

## **Knowledge and use of over-the-counter drugs in Italy: a survey-based study in the general population**

Stefania Chiappini<sup>1,2</sup>, Franca Ceci<sup>1</sup>, Alessio Mosca<sup>1</sup>, Francesco Di Carlo<sup>1</sup>, Julius Burkauskas<sup>3</sup>, Mauro Pettorruso<sup>1</sup>, Giovanni Martinotti<sup>1,2</sup>, Amira Guirguis<sup>4</sup>; John M. Corkery<sup>2</sup>; Norbert Scherbaum<sup>5</sup>, Fabrizio Schifano<sup>2</sup>, Massimo Di Giannantonio<sup>1</sup>

<sup>1</sup>Department of Neurosciences, Imaging and Clinical Sciences, Università degli Studi G. D'Annunzio, 66100 Chieti-Pescara, Italy; stefianiacchiappini9@gmail.com (S.C.); [franca.ceci@live.it](mailto:franca.ceci@live.it) (F.C.); alessio.mosca909@gmail.com (A.M.); francesco.dic@hotmail.it (F.D.C.); mauro.pettorruso@hotmail.it (M.P.); giovanni.martinotti@gmail.com (G.M.); digiannantonio@unich.it (M.D.G.)

<sup>2</sup>Psychopharmacology, Drug Misuse and Novel Psychoactive Substances Research Unit, School of Life and Medical Sciences, University of Hertfordshire, Hertfordshire AL10 9AB, UK; stefianiacchiappini9@gmail.com (S.C.); giovanni.martinotti@gmail.com (G.M.); [j.corkery@herts.ac.uk](mailto:j.corkery@herts.ac.uk) (J.M.C.); [f.schifano@herts.ac.uk](mailto:f.schifano@herts.ac.uk) (F.S.)

<sup>3</sup>Laboratory of Behavioral Medicine, Neuroscience Institute, Lithuanian University of Health Sciences, 00142 Palanga, Lithuania; [julius.burkauskas@ismuni.lt](mailto:julius.burkauskas@ismuni.lt) (J.B.)

<sup>4</sup>Swansea University Medical School, The Grove, Swansea University, Swansea, SA2 8PP, UK; amira.guirguis@swansea.ac.uk (A.G.)

<sup>5</sup> Department of Addictive Behaviour and Addiction Medicine, LVR-Klinikum Essen, Hospital of the University of Duisburg-Essen, Germany [norbert.scherbaum@uni-due.de](mailto:norbert.scherbaum@uni-due.de) (N.S.)

Corresponding author

Amira Guirguis

[amira.guirguis@swansea.ac.uk](mailto:amira.guirguis@swansea.ac.uk)

## **ABSTRACT (300/300 words)**

**BACKGROUND:** During the past decade the misuse of over-the-counter (OTC) medicines has become a global public health concern especially among young people. In this study, we aimed to identify current trends of OTC consumption and related misuse in Italy, exploring the level of knowledge on their diversion and eventual risk factors in the general population.

**METHODS:** The study consisted of an anonymous online survey distributed by direct contact and via the internet between June-November 2021 to the general population living in Italy. Descriptive statistics were reported, and regression analyses were performed to identify risk factors for lifetime misuse of OTC. The study was approved by the University of Hertfordshire (aLMS/SF/UH/02951).

**RESULTS:** A number of 717 subjects responded to the survey and were included in the study. Sample was mainly represented by female (69.3%) students (39.9%) in the 20-25 years age group (30.0%). Based on the survey responses, study participants were divided into two groups according to the presence/absence of OTC abuse/misuse (127 versus 590), which were compared for possible predictors of OTC diversion. Concomitant substances used with OTC were alcohol (8.8%), prescription medicines (6.1%), other OTC (4.7%), and cannabis (2.6%). Multivariate regression showed that the strongest predictor of OTC abuse/misuse was knowledge of the effects of OTC [odds ratio/OR of 2.711, 95% Confidence Interval/CI 1.794-4.097,  $p < 0.001$ ]. The probability of OTC abuse/misuse almost doubled when individuals purchased OTC without indication [OR = 1.54, 95% CI 1.02–2.34,  $p = 0.042$ ]. Finally, education was negatively correlated with OTC abuse/misuse [OR = 0.695, 95% CI 0.58–0.94,  $p = 0.016$ ].

