Off-label prescription of psychotropic medications in a sample of Italian psychiatrists working in private practice: a cross sectional study

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The Authors declare no conflict of interest

SUMMARY

Background
Off-label prescription refers to the use of a drug outside the terms of its Marketing Authorization. According to the literature, this practice is particularly common in clinical psychiatry.

Objective
To describe patterns of off-label prescription in a sample of Italian psychiatrists working in private practice.

Methods
An ad hoc questionnaire was developed and sent by e-mail to a sample of Italian psychiatrists working in private practice in the Region Emilia-Romagna. The questionnaire assessed frequency of off-label prescription, reasons associated with it, diagnostic categories more often associated with such practice, main sources of information used to support off-label prescription, and psychotropic agents most commonly prescribed off-label, as well as medical-legal implications. Data were analysed by means of univariate and multivariate ordered logistic regressions.

Results
Fifty psychiatrists (female: 44%) out of 129 who received the e-mail invitation responded (response rate: 39%). Off-label prescription was found to be inversely proportional to clinicians' age (OR = 10.53 [95% CI 2.13-52.13]). Most commonly, second-generation antipsychotics (SGAs) were prescribed to patients diagnosed with personality disorders (PDs) (OR = 0.08 [95% CI 0.02-0.36]). A higher rate of off-label prescription was also associated to relying more on pharmaceutical sales representatives (OR = 0.58 [95%CI 0.01-0.30]) or personal professionals' clinical experience (OR = 0.05 [95% CI 0.01-0.36]) and less on other colleagues' experience (OR = 11.80 [95% CI 4.16-33.50]) as source of information.

Conclusions
Off-label prescription is common, especially among young psychiatrists, who frequently rely on previous personal clinical experience, especially when prescribing SGAs for treating patients with PDs. Respondents pointed to the need for further research and training on the topic addressed by the present study.

Key words: *web survey, off-label prescription, psychiatry, private practice, psychotropic medications.*

Introduction

Off-label prescription is defined as the use in clinical practice of drugs already licensed by the competent regulatory institutions, though outside

the restricted terms of their market authorization [1]. Four main types of off-label prescription are recognized, depending on whether a drug is used for a different indication, a different group of patients, a different dosage, or a different therapeutic duration than the one approved [2]. Off-label prescription is a widespread phenomenon in various fields of medicine, especially in oncology, anaesthesia, neurology, general medicine, paediatric and child neuropsychiatry [3-7].

In psychiatry, knowledge on the extent of the phenomenon is very limited, though existing literature supports its wide diffusion in different sub-fields (e.g., adult psychiatry, child and adolescent psychiatry, geriatric psychiatry) [2]. A few reasons were hypothesized as explanations, some common to other medical disciplines, other more specific of psychiatry: first, the lack of licensed medications for many of the diagnostic categories described in the DSM [8]; second, the low rate of clinical effectiveness of licensed therapeutic approaches; third, the need to avoid side effects due to comorbidities [2]; fourth, limited knowledge on the pathogenesis of psychiatric disorders and on specific pharmacological targets [9]. Such reasons may lead psychiatrists to use psychotropic medication for unauthorized indications, or dosages, or to establish complex poly-pharmacotherapies [10]. During 2000-2001 Barbui et al. reported that nearly 50% of SGAs were dispensed off-label [11], having a more limited range of indications than first-generation antipsychotics (FGAs) and a generally more tolerable profile of side-effects. Aguglia and Salvi (2019) also estimated that nearly 50% of Italian psychiatrists prescribe SGAs off-label very often or often, particularly in case of severe PDs [12]. The very limited changes to the molecular targets of psychotropics since their pre-1960 prototypes, the overall poor knowledge on the mechanisms of action of not only SGAs but also Antidepressants (ADs) and "third-generation" drugs like aripi-/brexiprazole or cariprazine, combined with the low impact of psychotropics on disabling symptoms such as negative or cognitive symptoms of schizophrenia have resulted in a further increase of off-label or "near-label" prescriptions in the field of mental health [13-16], particularly when few effective treatments are available [17].

