



Association of knowledge and attitudes with practices of misuse of tranquilizers: A cohort study in Spain

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ABSTRACT

Background: Tranquilizer misuse represents a growing international public health problem with heavy social and economic consequences. We aimed to identify the psychosocial determinants of this misuse practice, focusing on modifiable factors including knowledge and attitudes towards these medications.

Methods: A prospective cohort study involving 847 adults accompanying children in primary care clinics was carried out in Spain. A validated Knowledge, Attitudes and Practices (KAP) questionnaire on tranquilizer use was self-administered at baseline, and then participants were followed-up bimonthly. A misuse event was defined as unprescribed intake of tranquilizers, storing/sharing leftovers of tranquilizers, and/or not adhering to the prescribed treatment period, timing or dosage. Poisson regression models were applied to estimate adjusted Incidence Rate Ratios (IRRs) of misuse and their 95 % Confidence Intervals (CIs).

Findings: Individuals' personal attitudes towards tranquilizers and treating physicians are strongly associated with the misuse of these drugs. These attitudes include: individuals' acceptance of taking tranquilizers to improve sleeping [IRR: 5.10 (95 %CI: 2.74–9.48)], to work better [IRR: 2.04 (95 %CI: 1.05–3.99)], or for recreational purposes [IRR: 1.85 (95 %CI: 1.04–3.32)]; willingness to prolong the course of tranquilizer treatment without medical consultation [IRR: 2.45 (95 %CI: 1.46–4.13)]; agreeing on storing tranquilizers for possible future need [IRR: 5.07 (95 %CI: 2.73–9.40)]; and untrusting the physician's decision about tranquilizer prescription [IRR: 1.92 (95 %CI: 1.12–3.30)]. The level of knowledge is marginally associated with tranquilizer misuse.

Conclusions: There is a strong association between individuals' attitudes towards tranquilizers and the misuse practices of these drugs. Educational interventional studies could help reduce the incidence of tranquilizer misuse.

1. Introduction

Tranquilizers are among the most prescribed psychoactive drugs (Moore and Mattison, 2017). These medications are considered safe and well-tolerated by patients, but they may have important consequences on the autonomic nervous system and carry a risk of dependence, especially when abused or consumed in high doses (O'Brien, 2005). Moreover, although tranquilizers have low toxicity profile, their ingestion with other medications such as opioids significantly contributes to the risk of overdose (Sun et al., 2017). The concurrent use of tranquilizers and opioids is salient internationally, particularly in the United

States and in some European countries (United Nations Office on Drugs and Crime, 2019).

In 2013, 11 % of the Europeans reported misusing tranquilizers some time in their lives and around 6% of the population misused these drugs in the last year (Novak et al., 2016). In the past decade, tranquilizer misuse has turned into a critical global public health issue (Votaw et al., 2019). Practices of misuse entail consuming tranquilizers without medical prescription and/or poor therapeutic compliance (United Nations Office on Drugs and Crime, 2011). These misuse practices include consumption at a higher dose or for a longer period than prescribed, but also shortening the course of treatment or reducing the dose as well

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(Cooper et al., 2007; Julius et al., 2009; Garrido and Boockvar, 2013). Recent reports indicated a worldwide worsening of public health indicators concerning tranquilizer misuse (Maree et al., 2016; United Nations Office on Drugs and Crime, 2018). The United States witnessed a 10-fold rise in fatal drug overdose including tranquilizers (National Institute on Drug Abuse, 2020), and a 90 % increase in emergency department visits for the same cause (Day, 2014). Furthermore, non-adherence, with drugs taken at a less quantity than prescribed may lead to lower quality of life, poorer management of comorbid physical illnesses, increased rates of hospitalization and higher healthcare costs (Garrido and Boockvar, 2013; Julius et al., 2009).