**CONCLUSION:** Although, according to our data, the phenomenon of OTC abuse appeared to be limited, increasing attention is needed because of its possible underestimation and high-risk outcomes. Preventive strategies, including a simplified access to information, may play a key role in the limitation of OTC drugs misuse.

**KEY WORDS:** over-the-counter drugs, OTC, drug misuse, drug diversion, survey

## **Plain Language Summary (PLS)**

### **Knowledge and use of over-the-counter drugs in Italy: a survey-based study in the general population**

Given the new trends in substance use emerged over the last decade, the abuse of over-the-counter (OTC) drugs has now becoming a global public health concern, especially in the young-adult category. In Italy, considered the little current evidence relating to the prevalence of OTC misuse and dependence, their extent has not been quantified yet, and types of drugs, modes of misuse, and total number of people affected have not been adequately determined. Therefore, here we aimed to identify current trends in OTC consumption and abuse in Italy, exploring the level of knowledge about their diversion and possible risk factors in the general population. The study consisted of an anonymous online survey distributed by direct contact and via internet between June-November 2021 to the general population residing in Italy.

A number of 717 subjects responded to the survey and were included in the study. The sample was mainly represented by female students in the age group 20-25 years. Based on survey responses, study participants were divided into two groups based on the presence/absence of OTC abuse/abuse (127 versus 590), which were compared for possible predictors of OTC diversion. Concomitant substances used with OTCs were alcohol (8.8%), prescription drugs (6.1%), other OTCs (4.7%), and cannabis (2.6%). The strongest predictor of OTC abuse/abuse was knowledge of the effects of OTCs; moreover, the probability of OTC misuse/abuse almost doubled when individuals purchased OTCs without indication. Finally, education was negatively related to OTC abuse.

Given the limited research in this area, the present study provided significant findings related to the misuse of OTC in Italy. Although, according to our data, the phenomenon of OTC abuse appeared to

be limited, more attention is needed because of its possible underestimation and high-risk outcomes, and preventive strategies may play a key role in limiting OTC drug abuse.

## **1. Introduction**

### *1.1 The 'pharming' phenomenon*

Over the counter medicines (OTC) are drugs that can be purchased from a pharmacy, online stores and supermarkets without a prescription and are available for self-medication, including several products used for the treatments of self-limiting conditions or minor illnesses, e.g., acute sore throat, conjunctivitis, coughs/colds and nasal congestions, diarrhoea, minor pain, travel sickness, etc. They are generally considered safe medications, however some of them may potentially be harmful due to an inappropriate intake, adverse drug reactions, and drug interactions, but also due to dependence and diversion issues (1–8). In fact, OTC might be abused and diverted to reach psychoactive recreational effects through idiosyncratic reactions related to unusual routes of administration, high or very-high dosages and combination of licit/illicit drugs to enhance effects (1,3,9,10). These issues are related to the phenomenon known as *pharming* (1,11) which identify the possibility of diversion of medicines in order to achieve psychoactive effects (11–13). OTC medications may be easily diverted due to several factors: i) they are ubiquitous and easily available and may be easily purchased at local stores and on the internet; ii) they are often inexpensive; and, finally, iii) they are legal and are perceived to be harmless (3,11). The most commonly abused OTC include: i) antihistamines, e.g., chlorphenamine, diphenhydramine and dimenhydrinate (3,14,15); ii) syrups based on codeine and/or promethazine (3,16–18); iii) dextromethorphan cough syrups (3,11,19); iv) drugs based on ephedrine and pseudoephedrine (3,20); v) loperamide (3,21,22); vi) and benzydamine-based anti-inflammatories (3,23,24).

### *1.2 Current prevalence of OTC diversion*

A major problem in assessing the extent of OTC misuse is the limited research on the problem as it is mostly focused on the abuse of illicit drugs (1,25). Currently, even though the problem of OTC abuse has been recognized and studied in recent decades (5,11,26), there is limited information on the prevalence of OTC misuse (12,13,27). According to a mixed-method systematic review, the prevalence reported via survey questionnaires with pharmacy customers and the general public ranged from 3.1 to 59% for misuse, 0.8 to 4.1% for abuse and 4.2 to 17.8% for dependence, while the prevalence of OTC medicines problematic use reported through national databases was variable,

