


# Italian prescribing patterns in obsessive–compulsive disorder

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## Abstract

The aim of the present study was to investigate psychopharmacological prescribing patterns in a large sample ( $n = 1815$ ) of patients suffering from obsessive–compulsive disorder (OCD) recruited in 4 Italian centers specialized in OCD, in comparison to available national and international guidelines.

The centers were asked to complete a specific data sheet questionnaire on patients' therapeutic status. Statistical analyses were carried out by SPSS.

The results showed that almost all patients referred to the centers of Milan, Pisa and Rome received psychotropic medications, whereas only 59.9% (313) did so in Turin. Selective serotonin reuptake inhibitors were the most used drugs ranging between 49.0% and 71.5%. Clomipramine was prescribed more often in Rome and Pisa than in Milan and Turin. The same was true for other tricyclic antidepressants. Second-generation antipsychotics were more often prescribed in Pisa and in Milan. Mood stabilizers were almost exclusively used in Pisa.

Taken together, the overall findings would suggest that, although the main Italian centers specialized in OCD follow available guidelines, a certain degree of variability does exist. This may depend on the different educational background, availability of other specific therapeutic strategies, as well as varying levels of severity and comorbidity of the patients.

## KEYWORDS

obsessive–compulsive disorder, psychopharmacological treatments, specialized OCD centers, treatment guidelines

## 1 | INTRODUCTION

Obsessive–compulsive disorder (OCD) is the fourth most common psychiatric disorder, with an incidence of approximately 2.5% in the general population (Angst, 1994; Karno, Golding, Sorenson, & Burnam, 1988), and a similar gender distribution, except in adolescence where the ratio male to female is 3:1 (Hollander & Stein, 1999). Minor differences seem to relate to different geographical areas and reflect some cross-cultural phenomena that in turn may affect different symptoms expression (Matsunaga et al., 2008; Stein & Rappaport, 1996).

The term “obsession” refers to an idea, a thought, a word, a memory, a feeling, an impulse, or a mental image that intrudes into the consciousness against the will of the subject that recognizes its irrational nature, at least at some point during the disturbance. It provokes marked anxiety or distress that the patient tries to neutralize with other thoughts or actions. “Compulsion” is defined as a drive, an

impulse, or a behavior that the patient feels forced to express often in response to an obsession: The aim is to reduce the discomfort or to prevent feared events. These behaviors may not be realistically linked with what they are supposed to prevent or neutralize, or they are clearly excessive. The obsessions and compulsive behaviors provoke significant subjective distress, sometimes consume a large part of the day (e.g., at least 1 hr per day) and interfere with the social and work function. Within the latest Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) (American Psychiatric Association Committee on Nomenclature and Statistics, 2013), a high relevance has been given to the concept of insight into the illness that might be reduced in some patients and even absent in others.

The current first-choice treatments of OCD are represented by pharmacotherapy and cognitive-behavioral therapy (CBT) including exposure and response prevention (ERP; Bandelow et al., 2008; Marazziti & Consoli, 2010; Marazziti, Consoli, Baroni, & Catena

Dell'Osso, 2010; Menchón et al., 2016; Montgomery, 1994). As far as pharmacotherapy is concerned, drugs enhancing the availability of serotonin (5-HT) in the synaptic cleft, such as clomipramine, a tricyclic antidepressant (TCA), and selective 5-HT reuptake inhibitors (SSRIs), now considered first-line drugs for their better side effect profile, are specifically effective in this condition [American Psychiatric Association, 2007; National Collaborating Centre for Mental Health (Nice, UK), 2006]. For patients unsuccessfully treated with SSRIs, practice guidelines suggest to add either one second-generation antipsychotic (SGA), mainly risperidone or aripiprazole, or CBT/ERP [American Psychiatric Association, 2007; Bloch et al., 2006; National Collaborating Centre for Mental Health (Nice, UK), 2006].

