'YOU MAY NEED TO READ THIS LEAFLET AGAIN': EPISTEMIC AND DEONTIC MODALITY IN US VS. ITALIAN ANTIDEPRESSANT PATIENT PACKAGE INSERTS

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Abstract

This contribution focuses on medicine Patient Package Inserts (PPIs). Aimed at popularizing specific procedural knowledge outside the framework of clinical medicine, these texts are cognitively designed to mediate key therapeutic protocols for non-specialized readers. In concert with the recent evolution of medical communication towards more socially mediated and interdiscursive practices, and enabling users to perform their own therapeutic routine (albeit under the guidance of a doctor), leaflets indeed offer a pro-active representation of patients as fully-fledged subjects within the empirical protocol of medical cure. Such a process is evidenced by the language of PPIs, and in particular by the way they construct deonticity and epistemicity, whereby what patients may, should or should not do with a medicine, and the effects that the medicine can, might or is expected to have on the patient, are an essential part of the referential and performative meanings conveyed by the leaflet. Different linguistic systems and healthcare environments, however, codify such meanings in different ways, and although active principles are marketed worldwide, the modal strategies deployed in leaflets can vary across languages and contexts. This paper analyses and compares the English and Italian texts accompanying all fluoxetine-based antidepressant products currently licensed by the US Food and Drug Administration and the Italian Agenzia del Farmaco. By investigating the grammatical and lexical construction of deontic and epistemic modality in PPIs, the study aims to highlight the linguistic strategies codifying both the pharmacological management of depression and the role of patients and doctors in the therapeutic process.

1. Introduction

This study presents a cross-cultural insight into a referential and performative genre widely used in everyday life, namely Patient Package Inserts (PPIs). These are instruction leaflets for the use of a pharmaceutical product, with which they are mandatorily supplied, and are targeted at the person the product was prescribed for. They

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usually present its key chemical and clinical properties, also providing directives as to dosage, precautions, adverse effects and other safety information. Aimed at disseminating specific procedural knowledge outside the disciplinary framework of pharmacology, PPIs are cognitively designed to spread and mediate therapeutic protocols throughout non-specialized audiences. This is particularly relevant in relation to the ethical and legal responsibility of pharmaceutical companies towards consumers. PPIs are usually drafted as an abridged and simplified version of full package inserts (PIs), that is, the substantial, lexically specialized prescribing information documents intended for the restricted audience of healthcare professionals, which convey a detailed evidence-based overview of a medicine's characteristics. Though lacking the competence required in order to fully understand how active ingredients treat certain conditions, patients are indeed assisted in implementing correct practices by the explanations, directions and caveats provided in PPIs. The issuing of PPIs is therefore subject to complex regulatory specifications, promulgated by competent agencies at both national and supranational level, such as the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA), jointly operating with country-specific agencies, such as Italy's Agenzia del Farmaco (AIFA).

PPIs have been a legal requirement for medicines sold within US borders as of 1966, that is, since the Fair Packaging and Labeling Act mandated that consumers be fully and transparently instructed on the use and risks of foods, drugs, medical devices and cosmetics (Nathan and Vider 2015). Since then, their contents and format have undergone several revisions, with a view to promoting general access to easy-to-consult and scientifically sound information: the most important amendment was implemented in 2006 [1], when the FDA required manufacturers to draft PPIs (or revise existing ones) following a specific model (FDA 2015). This includes a Highlights section (half a page in length, summarizing indications, dosage and administration of the drug), a Table of contents for quick reference, the original date of product approval, a toll-free telephone number and the URL of the manufacturer. In Italy, the issuing and periodic revising of PPIs is also a requirement for the labelling of medicines by AIFA. As of 2001 [2], PPIs must convey easily readable information to the widest possible audience, regardless of educational or linguistic background. In particular, the European Commission's Directive 2001/8/CE has ruled that sentences should not exceed 20 words and must privilege coordinated syntax, active voice and a direct style. Specialized lexis, acronyms and foreign loanwords must be replaced by general vocabulary and glosses; a sequence of six highlights must explain what the drug is for; what to know before taking it; how to use it; its possible side effects; how to store it; and the contents of the package (SEFAP 2009).

[1] See Title 21 of the Code of Federal Regulations, § 201.56 and § 201.57. Retrieved from https://www.ecfr.gov/cgi-bin/text-idx?SID=5408745407b957e41743749a0425e278&mc=true&node=se21.4.201_156&rgn=div8 and https://www.ecfr.gov/cgi-bin/retrieveECFR?gp=&SID=d4acf7c8f2c67d713a3c0890f983334c&mc=true&r=SECTION&n=se21.4.201_157.

[2] See Directive 2001/83/CE. Retrieved from http://www.agenziafarmaco.gov.it/sites/default/files/direttiva_83_2001.pdf.

From the standpoint of medical epistemology, as well as of the implications underpinning the placing on the global market of pharmaceutical products, the rationale behind PPIs is the "learned intermediary doctrine", positing the necessity of an intermediary figure between drug manufacturers and consumers, in order to guarantee that the clearest information about the benefits and risks connected to the product is disseminated as widely as possible (Johnson, Donahue and Sarti 2013). In line with the traditional mission of Hippocratic medicine, this function is generally associated with the prescribing physician, whereby the relationship between doctor and patient is one rooted in knowledge asymmetry, and therefore mediated by trust as a major vector for the social legitimization of competence. However, because of the rapid advancement of the pharmaceutical industry since the 1960s, and, even more so, given the proliferation of experimental data on the safety and efficacy of drugs brought about by today's leading paradigm for clinical research – i.e., evidence-based practice (Sackett *et al.* 1996) – PPIs have nowadays come to represent a supplementary and yet indispensable tool for knowledge mediation between drug manufacturers and end-users.

On the one hand, providing users with immediately available and concise information on the current standard of care for specific symptoms or conditions, PPIs perform a key role in terms of patient guidance. On the other hand, the discretion to which the patient is entitled (and which, to some extent, is expected) to access the general repository of scientific knowledge promptly made available by PPIs appears to be in line with the World Health Organization's seminal definition of patients as individuals endowed with the ability and responsibility to seek health, not simply intended as the absence of disease, but as "a state of complete physical, mental and social well-being", implying that everyone should realize "his or her own potential", and take action in order to keep or restore it (WHO 1946). Evidence as to drugs' efficacy and safety attained by means of clinical research is thus conceptually reified and linguistically transferred into PPIs, in such a format as to be rendered manageable for the general public.