Determinants of tranquilizer misuse remain understudied despite the deterioration of related public health indicators (Lembke et al., 2018). The available literature is limited to some studies that associated tranquilizer misuse with certain demographic characteristics such as sex, age, educational level, employment status, and other factors such as psychiatric distress, previous prescriptions and quality of life (Becker et al., 2007; Opaleye et al., 2013; Tahiri et al., 2017; Votaw et al., 2019). Therefore, international efforts should be considerably expanded to determine the risk factors of this misuse, and to establish health strategies that control this problem and enhance awareness about the proper prescription and administration of these medicines.

Knowledge, Attitude and Practice (KAP) questionnaires proved to be useful tools in identifying psychosocial properties related to the misuse of certain medicines as well as in designing intervention studies and related public health approaches. Studies about the association of knowledge and attitudes regarding tranquilizers with the misuse practices of these drugs are scarce. To the best of our knowledge, only two related surveys from the past century are available in the literature (Manheimer et al., 1973; Clinthorne et al., 1986).

Accordingly, in the present follow-up study we sought to explore the psychosocial determinants of the misuse of tranquilizers in a Spanish cohort, with a special focus on the following factors: 1) knowledge about tranquilizers, 2) personal attitudes towards tranquilizers and 3) patient-healthcare provider relationship.

2. Methods

2.1. Setting

The study was carried out in Galicia, a north-western region of Spain. The Spanish National Healthcare System (NHS) provides universal coverage to all Spanish citizens and the access to healthcare facilities is free of charge. The Spanish NHS also covers medicines that are approved and registered by the Agency of Medicines and Health Products. Outpatients may purchase the prescribed medicines at a reduced cost. The dispensing of medicines in general, and of psychoactive drugs in specific, is strictly controlled and is carried out electronically.

2.2. Study population and design

A prospective cohort study that involved adults (≥ 18 years old) from the general population was conducted in 2019. The participants consisted of 847 (as per our sample size calculation) adults accompanying a next-of-kin to primary care consultations at the University Hospital of Santiago de Compostela. The reason for choosing this population was the relative ease to have access to it and the high expected responsiveness. We contacted all subjects visiting the consultations during the recruitment period (May-December 2019). To avoid any misunderstanding, participants were informed that the questionnaire was about personal use of antibiotics, and not about the use in the offspring. No further restriction criteria were used in the inclusion of subjects.

A KAP questionnaire, previously validated in the Spanish general population, with Item Content Validity Index (I-CVI) from 0.78 to 1.00), Scale Content Validity Index (S-CVI/Ave) of 0.95) and Cronbach's alpha values > 0.6 , was applied in this study (Supplementary material, File S1)

(Mallah et al., 2021). Participants self-administered the questionnaire after signing an informed consent form and giving their approval to be followed-up every two months for a one-year period. This baseline questionnaire needed 10 min to be completed.

Subsequently, participants were telephoned every two months to inquire about their exposure to tranquilizers since the previous contact. When a participant doubted if the consumed medicine is classified as tranquilizer, we asked about the commercial name of that medicine and checked its pharmaceutical classification. If participants reported using tranquilizers, they were asked additional questions (Q18 to Q27 of the questionnaire) to determine any misuse practice. The follow-up phone interview lasted between 1 and 3 min.

During the follow-up, the participants were reminded about the date of the previous contact to help them recall better. Those participants who did not answer a follow-up phone call, were telephoned again four times subsequently before being excluded from the study.

2.3. Exposure assessment

The baseline questionnaire encompassed 16 items (Q1 to Q16) about Knowledge, Personal Attitudes towards tranquilizers and patient-healthcare provider relationship. These items were answered using a 0–10 Likert scale where 0 and 10 represent the lowest and highest degrees of agreement, respectively. The knowledge questions entailed the consequences of tranquilizer use such as increasing the risk of car accidents, reducing children's learning abilities and limiting self-control over certain behaviours. Statements of Personal Attitudes towards tranquilizers explored the participants' agreement to use tranquilizers in order to sleep or work better, or for recreational purposes. In addition, these statements examined the users' beliefs on how tranquilizers should be used. Items about patient-healthcare provider relationship examined the level of trust between the patients and their treating physicians as well as their satisfaction with the information provided regarding the motives of prescription or non-prescription of tranquilizers and the clarity of instructions of use given by these physicians.