with an overall pooled prevalence in the population-based studies recorded of 16.2% for misuse, 2.0% for abuse, and 7.2% for dependence (28). The same review study described analgesics (with or without codeine), sedative antihistamines, and cough mixtures containing dextromethorphan as the groups of OTC drugs most commonly involved in a problematic use (28). It is possible that the diversion of OTC may be underestimated because of the ease of purchasing OTC which promotes self-management which in turn, may increase diversion to the inherent abuse potential of some of these OTC medicines (25). Indeed, among pharmacists, there are increasing concerns about the possible inappropriate use of OTC in several countries, including the United Kingdom (UK) (4,25,26,29,30) and the United States of America (USA) (10,31,32). A further issue is the impact of the CoronaVirus Disease (CoViD)-19 pandemic on drug markets, which has introduced numerous changes in drug consumption habits e.g., an increase in drug amounts used, relapse, or shifts to other substances if access to illicit or other substances previously used has become limited. These changes have been associated with increased internet drug-seeking activities, increased access to websites promoting rogue/illicit pharmaceutical products, such as benzodiazepines, or the use of alternative drugs or medications, including OTC medications (33–36).

### *1.3 Data regarding OTC and self-medication in Italy*

According to the current literature available, there are several data concerning the patterns of use of certain OTC drugs in Italy, e.g., analgesic medications, including both opioids and non-opioids, used for the treatment of headache (37) or pain in general (38). OTC inappropriate use has been recorded mainly in specific categories, such as the elderly (38) and pregnancy women (39). A recently published study highlighted the value of the regulatory switch from prescription to non-prescription medicines in Italy, showing that greater availability of non-prescription/OTC drugs could determine a positive economic impact and promote greater adherence to therapy, resulting in more effective prevention or treatment of minor pathologies, but also, conversely, be associated with the risk of the misuse, requiring patient education and training (40). Despite of this, the current evidence relating to the prevalence of OTC misuse and dependence in Italy is still limited. Because of this, the extent of OTC misuse in Italy has not been quantified yet, and the types of drugs, modes of misuse, and total number of people affected have not been adequately determined.

*Aim of the study:* identify the trends and prevalence of OTC misuse in Italy to quantify this phenomenon, identify the demographic characteristics of people/individuals who are involved in OTC diversion, and the types and modes of misuse and diversion.

## 2. Methods

### 2.1 Questionnaire

The questionnaire used for the survey consisted of 15 multiple-choice questions aiming at collecting socio-demographic information of the participants, investigating the use and possible abuse/misuse of OTC, and eventual combination with other substances. The survey included:

i) general information, such as age, gender, occupation, level of education achieved, country of origin/residence;

and ii) information regarding the information about the abuse and misuse of OTC medicines: a) their purchase without a medical indication; b) type of OTC drug, including benzydamine mouth wash, spray, tablet or gel, e.g., Difflam®, Tantum Rosa®, Rosalgin®, and commercial brands; chlorphenamine-containing medicines, e.g., Piriton®, Allercalm®, Hayleve®, Chlortripton®, Panadol®, and commercial brands; codeine-containing medicines, e.g., Cocodamol®, Nurofen plus®, Adcodol®, and brand names; loperamide, e.g., Imodium®, and brand names; dextromethorphan-containing cough syrups, e.g., Coricidin®, Delsym®, Dimetapp®, Mucinex®, Robitussin®, Sucrets®, Vicks®, and store brands; diphenhydramine and dimenhydrinate medications, e.g., Benadryl®, Dramamine®, and store brands; ephedrine- and pseudoephedrine-containing medications, e.g., ActiPe®, Actifed®, Sudafed®, Claritin-D®, Panadol®, and store brands; hyoscine butyl bromide products, e.g., Buscopan®, and brand names; syrup and tablets containing promethazine, e.g., Phenergan®, and commercial brands; c) the effect sought, e.g. self-medication, psychoactive effects/recreational purposes, to increase/reduce the effects of concomitant drugs used; d) OTC dosage (e.g. above/below indication); e) licit or illicit concomitant substances; f) knowledge on OTC abuse/misuse potential effects and harms; etc.