In the wake of the WHO's definition, which is at the core of today's healthcare discourse, PPIs may then be said to perform a number of functions:

1) they carry out an informative function as to current standards of care, clarifying how, in what dosage and in what way the medicine works, etc.;

2) they activate specific procedural protocols in non-specialized users, providing the *do's* and *don'ts* of drug administering, thereby carrying out a directive function;

3) they perform a persuasive and performative function, interactionally codifying the patient's role in carrying out such therapeutic protocols.

PPIs may in sum be defined as key pragmatic mediators, as well as epistemological conductors, within the chain of evidence-based knowledge transmission underlying the practice of treatment (APA 2010; Hillhouse and Porter 2015). Enabling users to perform their own therapeutic routine, albeit under the guidance of a learned intermediary, PPIs instantiate a proactive representation of patients as fully-fledged subjects within the empirical protocol of medical care. As healthcare communication has shifted, in recent decades, from the traditional conservativeness of crystallized, gate-keeping formulae to more socially mediated and interdiscursive practices (Calsamiglia 2003; Calsamiglia and Van Dijk 2004; Jaime Sisó 2009; Gotti, Maci and Sala 2015; Myers 2003), the role of

patients in drug therapy has been notably foregrounded, as the recent evolution in the linguistic and argumentative format of both US and Italian PPIs shows.

Such intertwining of pragmatic and epistemological factors may be further investigated by means of a closer analysis of PPIs, at both micro- and macro-linguistic level. In this respect, this paper looks at the grammatical and lexical resources and strategies used in PPIs in order to construct modality, both epistemic (expressing judgement on the truth status of a given reality) and deontic (conveying some degree of intervention on a given reality). What a patient may, should, must, or must not do with a medicine, and the effects that the medicine might, can, is expected to, or will have on the patient is indeed an essential part of the referential and performative meanings conveyed by PPIs. Covering a spectrum of modalizing orientations standing between the paradigmatic concepts of Possibility and Necessity, the language of PPIs may be said to codify and reify a wide-ranging dominion of clinical and legal meanings, whose overarching function is to chart out for patients what therapy is likely to, may, must or will be like, and what it must, should, or is allowed to (or is forbidden to) be like.

More specifically, this paper considers a particular class of medicines, that is, Selective Serotonin Reuptake Inhibitors (SSRIs). These are used as the preferred treatment for moderate to severe symptomatology of depression and other related conditions, such as anxiety and panic disorders, obsessive-compulsive and post-traumatic stress disorder, and bulimia nervosa (APA 2010). By blocking the removal of serotonin upon synaptic transmission processes, SSRIs increase the amount of this neurotransmitter to the brain, producing mood-elevating and anti-anxiety effects [3]. According to the American Psychiatric Association, 12.7% of the US population between 12 and 60 took SSRIs in 2017, with a 64% increase in utilization rates over the last twenty years (Winerman 2017). This makes antidepressants the third most frequently prescribed drug to Americans of all ages (Pratt *et al.* 2011). Fairly similarly, the latest Mental Health Report issued by the Italian Ministry of Health (2017) reveals that, since 2006, the administration of SSRIs to patients aged 12 and over has increased by 30%. In 2016, 35 million packages were consumed by nearly 8 million people, that is, 12.6% of the Italian population (Ministero della Salute 2017; AIFA 2018).

Today's first-line and most frequently prescribed SSRI appears in particular to be fluoxetine (Hetrick *et al.* 2012). Interestingly, fluoxetine was also the first new-generation antidepressant to be approved by the FDA in 1987 (Hillhouse and Porter 2015). It was marketed in the US the following year under the trade name Prozac by the pharmaceutical company Eli Lilly, and was soon afterwards put on the global market. This study therefore examines PPIs accompanying all fluoxetine-based medicines currently licensed in the US and in Italy by, respectively, the FDA and the AIFA. By analysing

[3] A disorder of chronic and debilitating nature, impairing social and occupational functioning, depression has major consequences not only on the well-being of individuals, but also on the social and financial status of communities, triggering ever increasing medical and workplace-related costs (Greenberg et al. 2003). According to the Diagnostic and Statistical Manual of Mental Disorders-V (APA 2013), depression is signalled by a depressed mood (Criterion A1), a loss of interest in usually pleasurable activities (Criterion A2), significant changes in appetite or weight, sleep, psychomotor activity, loss of energy or fatigue, feelings of worthlessness, diminished ability to think and concentrate, and possible suicidal ideations (Criteria A3, A4, A5, A6, A7, A8, A9).

and comparing how the grammatical and lexical construction of epistemic and deontic modality in PPIs varies across languages and contexts, the study compares the ways in which different linguistic systems and healthcare environments codify therapeutic meanings, with particular regard to the linguistic representation of the pharmacological management of depression and the role of depressed patients (and prescribing physicians) in the treatment process.

2. Materials

In the US, a total of eighteen fluoxetine-based medicines (three brand-name and 15 generics [4]) are presently FDA-approved. They were first identified via the FDA's online search engine, filtering the search by active ingredient [5], while the corresponding PPIs were subsequently downloaded in PDF format from the National Library of Medicine's DailyMed archive, a public databank providing FDA-approved drug-labelling information [6]. The US subcorpus totals 36,339 running words. In Italy, there are currently 16 drugs licensed by the AIFA, both brand-name (four) and generic (12). These were identified via the AIFA's online Banca Dati Farmaci [7], a public databank which also provides the corresponding PPIs in PDF format. [8] The IT subcorpus consists of 84,538 running words. Materials were scanned using *AntConc* (Anthony 2016) and *WordSmith Tools* 7.0 (Scott 2017) software. However, given the multifunctional and polypragmatic nature of most modal markers in both English and Italian, further analysis was carried out manually on a case-by-case basis.

3. Method

The PPI corpus was analysed in order to quantify and compare the resources and strategies employed in the construction of epistemic and deontic modality in US vs. IT PPIs, so as to evidence possible patterns of commonality, variation and opposition. Modality tends to be expressed in English by (i) the nine central modals (*can*, *could*, *may*, *might*, *will*, *would*, *shall*, *should*, *must*); (ii) lexical-modal auxiliaries (*be*/*have* + infinitive); (iii) semi-modal verbs (*dare*, *need to*, *ought to*); (iv) other lexical items (semantic verbs, nouns, adjectives and adverbs), often combined so as to create modal harmony within sentences and discourses (Downing 2015: 343-352). In Italian, the same semantic load is carried out by (i) the two multifunctional modal verbs *potere* and *dovere*, in a variety of forms and moods (Palmer 2001: 102); (ii) lexical-modal auxiliaries (*essere*/

[4] Both in the US and in Italy, generic drugs must have the same labelling information as the brand-name drugs to which they are declared equivalent. However, this does not cover differences in formulation, bioavailability and pharmacokinetics. In general, generics appear both in the US and in Italy to have quite similar PPIs to one another, while brand-name drugs, such as Prozac or Xeredien, have definite linguistic features and argumentative strategies.