2.4. Assessment of misuse of tranquilizers

A misuse episode was detected when the participants reported using tranquilizers without medical prescription or not taking tranquilizers as instructed by the physician, including shortening the course of treatment, storing or sharing leftovers of tranquilizers, not taking tranquilizers regularly and/or changing the prescribed dosage without medical advice. These episodes were detected by asking about the use of tranquilizers in the past two months (Q17) and the practices showed with respect to the consumed tranquilizers (Q18 to Q28 of the questionnaire).

2.5. Statistical analysis

Each participant contributed person-time from the enrolment in the study until the date of misuse episode, drop-out, loss to follow-up, or the end of the study, whichever occurred first. Each of the 16 Knowledge/Attitude items represented an independent variable that was analysed separately. Answers were classified into percentiles of distribution of level of agreement or as a dichotomous category depending on the question.

We computed Incidence Rate Ratios (IRRs) and their 95 % Confidence Intervals (CIs) of tranquilizer misuse using Poisson Regression models. In the models, the quantile group that represented the highest level of knowledge or the perfect attitude was assigned as a reference category. Models were directly adjusted for sex and age due to the biological relevance of these variables. Other covariates evaluated as potential confounders were: employment status, educational level, family size, frequency of physician consultation in case of sickness, receiving medical prescription over the phone and alcohol consumption. They are shown on items Q28 to Q35 of the demographic section of the

questionnaire (Supplementary material, File S1). We carried out a univariate regression analysis for each of these covariates as an independent variable and tranquilizers misuse as the dependent variable. Covariates that showed a p-value smaller than 0.2 were considered as potential confounders, were introduced consecutively into the Poisson Regression model and only those that modified the IRR of the main exposure variable by at least 10 % were retained in the final model (Greenland, 1995). In our study, only employment status was deemed a confounder and was then included in the multivariate model. Participants with missing information on any of the covariates were not considered in the analysis.

2.6. Robustness analyses

2.6.1. Impact of cohort attrition

In the primary analysis, the IRRs were computed after excluding those participants who did not complete any follow-up assessment (dropouts). To explore the impact of dropouts and losses to follow up, we performed two sensitivity analyses with extreme scenarios. In the first analysis, we considered that no subject who dropped out had misused tranquilizers. In the second analysis, we assumed that all participants with incomplete follow-up had misused tranquilizers.

To examine the impact of missing data, we performed a multiple imputation by chained equations (MICE) procedure. We carried out 20 imputations using the “mi” suite commands of Stata that follows Rubin’s rules for the combination of results across the imputed datasets (Rubin, 2004). Adjusted IRRs and their 95%CI were then estimated using the imputed data.

2.6.2. Validation sub-study and exposure misclassification

Due to the absence of any superior instrument that could be considered as a “gold standard”, we estimated the specificity and the sensitivity of our questionnaire using the results of a reproducibility sub-study, carried out in parallel with the main cohort study. This sub-study consisted in asking 140 participants to answer our Knowledge and Attitudes questions on two occasions, with a one-month interval in between. The objective of this sub-study was to assess reproducibility. Reproducibility measures how stable over time the responses were, i.e. whether subjects did not answer differently after one month. In the analysis phase, each question had to be dichotomized into “good knowledge” and “poor knowledge” (or “risky attitude” and risk-free attitude” for attitude questions). We considered the answers of the first round as the reference, i.e. as the correct (or true) answers, and we compared the answers of the second round, assumed to be measured with a certain degree of misclassification, to the answers of the first round. Sensitivity is the proportion of questions answered as “poor knowledge” in the first round, which were answered correctly in the second round, while specificity is the proportion of questions answered as “good knowledge” in the first round, which were answered correctly in the second round. To assess the robustness of our results to exposure misclassification, in a secondary analysis, we used the estimated specificity and sensitivity values of each knowledge and attitude item to correct our relative risk estimates. We assumed that there was no loss to follow-up. We compared Odds Ratios (ORs) of each item before and after correction (Kleinbaum et al., 1982).

