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Please cite this article: DEVELOPMENT AND VALIDATION OF A QUESTIONNAIRE FOR MEASURING DRUG-INDUCED NAUSEA

Authors: Anđelka Prokić, Slobodan M. Janković; Vojnosanitetski pregled (2017); Online First September, 2017.

UDC:

DOI: https://doi.org/10.2298/VSP170421123P

When the final article is assigned to volumes/issues of the Journal, the Article in Press version will be removed and the final version appear in the associated published volumes/issues of the Journal. The date the article was made available online first will be carried over.
DEVELOPMENT AND VALIDATION OF A QUESTIONNAIRE FOR MEASURING DRUG-INDUCED NAUSEA

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Short title: MEASURING DRUG-INDUCED NAUSEA

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ABSTRACT

**Background:** There are several questionnaires for measurement of intensity of nausea after drug administration, but they are either too settings specific (like those measuring chemotherapy-induced nausea) or were not properly tested for reliability and validity.

**Objective:** The aim of this study was to develop and validate a reliable instrument that can measure drug-induced nausea.

**Method:** Cross-sectional study for assessing reliability and validity of a questionnaire. The questionnaire with 5 items and answers according to the Likert’s scale was developed during two brainstorming sessions of the research team. Its reliability, validity and temporal stability were tested on the sample of 128 outpatients taking iron salts orally.

**Results:** Final version of the Drug-Induced Nausea Scale (DINS) with 5 items showed excellent reliability, both when rated by the investigators (Cronbach’s alpha 0.892), and by the patients themselves (Cronbach’s alpha 0.897). It was temporally stable, and both divergent and convergent validity tests had very good results. Factorial analysis revealed only one factor, which means that whole scale is measuring only one phenomenon, intensity of nausea, as was originally intended.

**Conclusions:** DINS is reliable and valid instrument for measuring intensity of drug-induced nausea. Identification of patients with high intensity of drug-induced nausea by this questionnaire will help prescribers to decide whether the therapy should be stopped or the patient switched to less emetogenic therapy.

**Key Words:** drug-induced nausea; questionnaire; psychometric properties
INTRODUCTION

Drugs have varying potential to induce nausea and/or vomiting. Center for vomiting in medulla oblongata is under the influence of substances from blood, stimulation of nerve endings in gastrointestinal tract and impulses from chemioreceptor zone. Neurotransmitters with significant effect on the center are histamine, acetylcholine, dopamine, 5-hydroxytryptamine, substance P and endogenous cannabinoids (1). Cytostatic drugs cause nausea in as much as 10% (drugs with low emetogenic potential) to 90% (drugs with high emetogenic potential) patients (2), while opioids cause nausea in 48% of patients when used for treatment of cancer pain and in 27% when used for postoperative pain (3). Rate of nausea after oral administration of iron salts amounts to 11% (4), and it is probably caused by accumulation of free radicals in gastrointestinal mucosa (5). Drug-induced nausea is big problem in everyday clinical practice, as many patients are not compliant to the prescribed therapy or discontinue the therapy due to nausea.

There are several questionnaires for measurement of intensity of nausea after drug administration, usually developed specifically for certain drug groups, like Chemotherapy-Induced Nausea and Emesis Quality of Life questionnaire (CINI QOL) (6) or the Gastrointestinal Symptom Questionnaire (GSQ) designed to measure nausea after oral drug intake (7) and tested in patients taking iron salts. Within its program of developing standardized set of patient-reported outcomes (Patient-Reported Outcomes Measurement Information – PROMIS) National Institute of Health in USA created also Gastrointestinal Symptom Scales (GSS), and one of them is measuring nausea caused by either disease or drug (8). However, these scales are either too settings specific (like CINI QOL) or were not properly tested for reliability and validity after drug administration (like GSQ or PROMIS GSS-nausea). Reliable and valid questionnaire for measurement of drug-induced nausea as general phenomenon could be important clinical tool for assessing tolerability of emetogenic drugs and necessity to discontinue therapy or switch to less emetogenic one. If drug-induced nausea is mild, a prescriber could further decrease it through timing intake of the drug with food or giving only one daily dose before going to bed, and in this way preserve potentially very efficient drug for the patient instead of switching to other drugs (which could cause nausea, too). Besides, after adequate explanation and rating of nausea, the patients with mild form will be more compliant to the prescribed therapy.
The aim of our study was to develop questionnaire for measurement of intensity of drug-induced nausea, and test its reliability and validity on a sample of adult patients taking iron salts orally.