[5] Available at https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm.

[6] Available at https://dailymed.nlm.nih.gov/dailymed/.

[7] Available at https://farmaci.agenziafarmaco.gov.it/bancadatifarmaci/cerca-per-principio-attivo. The search was filtered by active ingredient.

[8] In Italy, the equivalent of a PPI is a Foglietto Illustrativo (FI), while a PI (meant for healthcare professionals) is referred to as a Riassunto delle Caratteristiche del Prodotto (RCP).

avere + adjective or infinitive; *avere da*/*essere da* + infinitive; *andare* + past participle); (iii) modalizing uses of mood or tense (e.g. epistemic or deontic future, conditional or subjunctive); (iv) lexical-modal resources (semantic verbs, nouns, adjectives and adverbs), including adjectival or nominal constructions based on *avere*/*esser(ci)* (e.g. 'Avere il dubbio', 'C'è la certezza', etc.), often combined so as to create modal harmony (Pietrandrea 2005).

3.1. *Epistemic resources*

Epistemicity (i.e. extrinsic, or propositional modality) expresses the truth status of a proposition, defining the range of the speaker's assumptions or assessments "that a certain hypothetical state of affairs under consideration (or some aspect of it) will occur, is occurring or has occurred in a possible world" (Nuyts 2001: 21), thereby encoding confidence (or lack thereof) in its adherence to accepted truth (Greenbaum and Quirk 1990: 66). This analysis considers expressions of the logical and representative status of events or situations, based on a specific (and usually limited) framework of knowledge coordinates. In particular, epistemic markers were identified on the basis of the following typology, comprising four modalizing orientations (Coates 1983; Palmer 2001; Pietrandrea 2005):

1) possibility: this orientation conveys weak commitment to the truth status of a proposition, as mainly linked to the presentation of speculation or hypotheses. It is realized as follows:

(a) English: modal verbs or auxiliaries such as *may*, *might*, *can*, *could*, *be supposed to*, etc.; hedging lexical-modal expressions (*possibly*, *apparent*, etc.);

(b) Italian: modal verb forms *può*, *potrebbe*; lexical-modal items (*possibile*, *presunto*, *potenziale*, *magari*, *forse*, etc.); epistemic future (e.g. 'L'avrai lasciato a casa'); conditional (e.g. 'Il colpevole sarebbe fuggito') or subjunctive mood (especially in subordinate clauses, e.g. 'Se persistesse');

2) probability: conveying flexible prediction, or plausible inference, based on logical deduction from known data. It is realized as follows:

(a) English: modal verbs, lexical-modal auxiliaries and semi-modals such as *should*, *ought to*, *be likely to*, etc.; hedging lexical-modal expressions (*likelihood*, *probability*, *infer*, etc.);

(b) Italian: modal verb form *dovrebbe*; modal auxiliary *è probabile*/*verosimile*, etc.; lexical-modal expressions (*verosimilmente*, *probabilmente*, etc.); epistemic future (e.g. 'Avrà fatto 100 km' (Sabbadini 1996));

3) necessity: this orientation indicates solid conviction based on logical deduction or inference from accepted evidence. It is realized as follows:

(a) English: modal verbs and auxiliaries such as *must*, *need to*, etc.; lexical-modal items (*actually*, *indicate*, *show*, etc.);

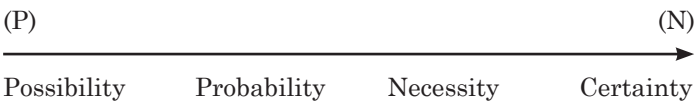
(b) Italian: modal verb form *deve*; lexical-modal auxiliary *è ragionevole*/*logico*, etc.; lexical-modal items (*di conseguenza*, *pertanto*, etc.);

4) certainty: indicating strong assumption or prediction, albeit conveyed as diminished certainty if compared to categorical assertions. It is realized as follows:

(a) English: modal verbs and auxiliaries *will*, *be due to*, *sure to*, etc.; lexical-modal items (*certain*, *truth*, *always*, etc.);

(b) Italian: modal verb form *deve*; lexical-modal auxiliary *è noto/certo/sicuro*; boosting lexical-modal expressions (*certo*, *sicuro*, *certamente*, *assolutamente*, etc.); epistemic future (e.g. 'Questo contribuirà a proteggere l'ambiente').

The four orientations can be placed along a spectrum of increasing epistemicity, that is, a semantic domain involving the apexes of Epistemic Possibility (EP) and Epistemic Necessity (EN) (Van der Auwera and Plungian 1998), where two orientations point to the concept of (EP), while two increasingly indicate the concept of (EN):



3.2. *Deontic resources*

Deonticity (i.e. intrinsic, or event modality) is concerned with the expression of some degree of human intervention upon reality, whereby changes are brought about by way of committing the speaker and/or others to certain courses of action (Greenbaum and Quirk 1990: 66). This is usually instantiated within a given ethical, legal and material setting of enabling or compelling principles (Pietrandrea and Cornillie 2012). For the purposes of this analysis, deontic markers were considered on the basis of the following typology, including three modalizing orientations (Coates 1983; Conte 1995; Palmer 2001):

1) Permission (or lack thereof, i.e. prohibition): this orientation signals the allowed (or forbidden) status of a certain course of action, usually with reference to a code of behaviour. It is realized as follows:

(a) English: for allowance, modal verbs *can* and *may*; lexical-modal auxiliary *be allowed*; for forbiddance, modal verbs *cannot*, *may not*, *must not*; lexical-modal auxiliary *not allowed*, etc.;

(b) Italian: for allowance, modal verb forms *può*, *potrebbe*; lexical-modal auxiliaries (*è ammesso/ammissibile/accettato*, etc.); for forbiddance, modal verb forms *non può*, *non deve*; lexical-modal auxiliaries (*è vietato/proibito*, etc.);

2) Recommendation: indicating a desirable, advisable, appropriate or convenient course of action in a certain context, usually conveying lack of absolute necessity, non-binding directions or suggestions, tact and/or politeness. It is realized as follows:

(a) English: modal verb *should*; semi-modal verb *ought to*; lexical-modal resources (*advisable*, *recommendation*, *preferably*, etc.);