The questionnaire was designed using Remark Office OMR 2014, version 9.2.0.20 (Gravic, Inc. 2014. Malvern, PA, USA). All analyses were carried out using Stata v12 (StataCorp. 2011. *Stata Statistical Software: Release 12*. College Station, TX: StataCorp LP.)

2.7. Ethics

This study was approved by the Ethics Committee of the University of Santiago de Compostela (R00002, No. 2019/179), and authorized by the Spanish Agency for Medication and Healthcare Products (AEMPS, Reference AFG-ANT-2018-01). The study was conducted in compliance

with the general requirements of the Ethics Committee and with the General Data Protection Regulation (Regulation (EU) 2016/679 and Organic Law 3/2018). Written informed consent form was obtained from the participants and the data were anonymized before analysis.

3. Results

Out of 847 recruited participants, 747 (88.19 %) were included in the main analysis. Five hundred sixty (74.97 %) were females, and half of them were between 36 and 45 years of age ($N = 373$, 49.93 %). Four hundred sixty-two (61.85 %) had university educational level and the majority were living in a household of a maximum of four members ($N = 609$, 81.53 %). Three-quarters of the participants were employed ($N = 561$, 75.10 %), half of them reported not always visiting the doctor in case of sickness ($N = 381$, 51.00 %) and 299 (40.02 %) individuals declared having received a medical prescription over the phone. Four hundred twenty-one (56.36 %) participants had never consumed alcohol (Table 1). Fifty-eight unique events of misuse of tranquilizers were identified in the cohort during the follow-up yielding an overall incidence rate of misuse of 0.17 year⁻¹.

3.1. Association of level of Knowledge with tranquilizer misuse

No association was observed between the low level of knowledge regarding the effect of tranquilizers and the misuse of these drugs. Not knowing that tranquilizers reduce people’s control over what they do [1st tertile IRR_{Q5}: 1.29 (95 %CI: 0.65–2.59)], affect children’s learning ability [1st tertile: IRR_{Q7}: 1.17 (95 %CI: 0.58–2.33)], or turn ineffective if consumed in excess [IRR_{Q10}: 1.31 (95 %CI: 0.74–2.32)], was not associated with increased risk of tranquilizer misuse (Table 2).

Table 1
General characteristic of the study population.

Characteristic	Total (N = 747)	Tranquilizer misusers (N = 58)
Sex		
Male	187 (25.03 %)	8 (13.79 %)
Female	560 (74.97 %)	50 (86.21 %)
Missing	0	0
Age		
<35 years	131 (17.54 %)	8 (13.79 %)
36–45 years	373 (49.93 %)	27 (46.55 %)
> = 46 years	243 (32.53 %)	23 (39.66 %)
Missing	0	0
Educational level		
Until high school	258 (34.54 %)	22 (37.93 %)
University	462 (61.85 %)	36 (62.07 %)
Missing	27 (3.61 %)	0
Family size		
≤4	609 (81.53 %)	52 (89.66 %)
>4	111 (14.86 %)	6 (10.34 %)
Missing	27 (3.61 %)	0
Consulting a doctor		
Not always	381 (51.00 %)	37 (63.79 %)
Always	338 (45.25 %)	21 (36.21 %)
Missing	28 (3.75 %)	0
Medical consultation over the phone		
No	419 (56.09 %)	29 (50.00 %)
Yes	299 (40.03 %)	28 (48.28 %)
Missing	29 (3.88 %)	1 (1.72 %)
Employment status		
Employed	561 (75.10 %)	39 (67.24 %)
Unemployed	160 (21.42 %)	19 (32.76 %)
Missing	26 (3.48 %)	0
Alcohol intake		
Never/less than once per month	421 (56.36 %)	35 (60.34 %)
Others	298 (39.89 %)	23 (39.66 %)
Missing	28 (3.75 %)	0

Table 2
Incidence Rate Ratio (IRR) of tranquilizers misuse according to quantiles of levels of agreement on knowledge and attitude statements.

