. These are: perceived sensitivity to medicines, nocebo, beliefs about medicines, side effects, pharmaceutical schema, generic substitution. Comment 2: Define PSM in the abstract as well. Reply 2: PSM is now defined in the abstract as well. Reviewer 1 Comment 1: You have quite a lot of data (table 1); i assume this kind of questionnaire / inventarisation took a lot of time from the patient ! please comment Reply 1: We agree that the questionnaire was extensive. The scope was to gain an in-depth understanding of the patients' medicine and health behaviours. Of course a downside is that it might have been time consuming for the patients. Indeed, multiple patients declined to participate in the study because of lack of time, as already acknowledged in the limitation. We have now amended the Limitation section, which reads: "The main reason given for declining was lack of time to complete the questionnaire, which was estimated to take about 15-20 minutes". However, it is important to acknowledge that we did not encounter substantial missing data in the responses. So, we believe that for those patients that participated in the study, the length of the questionnaire was probably not a concern. From an ethical standpoint, we have attempted to maximize the amount of data collected in the study, so that patients did not use their time unnecessarily. Comment 2: i'm not a specialist in statistics, so cannot give feedback on it Reply 2: Thank you for pointing this out. Comment 3: in the abstract: "sociodemographic and health behaviors were important factors" this is very generalising ; please specify in accordance with your findings Reply 3: Thank you for this remark. We have now amended the Abstract accordingly, as follows: "Female gender, having a non-native language, lower educational level and using generic medicines were important factors related to PSM." Comment 4: line 46: "a member of the research team, assisting patients" this is a possible source of bias! make a remark on it in the discussion part Reply 4: Thank you for this remark. This is indeed an important concern to acknowledge. A research team member was available to assist patients in completing the questionnaire, but this solely applied to technical support in what questions to answer/ways of answering (i.e., multiple choice answers, versus free-text). In view of this, the risk that the team member might have impacted the responses from the study participants is likely to be minimal. It is also important to highlight that the team member could not influence in any way on the PSM level reported by patients, since that had to be computed over summing up different question scores. Since PSM was our main outcome variable, we feel that the risk of bias in relation to the PSM prevalence and associated risk factors is likely to be minimal. However, we have now made this potential Limitation clearer, as follows: "The research team member could

solely provide technical supports to patients, i.e. where to fill out; thus, the risk of bias due to the team member influence on patients' responses is likely to be minimal."

Comment 5: line 58-59: you clarify the cut-off of PSM only in line 227-228 ; you should do it here.
Reply 5: This is been clarified.

Comment 6: line 67: looking for a version of BMQ-general, I find different versions and subscales (only harm and overuse); specify (in an appendix, like you do in box 1 for PMS) what questionnaire you have used
Reply 6: Thank you for this remark. The study by Prof Horne cited in our manuscript1, indeed relates to the original BMQ-General (named BMQ-G8) which comprises two 4-item factors assessing "harm" and "overuse". However, the BMQ-G12 also exists, which comprises a further 4 items general benefit scale assessing more positive views on medicines. See the paper by Wei et al.2 where the three BMQ factors (harm, overuse, benefit) were examined. Citation to this work has now been added to the manuscript. In the Methods section, we have stated "Patients' beliefs about medicines were explored via the 12-item Beliefs About Medicines in General Questionnaire (BMQ-General) [11], which comprises three subscales (4 items each): Harm, Overuse and Benefit". Since the main outcome variable of the work is the PSM (and not the BMQ) we prefer to present a box only for the PSM.

Comment 7: line 95: aiding with a list is another possible bias, you should mention it ; besides: just reporting some kind of experience does not mean there is a causal relation !
Reply 7: Thank you for this comment. We respectfully disagree with the reviewer that aiding recall to respondents is a source of bias. The converse, i.e. lack of aid to enhance recall, may introduce a greater risk of bias by misclassifying patients as "adverse event free", when in fact they did experience side effects. Low specificity can introduce greater bias than low sensitivity. We listed the side effects most commonly reported within the nocebo effect phenomenon, as stated in the Methods: "selected according to prior literature [15]". It has been established that patients report more symptoms/side effects e.g. in clinical trials when they are specifically asked about them, and this practice is likely to enhance the quality and completeness of data about possible side effects.

We did not assume any casual relation between exposure to a medicine and a specific side effect, and the question posed to patients in this regard was not meant to disentangle causal adverse drug effects. Our aim was to measure individual patient past experience with side effects, and relate this measure to the PSM level. Indeed, in our Discussion we call for future studies investigating the relation between PSM-side effects more closely. However, this association has also been identified by other studies in different population.3,4 To make this point clearer in the manuscript, we have now rephrased these symptoms as "suspected side effects". We have reworded to describe the list of side effects as 'a brief questionnaire' that participants were asked to complete, and that participants were further able to use free-text entry to provide additional information. This reads as follows: "Patients were asked about suspected side effects that they had experienced following the use of any medicine. Patients were asked to complete a brief questionnaire consisting of a list of ten commonly reported side effects (e.g., muscle pain, nausea, dizziness), selected according to prior literature [15]. For each side effect, patients were asked whether they had every experienced it (Yes/No), and were also able to make comments via free-text entry. The number of suspected side effects was then summed".