In the survey, the terms *non-medical use* or *misuse* or *abuse* in relation to a medication are considered as a single phenomenon and used interchangeably, even though referring to specific conditions. As a reference we could here consider the definitions available on the Medical Dictionary for Regulatory Activities-MedDRA (MedDRA) (41), which is a standardised medical terminology used worldwide in pharmacovigilance, where the term *misuse* describes the intentional use for a therapeutic purpose by a patient or consumer of a product, OTC or prescription, other than as prescribed or not in accordance with the authorised product information. Similarly, the European Monitoring Centre for Drugs and Drug Abuse (EMCDDA) indistinctly uses *diversion*, *misuse*, and *non-medical use* of medications, terms referring to situations where the medicinal product is intentionally and inappropriately used not in accordance with the authorised product information, e.g., a prolonged and continued use of medications, even after the original health problem for which the drug was prescribed has been resolved; or the use of a molecule in amounts exceeding the therapeutic dosage,

outside the indications, and in combination with other drugs or medicines(42). The National Institute on Drug Abuse (NIDA) uses *drug misuse* to distinguish improper or unhealthy use from use of a medication as prescribed, including the repeated use of drugs to produce pleasure, alleviate stress, and/or alter or avoid reality, using prescription drugs in ways other than prescribed, or using someone else's prescription(43). Similarly, NIDA uses the term *misuse*, as it is roughly equivalent to the term *abuse*, which is considered a diagnostic term that is increasingly avoided by professionals because it can be shaming and stigmatizing(43), whereas the MedDRA considers *drug abuse* the habitual use of drugs that are not needed for therapeutic purposes (e.g., to alter mood); to effect a body function unnecessarily (e.g., laxative); and non-medical use of drugs(41). Interestingly, highlighting its consequences, the UK Advisory Council on the Misuse of Drugs (ACMD), characterised *problematic drug use* as a condition that may cause an individual to experience social, psychological, physical, or legal problems related to intoxication and/or regular excessive consumption, and/or dependence(44). Indeed, misusing prescription drugs involves not only risks associated with the drugs themselves, but also with the general context in which they are consumed. These include side-effects, interactions between licensed medicines and other unlicensed substances or products (food and environmental chemicals), and individual variation in responses (genetic differences and possible comorbidities), which might be associated with a range of severe adverse reactions and fatalities (1,25,42,45,46).

## 2.2 Procedure

The survey was distributed to the general population by direct contact (e.g., acquaintances, students, psychiatrists working in hospitals and addiction centres) and via the internet (e.g., emails, social networks, online fora), through the snowball sampling technique (47), consisting in inviting participants to share the survey with their contacts. In fact, researchers encouraged participants to send the link to other participants, helping to reach an adequate study sample. However, the engagement rate was not monitored. A formal online consent was provided for each participant to tick before starting the survey. Participation to the survey was anonymous and free of compensation. The web-based survey platform was Microsoft Forms, which was used to collect the recorded data. Post recruitment, data were securely stored as Microsoft Excel sheets at the University of Chieti (Italy), Department of Neurosciences.

## 2.3 Data collection

The study was conducted between June 2021 and November 2021 and the survey was administered to the Italian general population from 15 years of age.

## *2.4 Statistical analysis*

All statistical analyses were performed using IBM SPSS windows version 22. Normality checking yielded adequate values. Groups of individuals (non-abusing/misusing vs. abusing/misusing) were compared using Chi-square test with paired Z test and Fisher's exact test, as appropriate. Binary logistic regressions were calculated to inspect how education, purchase OTC drugs without indication and have knowledge of OTC drugs misuse/abuse side effects predict the OTC drugs abuse/misuse (classified as 0, "non-abusing/non-misusing" or 1, "abusing/misusing"), controlling for age, gender, and employment status. With a given sample size and the number of 6 predictor variables, we were able to achieve power ranging from 0.82 to 0.99.

## *2.5 Ethical approval*

The study was approved by the Human Sciences Ethics Committee at the University of Hertfordshire (HSK/SF/UH/00104); protocol number is aLMS/SF/UH/02951(2). It complied with the Declaration of Helsinki and with the European General Data Protection Regulation (48).

# **3. Results**

## *3.1 Demographic characteristics*

All 717 subjects responded to the survey and were included in the study. About two-thirds (n= 497/717) of the participants were females (69.3%). In addition, about a third (n= 215/717) of the participants belonged to the 20-25 age group. Participants were mostly represented by students (39.9%) or workers (47.3%) and had a high-school diploma (50.9%). Based on the survey responses, study participants were divided into two groups according to the presence/absence of OTC abuse/misuse (127 versus 590), which were compared for possible predictors of OTC diversion. Thus, similar characteristics were reported when dividing the whole sample in the two groups considering the presence of OTC abusing/misusing issues (127/717 : 17.7%). Detailed socio-demographical data are reported in Table 1.