Knowledge or Attitude Statement Quantile of level of agreement	Level of agreement*	Person-weeks of observations	Misuse	Crude IRR (95%CI)	Adjusted IRR (95%CI)**	
					Without imputation	After imputation
Q1. I would agree to take tranquilizers in order to sleep better						
1 st tertile	0–5	9988	18	1	1	1
2 nd tertile	6–7	1893	13	3.81 (1.87, 7.78)	3.19 (1.54–6.61)	1.69 (1.16, 2.45)
3 rd tertile	8–10	2380	26	6.06 (3.32, 11.06)	5.10 (2.74–9.48)	2.16 (1.46, 3.19)
Q2. If I feel better after a few days, I sometimes keep taking my tranquilizers even after completing the prescribed course of treatment						
Totally disagree	0	9776	28	1	1	1
Not totally disagree	1–10	4027	29	2.51 (1.50, 4.22)	2.45 (1.46–4.13)	1.58 (1.11, 2.26)
Q3. I would take tranquilizers in order to enjoy myself with my family						
1 st tertile	0	8108	24	1	1	1
2 nd tertile	1–5	4146	22	1.79 (1.01, 3.20)	1.85 (1.04–3.32)	1.26 (0.85, 1.86)
3 rd tertile	6–10	1921	11	1.93 (0.95, 3.95)	1.87 (0.91–3.85)	1.64 (0.99, 2.70)
Q4. I would agree to take tranquilizers when I feel down and sad in order to work better						
1 st tertile	0–1	7779	23	1	1	1
2 nd tertile	2–5	4156	20	1.63 (0.89, 2.96)	1.63 (0.89–2.97)	1.11 (0.79, 1.57)
3 rd tertile	6–10	2190	14	2.16 (1.11, 4.20)	2.04 (1.05–3.99)	1.47 (0.98, 2.21)
Q5. Tranquilizers reduce people's control over what they do						
1 st tertile	0–5	6305	30	1.41 (0.71, 2.81)	1.29 (0.65–2.59)	1.37 (0.76, 2.47)
2 nd tertile	6–9	4324	15	1.03 (0.47, 2.23)	1.07 (0.49–2.32)	1.29 (0.86, 1.94)
3 rd tertile	10	3261	11	1	1	1
Q6. People taking tranquilizers are at increased risk of traffic accidents						
1 st tertile	0–5	4121	19	1.17 (0.64, 2.14)	1.08 (0.59–1.97)	1.26 (0.83, 1.90)
2 nd tertile	6–8	3868	12	0.80 (0.39, 1.58)	0.79 (0.40–1.59)	1.12 (0.81, 1.55)
3 rd tertile	9–10	6105	24	1	1	1
Q7. Psychotropic drugs (such as tranquilizers) may affect children's learning abilities when prescribed to them						
1 st tertile	0–5	5717	25	1.23 (0.62, 2.44)	1.17 (0.58–2.33)	1.13 (0.61, 2.07)
2 nd tertile	6–9	5013	18	1.01 (0.49, 2.09)	1.05 (0.51–2.18)	1.09 (0.71, 1.67)
3 rd tertile	10	3369	12	1	1	1
Q8. If I feel side effects during a course of treatment of tranquilizers, I should stop taking it as soon as possible						
Disagree	0–5	6498	25	1	1	1
Agree	6–10	7589	32	1.10 (0.65, 1.85)	1.19 (0.70–2.01)	0.80 (0.57, 1.12)
Q9. I take the tranquilizers according to the doctor's instructions						
Totally agree	10	9148	31	1	1	1
No totally agree or disagree	0–9	4827	26	1.59 (0.94, 2.68)	1.66 (0.98–2.80)	1.13 (0.78, 1.64)
Q10. If tranquilizers are consumed in excess, they won't work when they are really needed						
Disagree	0–5	3512	17	1.30 (0.73, 2.29)	1.31 (0.74–2.32)	1.08 (0.74, 1.57)
Agree	6–10	10452	39	1	1	1
Q11. I prefer to keep tranquilizers at home in case there is a need for them later						
1 st tertile	0	7521	15	1	1	1
2 nd tertile	1–5	3488	10	1.44 (0.65, 3.20)	1.46 (0.66–3.25)	1.32 (0.88, 1.97)
3 rd tertile	6–10	2975	32	5.39 (2.92, 9.96)	5.07 (2.73–9.40)	1.70 (1.13, 2.56)
Q12. I trust the doctor's decision if s/he decides to prescribe or not prescribe tranquilizers						
Totally agree	10	7318	22	1	1	1
No totally agree or disagree	0–9	6867	35	1.70 (0.99, 2.89)	1.92 (1.13–3.30)	1.29 (0.91, 1.83)