Comment 8: line 96-97: double
Reply 8: Thank you for notifying us. This has now been corrected.
Comment 9: line 122: i am no expert in statistics, but I do not understand why item 4 is excluded
Reply 9: Item 4 in the PSM scale measures if a patient has experienced side effects previously; "I have had a bad reaction to medicines in the past". So, the item 4 of the PSM and self-reported side effects measure overlapping concepts. By including item 4 in this analysis, we may have encountered collinearity because the two variables measures similar concepts. In the Methods we have stated the rationale for excluding item 4, as follows: "To test the robustness of the correlation with PSM and number of

reported side effects, item 4 was excluded".
Comment 10: line 193-194: i do not understand this: what is this concept ? a pharmaceutical schema is a list of medication (with specifications) ?
Reply 10: Thank you for your comment. In this context, a pharmaceutical schema is not a list of medications. Instead, it is a concept used in health psychology for understanding how people are organizing/structuring their beliefs and ideas about medicines which often are linked to their medication taking behaviour. E.g. if you have very negative pharmaceutical schema you might be very negative to medicines and instead more likely to use herbal remedies. We have now made this explicit in the main text, as follows: "This is often referred to as the concept of pharmaceutical schema: a pattern of beliefs about pharmaceuticals". For a more detailed reading see "Handbook of Health Psychology by Tracey A. Revenson, Regan A. R. Gurung – 2018".
Comment 11: line 203-204: you state that PSM presents a useful measure of ... i'm not convinced, see it more as some kind of possible indicator ; what about sensitivity and specificity ? please comment on it
Reply 11: Thank you for this remark. We agree to rephrase "measure" with the word "indicator". With respect to specificity and sensitivity, that is a challenging question to address in observational settings. Assessing whether patients with high PSM are truly cases experiencing a nocebo can probably be doable only in an experimental setting, where patients are blindly randomized to placebo vs a drug of interest. To the best of our knowledge, we could not retrieve information on sensitivity/specificity of PSM in the literature. However, as discussed in the manuscript, the PSM has been shown to have good psychometric properties: "Yet, this PSM version demonstrated good psychometric characteristics, and a criterion-related validity in the range and similar direction as previously described [2, 4, 5]".

Comment 12: table 2: the SD are rather extending ; does this not influence your conclusions ?
Reply 12: We did a priori power calculation, and stated this in the Methods: "We required a sample size of 246 patients to detect a 20% prevalence of high PSM with a precision of ±5% [5]." To the best of our knowledge, the SDs provided in Table 2 are not so large to invalidate our analyses. They simply reflect the variability of responses to the individual items of the PSM.

Reviewer 3:
Comment 1: This article addresses a topic which could be of general interest to curiosity driven readers within the clinical pharmacy community. It is not likely, at this stage of development, to have an impact on practice or patient outcomes. The big gap in the work relates to what does having a high score in the perceived sensitivity to medicines scale actually lead to within the population studied. This reviewer was surprised that a questionnaire like the MARS was not also included in the research to check if the self-reported sensitivity score was linked to self-reported changes in medication use behaviour. This gap makes the paper largely of academic interest only.
Reply 1: Thank you for your remark. We have added this limitation, which reads: "The study did not measure medication adherence and its association to PSM, as done in prior research".
No prior study has examined the extent of high PSM in patients in Norway. Because of this gap in the literature, the current study aimed to quantify this prevalence data, and patients' factor associated with higher PSM. Because of the exploratory nature of this study, we opted to not measure medication adherence for multiple reasons: 1) we expected to recruit mainly "prevalent users" of chronic medications rather than "new users" patients, and this could in turn affect our association measures with medication adherence; 2) we aimed to recruit about 250 patients with varying chronic diseases, and so we did not expect to have sufficient statistical power for conducting medication-specific analysis. Analysing medication adherence for any medication/treatment of any chronic disease would have been of little clinical value. Despite this limitation, we believe that our results are of clinical relevance and utility. Indeed, we measured and explored other patients' health behaviours (e.g., preference to generic switch, side effect reporting).
Comment 2: Specific comments
1. In the abstract, need to explain what the PSM measures. The term sensitivity could have a wide range of meanings which could be interpreted differently by different readers who are not familiar with the instrument.
Reply 2: PSM has now been defined in the abstract.

Comment 3: Although obviously not the case in Norway according to the paper, in some other countries patients will often not be aware that they have been dispensed a generic medicine, branded generic or the originator branded medicine. This point should be made clear in the introduction. There could be a particular issue with branded generics.
Reply 3: Thank you for this observation. We have now addressed this concern in the Limitation section (rather than in the Introduction), which reads: “In Norway patients are aware that they are being dispensed a generic medicine, which may not be the case in other countries. Thus, our observed negative association between taking generics and high PSM may not be of relevance in countries where patients are unaware of the dispensed medicine type (i.e., whether it is a generic medicine, a branded generic, or a branded medicine)”.

Comment 4: The nocebo effect should be explained more fully in the introduction.
Reply 4: We have added more information on the nocebo effect in the introduction, which now reads: “The placebo-nocebo phenomenon can help to better understand a treatment and how the words affect our brain. As a consequence the nocebo effect can reduce the potential effectiveness of and adherence to a prescribed treatment [6]”.

Comment 5: Unclear what 'symbolic gift card drawing' actually is and whether this was an actual tangible incentive to participate in the study.
Reply 5: Patients taking part in the study could take part in a lottery; a randomly chosen patient could receive a gift card for the value of 108 euro. This value of the gift card was not considered as a tangible incentive to participate by the research team, as well as by the Ethics Committee that examined the ethical integrity of our study. We have now made this clearer in the Methods, by stating the monetary value of the gift card: “Patients could participate in a symbolic (about 100 euro) gift card drawing”
Comment 6: A member of the research team was available in the pharmacies to assist patients filling out questionnaires. Need to make it clear if there was a standardised protocol related to what assistance could actually be given. It is usually not acceptable to help patients to interpret questions they are unsure of the meaning of, since the researcher's interpretation may differ from the interpretation of the general public (i.e. those who do not seek assistance).
Reply 6: Please see reply no. 4 to Reviewer 1.

