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REGULAR RESEARCH ARTICLE

Prescribing Patterns of Psychotropic Drugs and Risk of Violent Behavior: A Prospective, Multicenter Study in Italy

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Abstract

Background: This prospective cohort study aimed at evaluating patterns of polypharmacy and aggressive and violent behavior during a 1-year follow-up in patients with severe mental disorders.
Methods: A total of 340 patients (125 inpatients from residential facilities and 215 outpatients) were evaluated at baseline with the Structured Clinical Interview for DSM-IV Axis I and II, Brief Psychiatric Rating Scale, Specific Levels of Functioning scale, Brown-Goodwin Lifetime History of Aggression, Buss-Durkee Hostility Inventory, Barratt Impulsiveness Scale, and State-Trait Anger Expression Inventory-2. Aggressive behavior was rated every 15 days with the Modified Overt Aggression Scale and treatment compliance with the Medication Adherence Rating Scale.
Results: The whole sample was prescribed mainly antipsychotics with high levels of polypharmacy. Clozapine prescription and higher compliance were associated with lower levels of aggressive and violent behavior. Patients with a history of violence who took clozapine were prescribed the highest number of drugs. The patterns of cumulative Modified Overt Aggression Scale mean scores of patients taking clozapine (n = 46), other antipsychotics (n = 257), and no antipsychotics (n = 37) were significantly different (P = .001). Patients taking clozapine showed a time trend at 1-year follow-up (24 evaluations) indicating

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Significance Statement

- Patients affected by severe mental disorders, both inpatients and outpatients, show high levels of polypharmacy independently from their diagnosis.
- Clozapine administration is associated with the lowest rate of aggressive behaviors in patients with severe mental disorders during a 1-year follow up. Patients' higher (self-reported) compliance is also associated with lower rates of violent behaviors.

a significantly lower level of aggressive behavior. Patient higher compliance was also associated with lower Modified Overt Aggression Scale ratings during the 1-year follow-up.

Conclusion: Both inpatients and outpatients showed high levels of polypharmacy. Clozapine prescription was associated with lower Modified Overt Aggression Scale ratings compared with any other antipsychotics or other psychotropic drugs. Higher compliance was associated with lower levels of aggressive and violent behavior.

Keywords: aggressive behavior, clozapine, polypharmacy, severe mental illness, violence

Introduction

The simultaneous use of multiple psychotropic drugs by patients with mental disorders is a very common clinical practice in both outpatient and inpatient settings (Ghaemi, 2002). The commonly used definition of "psychiatric polypharmacy" refers to the use of 2 or more psychiatric medications in the same patient (Council NMD, 2001) or using 2 or more medications (of the same chemical class, with similar pharmacological actions, or belonging to different chemical classes) to treat the same condition (Kingsbury et al., 2001). One of the primary reasons for polypharmacy is that the treating clinician determines that the administration of a single medication is ineffective in adequately treating the individual's psychiatric symptoms (Council NMD, 2001; Procyshyn et al., 2001). However, there are other reasons for prescribing more than 1 medication: to target specific albeit different symptoms, to treat 2 distinct but comorbid disorders in the same patient, or to address unremitting symptoms (Preskorn, 2007).

Prevalence rates of polypharmacy in psychiatry vary between 13% and 90% (Möller et al, 2014). Antipsychotic (AP) polypharmacy (APP) is particularly common, being prescribed to 10% to 46% of psychiatric patients (McCue et al., 2003) with rising frequency in recent years (Toto et al., 2019). However, most widely used guidelines recommend avoiding combinations of APs unless multiple trials of monotherapy have failed because of limited evidence for the efficacy of combining APs and growing evidence about the increased side effects associated with such combinations (Barnes and Paton, 2011; Gupta and Cahill, 2016; Stahl, 2012). Discrepancies in the prevalence of polypharmacy across studies may also be accounted for by differences in the definition of drug combinations and also availability as well as clinical experience and knowledge of psychopharmacology by medical practitioners.

A clinical situation in which polypharmacy is particularly common in psychiatry is represented by the treatment of patients with severe mental disorders who were or currently are aggressive. Some studies have found that patients with severe mental disorders with a lifetime history of aggressive/violent behavior(s) received more medications compared with patients without a history of violence (Thibaut and Colonna, 1993; Sim et al., 2004; Kukreja et al., 2013; Iozzino et al., 2015; Jeon and Kim, 2017; James et al., 2017; Mauri et al., 2019).

In this regard, evidence for a specific anti-aggressive action (i.e., independent of AP or antimanic properties) of many psychotropic compounds is still very limited (Fuller, 1996; Fleischhacker and Uchida, 2014; de Jong and Neumann, 2018; Peeters et al., 2018). A specific anti-aggressive effect has been found so far only for clozapine (Wilson and Claussen, 1995; Essock et al., 2000; Bitter et al., 2005; Frogley et al., 2012).

This study reports the results of the detailed assessment of psycho-pharmacological treatments prescribed to a large sample of psychiatric patients in Italy. Approximately one-half of these patients had a history of serious violence, while the rest did not have any lifetime history of violent behavior. The study aimed at evaluating (1) patterns of polypharmacy in the whole sample and in specific subgroups, (2) variables associated with polypharmacy, and (3) the correlation between prescription patterns (involving clozapine, APs, or any other psychotropic drugs) and patterns of aggressive/violent behavior during 1-year follow-up.