(continued on next page)

Table 2 (continued)

Knowledge or Attitude Statement	Level of agreement*	Person-weeks of observations	Misuse	Crude IRR (95%CI)	Adjusted IRR (95%CI)**	
					Without imputation	After imputation
Q13. If I believe that I need a tranquilizer and the doctor did not prescribe it, I will get it at the pharmacy without a prescription						
Totally disagree	0	10882	38	1	1	1
No totally disagree or agree	1–10	3253	18	1.58 (0.90, 2.78)	1.55 (0.88–2.73)	1.19 (0.77, 1.84)
Q14. Doctors often explain clearly to the patient the reasons for prescribing or not prescribing tranquilizers						
1st tertile	0–5	6234	22	1.16 (0.56, 3.84)	1.30 (0.63–2.68)	1.35 (0.73, 2.49)
2nd tertile	6–9	4211	24	1.88 (0.92, 3.84)	1.98 (0.97–4.06)	1.31 (0.87, 1.95)
3rd tertile	10	3630	11	1	1	1
Q15. Doctors often explain clearly to the patient the instructions for the use of tranquilizers						
Not tally agree or disagree	0–7	7247	27	0.85 (0.50, 1.42)	0.91 (0.54–1.52)	1.10 (0.71, 1.72)
Totally agree	8–10	6810	30	1	1	1
Q16. When you buy tranquilizers, the pharmacist tells you about the importance of correct therapeutic compliance/ adherence						
1st tertile	0–4	3670	20	1.10 (0.58, 2.10)	1.16 (0.61–2.23)	1.39 (0.79, 2.44)
2nd tertile	5–8	6890	20	0.59 (0.31, 1.12)	0.62 (0.32–1.20)	1.12 (0.70, 1.79)
3rd tertile	9–10	3440	17	1	1	1

IRR: Incidence Rate Ratio; CI: Confidence Interval.

* Participants level of agreement on the corresponding statement expressed in a 0–10 Likert scale.

** IRR adjusted for sex, age and occupational status.

3.2. Association of personal Attitudes with tranquilizer misuse

Personal attitudes towards tranquilizers are strongly associated with their misuse.

Individuals who would agree to take tranquilizers to sleep (Q1) or work (Q4) better are at substantially higher risk of misusing these drugs as compared with those who disagree on using tranquilizers for these motives [3rd tertile: IRR_{Q1}: 5.10 (95%CI: 2.74–9.48) and IRR_{Q4}: 2.04 (95%CI: 1.05–3.99)] (Table 2).