MATERIALS AND METHODS

Design

The study was of a cross-sectional type, and assessed reliability and validity of newly developed questionnaire for measurement of drug-induced nausea (Drug-Induced Nausea Scale – DINS) among outpatients taking iron salts orally.

Construction of the new questionnaire

Developing of the new questionnaire was done according to the guidelines set by Robert F. DeVellis(9), through eight steps. In the first step (determining object of measurement) drug-induced nausea was chosen as an object of measurement, being one of the most frequent causes of discontinuation of effective drug therapy (10). The second step, generating an item pool, was conducted through two brainstorming sessions of the authors, one week apart. In the third step (determining format for measurement) each item was constructed in the form of positive statement which should reflect certain element of nausea. Five possible answers were offered for each statement, in the form of Likert’s scale: “never”, “rarely”, “sometimes”, “often”, and “always”. The answers were rated from 1 (“never”) to 5 (“always”). Total score of the questionnaire was calculated by summation of answers to individual items. The patients with the total score from 1 to 10 had mild nausea, those from 11 to 20 moderate nausea, and the patients with the score from 21 to 25 severe nausea. The fourth step (revision and correction of the initial pool of items) was made by the three member expert committee composed of a psychiatrist, a gastroenterologist and a clinical pharmacology specialist employed by Clinical Center Kragujevac, Serbia. Within the fifth step one validation item for discovering socially desirable behavior of respondents was included in the questionnaire: “I always try to help other people.” In the sixth step the initial pool of DINS’s items was tested on 5 PhD students (at Faculty of Medical Sciences, University of Kragujevac, Serbia) for clarity and comprehension. After the pilot a few
minor changes were made, and then final Serbian version of DINS was copied and prepared for reliability testing on the sample of 128 outpatients (Annex 1). The seventh (evaluating the items) and eighth (optimizing the questionnaire length) steps are described below.

Translation and cultural adaptation of supplementary questionnaire for validation purposes of the DINS instrument

Translation and cultural adaptation of the PROMIS-GSS-nausea questionnaire (4 items) was made according to International Society for Pharmacoeconomics and Outcomes Research (ISPOR) guidelines (11). Permission for translation of PROMIS-GSS-nausea (version with 4 items) from English to Serbian was granted by the National Institutes of Health Patient Reported Outcomes Measurement Information System. The original scale was first translated to Serbian by two investigators who were Serbian native language speakers (S. Jankovic and A. Prokic). They translated the scale independently of each other, and then the translations were harmonized to one Serbian version at the meeting of the study investigators. The harmonized Serbian version was then translated back to English by Dr. Zan Friscic, native English speaker, citizen of Australia. When translated back to English, Dr. Friscic was not aware of the original English version of the PROMIS-GSS-nausea. The back-translation to English was then compared with original English version by the study investigators, and at new meeting of investigators final Serbian version of the PROMIS-GSS-nausea was agreed on. The final translation of PROMIS-GSS-nausea to Serbian was then tested on 5 PhD students (at Faculty of Medical Sciences, University of Kragujevac, Serbia) for clarity and comprehension. After the pilot a few minor changes were made, and then final Serbian version of PROMIS-GSS-nausea was copied and prepared for reliability testing.