Comment 7: The desired sample size was not achieved. This is common in studies of this type, but in this case the researchers came very close to achieving the desired sample size. Unclear why some additional effort was not made to close this gap to make the study more complete.
Reply 7: We agree with the Reviewer that we should have achieved a larger sample, so that we could have reached a total of 250 patients after applying various exclusion criteria. However, the resources we had available for this project were limited, and so we could not recruit more patients.

Comment 8: I was unable to find Figure 1 in the online system.
Reply 8: We regret Figure 1 could not be seen in the submission system. We have now uploaded again Figure 1.

Comment 9: The authors suggest that since side-effects in the past explains about 20% of the PSM variance that this suggests that patients with high PSM hold negative expectations about treatments which contributes to the nocebo effect. The following piece on adherence mixes up actual side-effects and the expectation of side effects. I find this section very subjective and some redrafting is recommended.
Reply 9: We have rephrased slightly the passage, as follows: “These findings may suggest that patients with high self-reported PSM hold negative expectations about treatments, which could in turn trigger a nocebo effect. Likewise, it is also possible that negative past experiences with medicines may shape perceptions of medicine sensitivity”. We are trying to interpret the results of the study and possible explanations of these. We hope the added tone of uncertainty to the text makes the passage less subjective.

Comment 10: The fact that there was no association between perceived sensitivity and the number of prescription medicines taken is an important finding and should be

highlighted in the abstract.
Reply 10: Thank you, this result was added into the Abstract, as follows: “There was no association between PSM and the number of prescription medicines taken”.

Comment 11: The PSM focuses on increased sensitivity to medicines. It does not have any focus on decreased sensitivity, i.e. requiring a higher dose than normal to achieve the 'population norm' effect. There is no corresponding question on whether 'my body under-reacts to medicines'. It should be made clear throughout the paper that it is self-reported, increased sensitivity to medicines that is being discussed.
Reply 11: We have now tried to make this clearer throughout the manuscript, and added the following in the Aims: “The study focuses solely on increased perceived sensitivity to medicines”.

Comment 12: It appears from the findings that non-native Norwegians are more likely to have tertiary education. Does that map on to the actual situation in Norway
Reply 12: We did not report on the association between non-native language and educational level. The passage in lines 218-220 in the Discussion is interpreting two independent associations, i.e. of sole education and sole non-native language in relation to high PSM. To avoid confusion, we have now omitted part of the sentence, as follows: “Patients with high school education were less likely to report sensitivity to medicines...”

Comment 13: Box 1 does not add anything to paper since all details are available in a results table.
Reply 13: Thank you. We would like to keep box 1 to facilitate clarity of the outcome measure used in the study.

References
1.Horne R, Weinman J, Hankins M. The beliefs about medicines questionnaire: the development and evaluation of a new method for assessing the cognitive representation of medication. Psychol Health. 1999;14(1):1-24.
2.Wei L, Champman S, Li X, et al. Beliefs about medicines and non-adherence in patients with stroke, diabetes mellitus and rheumatoid arthritis: a cross-sectional study in China. BMJ open. 2017;7(10):e017293.
3.Faasse K, Grey A, Horne R, Petrie KJ. High perceived sensitivity to medicines is associated with higher medical care utilisation, increased symptom reporting and greater information-seeking about medication. Pharmacoepidemiol Drug Saf. 2015.
4.Horne R, Faasse K, Cooper V, et al. The perceived sensitivity to medicines (PSM) scale: an evaluation of validity and reliability. Br J Health Psychol. 2013;18(1):18-30.

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Submission of manuscript

Dear Editor-in-Chief,

We would like to submit our revised manuscript entitled **"Perceived sensitivity to medicines: a study among chronic medicine users in Norway"** as a research article in the *International Journal of Clinical Pharmacy*.

We have tried to address all concerns raised by the Editor and the Reviewers. We hope you will find the revised manuscript suitable for publication.

All authors contributed to the publication, are aware of the submission of the revised manuscript, and agree with it. Neither this manuscript, nor any similar manuscript is under review or consideration for publication elsewhere. We also want to declare that we have no conflict of interest regarding the content of this manuscript.

We look forward to hearing from you at your earliest convenience.

On behalf of all authors,

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Perceived sensitivity to medicines: a study among chronic medicine users in Norway

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Perceived sensitivity to medicines: a study among chronic medicine users in Norway

Introduction

Patients' beliefs and attitudes towards medicines are important drivers of health behaviors. Studies have consistently shown that these factors are strongly associated with patients' decisions about whether to start and/or continue a needed treatment [1-4]. Patients' beliefs about medicines may also be highly related to the expectations about the effect of a pharmacological treatment, in terms of effectiveness and/or potential side effects. In 2013 Horne *et al*. developed a five-item scale to measure patients' perceived sensitivity to medicines (PSM), defined as "the belief that one is especially sensitive to the actions and side effects of medicines" [2]. Despite the importance of understanding factors impacting patients' medicine taking behavior, little is known about patients' increased sensitivity to medicines. To date, only one study has explored the prevalence of PSM [5], and found it to be as high as 16% in the general population of New Zealand [5].