Methods

Design Overview and Participants

The Violence Risk and Mental Disorder (VIORMED) is a prospective cohort study with a baseline cross-sectional comparative design followed by a 1-year follow-up observation period. This study involved patients living in residential facilities and outpatients in treatment at 4 Departments of Mental Health in northern Italy. More details about both study settings and design can be found in previous publications (de Girolamo et al, 2016; Barlati et al., 2019). Inclusion criteria were a primary psychiatric diagnosis and age between 18 and 65 years. Exclusion criteria included a diagnosis of organic mental disorder, mental retardation, dementia, or sensory deficits. The selection of these patients was based solely on comprehensive and detailed documentation (as reported in clinical records) about a history of violent behavior(s). Violent patients ("cases") had to meet any of the following criteria: (1) admitted at least once to a forensic mental hospital for any violent act against people and then discharged, and/or (2) having a documented lifetime history of violent acts against people in the past 10 years that caused physical harm to the victim or having committed armed robbery, pyromania, or sexual violence; these behaviors led to legal prosecution or to arrest. The control group ("controls") included patients who did not meet any of these 2 conditions during their lifetime.

All participants provided written informed consent before entering the study. Ethical approval was granted by the ethical committee of the coordinating centre (IRCCS Saint John of God,

Fatebenefratelli; n° 64/2014) and by the ethical committees of all other recruiting centers.

Measures and Assessments

Sociodemographic characteristics, clinical and treatment-related data, and information about the history of violence were collected for all patients. The Structured Clinical Interview for DSM-IV Axis I (Mazzi et al., 2000; First et al., 2002) and Axis II (First et al., 1997) was administered to confirm clinical diagnoses. Symptom severity and psychosocial functioning were assessed using the Brief Psychiatric Rating Scale–Expanded (BPRS-E; Dazzi et al., 2016) and the Specific Levels of Functioning scale (Montemagni et al., 2015).

Aggressiveness, impulsiveness, and hostility were evaluated through a set of self-reported measures, notably the Brown-Goodwin Lifetime History of Aggression (BGLHA; Brown et al., 1979), the Buss-Durkee Hostility Inventory (BDHI; Buss & Durkee, 1957), and the Barratt Impulsiveness Scale–11 (BIS; Barratt, 1965). Anger was measured through the State-Trait Anger Expression Inventory-2 (Lievaart et al., 2016). Details about these tools can be found in Barlati et al. (2019).

Treatment compliance was rated with the Medication Adherence Rating Scale (MARS; Brown et al., 1979), a 10-item self-report questionnaire validated in patients with psychosis. As recommended by Fialko et al. (2008), we have given a score of 1 to patients answering "yes" to items 1–6 and 9–10 and "no" to items 7–8; item scores were added to obtain a total score. The MARS was administered only to outpatients, because medication compliance is granted to all patients living in residential facilities.

Monitoring of Aggressive and Violent Behavior

Aggressive and violent behavior exhibited by patients during the 1-year follow-up was rated fortnightly with the Modified Overt Aggression Scale (MOAS; Margari et al, 2005), for a total of 24 MOAS evaluations for each patient. All MOAS evaluators (psychiatric staff and patients' relatives) were very familiar with the patients and had daily, or very frequent, contact with them. The MOAS includes 4 aggression subdomains: verbal, against objects, against self, and physical-interpersonal. A score from 0 to 4 is assigned, with 0 indicating no aggressive behavior and higher scores showing increasing severity. The score in each category is multiplied by a factor assigned to that category, which is 1 for verbal aggression, 2 for aggression against objects, 3 for aggression against self, and 4 for aggression against other people. The total weighted score for each evaluation ranges from 0 (no aggression) to 40 (maximum grade of aggression); therefore, the individual MOAS total score for the 1-year period ranged from 0 to 960. We will subsequently refer to the weighted MOAS total score (our primary outcome) simply as the MOAS score.

Assessment of Drug Prescriptions

At baseline, information on current drug prescriptions of all recruited patients was collected. All psychotropic drugs were included in the study, grouped in 9 categories: first-generation antipsychotics (FGA), second-generation antipsychotics (SGA; i.e., aripiprazole, olanzapine, quetiapine, and risperidone, at that time marketed in Italy), clozapine, lithium, other mood stabilizers (e.g., valproate, carbamazepine, lamotrigine, gabapentin), first- and second-generation antidepressants (from now on considered as a single class, also in view of the very few prescriptions of first-generation antidepressants), and benzodiazepines (BDZ). For some additional analyses, we also considered long-acting antipsychotics (LAAs).

For the analysis of the association between prescription patterns at baseline and MOAS ratings during the 1-year follow-up, all patients (therefore merging cases and controls) were grouped into 3 categories: patients taking clozapine, alone or in association with any other psychotropic drugs ("clozapine group"); patients taking any other APs (and other psychotropic drugs, if any; "other AP group") but clozapine; and patients who did not receive any APs or clozapine, but were being prescribed any other psychotropic drugs (e.g., mood stabilizers, any antidepressants, and/or BDZ; "no AP group").

Statistical Analyses

To compare categorical data, a χ^2 test or the Fisher's exact test, whenever appropriate, was used. For quantitative data, ANOVA or a nonparametric Mann-Whitney test was used. The normality assumption was verified by visual inspection of the variable distribution through QQ-plots.