Data collection - population and the sample

Final Serbian versions of the both new (DINS) and translated (PROMIS-GSS-nausea) questionnaires were tested for reliability on outpatients who visited community pharmacies in Osečina, western Serbia. The visits took place during the year 2016. The inclusion criteria were oral intake of iron salts for at least two weeks, literacy, and age over 18. The exclusion criteria were previous gastrectomy, cognitive disorders (score at Mini-Mental State Examination below 24), mood disorders and mental retardation. The sample
of the patients was of consecutive nature, i.e. all patients who visited community pharmacies during the study period (and satisfied inclusion and exclusion criteria) were offered the questionnaire. During the first encounter the questionnaires were completed in two ways: at first, by the investigators who were questioning the patients, and second, by the patients themselves. At the second encounter, two weeks later, the patients were repeatedly interviewed by the study investigators who completed the same questionnaires again. The study was approved by the Ethics Committee of Clinical Center Kragujevac, Serbia. The patients were treated with due respect and care, according to the principles stated in Declaration of Helsinki.

Data analysis

Reliability testing

Reliability of the questionnaire was tested by three methods. First, internal consistency was determined through calculation of Cronbach’s alpha for the questionnaire as a whole. Second, the questionnaire was divided by split-half method to two parts with the same number of questions, and Cronbach’s alpha for each of the parts was calculated. Using the alphas for both parts, number of questions in each part and average correlation between questions in both parts of the original questionnaire, the Spearman-Brown coefficient for the questionnaire as a whole was calculated by the Spearman-Brown “prediction” formula (12). Third, for each question mean score and their variances were calculated, in order to check their suitability for measurement of whole extent of nausea severity.

Factorial analysis

Principal component analysis of the questionnaire was made in order to discover principal factors (13). Principal component analysis groups the items of a scale to a smaller number of principal components which describe most of the variance of the responses to the scale items. Each of the principal components identified covers part of the variance in the data, and they are not correlated between themselves. Components (factors) covering maximal variance are kept, while the others with small amount of variance are discarded. The amount of variance covered by each component is measured by its eigenvalue. First, suitability of the questionnaire and sample for factorial analysis was tested by Kaiser-
Meyer-Olkin measure of sampling adequacy and by the Bartlett's test of sphericity. Then, the factors were extracted at first without rotation, with conditions that Eigenvalues had to be greater than 1.0, and using Scree-plot (the extracted factors were above the “elbow” of the graph). Second, referent axes were rotated orthogonally, by the Varimax method, and another extraction of the factors was made, using the same criteria as for the unrotated solution. The following was reported for the extracted factors: loadings, eigenvalues, and percentage of variance explained. The extracted factors were then named accordingly. All calculations were performed by SPSS statistical software, version 18.0.

**Validity**

Content validity of the questionnaire was evaluated by an independent panel of three experienced clinicians at Clinical Center Kragujevac, Serbia: psychiatrist, gastroenterologist and clinical pharmacology specialist.

The criterion validity was tested by three methods: (1) comparison of the DINS scores when the questionnaire was completed by the investigators and by the patients themselves, (2) convergent validity testing by comparison of the DINS score with the PROMIS-GSS-nausea score, and (3) divergent validity testing by comparison of the DINS score with the score of the Intolerance of Uncertainty questionnaire (IU). The permission to use the Intolerance of Uncertainty questionnaire in Serbian language (which measures intolerance of uncertainty in everyday life, and was previously validated in Serbian population) was granted by Associated Professor Ljiljana Mihić, psychologist, University of Novi Sad, Serbia(14). The correlations between scores on the questionnaires were calculated and presented in Multi-method, multi-trait matrix. All calculations were performed by SPSS statistical software, version 18.0.