Side effects might be related to a known pharmacological or physiological mechanism, they can also be non-specific and driven by the nocebo effect, where negative expectations about a treatment – rather than active ingredients – cause side effects [6]. The nocebo effect is the less well known counterpart of the placebo effect [7]. The placebo-nocebo phenomenon can help to better understand a treatment and how the words affect our brain. As a consequence, the nocebo effect can reduce the potential effectiveness of and adherence to a prescribed treatment [6]. For example, Faasse *et al*, found a relationship between high PSM and increased symptom reporting compared with people who did not view themselves as sensitive to medicines [5]. Similarly, Horne *et al.* found that high PSM predicted elevated symptom reporting after vaccination (r=0.26) [2]. Moreover, other studies have shown that cancer patients who hold negative treatment expectations are more likely to experience unpleasant side effects [8, 9]. It is not yet understood how patients using medicines for chronic disorders perceive their own sensitivity to medicines, and what correlates are associated with high PSM.

Aim of the study

This study aimed to i) to explore the extent of and factors associated with high PSM in a Norwegian population of chronic medicine users, ii) and to assess the psychometric characteristics of the PSM in this population. The study focuses solely on increased perceived sensitivity to medicines.

Ethics approval

Ethics approval was received by the Norwegian Regional Committees for Medical and Health Research Ethics. The study was reported to the Data Protection Official at the Norwegian Centre for Research Data. Patient gave written informed consent and data were anonymized. Patients could participate in a symbolic (about 100 euro) gift card drawing.

Methods

Study design and data collection

This was a cross-sectional study conducted between October 2015 and January 2016 in three community pharmacies located in different areas of Oslo, Norway. Inclusion criteria were age over 18 years, understanding the Norwegian language, and filling a prescription to treat a self-reported chronic disorder (e.g. asthma). All patients filling a prescription were invited to participate in the study. Recruitment took place during different opening hours. Data were collected through a self-administered structured questionnaire. One member of the research team was available at the recruitment sites to answer questions and assist patients in filling out the questionnaires in a separate information room in the pharmacy. The questionnaire was first piloted. Data from the pilot were not included in the analysis. We required a sample size of 246 patients to detect a 20% prevalence of high PSM with a precision of ±5% [5].

Measures

Our outcome variable was patients' perceived sensitivity to medicines, measured via the validated psychometric instrument PSM [2]. The PSM is a structured, self-reported sensitivity measure with a satisfactory internal consistency (Cronbach's alpha) of 0.79–0.94 [2, 4, 5]. The PSM scale consists of five items (see Box 1) [2]; patients indicated their degree of agreement with each statement on a 5-point Likert scale (1=strongly disagree to 5=strongly agree).

Individual item scores were added, giving a total score of 5-25. A higher score indicates a greater increased sensitivity to medicines. The PSM score was then categorized into three groups: low (5-9), moderate (10-15) and high (16-25) PSM, based on a previous study [5]. Because previous research found no relevant differences between participants with low and moderate PSM scores, these groups were combined in some of the current analyses [5]. The translation from English (original version) to Norwegian, and the back-translation were done by two independent native speakers. Discrepancy between the two English versions was settled by discussion between the two translators. (See Appendix A for the translated version).

Patients' beliefs about medicines were explored via the 12-item Beliefs About Medicines in General Questionnaire (BMQ-General) [10, 11], which comprises three subscales (4 items each): Harm, Overuse and Benefit. BMQ-General was used to test the psychometric characteristics of the PSM-scale [2]. Patients indicated their degree of agreement with each statement on a 5-point Likert scale (1=strongly disagree to 5=strongly agree). Individual item scores were added, giving a total score of 4-20 for each subscale. Higher scores indicate stronger beliefs in the concepts represented by the subscale. The belief variables were used as continuous in the analysis. A validated Norwegian version of the BMQ-General was used [12].

Patients were asked to self-report which prescription medicine(s) they were dispensed at the pharmacy on the same day of recruitment into the study, by answering the question "Which medicine(s) have you been dispensed today"? Patients could report as free-text entry the name of each medicine, along with information whether this was a treatment for a chronic condition, and whether it was a generic (Yes/No). Based on this information, we estimated how many generics were dispensed at the pharmacy out of all prescriptions filled, and corrected this estimate by the availability of a generic option, using the Norwegian Medicine Agency as reference [13]. The generic variable was then divided into three groups: no generic use (even though there was an available generic option), using $< 75\%$ generic medicines, using $\geq 75\%$ generic medicines. Patients having no generic use option were grouped separately. The cut off was pragmatically chosen to provide equal group sizes. Patients were also questioned about any other medicine use via the question "Do you use other medicines (over-the-counter (OTC), e.g. paracetamol, or other prescription medicines)?" If yes, patients could report as free-text entry the name of the

other medicines, whether it was OTC or prescription, and frequency of use. All recorded medicines were coded into the corresponding Anatomical Therapeutic Chemical (ATC) codes in accordance with the World Health Organization ATC index [14]. The number of medicines regularly taken was calculated.

Patients were asked about suspected side effects that they had experienced following the use of any medicine. Patients were asked to complete a brief questionnaire consisting of a list of ten commonly reported side effects (e.g., muscle pain, nausea, dizziness), selected according to prior literature [15]. For each side effect, patients were asked whether they had every experienced it (Yes/No), and were also able to make comments via free-text entry. The number of suspected side effects was then summed.

Patients reported the number of visits they had made to their GP in the previous year (0, 1-2, 3-5, >5, cannot remember), whether they were currently using vitamins and/or supplements (Yes/No/Cannot remember) and if yes, which ones. The total number of all reported vitamins and supplements was also assessed and summed. Information about patient information leaflet (PIL) reading before starting a new medicine was collected.