Although representing a major problem that is easy to diagnose, OCD is still underdiagnosed and not properly treated. Besides that, there is the problem of treatment resistance (between 40% and 60% of patients do not respond to standard strategies), and delayed therapeutic effect of available compounds that is between 2 and 6 months (Albert, Aguglia, Bramante, Bogetto, & Maina, 2013; Albert et al., 2012; Marazziti & Dell'Osso, 2015; Tundo, Salvati, Busto, Di Spigno, & Falcini, 2007).

Additionally, some therapeutic failures may be due to different prescribing practices, as recently shown in an international study of prescribing practices in OCD (Brakoulias et al., 2016; Van Ameringen et al., 2014).

Understanding prescribing practices has important clinical implications. Where evidence-based treatment guidelines are not well adhered to, there may be local economic, service-related, or cultural factors that could be changed in order to improve prescribing practices. In this study, we aimed to compare the patterns of prescription of psychotropic agents amongst four Italian centers specialized in OCD treatment. Considering the variability between expert centers internationally (Karno et al., 1988; Menchón et al., 2016; Van Ameringen et al., 2014), we hypothesized that differences would also be apparent in expert centers at a national level.

## 2 | SUBJECTS AND METHODS

The first author (D. M.) invited the researchers of four Italian centers specialized in OCD treatment (Pisa, Milan, Turin, and Rome) to complete a standardized data collection sheet already used in previous study and approved by the ethics committee (Brakoulias et al., 2016). The centers were selected on the basis of their geographical locations (Northern, Central, and Central-Southern Italy), in order to obtain data from different Italian areas, as well as their recognized high degree of experience in the management of OCD. Moreover, the centers collaborate with each other since more than 2 decades and carry out different common research projects, under the umbrella of the organization called Italian group for OCD or International Council of Obsessive-Compulsive Spectrum Disorders. Moreover, all the centers are academic and, as such, are very similar and located in cities (Milan and Rome) or large towns (Turin, Pisa). All centers use the same assessment instruments, interviews, and guidelines. As such, they treat patients with pharmacotherapy, and two centers (Turin and Rome) are also specialized in the use of CBT/ERP for the treatment of OCD.

The survey assessed medication use cross-sectionally, upon referral to each research center. Information was collected in relation to the sample size, the years in which the sample was assessed, the mean age and gender distribution of the sample, the mean severity of OCD, the mode of referral of participants to the study, and the number of patients that were prescribed psychotropic medication. All the centers were asked to submit data regarding psychotropic use for OCD, specifically SSRIs, serotonin and norepinephrine reuptake inhibitors (SNRIs), clomipramine, other tricyclic antidepressants, mirtazapine, reboxetine, benzodiazepines (BDZs), SGAs, first-generation antipsychotics (FGAs), sodium valproate, lithium, and any other psychotropic compound.

The diagnosis of OCD was carried out by means of Structured Clinical Interview for DSM-IV-TR Axis I disorders (First, Spitzer, Gibbon, & Williams, 2007). The severity of OCD was assessed with the Yale-Brown Obsessive Compulsive Scale (Goodman et al., 1989).

### 2.1 | Statistical analyses

Chi-Squared tests (or Fisher's exact tests, when appropriate) were utilized to compare categorical variables (i.e., gender, referral type, and medication usage). Analysis of variance (ANOVA) followed by Bonferroni's tests for post hoc comparisons were utilized to compare parametric variables (i.e., age and Y-BOCS score). All statistical analyses were carried out with SPSS (version 22.0).

## 3 | RESULTS

All four invited centers agreed to participate and completed the survey based on their databases that collected prescribing data over a 10–15 year period.

A total of 1,815 patients (931 men and 884 women) were collected, the largest sample came from Pisa ( $n = 750$ ), followed by Turin ( $n = 522$ ), Rome ( $n = 406$ ), and Milan ( $n = 137$ ). Men and women were equally represented in the four centers. Patients from Turin were significantly younger than patients from the other centers ( $p < .001$ ; Table 1).