(b) Italian: modal verb forms *dovrebbe*, *potrebbe*; lexical-modal auxiliaries (*è opportuno/raccomandato/consigliabile*, etc.); other lexical-modal expressions (*si raccomanda*, *auspicabilmente*, etc.);

3) Obligation: this orientation expresses compulsion, inescapable duty or requirement, including deontic necessity (i.e., it is necessarily the case that something will happen, notwithstanding any form of human control, e.g. 'Plants need water and sunlight'). It is realized as follows:

(a) English: modal verbs *must*, *will*, *shall*; modal auxiliary *have (got) to*; semi-modal verb *need to*; lexical-modal resources (*urge*, *command*, *order*, *compulsory*, etc.); the imperative mood (Palmer 2001: 80);

(b) Italian: modal verb forms *deve*, *si deve*; lexical-modal auxiliaries (*è richiesto/obbligatorio/necessario*, etc.); *avere da*, *essere da* + infinitive, *andare* + past participle; lexical-modal expressions (*bisogna*, *occorre*, *per forza*, *necessariamente*, etc.); deontic future (e.g. 'Il candidato sarà in possesso dei seguenti requisiti'); mandative subjunctive (e.g. 'Si proceda'); the imperative mood.

These three orientations can be placed along a spectrum of increasing deonticity, i.e., a semantic domain involving the apexes of Deontic Possibility (DP) and Deontic Necessity (DN) (Van der Auwera and Plungian 1998), whereby Permission (in both its positive and negative meaning, i.e. Allowance and Prohibition) concerns (DP), while Recommendation and Obligation point to the concept of (DN):

(P) (N)

Permission Recommendation Obligation

4. Results

The distribution and frequency of epistemic and deontic markers in the two subcorpora (in normalized figures per 10,000 words) is presented in Tables 1 and 2.

	Epistemic				Deontic		
US SUBCORPUS (36,339 running words)	Poss.	Prob.	Nec.	Cert.	Permiss.	Recomm.	Oblig.
Fluoxetine Alembic	8.53	0	0	0.27	3.3	3.3	11
Fluoxetine Alvogen	8.53	0.27	0	0.27	3.02	3.3	10.73
Fluoxetine Aurobindo	8.25	0	0	0.27	3.3	3.3	11
Fluoxetine Heritage	8.8	0	0	0.27	3.3	3.3	11
Fluoxetine Lannett	9.1	0	0	0.27	3.3	3.3	10.73
Fluoxetine Mylan	7.98	0	0	0.27	3.02	2.48	9.08
Fluoxetine Pharm. Assoc.	8.8	0	0	0.27	3.3	3.02	10.46
Fluoxetine Reddy's	8.8	0	0	0.27	3.02	3.3	10.46
Fluoxetine Sandoz	8.8	0	0	0.27	3.3	3.3	10.46
Fluoxetine ScieGen	8.8	0	0	0.27	3.85	3.3	10.73
Fluoxetine Sun Pharms	8.8	0	0	0	3.3	3.02	9.9
Fluoxetine Torrent	7.7	0	0	0.27	3.3	2.2	9.08
Olanzapine + Fluoxetine Par	8.8	0	0	0.27	3.3	3.3	10.46
Olanzapine + Fluoxetine Sandoz	10.73	0.27	0	0.27	3.85	3.58	13.2
Olanzapine + Fluoxetine Teva	8.53	0	0	0.27	3.3	3.3	10.73
Prozac	8.8	0	0	0.27	3.3	3.3	11
Sarafem	7.7	0	0	0.27	3.02	2.75	8.53
Symbyax	11	0.27	0	0.27	4.4	3.58	15.41
SUBT.	158.51 (33.41%)	0.55 (0.11%)	0.00 (0%)	4.68 (0.99%)	60.54 (12.76%)	59.96 (12.64%)	193.46 (40.78%)
TOT. EPISTEMIC VS. DEONTIC	163.74 (34.49%)				310.96 (65.51%)		
TOT. EPISTEMIC + DEONTIC	474.70						

Table 1. Distribution of epistemic and deontic markers in the US subcorpus (normalized frequency per 10,000 words)

	Epistemic				Deontic		
IT SUBCORPUS (84,539 running words)	Poss.	Prob.	Necess.	Cert.	Permiss.	Recomm.	Oblig.
Diesan	11.24	0.24	0	0.71	0.71	3.19	10.53
Fluoxeren	7.57	0.24	0.24	1.06	1.77	2.48	11.47
Fluoxetina Accord	9.82	0.12	0.12	0.95	3.43	0.83	8.75
Fluoxetina Almus	7.8	0.12	0.12	0.35	3.07	0.95	9.94
Fluoxetina Angelini	11.23	0.24	0.12	0.95	1.77	2.96	13.6
Fluoxetina EG	8.52	0.35	0	1.18	1.77	0.59	10.65
Fluoxetina Eurogenerici	4.85	0.12	0	0.35	4.02	0.47	8.04
Fluoxetina Fidia	6.03	0.12	0.12	0.71	2.72	0.47	10.05
Fluoxetina Generics	7.1	0	0	0.35	3.31	0.71	6.27
Fluoxetina GERMED	8.16	0.24	0	1.06	2.72	2.48	9.58
Fluoxetina Sandoz Gmbh	6.15	0.24	0	0.71	2.36	0.59	9.46
Fluoxetina DOC Generici	6.86	0.35	0	0.59	2.72	0.71	8.87
Fluoxetina Mylan	7.69	0.24	0	0.95	3.43	0.83	8.52
Fluoxetina Ratiopharm	6.74	0.12	0	0.71	3.31	0.95	9.23
Prozac	9.58	0.24	0	1.18	2.72	0.95	9.23
Xeredien	6.62	0.35	0	0.59	1.66	2.25	7.45
SUBT.	125.98 (35.17%)	3.31 (0.92%)	0.71 (0.2%)	12.42 (3.46%)	43.17 (12.03%)	21.41 (5.97%)	151.65 (42.28%)
TOT. EPISTEMIC VS. DEONTIC	142.42 (39.71%)				216.23 (60.29%)		
TOT. EPISTEMIC + DEONTIC	358.65						

Table 2. Distribution of epistemic and deontic markers in the IT subcorpus

It can immediately be noticed that, although the US subcorpus is composed of roughly 57% fewer words, it has a higher frequency (+25%) of modality markers, both epistemic and deontic (474.70 vs. 358.65). In PPIs written in English, nearly five out of 100 words are either epistemic or deontic markers, whereas the proportion in Italian decreases to approximately 3.5 out of 100 words. A closer look at the two typologies of markers across the subcorpora shows that the distribution of epistemic vs. deontic resources is quite even in English and in Italian, with a distinct preference of both systems for deonticity. The US subcorpus appears to privilege (+5%) deontic over epistemic markers (65.5% vs. 34.5%). This suggests that, when communicating with the lay public of drug end-users, the language of PPIs tends to resort more to directive structures, specifically meant to guide patients along specific procedural protocols, than to resources which, encoding some forecast on the epistemological status of the information conveyed, presuppose some background knowledge on the part of addressees.