Patients sociodemographics included gender, age, native language, marital status, annual household income, level of education, and health-related education or a family member with health education (categorized as in Table 1). We assessed the study's external validity by comparing the distribution of age and gender in the sample with that of the Norwegian general population filling specific prescriptions in 2015 in Oslo (via the Norwegian Prescription Database) (Appendix B).

Statistical analyses

The Pearson chi-square and the Student's t-test were used to compare proportions and mean scores between independent groups, respectively. The psychometric characteristics of the PSM were assessed by measuring the extent of completion (%, acceptability), the internal consistency (Cronbach's alpha), and the PSM correlation with a) three BMQ-general subscales, and b) number of reported side effects c) total number of generics [2]. The Pearson and Spearman

correlation coefficients were used to relate the BMQ-general subscales with number of reported side effects and generics. This was done to test if PSM is a related, but a separate domain from BMQ. A p-value of <0.05 was considered statistically significant. To test the robustness of the correlation with PSM and number of reported side effects, item 4 was excluded.

Univariate and multivariate generalized estimation equations (GEE) with a binomial distribution (high versus moderate/low PSM) was fit to account for clustering within the reported chronic disorders [16]. The multivariate model was built after fitting the univariate model for all explanatory variables. Purposeful selection of candidate variables was done based on a univariate p-value<0.20. We fitted a reduced model by removing variables having no role (p-value>0.05) or yielding a change smaller than 15% in the beta coefficients of the retained variables [17]. A listwise deletion approach was applied. Data are presented as crude (OR) and adjusted odds ratios (aOR) with 95% confidence intervals (CI). As a sensitivity analysis a regular multivariate logistic model was carried out. All statistical analyses were performed using SPSS 22.0 (SPSS Inc., Chicago, IL, USA).

Results

The study included 218 chronic medicines users (response rate 36.7%) of which four were excluded, because of missing values on the PSM. This resulted in a final sample of 214 patients. The sample characteristics and the reported chronic disorders by PSM level are presented in Table 1 and Appendix C, respectively. Overall, 60.7% of participants were women and mean age was 62.3 years (SD: 15.2; range: 23-93 years). On average the patients used 5.7 regular medicines (SD: 2.7; range: 2-16), and 1.5 supplements (SD: 1.4; range: 1-7).

Table 2 outlines the degree of agreement with each individual PSM item. In the sample, the total PSM mean score was 12.2 (SD: 3.9; median 12) (Appendix D). On the basis of the PSM, 20.1% of the patients presented low perceived sensitivity to medicines, 61.7% moderate and 18.2% high (Appendix E). Patients with high PSM more often reported experiencing side effects such as dizziness, headache, constipation compared to patients with low/moderate PSM (Fig. 1).

The crude and adjusted results are presented in Table 3. Four factors were found to be independently associated with high PSM. Specifically, women or patients with a native language other than Norwegian had about 5-fold increased odds of having high PSM compared with men or native Norwegians. Acceptance of some generic substitution was associated with lower perceived sensitivity to medicines, and patients with high school education were less likely to view themselves as highly sensitive to medicines when compared to those with tertiary education. Similar association measures and overlapping confidence intervals were found in regular logistic analysis (results not shown).

The PSM was acceptable (98.2% completion), and with good internal consistency (Cronbach's alpha: 0.83. The PSM correlated negatively with the BMQ-benefit ($r=-0.22$; $p=0.001$), and total numbers of generics ($r=-0.14$; $p=0.038$). The PSM correlated positively with the BMQ-harm ($r=0.27$; $p<0.001$), BMQ-overuse ($r=0.22$; $p=0.002$), reported side effects ($r=0.46$; $p<0.001$; item 4 excluded: $r=0.39$; $p<0.001$). There was no significant correlation between any of the BMQ subscales and number of reported side effects. BMQ-overuse correlated negatively with numbers of generics ($r=-0.18$; $p<0.009$).

Discussion

In this study, almost one out of five patients had high self-reported PSM, and one out of two reported experiencing side effects to medicines in the past. High perceived sensitivity appears to be a common belief among Norwegian medicine users, and our estimate (18.2%) was similar to that observed in the general population in New Zealand (15.8%) [5]. The number of experienced side effects could explain about 20% of the PSM variance. These findings may suggest that patients with high self-reported PSM hold negative expectations about treatments, which could in turn trigger a nocebo effect. Likewise, it is also possible that negative past experiences with medicines may shape perceptions of medicine sensitivity. Regardless of the direction of this relationship, both negative expectations and the experience of unpleasant side effects can make patients reluctant to start or continue an otherwise beneficial and necessary treatment, as well as contributing to poor adherence [1, 2, 5, 18]. There is growing evidence that expecting side effects, makes them significantly more likely to occur [8, 19]. Indeed, patients have been found

to report similar rates of many side effects independent of being in the treatment or placebo control group, even in randomized controlled trials [5, 20, 21].