Subjects who did not totally disagree on keeping taking tranquilizers even after completing the prescribed course of treatment (Q2) are twice more likely to misuse tranquilizers than those who totally disagree on extending the use of tranquilizers beyond the prescribed period [IRR_{Q2}: 2.45 (95%CI: 1.46–4.13)] (Table 2).

Similarly, individuals who do not completely reject the use of tranquilizers for recreational purposes (Q3) are at higher risk of misusing these drugs in comparison with subjects who totally disagree on taking tranquilizers for this purpose [2nd tertile: IRR: 1.85 (95%CI: 1.04–3.32)] (Table 2). A similar association, albeit not statistically significant, was observed at higher levels of agreement [3rd tertile: IRR: 1.87 (95%CI: 0.91–3.85)] (Table 2).

The probability of tranquilizers misuse by individuals who prefer to store tranquilizers at home for a potential need in the future (Q11) is five times higher than that of subjects who totally disagree on storing tranquilizers [IRR: 5.07 (95%CI: 2.73–9.40)] (Table 2).

3.3. Association of patient's Attitudes towards their healthcare provider with tranquilizer misuse

Lack of trust and communication between patients and healthcare providers with regards to tranquilizer prescription is associated with their misuse.

Adults who do not fully trust the decision of their physician about tranquilizer prescription (Q12) are almost twice more likely to misuse these drugs when compared with subjects who fully trust their physician [IRR: 1.92 (95%CI: 1.12–3.30)] (Table 2).

Individuals who believe that doctors do not often explain clearly to

the patient the motives of prescribing or not prescribing tranquilizers (Q14) seem to be more likely to misuse these drugs, although the association observed is not statistically significant [2nd tertile: IRR: 1.98 (95%CI: 0.97–4.06)] (Table 2).

3.4. Robustness analyses

Assuming that all individuals who were lost to follow up had not misused tranquilizers yielded similar results to those of the main analysis. Conversely, under the assumption that all lost to follow-up were misusers, the magnitude of the effect was meaningfully smaller.

Our multiple imputation analysis (Table 2) confirmed the association of Knowledge and Attitudes with the misuse Practices of tranquilizers, yet with lower strength. The highest changes were observed in the IRR estimates of Q1 [agreeing to take tranquilizers in order to sleep better] (from 5.10, 95%CI: 2.74–9.48 to 2.16, 95%CI: 1.46–3.19), Q2 [taking tranquilizers even after completing the prescribed course of treatment] (from 2.45, 95%CI: 1.46–4.13 to 1.58, 95%CI: 1.11–2.26), and Q11 [storing tranquilizers for later use] (from 5.07, 95%CI: 2.73–9.40 to 1.70, 95%CI: 1.13–2.56).

After correction for non-differential exposure misclassification using our sensitivity and specificity estimates, the increase in the Odds Ratios was particularly high for Q2 [taking tranquilizers even after completing the prescribed course of treatment], Q3 [taking tranquilizers for recreational purposes], Q6 [whether tranquilizers increase the risk of traffic accidents], Q13 [trying to obtain tranquilizers at the pharmacy without a prescription], Q14 [whether doctors explain the reasons for prescribing or not prescribing tranquilizers] and Q16 [whether pharmacists explain the importance of therapeutic adherence] (data not shown).

4. Discussion

Our results show that tranquilizer misuse is substantially associated with *personal attitudes* toward tranquilizers and *patient - healthcare-provider relationship*. Conversely, previous *knowledge* does not seem to be related to misuse. These findings are not easily ascribed to confounding, misclassification, or bias from loss to follow-up.

The prospective study design ensured that usual *knowledge* and *attitudes* were assessed before the determination of misuse episodes, and thus prevented differential reporting of *knowledge* and *attitudes* between misusers and non-misusers.

Furthermore, we adjusted for factors potentially linked to misuse, and conducted sensitivity analyses to assess the influence of loss to follow-up, but the results did not materially change.