The overall proportions among all seven modal categories in the subcorpora can be further observed in Charts 1 and 2.

As to the distribution of epistemic markers, Possibility, Probability, Necessity and Certainty seem to have similar frequencies in English and in Italian. The most frequently used resource appears in both cases to be Possibility (33.4% and 35.2%), whose function is normally to alert patients about potential side effects or adverse reactions to the drug, as can be seen in (1) and (2):

(1) Stopping Prozac too quickly *may* cause serious symptoms [US 16]
(2) Nei pazienti che prendono fluoxetina *può* verificarsi una perdita di peso [IT 1]

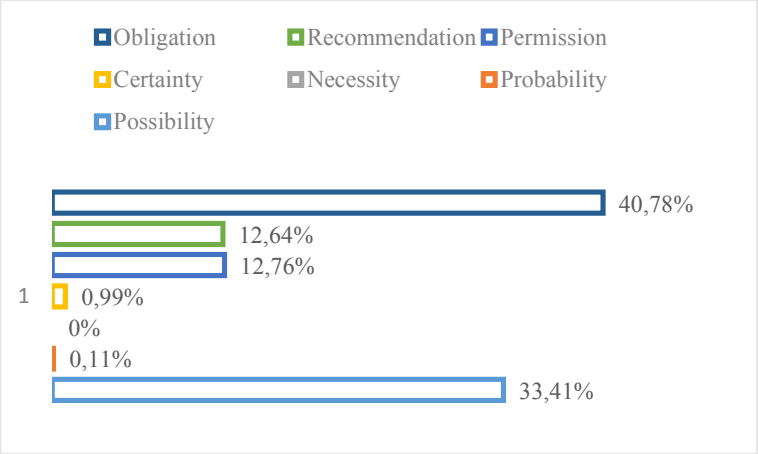


Chart 1. Breakdown of epistemic and deontic markers in the US subcorpus

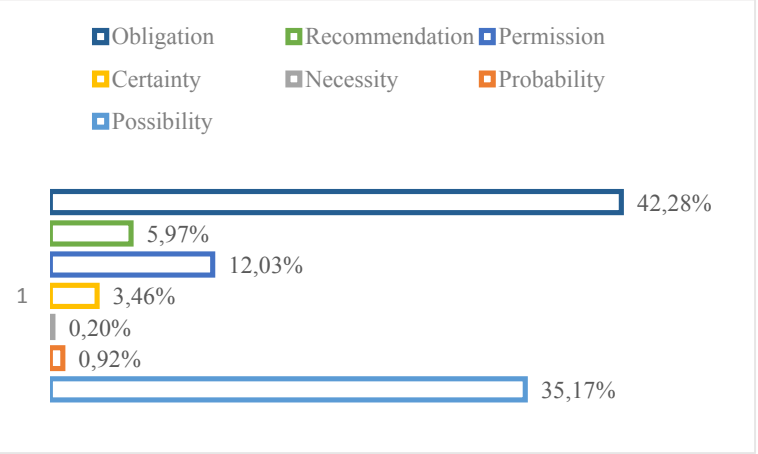


Chart 2. Breakdown of epistemic and deontic markers in the IT subcorpus

The least preferred strategies are Probability (0.11% vs. 0.92%) and Necessity (0% vs. 0.2%). These are used to warn patients about the likelihood, foreseeability or plausibility of particular events or situations connected to the use of the drug, typically on the basis of available experimental data, as is shown by (3), (4) and (5):

(3) Children and adolescents (10 to 17 years old) who received SYMBYAX were *more likely* to gain weight [US 18]
(4) Ciò è *più probabile* che accada durante le prime settimane di trattamento[9] [IT 2]

[9] This is more likely to happen during the first few weeks of treatment. (All translations are my own).

(5) Ciò *dovrebbe* aiutare a ridurre la probabilità di comparsa di effetti da sospensione [10] [IT 8]

In addition, there appears to be a difference in the frequency of Certainty markers in Italian (3.46%) compared to English (0.99%). These usually represent events and situations as logically predictable against the background of either experimental knowledge or indisputable principles, as evidenced by (6) and (7):

(6) Sarafem *will* harm your unborn baby [US 17]
(7) Questo *aiuterà* a proteggere l'ambiente [11] [IT 9]

With reference to the (EP)-(EN) spectrum of epistemicity presented in Paragraph 3.1, epistemic markers in the PPI corpora have a clear tendency to concentrate on the opposite extremes of the scale, either on Epistemic Possibility and Epistemic Necessity, with a prevalence of Epistemic Possibility. This seems to be in keeping with the chief pragmatic purposes of PPIs: informing patients about potential scenarios as to the action and effects of drugs (Epistemic Possibility), while reassuring them on evidence-based conclusions about their safety and efficacy (Epistemic Necessity).

As to distribution patterns among deontic markers, Permission (12.8% vs. 12.0%) and Obligation (40.8% vs. 42.3%) appear to have fairly similar trends in both subcorpora. These resources are privileged in the *do's* and *don'ts* sections of PPIs, defining the possibility (or impossibility) for patients to carry out certain courses of action, or clarifying conditions or precautions to be observed during treatment, as can be seen in, respectively, (8)-(9) and (10)-(11):

(8) You *may* report side effects to FDA at 1-800-FDA-1088 [US 18]
(9) La dose *può* essere gradualmente aumentata fino a un massimo di 60 mg [12] [IT 10]
(10) *Talk* with your healthcare provider if there is something you do not understand [US 10]
(11) L'uso di questo medicinale *deve* essere sempre associato alla psicoterapia [13] [IT 11]

Deontic markers in the PPI corpora also tend to be mainly placed on the opposite extremes of the (DP)-(DN) spectrum of deonticity presented in Paragraph 3.2, with a prevalence of Deontic Necessity. This again seems coherent with the crucial role of PPIs in providing patients with the *do's* and *don'ts* of drug administration, in terms of both Deontic Possibility (whenever existing norms of safety and efficacy permit the patient to engage in certain activities) and Deontic Necessity (whenever, as far as these norms are concerned, the patient's engagement in certain activities is necessary).