Monitoring of aggressive and violent behavior was carried out by analyzing MOAS scores across all 24 evaluations, and their trends were estimated by calculating the cumulative means, adapting the procedure described in Lawless and Nadeau (1995). This approach, based on the cumulative mean of all MOAS scores, allows a pictorial representation of the pattern of aggressive and violent behavior. In our study, the estimate of the cumulative means is straightforward. More specifically, if k is the number of patients (constant over time) under observation, t is the evaluation time ($t = 1, 2, \ldots, 24$), and $S(t)$ is the total MOAS score observed over the interval [1,t] calculated summing up all the individual MOAS scores observed from the first up to the t-th evaluation, the cumulative mean function of the MOAS score at evaluation t is calculated as $M(t) = S(t)/k$, that is, as the arithmetic mean of the total MOAS score up to evaluation t. If we indicate with $m(t)$ the mean of the MOAS scores at evaluation t, then $M(1) = m(1)$, $M(2) = m(1) + m(2)$, and, in general, $M(t) = m(1) + m(2) + \ldots + m(t)$ is the sum of the means of the MOAS score observed up to the evaluation time t. For example, if the means of the MOAS scores observed at evaluation times 1, 2, 3, and 4 are 1.20, 0.79, 0.99, and 0.88, the corresponding cumulative means of the MOAS scores are 1.20, 1.99, 2.98, and 3.86, respectively.

To compare 2 or more cumulative functions, the areas under the corresponding graphs were calculated using a trapezoidal rule. Interestingly, it is also possible to calculate an area under the graph of the 24 cumulative MOAS scores for each participant, and as a consequence of the properties of the arithmetic mean, the mean of the participants' areas corresponds to the area under the graph of cumulative means of MOAS scores. Areas were compared employing a permutation test: this test is based on the assumption that, if there is no difference, the distribution of the areas observed in n groups under comparison will be one of the most likely resulting from randomly allocating the entire sample in n subsamples. If D is the test statistic employed to compare the areas of the n groups, the permutation test involves comparing the observed statistic D with the distribution of the same statistic found performing random allocations a great number of times (10 000 in our case). If D is unusually extreme, then the data are unlikely to have arisen if the null hypothesis is true. The 2-sided P value of this test is twice the proportion of replications giving a value of the test statistic equal to or more

extreme than *D*. All statistical analyses were performed using R: A language and environment for statistical computing (R Core Team, 2018).

Results

Sample Characteristics

A total sample of 340 patients was recruited: 181 (53.2%) were cases and 159 (46.8%) controls. Among these 340 patients, 177 (52.1%) had a diagnosis of schizophrenia, 90 (26.5%) suffered from a personality disorder, while the remaining 73 (21.5%) had other mental disorders. Furthermore, 125 (36.8%) patients were living in residences and 215 (63.2%) were outpatients. Most (81.5%) were males. The mean age was 45.3 ± 10.3 years.

Table 1 shows the sociodemographic and clinical characteristics of cases and controls by diagnostic groups. There were significantly more males among cases (83.2% vs 69.7%, $P = .037$). While the percentage of single participants was not significantly different between cases and controls, a highly significant difference ($P < .001$) was found when diagnostic groups were considered: single were 92.7% of schizophrenic patients, 78.4% of personality disorders, and 79.8% of other diagnoses. Cases had a significantly lower level of education ($P = .019$); educational level was also significantly different among diagnostic groups ($P = .027$): patients achieving a medium-high educational level were 25.4% among schizophrenic patients, 36.7% among patients with personality disorders, and 41.1% among patients with other diagnoses. While the percentage of unemployed participants was not significantly different between cases and controls, a significant difference ($P = .032$) was found when diagnostic groups were considered: unemployed were 73.3% of schizophrenic patients, 59.1% of personality disorders, and 61.1% of other diagnoses. In terms of clinical characteristics, BPTS-E total score was higher among cases in all the 3 diagnostic groups.

With regard to the distribution of aggressive behavior across diagnoses, the history of aggressive behavior was not significantly different across diagnoses: "cases" (patients with an history of violence) were 54.8% (97 of 177) among people with schizophrenia, 55.6% (50 of 90) among patients with personality disorders, and 46.6% (34 of 73) among patients with "other" diagnoses ($\chi^2 = 1.67$, $P = .43$).

We then stratified cases and controls according to the 3 groups based on prescription patterns (i.e., clozapine group, other AP group, no AP group) (Table 2). None of the sociodemographic variables considered showed a significant association with the prescription pattern.

BPRS-E scores were significantly different in the level of activation both between cases and controls; that is, cases

Table 1. Sociodemographic and Clinical Characteristics of Cases and Controls by Diagnostic Group