## *3.2 Drug knowledge and use*

Overall, a significant percentage of respondents (567 subjects : 79.1%) purchased OTC medicines without any licensed indication. Of these, approximately 43.7 % had been advised to use the medicine by a family member and 21.7% by an acquaintance / friend, while others had found the suggestion on a web page (8.6%) or on an online forum (1.6%). About 12.8% of the respondents recorded to have used OTC in combination with one or more other substances. The substances most used in

combination with OTC medicines were alcohol (8.8%), prescription only medicines (6.1%), other OTC products (4.7%), and cannabis (2.6%). Results regarding cocaine, opioids and ketamine were not statistically significant. Finally, the majority (66.0%) of the participants declared that they knew the side effects of OTC abuse/misuse. Of the entire sample 17.7% (n=127 subjects) declared of having made an abuse/misuse of OTC. In the abusing / misusing group, data recorded were similar, however, interestingly, about 15% declared they abused other substances than OTC medicines, such as cocaine and cannabis. The percentage of respondents who stated that they had no knowledge of the side effects of OTC drug abuse was significant (55.9%). Full data of the entire participant sample and of the two groups of subjects are shown in Table 1.

**Table 1. Demographic characteristics of study participants**

|   | <b>Total</b> | <b>Non abusing/<br/>misusing</b> | <b>Abusing/<br/>misusing</b> | $\chi^2$ | <b>p</b>    |
|---|--------------|----------------------------------|------------------------------|----------|-------------|
|   | <b>N=717</b> | <b>n=590</b>                     | <b>n=127</b>                 |          |             |
| Age:                                      |              |                                  |                              | 14.527   | <b>.024</b> |
| 15-20 yrs.                                | 53(7.4%)     | 42(7.1%)                         | 11(8.7%)                     |          |             |
| 20-25 yrs.                                | 215(30.0%)   | 170(28.8%)                       | 45(35.4%)                    |          |             |
| 25-30 yrs.                                | 133(18.5%)   | 114(19.3%)                       | 19(15.0%)                    |          |             |
| 30-35 yrs.                                | 76(10.6%)    | 67(11.4%)                        | 9(7.1%)                      |          |             |
| 35-45 yrs.                                | 94(13.1%)    | 86(14.6%)                        | 8(6.3%)                      |          | <b>.012</b> |
| 45-65 yrs.                                | 125(17.4%)   | 94(15.9%)                        | 31(24.4%)                    |          | <b>.022</b> |
| over 65 yrs.                              | 21(2.9%)     | 17(2.9%)                         | 4(3.1%)                      |          |             |
| Gender:                                   |              |                                  |                              | 5.476    | <b>.019</b> |
| Male                                      | 220(30.7%)   | 170(28.8%)                       | 50(39.4%)                    |          |             |
| Female                                    | 497(69.3%)   | 420(71.2%)                       | 77(60.6%)                    |          |             |
| Occupation:                               |              |                                  |                              | 6.760    | .080        |
| Student                                   | 286(39.9%)   | 229(38.8%)                       | 57(44.9%)                    |          |             |
| Worker                                    | 339(47.3%)   | 291(49.3%)                       | 48(37.8%)                    |          | <b>.019</b> |
| Unemployed                                | 51(7.1%)     | 40(6.8%)                         | 11(8.7%)                     |          |             |
| Retired                                   | 41(5.7%)     | 30(5.1%)                         | 11(8.7%)                     |          |             |
| Employed:                                 |              |                                  |                              | 5.571    | <b>.018</b> |
| No  | 378(52.7%)   | 299(50.7%)                       | 79(62.2%)                    |          |             |
| Yes                                       | 339(47.3%)   | 291(49.3%)                       | 48(37.8%)                    |          |             |
| Education:                                |              |                                  |                              | 12.957   | <b>.004</b> |
| Middle School diploma                     | 65(9.1%)     | 46(7.8%)                         | 19(15.0%)                    |          | <b>.011</b> |
| High School diploma                       | 365(50.9%)   | 293(49.7%)                       | 72(56.7%)                    |          |             |
| Degree                                    | 235(32.8%)   | 203(34.4%)                       | 32(25.2%)                    |          | <b>.045</b> |
| Postgraduate qualification                | 52(7.3%)     | 48(8.1%)                         | 4(3.1%)                      |          | <b>.048</b> |
| Purchased an OTC drug without indication: |              |                                  |                              | 4.111    | <b>.043</b> |
| No  | 150(20.9%)   | 115(19.5%)                       | 35(27.6%)                    |          |             |
| Yes                                       | 567(79.1%)   | 475(80.5%)                       | 92(72.4%)                    |          |             |
| Familiar                                  | 248(43.7%)   | 207(43.6%)                       | 41(44.6%)                    | 0.030    | .861        |
| Acquaintance/friend                       | 123(21.7%)   | 99(20.8%)                        | 24(26.1%)                    | 1.248    | .264        |
| Web page                                  | 49(8.6%)     | 42(8.8%)                         | 7(7.6%)                      | 0.149    | .700        |
| Forum online                              | 9(1.6%)      | 7(1.5%)                          | 2(2.2%)                      | 0.242    | .644        |
| Substance use:                            |              |                                  |                              | 0.626    | .429        |
| No  | 625(87.2%)   | 517(87.3%)                       | 108(85.0%)                   |          |             |
| Yes                                       | 92(12.8%)    | 73(12.4%)                        | 19(15.0%)                    |          |             |
| Alcohol                                   | 63(8.8%)     | 54(9.2%)                         | 9(7.1%)                      | 0.557    | .456        |
| Prescription drugs                        | 44(6.1%)     | 36(6.1%)                         | 8(6.3%)                      | 0.007    | .933        |
| Over-the-counter medications              | 34(4.7%)     | 24(4.1%)                         | 10(7.9%)                     | 3.352    | <b>.067</b> |
| Cannabis                                  | 19(2.6%)     | 15(2.5%)                         | 4(3.1%)                      | 0.149    | .759        |
| Cocaine                                   | 3(0.4%)      | 2(0.3%)                          | 1(0.8%)                      | 0.504    | .443        |
| Opioids                                   | 2(0.3%)      | 0(0.0%)                          | 2(1.6%)                      | 9.317    | <b>.031</b> |