Recommendation appears to be more frequent in the US than in the IT subcorpus (12.6% vs. 6.0%). This resource typically occurs in the "How *should* I take the drug?" and "What *should* I avoid while taking the drug?" sections, where directives on posology or contraindications are provided in the form of beneficial, non-binding specifications, as evidenced by (12) and (13):

[10] This should help to reduce the likelihood of withdrawal effects.
[11] This will help protect the environment.
[12] The dose can be gradually increased up to a maximum of 60 mg.
[13] The use of this medicine must always be associated with psychotherapy.

(12) What is the most important information I *should* know before taking fluoxetine capsules? [US 1]
(13) La dose *raccomandata* è 20 mg al giorno [14] [IT 12]

The higher frequency of Recommendation markers in the US subcorpus may indicate a clearer preference for the use of mild directions, usually in the form of polite suggestions pointing to advisable or convenient actions, procedures or precautions, therefore performing a persuasive rather than a coercive function with respect to end-users. As will be argued in the Discussion section, resort to persuasion, in order to construe some degree of agency and accountability of drug consumers within therapeutic protocols, seems to be in line with the WHO's (1946) definition of patients as responsible health-seeking individuals.

The charts overall elucidate that, among all seven categories in consideration, the most popular strategies in both US and IT PPIs are Obligation (i.e. Deontic Necessity) and Possibility (i.e. Epistemic Possibility), representing respectively 74.2% and 77.4% of occurrences. This again seems in line with the chief pragmatic functions of PPIs, namely the directive and the informative function, whereby Obligation is the leading approach when training patients to use the medicine correctly, lest they unwittingly nullify its beneficial effects or trigger adverse reactions, while Possibility is a major resource for making them aware of the effects (positive or otherwise) of the medicine.

4.1. *Obligation resources*

Although the overall frequency of Obligation markers in the US and IT subcorpus appears to be fairly similar (40.8% vs. 42.3%), the array and distribution of different types of such markers within each subcorpus varies considerably. There are three most frequently used resources for Obligation in the PPI corpora, namely (i) the imperative mood (in both languages (Palmer 2001: 80)); (ii) the modal and semi-modal verbs *must* and *need to*, or the modal verb form *deve*; (iii) other lexical-modal expressions, such as *necessary*, *directed*, etc., or *occorre*, *bisogna*, *necessità*, and deontic future (e.g. 'Il medico prescriverà la dose corretta'). Tables 3 and 4 detail the distribution of Obligation markers (in normalized figures per 10,000 words).

As can be observed in the Tables, the US subcorpus has over twice as many imperatives as the IT subcorpus (87.6% vs. 42.6%), while the modal verb form *deve* in the IT subcorpus has approximately seven times the frequency of *must*/*need to* in the US subcorpus (34.6% vs. 4.8%). Other lexical-modal resources in the IT subcorpus are three times more frequent (22.6%) than in the US one (7.6%).

Table 3, moreover, shows that the US subcorpus tends to encode Obligation almost exclusively through the use of imperatives, at the cost of alternative lexical-modal expressions (7.6%) and, especially, of expressions with *must* and *need to* (4.8%). The use of the latter seems in particular to be restricted to necessary (or required) course of action on the part of prescribing physicians, not of patients, whose conduct is instead typically ruled by means of direct and concise imperatives, as (14) and (15) clarify:

[14] The recommended dose is 20 mg per day.

(14) Your healthcare provider may *need to* change the dose of your diabetes medicines [US 10]
(15) *Watch* for these changes and *call* your healthcare provider right away if you notice [US 8]

When describing doctors' duties and responsibilities, US PPIs privilege the use of the modal and semi-modal verbs *must* and *need to*, followed by a full verb, such as *change* in (14), thus keeping the semantic load of 'obligation' split from the predicate meaning of the lexical verb. This may possibly have the function of marking off the legitimacy and authoritativeness of doctors' initiatives, which are presented as necessary

OBLIGATION - US SUBCORPUS	Imperative	*Must/Need to*	Other resources
Fluoxetine Alembic	9.36	0.27	1.37
Fluoxetine Alvogen	9.08	0.27	1.37
Fluoxetine Auroindo	9.36	0.27	1.37
Fluoxetine Heritage	9.08	0.55	1.37
Fluoxetine Lannett	9.36	0.27	1.1
Fluoxetine Mylan	6.88	0.55	1.65
Fluoxetine Pharm. Assoc.	10.18	0.27	0
Fluoxetine Reddy's	9.36	0.55	0.55
Fluoxetine Sandoz	9.9	0.55	0
Fluoxetine ScieGen	10.18	0.55	0
Fluoxetine Sun Pharms	9.08	0.27	0.55
Fluoxetine Torrent	8.26	0.55	0.27
Olanzapine + Fluoxetine Par	9.08	0.27	1.1
Olanzapine + Fluoxetine Sandoz	11.56	1.37	0.27
Olanzapine + Fluoxetine Teva	9.08	0.27	1.37
Prozac	9.9	0.55	0.55
Sarafem	7.8	0.27	0.55
Symbyax	12.38	1.65	1.37
TOTAL	169.88 (87.57%)	9.3 (4.8%)	14.81 (7.63%)

Table 3. Distribution of Obligation markers in the US subcorpus (normalized frequency per 10,000 words)

OBLIGATION - IT SUBCORPUS	Imperative	*Deve*	Other resources
Diesan	1.77	7.33	1.42
Fluoxeren	3.31	6.03	2.13
Fluoxetina Accord	4.49	1.89	2.36
Fluoxetina Almus	5.44	1.77	2.72
Fluoxetina Angelini	4.38	6.74	2.48
Fluoxetina EG	4.61	3.43	2.6
Fluoxetina Eurogenerici	4.85	1.54	1.66
Fluoxetina Fidia	4.73	2.36	2.96
Fluoxetina Generics	2.96	2.25	1.06
Fluoxetina GERMED	2.72	5.2	1.66
Fluoxetina Sandoz Gmbh	4.73	2.36	2.36
Fluoxetina DOC Generici	5.2	1.89	1.77
Fluoxetina Mylan	3.9	2.01	2.6
Fluoxetina Ratiopharm	4.61	2.36	2.25
Prozac	4.97	1.77	2.48
Xeredien	2.13	3.55	1.77
TOTAL	64.8 (42.75%)	52.48 (34.63%)	34.28 (22.62%)

Table 4. Distribution of Obligation markers in the IT subcorpus (normalized frequency per 10,000 words)

within the framework of scientific competence, from which patients are excluded. When the latter are directly addressed, the full semantic load is instead condensed in imperative verbs, mainly because of their immediate and concise performativity.