**Temporal stability**

Temporal stability of the DINS and the PROMIS-GSS-nausea results was tested by second completion of the questionnaires by the investigators who repeatedly interviewed the patients two weeks after the first encounter. The patients were invited to the second encounter by phone.
RESULTS

The first version of the DINS questionnaire contained 5 questions, which after the pilot and minor adjustments was tested on the sample of 128 outpatients: mean age 45.8 ± 13.5 years, male/female ratio 16/112 (12.5%/87.5%), education elementary school / high school / university = 26.6% / 51.6% / 21.6%, place of residence, urban/rural = 83/45 (64.8%/35.2%), and all patients except 2 (1.6%) were prescribed with oral iron for treatment of anemia. Thirty-eight patients (29.7%) were taking iron salts before a meal, 7 (5.5%) during a meal, 68 (53.1%) after a meal and remaining 15 (11.7%) did not take care about the timing of drug intake. Seventy patients (54.7%) were previously introduced with gastrointestinal adverse effects of iron preparations, and the remaining 58 patients (45.3%) were not. Sixteen patients (12.5%) did have previous experience with nausea after oral drug intake, and the remaining 112 (87.5%) did not. Finally, 53 patients (41.4%) suffered from at least one chronic non-contagious disease, and 75 (58.6%) did not.

Mean score of the DINS was 8.6 ± 5.1 (range from 5 to 25). There were no significant differences in severity of nausea (the DINS score) according to the sex (females 8.6 ± 5.1, males 8.3 ± 4.7, p = 0.781), education (elementary school 8.9 ± 4.5, high school 8.7 ± 5.3, higher education 8.3 ± 4.4, p = 0.910) or place of living (urban 8.6 ± 5.4, rural 8.5 ± 4.4, p = 0.962) of the study participants.

Reliability testing

After testing original 5 items from the questionnaire, and examining results of correlation matrix, mean values, variance, skewness and kurtosis of distributions of responses for each of the items, none of the items was removed, leaving final version of the DINS questionnaire with 5 items. Criteria for removing the items were extreme means, near zero variances and correlation coefficients with majority of other items below 0.2. Cronbach’s alpha of the final version with 5 items was 0.892, when the scale was rated by the investigators. Mean values of responses, standard deviations, skewness and kurtosis for each item of DINS are shown in the Table 1. After division of the DINS questionnaire by the split-half method the Spearman-Brown coefficient for the questionnaire as a whole
was calculated by the Spearman-Brown “prediction” formula, and its value was 0.834. When the scale was rated by the patients themselves, Cronbach’s alpha was 0.897.

Cronbach’s alpha of the PROMIS-GSS-nausea questionnaire with 4 items was 0.739, when the scale was rated by the investigators. After division of the PROMIS-GSS-nausea questionnaire by the split-half method the Spearman-Brown coefficient for the questionnaire as a whole was calculated by the Spearman-Brown “prediction” formula, and its value was 0.662. When the scale was rated by the patients themselves, Cronbach’s alpha was 0.737.

**Factorial analysis**

Factorial analysis of DINS was made by the principal components method. The Kaiser-Meyer-Olkin measure of sampling adequacy was 0.815 and the Bartlett's test of sphericity was significant (p = 0.000). Only one factor was extracted, explaining in total 70.1% of variance, and with eigenvalue 3.503.

Factorial analysis of PROMIS-GSS-nausea questionnaire was made also by the principal components method. The Kaiser-Meyer-Olkin measure of sampling adequacy was 0.614 and the Bartlett's test of sphericity was significant (p = 0.000). Only one factor was extracted, explaining in total 56.22% of variance, and with eigenvalue 2.249.

**Validity**

Construct validity of the questionnaire was confirmed by the panel of experts, who also helped with slight re-phrasing of the questions.

Divergent criterion validity was tested through non-parametric correlation between scores of the DINS scale (when it was rated by investigator and by patients themselves) and scores of the IU scale (when it was rated by investigator and by patients themselves).

Convergent criterion validity was tested through non-parametric correlation between scores of the DINS scale (when it was rated by investigator and by patients themselves), scores of the PROMIS-GSS-nausea scale (when it was rated by investigator and by patients themselves). Correlation coefficients between the DINS and IU scales and between PROMIS-GSS-nausea and IU scales were below 0.2 and statistically insignificant. Non-parametric
correlation was chosen due to non-normal distribution of some of the scores. Spearman’s correlation coefficients are shown in the Multi-trait, multi-method matrix (Table 2).