Three findings from the current study point to PSM being part of a more general network of negative beliefs about medicines, and not just a specific response to an unpleasant medicine experience. First, PSM scores were negatively correlated with beliefs about the broad benefits of medicines, and positively correlated with perceptions of medicines as being harmful and overused. Second, there was no association between perceived sensitivity and the number of prescription medicines that patients reported taking. Third, while 54.2% of respondents reported having a bad reaction to medicines in the past, only 20.6% endorsed the idea that their body was very sensitive to medicines. These findings indicate that experience of poor reactions to medicines, alone, are not sufficient to generate the perception of heightened sensitivity. We propose that the perception of high personal sensitivity to medicines may contribute to a vicious cycle, in which negative expectations (high PSM) contribute to the experience of more treatment side effects via the nocebo effect, which further reinforces perceived sensitivity. This is often referred to as the concept of pharmaceutical schema: a pattern of beliefs about pharmaceuticals [10, 22, 23].

A key finding is that patients who accepted generic substitution were less likely to be categorized as having high PSM compared to users of branded drugs alone (59-88% odds reduction). This association supports a link between a belief (PSM), and an objectively assessed behavioral outcome (use of generic medicines). Patients often state that generics are not an equal alternative to branded drugs [24]. Brand name medicines may offer a sense of reassurance and a promise of efficacy and safety to already concerned patients [25]. Patients' trust in and willingness to use generic medicines varies, and depends on both sociodemographic factors as well as attitudes, beliefs, and experiences [26]. Thus, the PSM presents a useful indicator of general side effect expectations, which is conceptually related to both nocebo effects and generic medicine use [2, 26].

Gender, immigrant status, and educational level, were the sole patients' characteristics independently associated with high PSM. This battery of correlates can however aid health care

providers in the identification of patients at risk of high sensitivity to medicines. Women viewed themselves as more sensitive to medicines compared to men, as identified in earlier studies [5, 18]. The established gender differences in pharmacokinetics and pharmacodynamics, health behavior and physical symptom reporting, may not entirely explain the association between PSM and gender [27-29]. It is possible that females are more inclined to information seeking [30-32], including information about possible treatment side effects [33]. Patients with high school education were less likely to report sensitivity to medicines. Less educated people appear to be less likely to seek health information [34] or ask questions during medical encounters [35]. It might be that that less information about side effects may have a 'protective' effect on some patients. The results of the current study parallel the finding that parents with lower levels of education held more positive views of vaccination [36].

One strength of this study is the focus on patients taking medicines for chronic disorders, an important group of the population in relation to perceived sensitivity to medicines and the reporting of adjusted measures of association with PSM. The PSM scale has been previously validated although this study was the first utilizing the Norwegian version of the PSM [2]. Yet, this PSM version demonstrated good psychometric characteristics, and a criterion-related validity in the range and similar direction as previously described [2, 4, 5]. The PSM cut-off scores are not validated, instead based on a previous study [5]. Further, all items on the PSM scale are negatively worded, which can influence participant responding. One notable limitation is the low response rate (36.7%). The main reason given for declining was lack of time to complete the questionnaire, which was estimated to take about 15-20 minutes. The proportion of patients within some subgroups, such as non-Norwegian native language, was low. Another limitation is the cross-sectional nature of the study: we cannot establish whether high perceived sensitivity resulted in more side effects, or the converse. Patients filling a prescription were randomly asked to participate in the study, however we cannot rule out the possibility of selection bias. The study did not measure medication adherence and its association to PSM, as done in prior research [2]. The research team member could solely provide technical supports to patients, i.e. where to fill out; thus, the risk of bias due to the team member influence on patients' responses is likely to be minimal. In Norway patients are aware that they are being dispensed a generic medicine, which may not be the case in other countries. Thus, our observed negative

association between taking generics and high PSM may not be of relevance in countries where patients are unaware of the dispensed medicine type (i.e., whether it is a generic medicine, a branded generic, or a branded medicine). Recruitment took place only in the capital of Norway; thus extrapolation of our finding to the general Norwegian population of medicine users should be done keeping these limitations in mind. Nevertheless, the characteristics of the sample were similar to those of the general prescription fillers in Oslo as regards age and gender. The precision of detecting high PSM in our sample is +/-6.0%. Still, our findings must be interpreted with these limitations in mind.

Conclusion

In this Norwegian population of patients using medicines for chronic disorders, almost one out of five patients had a high self-reported perceived sensitivity to medicines, and the Norwegian PSM version presented good validity. The factors positively associated with high PSM were female gender and having a non-native language; lower educational level and using generic medicines were negatively associated with high PSM. These findings points to the need for greater awareness about patient perceptions of their personal sensitivity to medicines among health care providers.

Conflicts of interest

No conflict of interest.

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Table 1. Frequency of background characteristics of the study population, according to level of perceived sensitivity to medicines (PSM).