As Table 4 reveals, the IT subcorpus tends towards a more evenly balanced use of the resources, and while imperatives are still predominant in addressing the lay public of patients (42.8%), the modal verb form *deve* and other lexical-modal items are also popular strategies (34.6% and 22.6% respectively), as evidenced by the following examples:

(16) Cosa *deve* sapere prima di prendere Fluoxetina Mylan Generics [15] [IT 13]
(17) *Chieda* consiglio al medico o al farmacista prima di prendere questo medicinale [16] [IT 14]
(18) Può essere *necessario* interrompere l'assunzione di Prozac [17] [IT 15]

Obligation strategies in Italian thus appear to be more varied – or less clearly definite – than in English. As will be argued in the Discussion section, these differences cannot be fully explained in terms of codification in one language or another. The simultaneous multilingual production of medical documents meant for international circulation, such as PPIs accompanying drugs marketed worldwide [18], is indeed linked to institutional and cultural factors, such as the different legal and healthcare environments represented by the US and Italy, and the different ways in which these depict the role of the depressed patient, and of learned intermediaries, within the treatment process.

4.2. *Permission resources*

The frequency and distribution of Permission resources also deserve further analysis. Although the overall frequency of markers is very similar in both subcorpora (12.8% vs. 12.0%), Tables 5 and 6 show that different types of markers are used in different ways within each subcorpus. There are two main meanings connected with Permission in the PPI corpus, namely: (i) Allowance, normally signalled by the modal verbs *can* and *may* and the lexical-modal auxiliary *be allowed to*, or the modal verb forms *può*, *potrà* and lexical-modal items (*ammesso*, *ammissibile*, etc.); (ii) Forbiddance, typically conveyed via negative imperatives (in both languages), *never*-constructions, or modal verb forms *non deve* and lexical-modal items (*vietato*, *evitare*, etc.).

In both subcorpora, markers indicating Forbiddance are clearly more frequent than those indicating Allowance, yet their proportions are very dissimilar: in the US subcorpus, the ratio is 4:1; in the IT subcorpus, it is approximately 3:2. The IT subcorpus has over twice as many markers for Allowance than the US subcorpus, while the latter has 20% more markers indicating Forbiddance.

More specifically, in the US subcorpus the use of Allowance or Forbiddance tends to be ruled by an epistemological principle, whereby Permission is generally granted

[15] What you need to know before you are given Fluoxetine Mylan Generics.
[16] Ask your doctor or pharmacist for advice before taking this medicine.
[17] It may be necessary to stop taking Prozac.
[18] This is actually a major concern for pharmaceutical companies, to which the EU has been responsive, for instance through the PILLS project (Patient Information Language Localisation System; see Bouayad-Agha et al. 2002).

PERMISSION – US SUBCORPUS	Allowed	Forbidden
Fluoxetine Alembic	0.82	2.48
Fluoxetine Alvogen	0.82	2.48
Fluoxetine Aurobindo	0.82	2.48
Fluoxetine Heritage	0.82	2.48
Fluoxetine Lannett	0.82	2.48
Fluoxetine Mylan	0.55	2.48
Fluoxetine Pharm. Assoc.	0.55	2.75
Fluoxetine Reddy's	0.27	2.75
Fluoxetine Sandoz	0.55	2.75
Fluoxetine ScieGen	1.1	2.75
Fluoxetine Sun Pharms	0.55	2.75
Fluoxetine Torrent	0.82	2.48
Olanzapine + Fluoxetine Par	0.82	2.48
Olanzapine + Fluoxetine Sandoz	0.55	3.3
Olanzapine + Fluoxetine Teva	0.82	2.48
Prozac	0.55	2.75
Sarafem	0.55	2.48
Symbyax	0.55	3.85
TOTAL	12.33 (20.29%)	48.45 (79.71%)

Table 5. Distribution of Permission markers in the US subcorpus (normalized frequency per 10,000 words)

PERMISSION – IT SUBCORPUS	Allowed	Forbidden
Diesan	0.24	0.47
Fluoxeren	1.3	0.47
Fluoxetina Accord	1.06	2.36
Fluoxetina Almus	0.95	2.13
Fluoxetina Angelini	1.18	0.59
Fluoxetina EG	1.41	2.6
Fluoxetina Eurogenerici	0.95	1.77
Fluoxetina Fidia	1.41	1.89
Fluoxetina Generics	1.3	1.41
Fluoxetina GERMED	1.41	0.95
Fluoxetina Sandoz Gmbh	1.06	1.66
Fluoxetina DOC Generici	1.18	2.25
Fluoxetina Mylan	1.3	2.01
Fluoxetina Ratiopharm	0.95	1.77
Prozac	1.18	2.25
Xeredien	0.95	0.71
TOTAL	17.83 (41.35%)	25.29 (58.65%)

Table 6. Distribution of Permission markers in the IT subcorpus (normalized frequency per 10,000 words)

to patients when their initiatives pertain to appropriate communication with doctors, whereas Forbiddance applies in all other cases, as exemplified by (19) and (20):

(19) You *may* ask your healthcare provider or pharmacist for information about fluoxetine delayed-release capsules [US 8]
(20) *Do not stop* taking Sarafem without first talking to your healthcare provider [US 17]

This suggests that – probably on account of the ethical and legal principles underpinning the merchantability of medicines in the US – these PPIs tend to resort to Allowance only when meanings point to the mediatory function performed by prescribing physicians.

In the IT subcorpus, however, while Forbiddance markers are also exclusively used for providing patients with caveats as to the drug's risks and side effects, the semantic domain of Allowance is crucially extended to include physicians themselves over the course of therapy, as shown by (21) and (22):

(21) Dopo 1-2 settimane, il medico *può* aumentare la dose fino a 20 mg al giorno [19] [IT 15]
(22) Successivamente il medico *può* continuare a ridurre la dose [20] [IT 2]

This is not the case with the US subcorpus, where the prescribing physician is never represented *in praesentia*, as *allowed* to do something in the performance of his/her duties. S/he is rather represented as *compelled* to do something, by virtue of his/her clinical expertise. Italian PPIs thus seem more concerned about providing substance to patients' awareness of (and trust in) the conduct of prescribing physicians, whereas they tend to be implied, albeit tacitly embedded, in US PPIs. This difference is important inasmuch as the practical indications conveyed by PPIs are the same in both languages and contexts: patients are supposed to take one tablet of fluoxetine a day, for instance, and may not take two or more. And yet, this is codified via different modal strategies, in which the social actors involved in the therapeutic process are represented as playing similar, though not identical, roles. This brings about, as will now be argued, the issue of PPIs' representative and ideological efficacy across different cultural and institutional systems.