Patients' decision of using a certain medicine and their adherence to the treatment instructions is highly affected by their awareness of the risks associated with the medication (Von Wartburg, 1984). In addition, in the case of tranquilizers, individuals' perception of prescription drugs as being socially accepted, safe and easily obtainable encourage their use (Quintero et al., 2006; Weyandt et al., 2009). In Spain, tranquilizers cannot be obtained without a medical prescription. Nonetheless, misuse can still take place as patients may fail to adhere to the treatment regimen, store leftovers of tranquilizers or share these drugs with someone else. The high obtainability of drugs influences the individual's perception or behaviour towards those drugs and promote their misuse (Gillespie et al., 2009; Gras et al., 2020; Wills et al., 1996). A recent study reported an increased prevalence of self-medication in Spain (Niclos et al., 2018), and previous prescriptions and friends were identified as the most common sources of self-medication (Bennadi, 2013). Almost all participants in our study were in the working age and one-third of the misusers of tranquilizers were unemployed when they enrolled in the study. Unemployment has a negative impact on the psychological state and mental health of the working-age population and thus, may increase the consumption of tranquilizers (Batic-Mujanovic et al., 2017; Navarro-Mateu et al., 2015).

We reported that individuals who would accept prolonging the use of tranquilizers even after improving are at substantial higher risk of misusing tranquilizers. Patients who use tranquilizers for a long time can experience physical dependence on these drugs. In fact, benzodiazepines, which represent the major class of tranquilizers, are safe if used for two to four weeks. Beyond the one-month use, half of patients start to develop dependence (De las Cuevas et al., 2003; Lader, 2011). Benzodiazepines affect the central nervous system, and their mechanisms of action is similar to that of other addiction drugs (Luscher and Ungless, 2006; Saal et al., 2003; Tan et al., 2010).

The present study suffers from some limitations. Studies relying on observations of individuals are prone to a bias known as "Hawthorne effect", i.e. individuals participating in research studies tend to enhance their behavior due to the feeling of being invigilated (McCambridge et al., 2014). Another related bias is "social desirability bias" (Tourangeau and Yan, 2007), where participants fail to report their misuse practices towards tranquilizers and tend to give socially accepted answers. In our study, we measured the exposure (Knowledge and Attitude) at baseline only, and thus it is possible that some participants might have changed their exposure category during the follow-up and improved their use of tranquilizers.

Previous studies showed that individuals with low level of knowledge are less likely to respond to research studies (Purdie et al., 2002; Tolonen et al., 2005), and may then abandon follow-up more frequently, therefore introducing a selection bias. Nonetheless, this was unlikely to take place in our study as individuals who abandoned the study after baseline assessment and those who completed the follow-up questionnaires had similar levels of knowledge and attitudes. Furthermore, loss to follow-up in our study, although limited to 11 % of the population, may have reduced the number of events of misuse of tranquilizers during the follow up, decreasing therefore the statistical power of the observed associations.

In summary, we found substantial evidence of an association between inappropriate attitudes and tranquilizer misuse. The association persisted after control for several potential determinants. Future studies in different settings and cultures are needed to confirm further these associations. These findings might help design intervention studies to enhance the rationale use of tranquilizers.

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None declared.

Contributors

NM conceived the research idea, collected, analyzed, and interpreted the data, and designed and wrote the manuscript. NM, AF and BT designed the study. HHM participated in data analysis. AF and BT supervised data analyses and interpretation. All authors reviewed and revised the manuscript and counted responsible for its content.

Data statement

The dataset generated and analysed in this study is available the data repository FigShare at the following link: <https://figshare.com/s/d69b99d1ab0299e83aba> [Reserved DOI: <https://doi.org/10.6084/m9.figshare.13453805>].

Declaration of Competing Interest

The authors report no declarations of interest.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.drugalcdep.2021.108793>.

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