	Low/moderate PSM (n=175)	**High PSM (n=39)**	**Total (n=214)**
Gender n (%)			
Female***	97 (55.4)	33 (84.6)	130 (60.7)
Age (years) mean ± SD	63.1; 15.3	58.7; 14.3	62.3; 15.2
Native language n (%)			
Norwegian	147 (84.0)	29 (74.4)	176 (82.2)
Other	26 (14.9)	10 (25.6)	36 (16.8)
Marital status n (%)			
Married or cohabiting	100 (57.1)	22 (56.4)	122 (57.0)
Other†	75 (42.9)	17 (43.6)	92 (43.0)
Annual income for the household (€)‡* n (%)			
Low	47 (29.9)	11 (28.2)	58 (27.1)
Medium	59 (33.7)	16 (41.0)	75 (35.0)
High	51 (29.1)	8 (20.5)	59 (27.6)
Educational level§* n (%)			
High school	81 (46.3)	16 (41.0)	97 (45.3)
University/College	63 (36.0)	21 (53.8)	84 (39.3)
Other education	30 (17.1)	2 (5.1)	32 (15.0)
Health-related education* n (%)			
Yes	39 (22.3)	14 (35.9)	53 (24.8)
No	132 (75.4)	22 (56.4)	154 (72.0)
I do not know	4 (2.3)	3 (7.7)	7 (3.3)
Family member with health-related education n (%)			
Yes	62 (35.4)	21 (53.8)	83 (38.8)
No	111 (63.4)	18 (46.2)	129 (60.3)
I do not know	2 (1.1)		2 (0.1)
Number of regular medicines taken m ± SD	5.9; 2.7	5.3; 2.8	5.7; 2.7
Use of OTC n (%)			
No	99 (56.6)	24 (61.5)	123 (57.5)
Yes	76 (43.4)	15 (38.5)	91 (42.5)
Number of supplements taken m ± SD	1.4; 1.4	1.7; 1.6	1.5; 1.4
Generic substitution¶ n (%)			
No	52 (29.7)	17 (43.6)	69 (32.2)
< 75%	49 (28.0)	5 (12.8)	54 (25.2)
≥ 75%	49 (28.0)	11 (28.2)	60 (28.0)
Patient information leaflet reading n (%)**			
Never/sometimes	86 (49.1)	10 (25.6)	96 (44.9)
Always	89 (50.9)	29 (74.4)	118 (55.1)
GP visits in a year n (%)			
0-2	49 (28.0)	10 (25.6)	59 (27.6)
3-5	68 (38.9)	15 (38.5)	83 (38.8)
>5	51 (29.1)	12 (30.8)	63 (29.4)

Cannot remember	7 (4.0)	2 (5.1)	9 (4.2)

Numbers do not add up due to missing numbers. Missing values were < 4 % for all variables, except annual income (n=22; 10.3%).

*< 0.05; **≤ 0.01 ***≤ 0.001

†: Single, divorced or other.

‡: If one was married or registered partnership and had total income: <43 057 or 43 057 -64 478€, was categorized as low income; 64 586-86 006 € you were categorized as medium income; >86 114€ you were categorized as high income. If you were divorced/ widow/widower/not married or other and had total income: < 43 057€ you were categorized as medium income; > 43 057€ you were categorized as high income. 1 Euro= 9.29 NOK, annual exchange rate for 2016.[10]

§: High school education indicates secondary education with 9-12 years of education, and also education other than tertiary.

¶: The generic variable was then divided into three groups: no generic use (even though there was an available generic brand), using < 75% generic medicines, using ≥ 75% generic medicines. Patients with no choice of a generic substitution n=34 (14.2%).

Table 2. Mean (±SD) and median for the Perceived Sensitivity to Medicines (PSM) scale of individual items and numbers and percentages of individuals who agreed disagreed with the items (n=214).

Item	Mean (SD)	Strongly disagree	Disagree	Neither agree or disagree	Agree	Strongly agree
		n (%)	n (%)	n (%)	n (%)	n (%)
My body is very sensitive to medicines	2.5 (1.1)	25 (11.7)	107 (50.0)	38 (17.8)	31 (14.5)	13 (6.1)
My body overacts to medicines	2.2 (0.9)	34 (15.9)	129 (60.3)	32 (15.0)	15 (7.0)	4 (1.9)
I usually have a stronger reaction to medicines than most people I know	2.0 (0.9)	55 (25.7)	115 (53.7)	30 (14.0)	9 (4.2)	5 (2.3)
I have had a bad reaction to medicines in the past	3.2 (1.2)	21 (9.8)	51 (23.8)	26 (12.1)	101 (47.2)	15 (7.0)
Even small amounts of medicine can upset my body	2.2 (1.0)	46 (21.5)	108 (50.5)	34 (15.9)	20 (9.3)	6 (2.8)

Table 3: Prediction model of factors associated with high Perceived Sensitivity to Medicines PSM (n=214).

	Model 1[†]		Model 2[‡]	
	OR	**95% CI**	**OR**	**95% CI**
Gender				
Male	1		1	
Female	**4.42**	**1.76-11.09**	**5.33**	**1.52-18.72**
Age (years)[§]	0.98	0.96-1.00		
Native language				
Norwegian	1		1	
Others	1.95	0.85-4.48	**4.76**	**1.48-15.30**
Marital status				
Married/registered partnership	1			
Other	1.03	0.51-2.08		
Household income[¶]				
Medium	1			
Low	0.86	0.37-2.04		
High	0.58	0.23-1.46		
Educational level[Ī]				
University/College	1		1	
High school	**0.49**	**0.24-0.98**	**0.43**	**0.17-1.07**
Health-related education				
No	1			
Yes	**2.15**	**1.01-4.60**		
Family member with health-related education				
No	1			
Yes	**2.09**	**1.04-4.22**		
Number of regular medicines taken	0.92	0.80-1.07		
Use of OTC				
No	1			
Yes	0.81	0.40-1.66		
Number of supplements taken	1.15	0.93-1.43		
Generic substitution[Φ]				
No	1		1	
< 75%	**0.31**	**0.11-0.91**	**0.12**	**0.03-0.57**
≥ 75%	0.69	0.29-1.61	**0.41**	**0.15-1.13**
Patient information leaflet reading				
Never/sometimes	1			
Always	**2.80**	**1.29-6.10**		
GP visits in a year				
0-2	1			
3-5	1.08	0.45-2.61		
>5	1.15	0.46-2.91		
Cannot remember	1.40	0.25-7.78		

OR= odds ratio; CI= confidence interval

†: Univariate analysis adjusted only for clustering on patients chronic disorder.