5. Discussion and conclusions

The overall preference for deontic over epistemic modality shown by both US and IT PPIs (see Tables 1 and 2), along with the prevalence, among all seven modal categories, of Obligation (Deontic Necessity) and Possibility (Epistemic Possibility) (see Charts 1 and 2), may be revealing as regards the semantic strategies used in pharmacological language in order to codify the management of depression as well as the role of patients and doctors in this process. On the one hand, in privileging the construction of treatment as ruled by specific procedures which patients are obliged to respect (Deontic Necessity), PPIs may be said to create for depressed patients a sheltered, authority-invigilated environment for care, where drug safety and efficacy are guaranteed by observance of the instructions provided, and where they are operatively supported (and overtly committed) to stick to such a conduct. The overarching semantic domain of Deontic Necessity may in fact contribute to relieving the pressure of individual agency and accountability from patients who, according to the Diagnostic and Statistical Manual of Mental Disorders-V, are highly likely to feel physically and emotionally depleted, and to benefit from clear-cut guidelines (APA 2013; see Note 4).

On the other hand, by giving prominence to the semantic domain of Epistemic Possibility, PPIs also stimulate patients' awareness of the potential occurrence of side effects or unexpected reactions to the medicine, especially when directions for use are not fully respected, thus positing explicit operative parameters and cognitive criteria for

[19] After 1-2 weeks, the doctor may increase the dose to 20 mg per day.
[20] The doctor may then continue to reduce the dose.

self-vigilance. Also, the construction of a pro-active role for patients is a precondition for the "therapeutic alliance" needed in order to build an "empathic and trusting environment" for healing (APA 2010). As Charts 1 and 2 indicate, the semantic domain of Recommendation contributes to reinforce this tendency – especially in dosage and precautions sections, as shown by examples (12) and (13) – whereby appealing to the patient's collaboration by means of persuasive (instead of directive) strategies may result in augmenting the perceived self-efficacy of patients, and in strengthening team-building interactions between patient and doctor. Although it is beyond the scope of this study to ascertain whether, and to what extent, depressed patients may be affected by the semantic strategies of psychopharmacological literature, further and more extended research may perhaps investigate the potential correlations between the linguistic identity and the therapeutic indications of medicinal products.

Cross-cultural fault-lines between the US and the Italian healthcare environment are instead evidenced by the diverging strategies used in PPIs in order to represent the learned intermediary figure doctrine, as well as the chain of evidence-based knowledge transmission connecting patients, prescribing physicians and PPIs themselves. As Tables 3 and 4 show, the codification of Obligation with regard to the duties and responsibilities of physicians and patients follows different criteria in the two contexts (see examples (14) and (15)). While US literature tends to differentiate between the legitimate and authoritative conduct expected from professionals fulfilling their Hippocratic function (signalled by the dedicated use of the semi-modal verbs *must*/*need to*) and the respect of safety rules expected from patients (simply conveyed by imperatives), Italian literature makes no such distinction. Deontic Necessity is expressed quite indistinctly in Italian PPIs, as examples (16), (17) and (18) indicate. Along with country-specific compliance with different institutional regulations for products liability [21], this discrepancy may indicate dissimilar cultural perceptions of the tutoring function played by doctors with regard to patients, whereby US literature takes on a specific legal overtone expressly stressing the ethical and material mission of the former in safeguarding the latter's well-being and statutory rights.

Likewise, as Tables 5 and 6 show, the semantic domain of Permission (Deontic Possibility) is represented in different ways in the corpus. There is a clear orientation in US PPIs towards patient/consumer protection and the neutralization of potential harm (including self-harm), whereby an extensive spectrum of patient activities is banned on account of its possible interference with safety conditions, as example (20) shows. In accordance with products liability legislation, Allowance is instead granted to initiatives, such as (19), anchoring the patient's use of medicines to the competent supervision of a doctor. In Italian literature, on the other hand, the social domain of Allowance is substantially reformulated, so as to include a superordinate actor in the knowledge dissemination chain, that is, the physician him/herself, who thus becomes part of the community which PPIs – as pragmatic and epistemological mediators – are designed to invigilate and guide on behalf (and for the benefit) of drug end-users. As examples (21)

[21] Although drug manufacturers are required to warn patients about any risk associated with their products, 22 Supreme State Courts and legislatures in the US have ruled that this does not apply when certain types of products are prescribed by a learned third party. This can partially discharge pharmaceutical companies, while making doctors responsible for informing the patient about the potential benefits and risks of the medicine (Johnson, Donahue and Sarti 2013).

and (22) indicate, Italian doctors' initiatives, such as adjusting dosages as treatment goes, are subject to monitoring and verification on account of their conformity to the guidelines provided in PPIs. US doctors *need to* adjust dosages; their Italian peers *may* do so.

Such a need to put down on paper the degree of permissibility granted to the discretionary powers of the healthcare elite may be interpreted as a peculiarity of the Italian system. While it exceeds the scope of this study to investigate the psycho-sociology of Italian attitudes towards issues of trust, mistrust and control (Carli 2018), it is here worthwhile noticing that, although the exact designation of PPIs in Italian is Foglietti Illustrativi ('explanatory leaflets'), they are popularly referred to, in written as well as spoken discourse, as *bugiardini* (literally, 'small and deceitful [texts]'). As clarified by the *Accademia della Crusca* (Setti 2003), this noun is a traditional diminutive form (hence, the meaning of 'small') from the adjective *bugiardo* ('deceitful'). This choice of words appears to both reflect a typically Italian ironical stance towards the ample format (and small print) of PPIs, as well as to – ideologically – suggest that the information they convey should not be fully trusted, because possibly insufficient or inaccurate. It is precisely with the meaning of concise informative text (e.g. package inserts, book back covers, promotional brochures, etc.) believed to cover up a deceitful referent of sorts, that the word is nowadays being used in a variety of Italian contexts, including institutional discourse by health authorities (Setti 2003).

In conclusion, although medicinal products – such as world best- and long-seller SSRIs – are marketed worldwide, different linguistic, institutional and ideological settings will invariably tend to produce dissimilar and yet interrelated understandings, which will in turn influence the knowledge dissemination process that is the discursive keystone of pharmacological therapy, along with the various social actors it involves. Stemming from their key epistemological and pragmatic functions, PPIs will produce a variety of semantic strategies according not only to their informative, directive or performative purposes, but also to the cultural milieus they will be instantiated in, of their rules and regulations as well as authority and legitimacy frameworks, and of their relationships with what is possible and/or necessary in order for people to stay, or get, healthy.

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