As elsewhere in the world, in Italy off-label prescription is strictly regulated, with the aim to safeguard the health of patients and to prevent waste of resources [1]. Specifically, three conditions must be satisfied: 1. the patient cannot be treated effectively with any on-label medication; 2. the patient must provide an informed consent; 3. the prescription must be supported by scientific evidence [2,18-20].

Aim of this study was to assess patterns of off-label prescriptions in a sample of psychiatrists working in their private practice in the Emilia-Romagna Region (Italy), highlighting frequency and features of prescriptions, and further investigating general knowledge and opinions of clinicians as well as some medico-legal implications of the topic. Our initial assumption was that the practice of off-label prescription would have been found to be very common in this sample.

Materials and method

Study design, development and delivery of the research questionnaire

This was a cross-sectional study, carried out by means of an *ad hoc* questionnaire.

A search of relevant scientific literature published on Medline and Scopus since 2000 was initially performed. Further information was derived from the database of the Italian Drug Association (Agenzia italiana del Farmaco, AIFA), specifically guidelines and technical information concerning specific classes of medications.

The most relevant topics were then selected to be addressed by the questionnaire, up to a final choice of 15 items. The questionnaire was developed using the "Online Survey" platform, available on the website www.sondaggio-online.com. Most of the questions were multiple-choice, only one was open-ended and the last two questions were yes/no items. None of the questions were mandatory.

After sociodemographic information (gender, age, years of clinical practice), prescription habits related to off-label use were investigated, consisting of: [a] frequency rate, [b] types and motivations [c], respect of ethical and institutional regulations. Finally, based on results of literature search, a list of the most frequent matches between certain types of psychotropic medications and their off-label use in psychiatric disorders was provided (e.g. olanzapine for anorexia nervosa, or SGAs for PDs) and respondents were asked to mark the matches they used 'frequently' in out-patient care. The questionnaire is available upon request to the corresponding author.

The questionnaire was sent to the e-mail contacts of psychiatrists working as private practitioners in the Emilia-Romagna Region (Italy). Names and contacts were searched online referring to the different provinces of the Region, using the keyword "psychiatrist" and after double-checking the professional profiles. A final selection of 129 contacts was obtained and three subsequent rounds of invitations were made between 1st April 2018 and 31st May 2018.

Ethical issues

Given the study design, the topic and the population investigated, and after discussing this with referents of the local ethical committee, institutional review board approval was considered unnecessary. Results were

anonymous and sending e-mail addresses were untraceable. Acceptance to fill-in the questionnaire by respondents included consent to analysis and public distribution of results.

Statistical analysis

Descriptive analysis was carried out using means, medians, frequencies, standard deviations and ranges. Inferential analysis was carried out by ordered logistic regression models, using HAC standard errors. Univariate regressions were initially run, assessing the association of each co-variable with dependent variables, i.e. answer to item 5 of the questionnaire, the frequency of off-label prescription. All co-variables that reached a p-value < 0.25 (to reduce type-II error) were then included in the multiple regression analysis. Finally, the usual level of significance was used (p < 0.05) to identify significant associations. The software Gretl was used for the analysis.

Results

Description of the sample

Of the 129 psychiatrists working in the Emilia-Romagna Region invited to take part to the study, 50 responded to the survey (response rate: 39%). Since the structure of the online questionnaire allowed respondents to skip questions leaving them unanswered, not every question received 50 answers.

The 44% of respondents were females (n = 22). Mean age was 50 ± 11 years and median age was 54 years (range: 32-72 years). Respondents had a mean number of years of clinical practice after specialization of 20 ± 11 years, and a median of 24 years (range: 1-42 years).

The 26% of respondents declared to prescribe off-label psychotropics "often", 38% "sometimes", 22% "seldom" and 6% "never". Four participants (2.0%) of the sample did not answer to this question. Further details are included in Table I.