The OCD severity, as assessed by the mean Yale-Brown Obsessive Compulsive Scale total score (mean  $\pm$  SD), was significantly higher in the Pisa sample ( $30 \pm 8$ ) than in those from the other three centers (Rome  $25.8 \pm 4$ ; Milan,  $25.2 \pm 6.8$ ; and Turin,  $24.7 \pm 6.4$ ;  $p < .001$ ).

The majority of the participants in the Turin sample ( $n = 308$ ; 59%) were referred by a general practitioner, whereas those from Pisa ( $n = 270$ ; 36%) were self-referred ( $p < .001$ ; Milan and Rome did not provide these data).

As shown in Table 2, the large majority of the total sample (1,606 out of 1,815 patients; 88.5%) had received a psychotropic drug prescription when referred to one of the centers; however, the rate of pharmacotherapy was significantly different ranging between 59.9% in Turin and 100% in the other three centers ( $p < .001$ ).

All comparisons amongst the four centers on medication use were statistically significant ( $p < .001$ ). As percentage of prescriptions, the highest rate of SSRIs was in Milan ( $n = 98$ ; 71.5%), followed by Pisa ( $n = 520$ ; 69.3%) and Rome ( $n = 276$ ; 67.98%), with the lowest in Turin ( $n = 256$ ; 49.04%). Post hoc comparisons showed that

**TABLE 1** Characteristics of the patients of the four Italian sites

	Sample size n (%)	Gender M/F n (%)	Mean age (years) M (SD)	Mean total Y- BOCS M (SD)	Referral by a doctor n (%)	Referral by other health profession. n (%)	Self-referral n (%)	Diagnosis
Milan	137 (7.5)	69 (50.1)/68 (49.9)	39.6 (14.5)	25.2 (6.8)	—	—	—	SCID IV
Pisa	750 (41.3)	368 (40.1)/382 (50.9)	39.0 (11.0)	30.0 (8.0)	250 (33.3%)	230 (30.7%)	270 (36.0%)	SCID IV
Rome	406 (22.4)	223 (54.9)/183 (45.1)	38.1 (13.9)	25.8 (4.0)	—	—	—	SCID IV
Turin	522 (28.8)	271 (51.9)/251(48.1)	34.8 (12.3)	24.7 (6.4)	308 (59.0%)	112 (21.4)	102 (19.6%)	SCID IV
Total survey sample	1815 (1.0)	931 (51.3)/884 (48.7)	37.7 (12.9)	26.4 (6.3)	558 (43.9)	342 (26.9)	372 (29.2)	SCID IV
Overall comparison	$p < .001$	$p = .388$	$p < .001$	$p < .001$	$p = .001$	$p < .001$	$p < .001$	—
Pairwise post hoc comparison ( $p < .05$ )	M < R, M < T, M < P, R < T, R < P, T < P	—	T < R, T < M, T < P	P > R, P > M, P > T, R > T	T > P	P > T	P > T	—

Note. SCID = Structured Clinical Interview for DSM IV-TR; Y-BOCS = Yale-Brown Obsessive Compulsive Scale. Referral source was not specified for Milan and Rome sample.