|   |            |            |           |        |       |
|---|------------|------------|-----------|--------|-------|
| Ketamine  | 1(0.1%)    | 0(0.0%)    | 1(0.8%)   | 4.652  | .177  |
| Knowledge of OTC drugs misuse/abuse side effects: |            |            |           | 32.896 | <.001 |
| Yes   | 473(66.0%) | 417(70.7%) | 56(44.1%) |        |       |
| No  | 244(34.0%) | 173(29.3%) | 71(55.9%) |        |       |

Abbreviations: OTC: over-the-counter; yrs: years

### 3.3 Regression analysis

Logistic regression on OTC drug abuse/misuse [classified as 0, “non-abusing/non-misusing” or 1, “abusing/misusing”] in the model included: i) education; ii) the purchase of OTC drugs without indication (0, “no”; 1, “yes”); iii) having a knowledge on OCT drugs side effects (0, “have knowledge”; 1, “have no knowledge”); iv) age; v) gender; and vi) employment status. The strongest predictor of OTC abuse/misuse, with an odds ratio (OR) of 2.711, 95% Confidence Interval (CI) 1.79–4.10,  $p < 0.001$ , was the knowledge on the substance use side effects. The probability of OTC drugs abuse/misuse almost doubled when individuals purchased OTC without indication [OR = 1.54, 95% CI 1.02–2.34,  $p = 0.042$ ]. Education was also significant and was negatively related with OTC drugs abuse/misuse [OR = 0.695, 95% CI 0.58–0.94,  $p = 0.016$ ] (Table 2).