	Cases			Controls				
	Schizophrenia	Pers Dis	Other	Schizophrenia	Pers Dis	Other	*P* (group)	*P* (diagnosis)
Gender							.037	<.001
Male	86	39	30	67	22	33		
Female	11	11	4	13	18	6		
Age, y							.693	.040
18–35	18	14	4	11	9	6		
36–50	44	25	18	36	21	24		
51+	35	11	12	33	10	9		
Marital status							.476	<.001
Married or cohabiting	4	16	9	9	7	15		
Single	93	34	25	71	33	24		
Education							.019	.027
Low level	78	34	222	54	23	21		
Medium-high level	19	16	12	26	17	18		
Occupation							.247	.032
Employed	23	22	9	24	14	19		
Unemployed	73	27	25	56	25	19		
BPRS-E								
Total score (range 24–168)	50.5 ± 21.5	39.2 ± 13.0	39.7 ± 14.8	48.8 ± 19.2	38.7 ± 9.5	37.7 ± 10.8	.672	<.001
BGLHA								
Total score (range 22–88)	36.4 ± 12.3	43.7 ± 13.0	35.8 ± 9.0	30.8 ± 8.7	38.5 ± 13.9	33.1 ± 7.7	<.001	<.001
BIS-11								
Total score (range 30–120)	63.3 ± 11.3	67.7 ± 13.6	66.5 ± 9.9	63.7 ± 11.9	64.7 ± 12.8	63.7 ± 10.1	.584	.401
BDHI								
Total score (range 0–75)	34.2 ± 13.0	37.9 ± 13.6	37.2 ± 12.4	33.0 ± 12.8	38.7 ± 11.2	32.0 ± 9.6	.395	.060
STAXI-2								
Anger expression index (range 0–96)	39.4 ± 15.4	45.8 ± 15.2	46.8 ± 16.0	35.3 ± 13.4	47.2 ± 14.4	41.6 ± 14.8	.138	<.001
Mean number of psychotropic drugs	2.63 ± 1.2	2.6 ± 1.2	2.8 ± 0.9	2.2 ± 1.1	2.7 ± 1.0	3.0 ± 1.28	.232	.011

Abbreviations: BDHI, Buss-Durkee Hostility Inventory; BGLHA, Brown-Goodwin Lifetime History of Aggression; BIS-11, Barratt Impulsiveness Scale–11; BPRS-E, Brief Psychiatric Rating Scale–Expanded; STAXI-2, State-Trait Anger Expression Inventory-2.

Table 2. Sociodemographic and Clinical Characteristics of Cases and Controls by Prescription Patterns

	Cases			Controls			P (pharm.)
	No AP	Other AP	Clozapine	No AP	Other AP	Clozapine	
Gender							.544
Male	16	119	20	12	91	19	
Female	5	17	4	4	30	3	
Age, y							.601
18–35	6	27	3	3	21	2	
36–50	8	69	10	9	58	14	
51+	7	40	11	4	42	6	
Marital status							.083
Married or cohabiting	5	21	3	6	23	2	
Single	16	115	21	10	98	20	
Education							.695
Low level	16	101	17	7	76	15	
Medium-high level	5	35	7	9	45	7	
Occupation							.146
Employed	8	44	2	8	40	9	
Unemployed	12	91	22	8	79	13	
BPRS-E							
Total score (range 24–168)	40.8 ± 15.9	44.8 ± 17.7	56.9 ± 25.0	31.8 ± 5.6	44.6 ± 15.9	46.2 ± 19.6	.001
BGLHA							
Total score (range 22–88)	37.0 ± 14.7	37.5 ± 11.1	42 ± 15.6	31.2 ± 5.9	33.6 ± 11.1	32.4 ± 9.8	.891
BIS-11							
Total score (range 30–120)	67.9 ± 12.9	64.5 ± 11.6	66.1 ± 12.3	63 ± 12.3	64.4 ± 11.1	62.5 ± 16.1	.870
BDHI							
Total score (range 0–75)	39.3 ± 10.7	35 ± 13.4	36.8 ± 12.8	30.3 ± 10.2	34.4 ± 12	35.4 ± 13.3	.833
STAXI-2							
Anger expression index (range 0–96)	50.0 ± 15.8	41.1 ± 15.8	45.6 ± 13.1	40.1 ± 15.6	40.2 ± 15	37.2 ± 13.5	.344
Mean number of psychotropic drugs	1.9 ± .7	2.7 ± 1.1	3.1 ± 1.2	1.9 ± .8	2.6 ± 1.2	2.6 ± 1.1	<.001

Abbreviations: AP, Antypsychotics; BDHI, Buss-Durkee Hostility Inventory; BGLHA, Brown-Goodwin Lifetime History of Aggression; BIS-11, Barratt Impulsiveness Scale–11; BPRS-E, Brief Psychiatric Rating Scale–Expanded; STAXI-2, State-Trait Anger Expression Inventory-2.

had higher scores than controls in general as well as in the 3 pharmacological groups. Negative symptoms, psychotic symptoms, and total scores were also significantly different between the 3 pharmacological groups: the clozapine group showed higher total scores than the other 2 groups.

Specific Levels of Functioning scale ratings differed significantly among the 3 pharmacological groups in self-care, activities, and work skills areas: patients in treatment with clozapine showed the worst ratings. Cases treated with clozapine showed the highest BGLHA score (which rates their lifetime history of violence).

Prescription Patterns

The whole sample was prescribed mainly APs: 55.3% of the entire sample took SGAs, while 29.4% took FGAs. Overall, 13.5% of all patients were prescribed clozapine, and 21.2% received an LAA; 33.5% were prescribed mood stabilizers, with a minority (5.0%) of them treated with lithium. Finally, 35.9% of patients were prescribed antidepressants, and nearly 60% were receiving BDZ (see Table 3).