**TABLE 2** Rates of psychotropic prescribing for obsessive-compulsive disorder across four Italian centers

	Any psychotropic medication n (%)	SSRIs n (%)	SGA n (%)	BDZs n (%)	Clomipramine n (%)	SNRIs n (%)	Sodium valproate n (%)	Lithium n (%)
Milan (n = 137)	137 (100%)	98 (71.5)	45 (32.9)	25 (18.3)	13 (9.5)	11 (8.0)	4 (2.9)	3 (2.2)
Pisa (n = 750)	750 (100%)	520 (69.3)	251 (33.5)	94 (12.5)	192 (25.6)	180 (24.0)	253 (37.7)	120 (16.0)
Rome (n = 406)	406 (100%)	276 (68.0)	73 (18.0)	203 (50.0)	170 (41.9)	32 (7.9)	74 (18.2)	0 (0.0)
Turin (n = 522)	313 (60.0)	256 (49.0)	78 (15.0)	26 (5.0)	51 (9.8)	17 (3.3)	7 (1.3)	11 (2.1%)
Total survey sample	1606 (88.5)	1150 (63.4)	447 (24.6)	348 (19.2)	426 (23.5)	240 (13.2)	338 (18.6)	134 (7.4)
Overall comparison	p < .001	p < .001	p < .001	p < .001	p < .001	p < .001	p < .001	p < .001
Pairwise post hoc comparison (p < .05)	T < R, T < P, T < M	T < M, T < P, T < R	T < P, T < M, R < P, R < M	T < P, T < M, T < R P < M, M < R	T < R, T < P, M < R, M < P, P < R	T < R, T < P, T < M R < P, M < P	T < R, T < P, M < P, M < R, R < P	R < M, R < P, R < T, M < P, T < P

Note. SSRIs = Selective serotonin re-uptake inhibitors; SGA = second-generation antipsychotic; BDZs = benzodiazepines; SNRIs = serotonin norepinephrine reuptake inhibitors; Denominator for percentages is the number of any psychotropic medication. In Italy, gabapentin (n = 98; 13.1%) and pregabalin (n = 92; 12.3%) were used. Psychotropic drugs used by less than 5% of the total survey sample are not included in this table.

percentages of prescriptions in Turin were significantly lower than in the others ( $p < .05$ ).

SNRI (especially venlafaxine) use was significantly lower in Turin ( $n = 17$ ; 3.3%) than in Rome ( $n = 32$ ; 7.9%), Milan ( $n = 11$ ; 8.0%), and Pisa ( $n = 180$ ; 24.0%;  $p < .05$ ). Duloxetine was prescribed only in four patients in Milan and three in Pisa.

The rate of clomipramine use were significantly ( $p < .05$ ) higher in Rome ( $n = 170$ ; 41.9%) than in Pisa ( $n = 192$ ; 25.6%) where, in turn, it was significantly higher with respect to Milan and Turin ( $n = 51$ ; 9.8%) or Milan ( $n = 13$ , 9.5%;  $p < .05$ ).

In a small number of cases, the Pisa ( $n = 72$ ; 9.6%) and Rome ( $n = 10$ ; 4.4%) patients were treated with TCAs other than clomipramine. TCAs were much less likely to be used in Turin ( $n = 1$ ) and Milan ( $n = 0$ ). Pisa and Rome were also associated with a higher prescription rate for mirtazapine (Pisa,  $n = 59$ ; 7.9% and Rome,  $n = 9$ ; 2.2%;  $\chi^2 = 77.10$ ,  $p$ -value  $< .001$ ).

BDZs were used significantly more often ( $p < .05$ ) in Rome ( $n = 203$ ; 50%) than in Milan ( $n = 25$ ; 18.25%), Pisa ( $n = 94$ ; 12.53%), and Turin ( $n = 26$ ; 5.0%). The lowest use of BDZs was recorded in Turin ( $p < .05$ ).

Antipsychotics were prescribed most often in Pisa ( $n = 311$ ; 41.5%) and in Milan ( $n = 55$ ; 40.2%), with a preference for SGAs (Pisa,  $n = 251$ ; 33.5%; Milan,  $n = 45$ ; 32.8%), while FGAs were minimally used in Turin ( $n = 11$ ; 2.1%) and not used in Rome. Prescription of trazodone was highest in Pisa ( $n = 112$ ; 14.9%) and absent in the other centers ( $p < .001$ ).