**Table 2. Logistic regression model of factors associated with OCT abuse/misuse**

| Total N=717<br>(Non abusing/<br>misusing: n =<br>590)/ Abusing/<br>misusing: n = 127) | Variables   | B            | Standard Error | OR           | CI           |              | p                |
|---|---|--------------|----------------|--------------|--------------|--------------|------------------|
|   |   |              |                |              | Min          | Max          |                  |
|   | Age   | -.006        | .063           | .994         | .878         | 1.125        | .923             |
|   | Gender  | -.196        | .220           | .822         | .534         | 1.265        | .373             |
|   | Employed  | -.265        | .243           | .767         | .477         | 1.235        | .275             |
|   | <b>Educational level</b>                                  | <b>-.364</b> | <b>.151</b>    | <b>.695</b>  | <b>.517</b>  | <b>.935</b>  | <b>.016</b>      |
|   | <b>Purchase of OTC drugs without indication</b>           | <b>.433</b>  | <b>.213</b>    | <b>1.542</b> | <b>1.017</b> | <b>2.339</b> | <b>.042</b>      |
|   | <b>Knowledge of OTC drugs misuse / abuse side effects</b> | <b>.997</b>  | <b>.211</b>    | <b>2.711</b> | <b>1.794</b> | <b>4.097</b> | <b>&lt; .001</b> |
|   | Constant  | -.893        | .577           | .410         |              |              | .122             |

Abbreviations: CI: Confidence Interval; Odds Ratio: OR; OTC: over-the-counter

Gender – male (1)/female (2); Employed – No (0), Yes (1); Purchase Over-the-er drug without indication – No (0), Yes (1); Have no knowledge – have (0), No have/I have never used the previous drugs (1).

## 4. Discussion

Given the limited research in this area, the present study provided significant findings related to the misuse of OTC in Italy. Indeed, the aim of the present study was to identify trends and patterns of OTC consumption in Italy through a cross-sectional, observational design. Frequency of use, type of

OTC used, risk for abuse/misuse were the main aspects investigated. Predictors and eventual factors which might constitute a risk for OTC abuse/misuse were also explored.

Firstly, due to the heterogeneity regarding data focusing on prescription drug misuse and the issues in identifying misusing practices, we have here considered the United Nations Office on Drugs and Crime (UNODC) definition of misuse of medicines, described as ‘the problematic consumption outside of acceptable medical practice or medical guidelines, when self-medicating at higher doses and for longer than is advisable, for intoxicating purposes and when risks and adverse consequences outweigh the benefit’ (12,13,49). Indeed, abuse and misuse of OTC medicines refers to an inappropriate use of the product in excessive dosages or not in accordance with the marketing authorization. As shown by the data presented here, this is a considerable problem associated with substantial risk of harm in the Italian scenario. Data from international surveys such as the National Surveys on Drug Use and Health in the US, equally showed similar trends with increasing misuse of medications, prescription psychotropics, and OTC medicines, especially in the age range 18-25 years during 2019-2020 (50). A relevant part of our sample declared to misuse OTC in combination with other substances (3,11,25,51), possibly for recreational purposes (*high*) or to relax and relieve anxiety. However, many other reasons for the problematic use of OTC medicines were previously described (2,11,31), and included the need to manage frequent headaches and chronic pains with OTC analgesics, or the management of opioid withdrawal symptoms with codeine-based medications or loperamide. Among OTC medicines, opiate-based products and cough/cold products containing dextromethorphan, sleep aids, sedative antihistamines, analgesics, hypnotics, and laxatives have been highlighted as having abuse potential (2,42). The OTC codeine or other opioid-containing products, and OTC cough and cold medications have been identified as the most commonly implicated medications with abuse potential (26,52). Moreover, together with opioids, dextromethorphan, some antihistamines such as chlorpheniramine or promethazine, and pseudoephedrine prolonged use and overdosing might result in physical, psychological, and social life consequences, but also in a full substance dependence (2,23,26,53) and severe outcomes which might lead to life-threatening or fatal conditions, such as the serotonin syndrome (3,23,54). All these consequences might clearly involve an economic cost to the health care system due to increasing hospitalisation and multiple admissions (42). Therefore, this supports the need for interventions reducing the risk of OTC medicines’ problematic use, including drug up-scheduling, e.g. codeine was rescheduled as a prescription only medicine in some countries (55), or size and type sale limits, e.g. loperamide has been restricted to no more than 48 mg and requiring unit-dose blister packaging in the USA by the Food and Drug Administration (FDA) (56).

Our study showed that lower levels of educational attainment, purchasing OTC without licensed indications, and having no or a lacking knowledge about their side effects are factors which might contribute to the OTC medicines' problematic use, which is consistent with previous studies recording users' limited knowledge about OTC medications uses, indications, side effects, and safety risks with prolonged use (5,6,31,32). A survey previously conducted in Italy collected data regarding the use of OTC medications from 1,206 adults aged 18 years and older through a self-administered questionnaire, finding uncertain results regarding the non-medical use of OTC medicines (around 42% confused the concept of 'contraindications' with that of 'side effects') and potential side effects, e.g. most respondents were aware of the OTC general potential for side effects but 64.3% did not know about potential harms related to the use of painkillers in people with high blood pressure and the risks of long-term use of laxatives and codeine-based nasal decongestants (57).