Cases who took clozapine were prescribed the highest number of drugs, with a statistical significance in the average number of drugs among the 3 pharmacological groups, as shown in the last row of Table 2. There were 62 different association patterns of psychotropic drugs: the first 10 patterns were prescribed to 50.6% of the overall sample. The most frequently prescribed pattern was SGA + antidepressants + BDZ (n = 27), followed by SGA (n = 24), LAA (n = 23), and SGA + BDZ (n = 23). Considering associations between drugs from 2 different categories only, the 5 most common associations were SGA and BDZ (n = 119, 35.0%), antidepressants and BDZ (n = 80, 23.5%), FGA and BDZ (n = 76, 22.4%), mood stabilizer and BDZ (n = 76, 22.4%), and SGA and antidepressants (n = 74, 21.8%).

Patients with a diagnosis of schizophrenia were prescribed clozapine significantly more frequently than patients with personality disorders (PDs) or with other mental disorders (22.0% vs 5.6% and 2.7%, respectively; $P < .001$), while the latter group was prescribed lithium (17.8% vs 0% among PD patients and 2.3% among patients with schizophrenia; $P < .001$) with a significantly higher frequency. Prescription of FGA and SGA, as well as of mood stabilizers, did not differ significantly among the diagnostic groups (FGA: 33.3% in patients with schizophrenia, 26.7% in patients with PDs, and 23.3% in patients with other diagnoses, $P = .228$; SGA: 55.4% in patients with schizophrenia, 55.6% in patients with PDs, and 54.8% in patients with other diagnoses, $P = .995$; mood stabilizer: 26.6% in patients with schizophrenia, 38.9% in patients with PDs, and 30.1% in patients with other diagnoses, $P = .117$). LAAs were prescribed with significantly higher frequency in people with schizophrenia (28.8% vs 12.2% in PDs and 13.7% in other diagnoses; $P = .002$). Antidepressants were given significantly more often to patients with PDs (55.6%) or with other diagnoses (58.9%) than to participants with schizophrenia (13.0%; $P < .001$). BDZ were widely prescribed, particularly in patients with PDs (63.3%) and in patients with other diagnoses (68.5%), followed by patients with schizophrenia (52.5%; $P = .040$).

Table 3. Different Drug Classes, Number of Drugs in Each Category, and Patterns of Prescriptions

Drug category	No. of drugs in category	No. of patients receiving any drugs from category	No. of different drugs in category administered to each patient
First-generation antipsychotics	7	100 (29.4%)	1 = 83 2 = 17
Second-generation antipsychotics	4	188 (55.3%)	1 = 177 2 = 10 3 = 1
LAA	8	72 (21.2%)	1 = 72
Clozapine	1	46 (13.5%)	46
Lithium	1	17 (5.0%)	1 = 17
Mood stabilizers	6	104 (30.6%)	1 = 97 2 = 7
First generation antidepressants	4	14 (4.1%)	1 = 14
Second-generation antidepressants	12	108 (31.8%)	1 = 101 2 = 7
Benzodiazepines	—	200 (58.8%)	200

Table 4 shows the number of drugs in the 3 main diagnostic groups: schizophrenia, patients with PD, and other major mental disorders. Patients with schizophrenia were prescribed 2 different psychotropic drugs in 30.5% and only 1 in 25.4% of this diagnostic group, while patients with PDs and patients with other diagnoses received 2 (31.1% and 28.8%, respectively) or 3 (27.8% and 35.6%, respectively) different psychotropic drugs ($P = .011$). Those drugs mainly belonged to 2 different categories in all groups (see Table 2). Schizophrenia was the diagnostic group that more frequently was prescribed the lowest number of different drug categories: 26.0% of them took compounds belonging to just 1 category against 14.4% of patients with PDs and 9.6% of patients suffering from other disorders; on the other hand, 17.0% of patients with schizophrenia took medications belonging to 4 or 5 different categories against 22.2% of patients with PDs and 21.9% of patients with other diagnoses ($P = .015$).

Trends in Violent Behavior

The analysis of the MOAS scores during the 24 fortnightly evaluations showed that, among controls, cumulative MOAS mean scores (cMOAS) increased constantly, with an evident linear trend (Figure 1); the correlation between time of evaluation and cMOAS was 0.9986. A linear trend in cMOAS scores means that from one evaluation to the other, the MOAS means remain approximately constant over the entire evaluation period (around the value of 0.345, i.e., the MOAS mean calculated considering together all the 24 evaluations).

A linear trend was also found in cases but with an important difference (Figure 1). A linear increase was observed between the first and the seventh MOAS evaluation; the correlation between time of evaluation and the first 7 cMOAS was 0.9974: therefore, in this time span, the MOAS means remained approximately constant (around the value of 1.309). After the seventh MOAS and up to the last evaluation, the observed pattern of cMOAS was again linear (with a correlation of 0.9986), but with a lower slope; that is, from MOAS points 7 to 24, the MOAS mean remained approximately constant (around the value of 0.602).

Both of these trends in the pattern of the cMOAS are shown in Figure 1. The comparison between prescribing patterns in cases and controls shows that significantly ($P = .001$) more controls than cases (n = 274, 45.3% vs n = 106, 27.1%, respectively) showed an area equal to 0 (i.e., all the MOAS scores are equal to 0). If we consider only those subjects with an area greater than 0, the area estimates for these subjects were 375 among cases and 194 among controls: the area of cases was about 1.9 times greater than the area of controls. A 95% bootstrap confidence interval (CI) for the ratio of the 2 areas (cases vs controls) was between 1.74 and 3.95.