Mood stabilizers, particularly lithium and valproate, were used almost exclusively in Pisa (Lithium:  $n = 120$ ; 16.0%; Valproate:  $n = 253$ ; 37.7%), but they were not prescribed in Turin or Rome and just prescribed in four patients in Milan. Gabapentin and pregabalin were also rarely used in centers outside Pisa.

## 4 | DISCUSSION

The present study aimed to explore possible differences in the prescription of psychotropic agents to OCD patients referred to four Italian centers that specialize in OCD treatment, through a specific survey.

The total number of patients recruited was 1,815 and, to our knowledge, constitutes the largest national sample of OCD patients analyzed so far. Men and women were almost equally represented in the four centers, in agreement with the literature (Angst, 1994; Hollander & Stein, 1999; Karno et al., 1988).

The most numerous group was that of Pisa, followed by Turin, Rome, and Milan. This finding is related to the evidence that Pisa and Turin share a longer tradition in OCD research, management, and treatment that dates back to the end of the 1980s. Pisa is a national referral center for different psychiatric disorders and attracts patients from all the country, so it is not surprising that the most severe patients are those visited there and are mainly self-referred. On the contrary, the patients visited in Turin are sent by general practitioners.

The large majority of patients, 1,606 out of a total of 1,815, were taking psychopharmacological treatments, with Milan, Rome, and Pisa reaching almost 100%, and Turin showing significantly lower rates (60%). This might be due to the fact that Turin center widely uses

CBT. Taking into consideration the specific model of treatment delivery in Turin, this is not surprising: OCD patients in that area are sent to the specialized center even before any drug prescription is made, with 40% of patients not receiving any medication at referral (patients are younger, presumably with a shorter duration of illness, less severe, and maybe more frequently treated with CBT than in the other centers). Another factor that could explain this difference is that CBT/ERP is generally not supported by the public welfare in all Italian regions and not available in public hospitals, as Pisa and Milano centers, whereas at the Rome center—a private outpatient clinic—CBT/ERP is usually used as augmentation for patients who do not respond to pharmacotherapy (American Psychiatric Association, 2007; Bloch et al., 2006).

Overall, the prescribing practices in the four Italian centers involved in the study are in agreement with international treatment guidelines for OCD (Koran et al., 2007); the majority of patients were treated with SSRIs that are considered the first-line treatment together with CBT [National Collaborating Centre for Mental Health (Nice, UK), 2006; American Psychiatric Association, 2007; Koran et al., 2007; Marazziti, 2013]. The rate of SSRI use was almost the same in percentage (between 71% and 68%) in Milan, Pisa, and Rome, being lower in Turin (49%). This difference may be due to the cultural factors, that is to say, more pharmacological treatments in Milan, Pisa, and Rome due to cultural background coupled with a lower availability of psychologists in the staff, and more availability of CBT and other psychological techniques in Turin. However, when considering Turin patients who had been prescribed medications ( $N = 313$ ), the vast majority of them (in agreement with the other three Italian centers) were prescribed SSRIs ( $256/313 = 81.8\%$ ).

Clomipramine was the second most used drug after SSRIs, with the highest percentage in Rome, followed by Pisa, Turin, and Milan. This difference might be explained by the fact that in Rome center, clomipramine and not SGA augmentation, is the recommended treatment option for patients who do not respond to SSRIs. This strategy is consistent with the results of some studies showing that clomipramine is more effective than SSRIs in resistant patients [The Clomipramine Collaborative Study Group, 1991; Song et al., 1993; Danish University Antidepressant Group (DUAG), 1986; Danish University Antidepressant Group (DUAG), 1990], although current guidelines do not recommend it as first-line treatment for its side effect profile. It is, however, true that clomipramine is cheaper than SSRIs, so that the recent economic crisis might be another factor influencing medical prescriptions (Walbeck & McDaid, 2012).