Prevention approaches should focus on health education in order to support people to learn the appropriate use of OTC drugs while eliminating their misuse. Patients can take steps to ensure that they use prescription medications appropriately by: i) following the directions as explained on the label or by the pharmacist; ii) being aware of potential interactions with other drugs as well as alcohol, iii) never stopping or changing a dosing regimen without first discussing it with the doctor; iv) never using another person's prescription; v) never giving their prescription medications to others; vi) and safely storing prescription stimulants, sedatives, and opioids (58).

Healthcare professionals should be trained to identify and treat problematic use, and know how to address signs of non-medical use of medicines optimising the appropriateness, use and safety of OTC drugs (59). Moreover, offering support in primary care settings may be appropriate for people with problems associated with the non-medical use of medicines who are reluctant to seek help from traditional drug treatment services, such as professionals or non-regular drug users. Good clinical practice, supported by clear guidelines, can lower the risk that medicines being diverted and misused. In addition, pharmacists should play an increasing role in preventing the inappropriate use of medicines and reducing the associated risks and potential harms, and should therefore be included in educational programmes (2,8). Finally, public awareness and knowledge should be increased about the safe use of medications in people who might be identified as most vulnerable or at risk. Developing and implementing such responses, whether at EU, national, local, or individual level, should involve several steps, such as the identification of the nature of the drug problems to be addressed; the selection of potentially effective interventions to tackle these problems; and the implementation and monitoring of these interventions (42). Finally, a multidisciplinary team working, and holistic non-stigmatizing approaches should be helpful and effective during the overall process of patient care.

### *Limitations*

Despite the novelty of the study, it presented several limitations. Firstly, study enrolled a self-selected sample through an online questionnaire, and thus the generalisability of the findings could be reduced. A further limitation is related to the terminology used with regard to the definitions of *abuse*, *misuse*, and *non-medical use* of OTCs, which have been interchangeably used in the survey. In addition, some variables which could have been of interest were excluded due to the low statistical significance, e.g. the type of abuse/misuse ('in lower dosage'; 'in higher dosage'; 'number of different administrations'; 'for different indications'); or the reason for OTC abuse/misuse ('to have a psychotropic ("high") / recreational effect'; 'in combination with other drugs or substances to reduce their (side) effect'; 'in combination with other drugs or substances to accentuate their effect'). Moreover, the engagement rate was not monitored. However, all the participating respondents provided data sufficient for the analysis of the study variables. Also, due to the cross-sectional nature of the data, no causal relationship can be drawn between the variables. Finally, the use of an Italian-only sample could reduce the applicability of our findings to different cultural settings.

### **Conclusions**

The misuse of OTC medicines is a matter of increasing concern in Europe and is associated with a range of both acute health harms and chronic problems, such as dependence. Despite the limitations, the present study can provide important insight on the phenomenon of OTC abuse and misuse in Italy. Social education about the risks deriving from a misuse of OTC drugs should play a key role in preventing strategies, particularly among those individuals at increased risk as the youngest. Policies to prevent the diffusion of OTC without prescription through the web may also be improved. Comparative data for other countries across the European Union and beyond are needed to extend and generalize our findings, as well as to improve common preventive strategies.

### **Author Contributions**

Conceptualization, S.C., G.M., M.D.G., and F.S; writing—original draft preparation, A.M., A.Mi., F.C., and S.C.; statistical analysis: J.B.; writing—review and editing, S.C., G.M., F.D.C, N.S., M.P., M.D.G., A.G., and J.C. All authors have read and agreed to the published version of the manuscript.

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### **Conflicts of Interest**

F.S. was a member of the UK Advisory Council on the Misuse of Drugs (ACMD; 2011–2019) and is currently a member of the EMA Advisory Board (Psychiatry).

J.C. is a member of the ACMD's Novel Psychoactive Substances and Technical Committees.

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S.C., F.C., A.M., F.D.C., M.P., A. Mi., A.G., N.S., and J.B. have nothing to declare.

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