‡: Adjustment was done for clustering on patients' chronic disorder, health-related education, having family member with health-related education, age and number of vitamins/supplements (as continuous variables), and frequency of SPC reading.

§: Age was used as a continuous variable.

¶: If one was married or registered partnership and had total income: <43 057 or 43 057 -64 478€, was categorized as low income; 64 586-86 006 € you were categorized as medium income; >86 114€ you were categorized as high income. If you were divorced/ widow/widower/not married or other and had total income: < 43 057€ you were categorized as medium income; > 43 057€ you were categorized as high income. 1 Euro= 9.29 NOK, annual exchange rate for 2016.[10]

Ï: High school education indicates secondary education with 9-12 years of education, and also education other than tertiary.

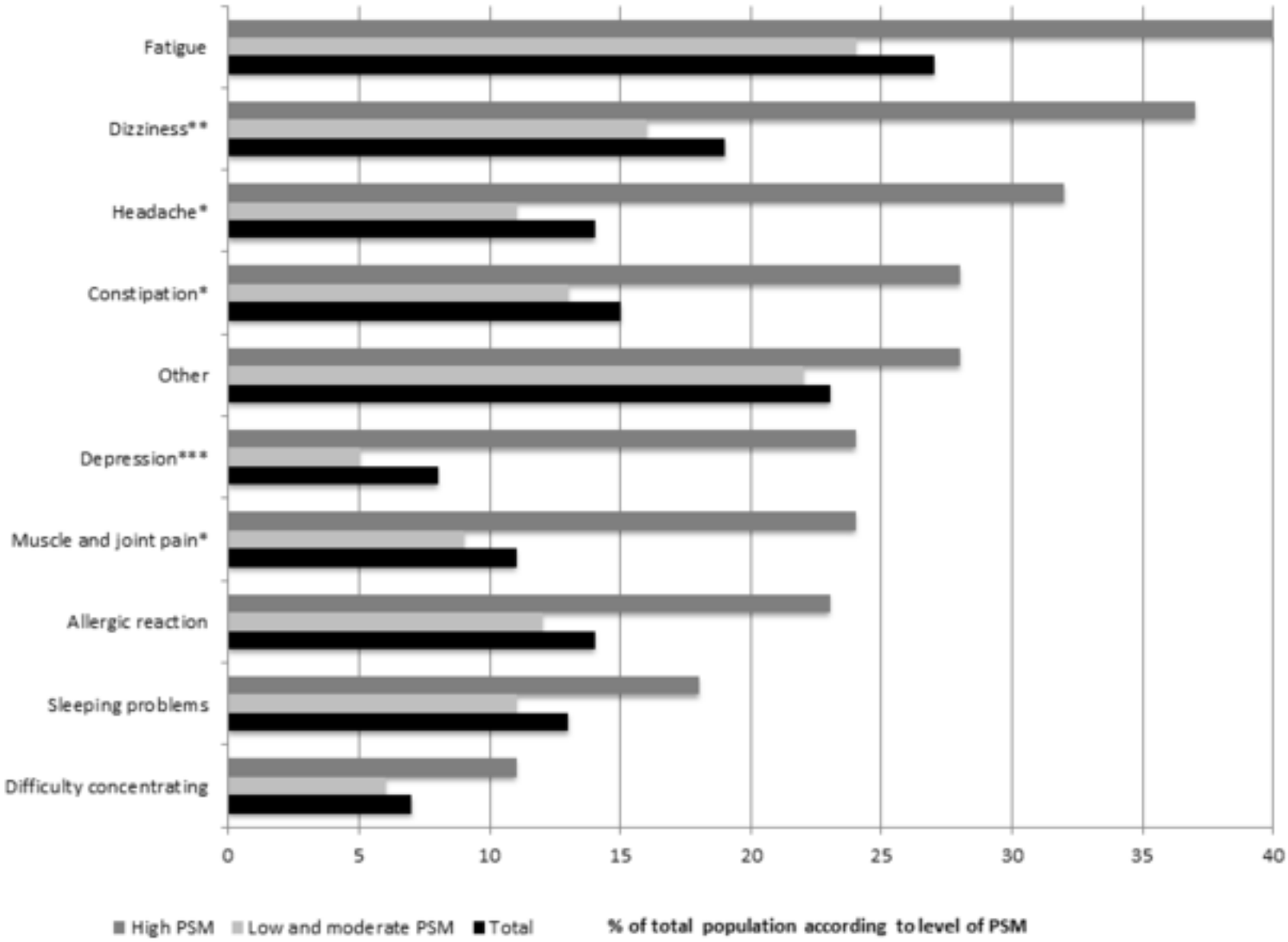
Φ: The generic variable was then divided into three groups: no generic use (even though there was an available generic brand), using < 75% generic medicines, using ≥ 75% generic medicines. Patients with no choice of a generic substitution n=34 (14.2%).

Box 1. Individual items of the Perceived Sensitivity to Medicines scale (PSM).

1. My body is very sensitive to medicines
2. My body overreacts to medicines
3. I usually have stronger reactions to medicines than most people
4. I have had a bad reaction to medicines in the past
5. Even very small amounts of medicines can upset my body.

Figure 1

Figure 1. Distribution of reported side effects among the study population by high respectively low/moderate Perceived Sensitivity to Medicines (PSM) (n=214)



Chi-square test for independence for experience of side effects for low/moderate PSM and High PSM* p≤0.05; ** p≤0.01; ***p≤0.00.

attachment A

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attachment B

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attachment C

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attachment D

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attachment E

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