TABLE I. *Frequency and reasons for off-label prescription.*

Frequency of off-label-prescription	Respondents	Younger*	Older*	Women	Men
Never	3(6.0)	2(66.7)	1(33.3)	1(33.3)	2(66.7)
Seldom	11(22.0)	5(45.5)	6(54.5)	4(36.4)	7(63.6)
Sometimes	19(38.0)	8(42.1)	11(57.9)	10(52.6)	9(47.4)
Often	13(26.0)	10(76.9)	3 (23.1)	5(38.5)	8(61.55)
Motivations for off-label prescription					
Ineffectiveness of previous medication	36(72.0)	18(50.0)	18(50.0)	16(44.4)	20(55.6)
Unavailable on-label medication	20(40.0)	13(65.0)	7(35.0)	6(30.0)	14(70.0)
Medical risk with on-label medication	13(26.0)	5(38.5)	8(61.5)	9(69.2)	4(30.8)
Previous effective off-label medication	11(22.0)	7(63.6)	4(36.4)	5(45.5)	6(54.5)
Side effects of on-going medication	7(14.0)	2(28.6)	5(71.4)	2(28.6)	5(71.4)
Reason to avoid off-label prescription					
Fear of possible side effects	12(24.0)	4 (33.3)	8(66.7)	6(50.0)	6(50.0)
Fear of medical-legal consequences	22(44.0)	12(54.5)	10(45.5)	8(36.4)	14(63.6)
Lack of reliable data on effectiveness	22(44.0)	8(36.4)	14(63.6)	10(45.5)	12(54.5)
Off-label use in DSM 5 categories					
Personality Disorders	35(70.0)	20(57.1)	15(42.9)	18(51.4)	17(48.6)
Neurocognitive Disorder	15(30.0)	6(40.0)	9(60.0)	9(60.0)	6(40.0)
Sleep disorders	14(28.0)	6(42.9)	8(57.1)	7(50.0)	7(50.0)
Obsessive-Compulsive Disorder	11(22.0)	7(63.6)	4(36.4)	4(36.4)	7(63.6)
Major Depressive Disorder	11(22.0)	6(54.5)	5(45.5)	3(27.3)	8(72.7)
Eating Behaviour Disorders	11(22.0)	4(36.4)	7(63.6)	5(45.5)	6(54.5)
Intellectual Disability	10(20.0)	6(60.0)	4(40.0)	5(50.0)	5(50.0)
Bipolar disorder	6(12.0)	4(66.7)	2(33.3)	2(33.3)	4(66.7)
Anxiety disorder	5(10.0)	1(20.0)	4(80.0)	1(20.0)	4(80.0)