We then evaluated the longitudinal pattern of violent behavior (employing the cumulative means of total MOAS) separately in the 3 diagnostic groups: the results are shown in 3 figures (see supplementary files; supplementary Figures 1–3), which confirm that cases display more aggressive behavior than controls irrespective of the diagnosis. The 95% bootstrap CI for the ratio of the 2 areas (cases vs controls) calculated after having taken into account the diagnosis (1.77–3.85) was quite similar to that previously found.

Prescription of Selected Medications and MOAS Scores

Taking into account the 3 groups based on prescribing profiles, the patterns of cMOAS for patients taking clozapine (46 participants), any other APs (257 participants), and no APs (37 participants) are shown in Figure 2.

Among cases, the areas were 204 (clozapine), 282 (other APs), and 297 (no APs); among controls, the areas were 42 (clozapine), 119 (other APs), and 99 (no APs). After adjustment for the difference between cases and controls, a significant difference was found among the 3 areas ($P = .023$): the area of patients taking clozapine was significantly lower compared with the area of all participants not taking clozapine, while the areas of participants treated with other APs and of participants treated with no APs were fairly similar. Twenty-three of 46 (50.0%) participants taking clozapine showed an area equal to 0 (i.e., all MOAS scores were equal to 0) compared with 91 of 257 (35.4%) patients taking other APs, and 7 of 37 (18.9%) patients taking no APs. Also, after having adjusted for the difference between cases and controls, these percentages were significantly different (chi-square = 8.82, $df = 2$, $P = .012$).

On the other hand, when comparing the mean values of logarithmically transformed positive areas, no difference was found among the 3 groups based on prescription profiles taking into account the difference between cases and controls ($P > .5$). Among all cases, these areas were 307, 392, and 346, respectively, in patients taking clozapine, other APs, and no APs, respectively.

Table 4. Number of Patients Receiving Different Number of Psychotropic Drugs in 3 Main Diagnostic Groups

No. of drugs	No. of patients by diagnostic groups			
	Schizophrenia	Personality disorders	Other diagnoses	Total
1	45	13	6	64
2	54	28	21	103
3	39	25	26	90
4	30	20	15	65
5	9	4	3	16
6	–	–	2	2

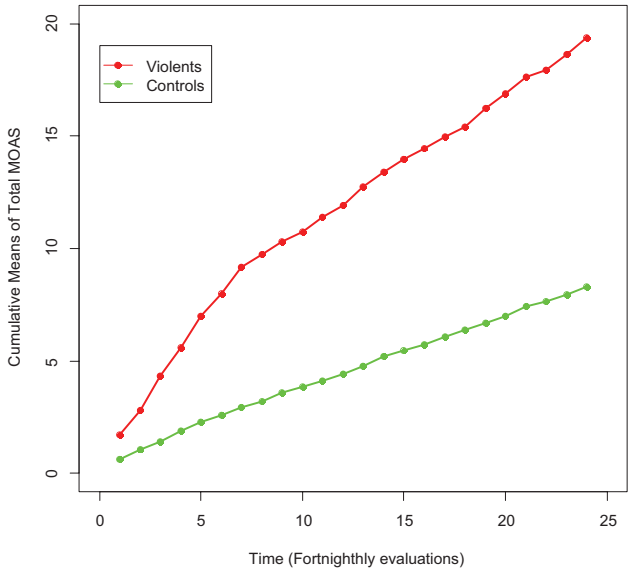

Figure 1. Cumulative means of total Modified Overt Aggression Scale (MOAS).

The corresponding values observed in the control group were 131, 211, and 132, respectively. Among cases, the area estimates were 204 (clozapine), 282 (other APs), and 297 (no APs); among controls, the corresponding estimates were 42 (clozapine), 119 (other APs), and 99 (no APs). After having adjusted for the difference between cases and controls, a significant difference was found among the 3 areas ($P = .023$). The area of patients taking other APs was 1.62 times the area of participants taking clozapine, with a 95% CI ranging from 0.91 to 3.65; the wideness of this interval is mainly due to the relatively small number of patients taking clozapine.

If we restrict our analysis to 177 patients with schizophrenia, 39 were prescribed clozapine, 137 Aps, and only 1 other drug. Supplemental Figure 4 shows rates of aggressive behavior of 176 patients with schizophrenia taking either clozapine or APs and confirms a lower rate of violent behavior among those taking clozapine at baseline.

MOAS Scores and Compliance Rates

Residential patients showed less overt aggression than outpatients (Figure 3). The area under the cMOAS for residential patients was 143, while for outpatients the corresponding area was 226 (i.e., 1.6 times higher); the 95% bootstrap CI for this ratio was between 1.03 and 2.49.

With regard to medication compliance, perhaps the main difference between residential patients and outpatients is that in residential facilities, treatment compliance is granted by a 24-hour cover. For this reason, the MARS was administered only to outpatients; there were 51 refusals among patients who were administered the MARS. Eighteen patients (11.0%) showed a maximal adherence to medication; 37 (22.6%) and 27 (16.5%) scored equally high on the MARS. A new binary variable was therefore defined, classifying as compliant all patients living in residential facilities and outpatients with a MARS score ≤2 (207 of 289, 71.6%), while outpatients with a MARS score >2 were considered noncompliant (82 of 289; 28.4%). Noncompliant patients showed higher cMOAS values compared with compliant patients (supplementary Figure 5). The ratio of the 2 areas was 2.1 (285/138), with a 95% bootstrap CI between 1.2 and 3.3.