The use of SGAs was present in all centers: This is consistent with guidelines recommending their addition to augment SSRI response (Dold, Aigner, Lanzenberger, & Kasper, 2012; Maina, Pessina, Albert, & Bogetto, 2008). The percentages ranged between 40% and one third of patients, as widely reported in the literature (Van Ameringen et al., 2014). The higher prescription in Pisa and Milan, where even FGAs were prescribed, may be related to a greater proportion of more severe OCD patients with poor or no insight (ranging between 18% and 20%). Another possible explanation is that more resistant patients are referred to the centers of Pisa and Milan than to Turin for reasons related to the model of psychiatric treatment delivery in different regions of Italy (e.g., OCD patients are referred to the specialized center of Turin earlier than to other centers, so that it is possible that



they are less treatment-resistant and the consequent use of SGAs is lower; Dell'Osso, Benatti, Hollander, & Altamura, 2016).

A great difference amongst the centers was particularly robust for the use of mood stabilizers (lithium, valproate, gabapentin, and pregabalin), in that they were almost exclusively used in Pisa. This might be due to the prevalence of the most severe patients in this center, and the high comorbidity rate with bipolar disorders (15.7% reaching 55% and including bipolar spectrum disorders). This comorbidity pattern is common and generally considered a negative predictor of response (Amerio, Odone, Marchesi, & Ghaemi, 2014; Milanfranchi et al., 1995; Perugi et al., 1997; Perugi et al., 2002).

The use of BDZs was minimal in Turin, Milan, and Pisa samples and high in Rome sample where reach the rate of 50%. This rate is amazing considering that BDZ are not recommended for OCD in treatment guidelines, and there is no evidence of their utility (Perugi et al., 1997). Because Rome center is an outpatient clinic specialized in mood and anxiety disorders, we hypothesize the presence in Rome sample of patients with high level of anxiety and/or of anxiety disorders comorbidity requiring BDZs for decreasing the anxiety levels, at least for limited periods. However, this survey did not collect data on comorbidity and assessed medication use cross-sectionally, so we are unable to confirm our hypothesis.

SNRIs were mostly used for anxiety in OCD, specifically venlafaxine that was the most prescribed SNRI, with the highest rate in Pisa. Venlafaxine is generally used as an augmenting agent in OCD and also to target comorbid depression or anxiety (Amerio et al., 2014; Dell'Osso & Lader, 2013).

A few studies, mainly case reports, support the use of trazodone (Pigott et al., 1992; Marazziti, Gemignani & Dell'Osso, 1999) and mirtazapine in OCD (Albert, Aguglia, Maina, & Bogetto, 2002; Marazziti, 2003; Koran et al., 2005): The first drug was exclusively used in Pisa center to revert the sexual side effects of SSRIs, the second in Pisa and Rome centers as SSRI augmentation.

The main bias of the present study is that data were collected in tertiary clinics specialized centers for OCD treatment so that they may not reflect the "real" prescribing practice of the country. However, surveying specialized centers could also be regarded as a strength of the study, because each center, 37 used the same diagnostic criteria, assessment scale for diagnosis, and followed the available guidelines. It should be also underlined that the overall sample size is one of the largest reported in the literature.

In conclusion, the ensuing findings indicate that OCD patients in Italy, at least those visited in specialized centers generally receive pharmacological treatment. The prescriptions generally follow international and national guidelines [American Psychiatric Association, 2007; Angst, 1994; Bandelow et al., 2008; Bloch et al., 2006; Menchón et al., 2016; National Collaborating Centre for Mental Health (Nice, UK), 2006], with SSRIs being the most used drugs. The differences observed amongst the centers may be related to clinical heterogeneity of the patients, in particular their clinical characteristics, severity, and comorbid patterns and also to uncontrolled influences related to doctors (e.g., different trainings, ages, or genders). Besides these, other cultural factors related to the local setting (traditional preference for some drugs over other), and socio-economic variables may influence prescriptions (Walbeck & McDaid, 2012).

## CONFLICT OF INTEREST

None

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