TABLE I. *continue*

Off-label use in DSM 5 categories	Respondents	Younger*	Older*	Women	Men
Schizophrenia spectrum disorders	4(8.0)	2(50)	2(50)	0(0.0)	4(100.0)
Autism spectrum disorder	3(6.0)	2(66.7)	1(33.3)	1(33.3)	2(66.7)
Subsequent specific clinical actions					
Written informed consent	18(36.0)	10(55.6)	8(44.4)	9(50.0)	9(50.0)
Oral informed consent	24(48.0)	11(45.8)	13 (54.2)	10(41.7)	14(58.3)
Increased frequency of visits and exams	14(28.0)	5(35.7)	9(64.3)	9(64.3)	5(35.7)
Update medical records	18(36.0)	12(66.7)	6(33.3)	8(44.4)	10(55.6)
None	3(6.0)				
Sources of information					
Personal clinical experience	31(62.0)	15(48.4)	16(51.6)	14(45.2)	17(54.8)
PubMed	26(52.0)	18(69.2)	8(30.8)	11(42.3)	15(57.7)
Psychiatric scientific literature	25(50.0)	13(52.0)	12(48.0)	10(40.0)	15(60.0)
Clinical experience by colleagues	22(44.0)	12(54.5)	10(45.5)	13(59.1)	9(40.9)
Scientific events	21(42.0)	12(57.1)	9(42.9)	10(17.6)	11(52.4)
Institutional websites	9(18.0)	3(33.3)	6(66.7)	8(88.9)	1(11.1)
Pharmaceutical representatives	7(14.0)	4(57.1)	3(42.9)	4(57.1)	3(42.9)
Most common matches medication/disorder					
SGAs – PDs	34(68.0)	20(58.8)	14(41.2)	14(41.2)	20(58.8)
Mood stabilizers – PDs	32(64.0)	19(59.4)	13(40.6)	12(42.9)	16(57.1)
SSRIs – PDs	34(68.0)	14(41.1)	20(58.8)	5(33.3)	10(66.7)
SGAs – NCDs	27(54.0)	16(59.3)	11(40.7)	11(40.7)	16(59.3)
Trazodone – sleep disturbance	25(50.0)	12(48.0)	13(52.0)	13(52.0)	12(48.0)
Mirtazapine – sleep disturbance	20(40.0)	12(60.0)	8(40.0)	7(35.0)	13(65.0)
Quetiapine – sleep disturbance	18(36.0)	10(55.6)	8(44.4)	7(38.9)	11(61.1)
SGAs – OCDs	23(46.0)	13(56.5)	10(43.5)	6(26.1)	17(73.9)
SSRIs – EBDs	15(30.0)	5(33.3)	10(66.7)	5(33.3)	10(66.7)
Olanzapine – EBDs	5(10.0)	0(0.0)	5(100.0)	2(40.0)	3(60.0)
Quetiapine – GADs	15(30.0)	8(57.1)	6(42.9)	5(35.7)	9(64.3)
Gabapentin – bipolar disorders	9(18.0)	5(55.6)	4(44.4)	5(55.6)	4(44.4)
Trazodone – GADs	9(18.0)	4(44.4)	5(55.6)	5(55.6)	4(44.4)
Valproate – NCDs	4(8.0)	3(75.0)	1(25.0)	0(0.0)	4(100.0)
Paliperidone LAI – schizoaffective disorders	4(8.0)	3(75.0)	1(25.0)	1(25.0)	3(75.0)
Lithium – suicidal behaviours	12(24.0)	9(75.0)	3(25.0)	3(25.0)	9(75.0)

Data expressed as absolute number (percentage).
Young(er) psychiatrist ≤ 54 years old **vs old(er) psychiatrist > 54 years old (based on median value of 54 years in the distribution of age of respondents); SSRIs, selective serotonin reuptake inhibitors; PDs, personality disorders; OCDs, obsessive compulsive disorders; EBDs, eating behaviour disorders; GADs, general anxiety disorders; LAI, long-acting injection; Age, personal clinical experience, pharmaceutical representatives and SGAs – PDs were p < 0.25 at univariate logistic regression.*

The most common reason for off-label prescription was ineffectiveness of previous therapies (72%) or unavailability of on-label medications for specific psychiatric disorders (40%). Reasons against off-label prescription were instead the fear of side effects (24%) or of legal consequences (44%) or the lack of reliable data on effectiveness (44%). The respondents reported more frequent off-label prescriptions when dealing with the following psychiatric

disorders: PDs (70%), Neurocognitive Disorders (NCDs 30%), sleep disorders (28%), Obsessive Compulsive Disorders (OCDs 22%), Major Depressive Disorder (MDD 22%), Eating Behaviour Disorders (EBDs 22%), Intellectual Disability (ID, 20%) and Bipolar Disorder (BP, 12%).

All respondents confirmed that they collect their patients' informed consent when prescribing off-label, but only in the 36% of cases in a written form.

The most common sources of information supporting off-label prescriptions were personal previous clinical experience (62%), PubMed (52%) and other sources of scientific literature (50%).

The most common matches between off-label medications and psychiatric disorders were the following: SGAs, mood stabilizers and SSRIs and PDs (68, 64 and 68% respectively); trazodone, mirtazapine and quetiapine for sleep disturbances (50, 40 and 36% respectively); and SGAs for NCDs (54%).

The majority of respondents deemed the topic of the survey relevant (96%), reporting (60%) that they would like to receive more information on it; respondents rated the questionnaire as being clear and easy to fill in (90 and 96%, respectively).

Inferential statistical analysis

Table II displays the results of the multivariate regression. The propensity toward off-label prescription was found to be inversely proportional to the age of respondents; moreover, it was associated with a prescription of SGAs in the treatment of PDs and to a higher propensity to rely on personal clinical experience or on information received by pharmaceutical representatives.