Both cases and controls showed a similar compliance (72.0%, 108 of 150 cases; 71.2%, 99 of 139 controls; supplementary Figure 6 shows the pattern of cMOAS taking into account both compliance and violence).

Noncompliant cases showed the highest MOAS values (with an area of 395), while compliant controls showed the lowest MOAS scores (with an area of 75; 95% bootstrap CI between 2.6 and 10.8). On the other hand, compliant cases and noncompliant controls showed a rather similar cMOAS pattern (the 2 areas were 196 and 170 with a 95% bootstrap CI between 0.6 and 2.4). Overall, 3 main patterns emerged with respect to compliance and violence (as rated with the MOAS), listed from the most to the least violent: (1) noncompliant cases, (2) compliant cases and noncompliant controls, and (3) compliant controls. A similar result was found when we assessed compliance and MOAS ratings by diagnosis: in all 3 diagnostic groups, compliant patients confirmed a less aggressive behavior compared with not-compliant participants (see supplemental Figures 7–9).

We have also evaluated (1) patients taking clozapine (considered as 1 group); (2) patients not taking clozapine, but rated as compliant (based on MARS scores); and (3) patients not taking clozapine and not compliant (again based on MARS scores). Interestingly, the main difference was between noncompliant patients who did not take clozapine (group 3) and the other 2 groups, with patients taking clozapine (group 1) showing lower rates of aggressive behavior similar (and numerically lower with respect) to rates found in compliant patients not taking clozapine (group 2).

Discussion

This is, to our knowledge, the first extensive research aimed at analyzing psychotropic prescription patterns in a large sample of residential patients and outpatients with and without a lifetime history of violent behavior and the associations between pharmacological treatments and aggressive/violent behavior(s) shown during a 1-year monitoring period.

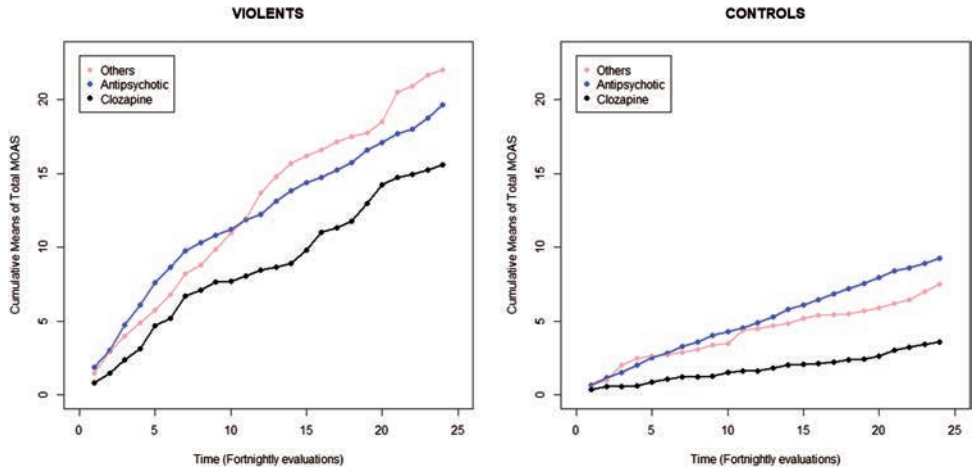

Figure 2. Cumulative means of total Modified Overt Aggression Scale (MOAS) in different pharmacological groups.

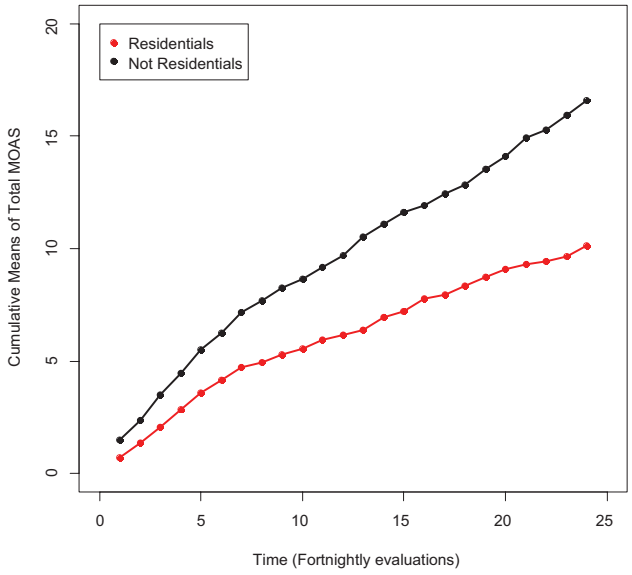

Figure 3. Cumulative means of total Modified Overt Aggression Scale (MOAS) in different clinical groups according to residential setting.

Patterns of Polypharmacy

About three-quarters of our sample took at least 1 AP, independently from any history of violence. BDZ were widely prescribed, independent of any diagnostic groupings. Clozapine was prescribed significantly more often to people with schizophrenia, while lithium was more frequently administered to people with other disorders, including bipolar disorder. Patients affected by schizophrenia received a lower number of medications belonging to fewer categories compared with those with PDs or other disorders (including bipolar disorder); they were also receiving LAAs with the highest frequency. In contrast, people with PDs showed the largest number of different drugs from different categories.