**Temporal stability**

The DINS scale showed excellent temporal stability: when rating (by the investigator) was repeated on the same patients two weeks later, the correlation between the scores (Spearman’s coefficient) was 0.965 (p < 0.001). Cronbach’s alpha after the repeated rating was 0.901.

The PROMIS-GSS-nausea scale also showed excellent temporal stability: when rating (by the investigator) was repeated on the same patients two weeks later, the correlation between the scores (Spearman’s coefficient) was 0.947 (p < 0.001). Cronbach’s alpha after the repeated rating was 0.742.

**DISCUSSION**

Final version of the DINS scale with 5 items showed excellent reliability, both when rated by the investigators, and by the patients themselves. It was temporally stable, and both divergent and convergent validity tests had very good results. Factorial analysis revealed only one factor, which means that whole scale is measuring only one phenomenon, intensity of nausea, as was originally intended. DINS scale was also more reliable than previously validated PROMIS-GSS-nausea scale.

Although PROMIS-GSS-nausea scale was used for measuring intensity of nausea in a variety of gastrointestinal diseases, showing high ability to discriminate between subtle changes in the nausea intensity (15), it was not previously used to measure drug-induced nausea. In our study it showed necessary level of reliability for this purpose, but DINS surpassed it by far with its high Cronbach’s alpha around 0.9.

Since nausea and vomiting are particularly severe in patient receiving chemotherapy, it is not surprising that the largest number of instruments for measuring drug-induced vomiting was specifically developed in this area. Recent systematic review found seven instruments for measuring chemotherapy-induced nausea, retching and vomiting (16). Majority of these instruments cover three key domains (nausea, vomiting and retching) and are prepared in several forms which are adjusted for three different phases
of nausea-vomiting-retching phenomenon: anticipatory, acute and delayed. Our instrument DINS is focused on nausea domain, which is usually the only one present when patients take less emetogenic drugs other than cytostatics (17). Therefore, DINS should not be used for measurement of chemotherapy induced nausea, retching and vomiting, but for estimation of nausea caused by less emetogenic drugs prescribed to outpatients.

Although limited to measurement of nausea, items from the DINS instrument cover essential aspects of this phenomenon, which could be applied also to vomiting and retching: occurrence (item 2), duration (item 1) and severity (items 3, 4 and 5) (17). The Gastrointestinal Symptom Questionnaire by Pereira et al (7) also covered these aspects of nausea, but the answers to questions had only three modalities, “mild”, “moderate” and “severe”, limiting discriminative power of the scale. Although in their study Pereira and associates did not measure internal consistency of their questionnaire, most likely it would not be too high, since the questionnaire relates only to condition of a patient on the day of rating, and misses chronicity as important aspect of drug-induced nausea. We also would like to point out that second question (During drug therapy, did you feel nausea always in the same time during a day?) could be betterformulated in a way which would take into account timing of a drug intake during the day (e.g., During drug therapy, did you feel nausea always after its administration?) in order to capture causality between intake of a drug and emergence of nausea. However, this new formulation would have to be tested in a future study.

Main limitations of this study were non-homogenous nature of the study sample, i.e. some of the patients had previous experience with nausea after oral drug intake, some did not, and female sex was largely predominant, due to higher incidence of iron-deficiency anemia. This non-homogeneity could be responsible for somewhat wider dispersion of patients’ responses. Besides, the patients were taking only one drug (iron salts) which causes nausea, so the results could be drug type – specific, and may not apply to nausea caused by other drugs. Future studies with the same questionnaire should be conducted on several patient subgroups which are taking other emetogenic drugs in order to get complete insight into its functionality.