Discussion

Aim of the present study was to analyse the phenomenon of off-label prescription of psychotropic medications in a sample of Italian psychiatrists working in private settings.

The majority of the sample confirmed resorting to off-label prescription "often" and "sometimes", consistently with available literature [21-24].

The two most common reasons for starting an off-label medication were partial or total ineffectiveness of previous on-label therapeutic actions (72%), or absence of on-label medications for a specific psychiatric disorder (40%). The only partial response to licensed medications of many psychiatric disorders is well documented in international scientific literature: over 20-30% of patients with schizophrenia are resistant to antipsychotics (clozapine included) [25], more than 40% of people affected by OCDs are resistant to first-line treatments with SSRI [26], at least 20% of patients with MDD do not experience a remission after AD therapy [27], in Bipolar Depression, finally, mood stabilizers and atypical antipsychotics may provide only suboptimal relief of depressive symptoms [28]. Moreover, for many diagnostic categories there is no licensed drug: in this case, if medications are needed, these are off-label by definition [8]. For example, SSRIs are often used to manage depression and anxiety symptoms, in addition to self-harm behaviours in patients with Intellectual Disabilities [29]. This is also the case for PDs, NCDs, sleep disorders that were consistently associated with higher off-label prescription in the present study.

Younger psychiatrists were found to be more prone to off-label prescription: they may be generally more prone to a so-called 'risky behaviour', i.e. the tendency to underestimate the possible risks and consequences associated with off-label prescription, out of greater clinical inexperience, but they also may have a less rigid clinical attitude. Also, younger specialists may have access to a wider range of information, leading to higher pressure to implement off-label prescription in their clinical practice. Last but not least, higher levels of burnout syndrome described among young psychiatrists may impact also on their prescriptive style [30].

A higher tendency to off-label prescription was also associated to personal clinical experience as motivation: the risks connected to overestimation, excessive self-confidence or being self-referential are well-known and described [31].

Finally, the attitude toward off-label prescription was found to be associated with the tendency to rely on information received by pharmaceutical representatives.

TABLE II. *Results of the multivariate regression analysis. Dependent variable: off-label prescription declared as "**often**".*

	O.R.	95.0% C.I.		P-value
		Lower	*Upper*	
Age	10.53	2.13	52.13	< 0.01
SGAs-PDs	0.08	0.02	0.36	< 0.01
Personal clinical experience	0.05	0.01	0.36	< 0.01
Pharmaceutical representatives	0.58	0.01	0.31	< 0.01

Considering that representatives from pharmaceutical industries should only describe on-label approved use and indications of their Company's medications, this finding may reflect a tendency of clinicians in applying the information received more broadly, possibly as a result of limited pharmaceutical options to deal with very challenging clinical situations, as already discussed [32]. A clear need for non-sponsored and ethical clinical research and training over this topic emerges as a significant result of the study here discussed.

Several limitations affecting the present research need to be acknowledged. First, we enrolled a purpose sample of psychiatrists, and no random selection procedures were used other than the systematic inclusion of all online sources. Moreover, only psychiatrists working in the Region Emilia-Romagna and operating in private contexts of care were invited to take part to the study. This led to a sample size of 50 professionals, that may not be representative for the entire Italian population of psychiatrists. These recruitment procedures partly impair the generalizability of our findings. The choice to rely on the online delivery of an *ad hoc* questionnaire, used to maximize feasibility, could have introduced response and self-selection biases, i.e. selection of a younger and more "technology-prone" sample of respondents. Despite all this, we obtained results in line with current literature on this topic, and particularly to one of the few existing similar studies performed in Italy [33]. Also, the present research was intended as pilot study for a nation-wide data collection currently on our research agenda, which aims to overcome the limitations hereby recalled.

Conclusions

Off-label prescription of psychotropics is common among psychiatrists working in private practices. It is favoured by younger professionals, that frequently rely, when prescribing, on their previous personal clinical experience; off-label prescriptions are more often associated to the treatment of some diagnostic groups, e.g. PDs. A need for extensive and detailed clinical research and training activities on this topic emerged, to be taken into account in the next future.

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