In general terms, our data show that most patients (81.2%) took more than 1 psychotropic drug and many received APP. This happens despite the fact that the evidence for APP efficacy and tolerability is weak (Barbui et al., 2009; Correll et al., 2009; Constantine et al., 2015; Galling et al., 2017), and most guidelines recommend the addition of a second AP as a last-stage treatment option, after clozapine failure, intolerability, or rejection (Falkai et al., 2005; Goodwin et al., 2009). Indeed, APP may cause problematic drug-drug interactions, decreased adherence due to complex drug regimes, higher costs (Rupnow et al., 2007; Baandrup et al., 2012), and increased adverse effects (Goodwin et al., 2009; De Hert et al., 2011; Gallego et al., 2012).

Patterns of Psychotropic Prescriptions and Aggressive/Violent Behavior

Our results show that all patients with an history of violence displayed higher rates of aggressive and violent behavior during the follow-up; this finding was also confirmed when separate analyses were made within the 3 diagnostic groups (see supplementary Figures 1–3). Very few studies have analyzed the effects of pharmacotherapy on violent behavior and often compare different APs at a single time point without any prospective evaluation of participants' violent behavior (Swanson et al., 2004, 2008; Bitter et al., 2005; Volavka et al., 2011). Some studies have explored the possible differences between oral APs and LAAs, documenting a higher efficacy for LAAs (Arango et al., 2006), probably because of better medication adherence associated with the depot administration. Indeed, poor or partial adherence to medications has been found to be associated with a significantly higher risk of violence among patients suffering from psychotic disorders (Ascher-Svanum et al., 2006; Alia-Klein et al., 2007), while medication adherence has been regarded as essential to manage violence in people with schizophrenia (Topiwala and Fazel, 2011). In agreement with such findings, our results indicate that noncompliant patients (as shown by MARS ratings and by treatment setting) displayed more aggressive/violent behaviors than compliant patients; also, in this case, this result was confirmed when separate analyses were made within the 3 diagnostic groups (supplementary Figures 6–8).

In the present study, patients with lower MOAS scores were prescribed more psychotropic drugs compared with those with moderate or high scores. This finding may be explained by the sedative properties of most psychotropic drugs: patients receiving more psychotropic drugs are more sedated and then display less aggression and violence. It may also be possible that these patients were characterized by more comorbid mental disorders and for this reason were prescribed more medications, which led to lower rates of aggression/violence.

Interestingly, our findings show that clozapine-treated patients had the highest BGLHA scores, when evaluating the lifetime history of violence, and highest BPRS-E scores, but they were characterized by no or lower aggressive and/or violent behavior (as shown by statistically lower MOAS scores) during the 1-year follow-up; this result was confirmed in a separate analysis that considered only schizophrenic patients (clozapine was prescribed almost exclusively to these patients). Our results are in line with previous literature on severe mental disorders and violence in which clozapine has been found to have effective anti-aggressive properties (independent of its sedative or AP effect; Volavka et al., 2004; Quinn and Kolla, 2017), reducing violent behavior particularly in patients with schizophrenia (Krakowski et al., 2008; Swanson et al., 2008; Volavka et al., 2014).

It should be noted that clozapine is often regarded as the AP agent of last resort prescribed to patients with schizophrenia and other psychotic disorders who cannot tolerate or do not respond to other APs. This is due to an increased risk of agranulocytosis, which requires regular hematologic monitoring for neutropenia for the entire duration of the treatment (weekly from initiation to 6 months, every 2 weeks from 6 to 12 months, and monthly after the 12th month). For this reason, the extent of clozapine use is below the estimated prevalence of treatment-resistant schizophrenia (Leslie and Rosenheck, 2001; Weissman, 2002). However, as also shown in our study, treatment with clozapine should be considered an important component of violence risk management, especially in patients with a history of violence. It may have important implications in facilitating discharge planning and reintegration of difficult patients back into the community (Krakowski et al., 2006).

Limitations

The first limitation is that drug prescriptions were assessed only at baseline, so it may be possible that patients underwent drug switches during the 1-year period, and this may have affected the MOAS ratings. It should, however, be highlighted that clozapine prescription in Italy is regulated by tight official rules, and for this reason, it is rather uncommon to start clozapine and then switch to other medications (unless there are serious side effects due to clozapine). With regard to the comparison of the clozapine, other APs, and no APs groups, all patients were also receiving other psychotropic medications; therefore, the finding of a lower rate of aggression and violence in the clozapine group may also be due to the other medications prescribed in association.

Another limitation is that patients' compliance was not assessed with laboratory examinations; compliance was rated only through the MARS, a self-report test.

Conclusions

Our study demonstrates that polypharmacy is common among patients in treatment in different settings. Even the association between specific diagnostic profiles and medication prescribing is often weak, as demonstrated by the widespread prescription of BDZ.

AP prescription has an important role in preventing and managing aggressive and violent behavior in people with severe mental disorders, and clozapine has a special role in the clinical management of patients with an history of aggressive and violent behavior. Finally, patient compliance is also of paramount importance to prevent and effectively treat aggressive and violent behavior.

Supplementary Materials

Supplementary data are available at *International Journal of Neuropsychopharmacology (IJNPPY)* online.

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Interest Statement

None.

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