CONCLUSION
In conclusion, DINS is reliable and valid instrument for measuring intensity of drug-induced nausea. Identification of patients with high intensity of drug-induced nausea by this questionnaire will help prescribers to decide whether the therapy should be stopped or the patient switched to less emetogenic therapy.

ACKNOWLEDGEMENTS

The authors are grateful to Dr Zan Frisčić, MD, specialist of orthopedic surgery and native English language speaker, who helped with backward translation from Serbian to English of the PROMIS-GSS-nausea scale. The authors also thank to Associated Professor Ljiljana Mihić, psychologist, University of Novi Sad, Serbia, for giving permission to use the Intolerance of Uncertainty questionnaire for testing divergent validity of the DINS scale.

REFERENCES:


Table 1. Mean values, standard deviation, skewness and kurtosis of responses to items of DINS questionnaire (the responses are rated from 1 to 5 on a Likert scale).

<table>
<thead>
<tr>
<th>Item</th>
<th>Mean response</th>
<th>Standard deviation</th>
<th>Skewness</th>
<th>Kurtosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Did you feel nausea during drug therapy?</td>
<td>1.97</td>
<td>1.386</td>
<td>1.157</td>
<td>-0.084</td>
</tr>
<tr>
<td>During drug therapy, did you feel nausea always in the same time during a day?</td>
<td>1.89</td>
<td>1.399</td>
<td>1.338</td>
<td>0.319</td>
</tr>
<tr>
<td>During drug therapy, how often you could not perform your daily activities due to nausea?</td>
<td>1.71</td>
<td>1.243</td>
<td>1.641</td>
<td>1.404</td>
</tr>
<tr>
<td>Was your appetite decreased due to nausea during drug therapy?</td>
<td>1.36</td>
<td>.858</td>
<td>2.651</td>
<td>6.599</td>
</tr>
<tr>
<td>Did you feel an urge to vomit during drug therapy?</td>
<td>1.63</td>
<td>1.100</td>
<td>1.746</td>
<td>2.083</td>
</tr>
</tbody>
</table>
Table 2. Multi-trait, multi-method correlation matrix (non-parametric Spearman’s coefficients).

<table>
<thead>
<tr>
<th></th>
<th>DINS score, rated by an investigator</th>
<th>DINS score, rated by a patient</th>
<th>PROMIS-GSS-nausea score, rated by an investigator</th>
<th>PROMIS-GSS-nausea score, rated by a patient</th>
<th>IU score, rated by an investigator</th>
<th>IU score, rated by a patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>DINS score, rated by an investigator</td>
<td>1</td>
<td>0.956**</td>
<td>0.765**</td>
<td>0.765**</td>
<td>0.131</td>
<td>0.126</td>
</tr>
<tr>
<td>DINS score, rated by a patient</td>
<td>0.956**</td>
<td>1</td>
<td>0.757**</td>
<td>0.759**</td>
<td>0.127</td>
<td>0.123</td>
</tr>
<tr>
<td>PROMIS-GSS-nausea score, rated by an investigator</td>
<td>0.765**</td>
<td>0.757**</td>
<td>1</td>
<td>0.961**</td>
<td>0.052</td>
<td>0.037</td>
</tr>
<tr>
<td>PROMIS-GSS-nausea score, rated by a patient</td>
<td>0.765**</td>
<td>0.759**</td>
<td>0.961**</td>
<td>1</td>
<td>0.018</td>
<td>0.013</td>
</tr>
<tr>
<td>IU score, rated by an investigator</td>
<td>0.131</td>
<td>0.127</td>
<td>0.052</td>
<td>0.018</td>
<td>1</td>
<td>0.972**</td>
</tr>
<tr>
<td>IU score, rated by a patient</td>
<td>0.126</td>
<td>0.123</td>
<td>0.037</td>
<td>0.013</td>
<td>0.972**</td>
<td>1</td>
</tr>
</tbody>
</table>

**Significant correlation at p<0.001**