



Substance Abuse Associated with Aggressive/Violent Behaviors in Psychiatric Outpatients and Related Psychotropic Prescription

Massimo Carlo Mauri¹ · Giovanna Cirnigliaro² · Eleonora Piccoli² · Matteo Vismara² · Vera De Carlo² · Nicolaja Girone² · Bernardo Dell'Osso^{2,3,4,5}

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Abstract

Psychiatric disorders with substance abuse are considered the leading causes of most violent and aggressive behaviors in the general population. This study was aimed to assess the impact of substance abuse and the therapeutic approaches adopted by psychiatrists in aggressive vs non-aggressive outpatients ($n = 400$) attending community-based psychiatric services and recruited over a 3-year period. Clinical and therapeutic variables were collected from medical records and the Modified Overt Aggression Scale (MOAS) was used to assess any aggressive/violent behavior. Violent behaviors were significantly higher in alcohol and substance abusers compared to non-abusers ($p < 0.01$), except for heroin abusers. Mean weighted MOAS score was significantly higher in patients taking antipsychotics ($p < 0.005$). The administration of Haloperidol, Zuclopenthixol, and Clozapine was more frequent in aggressive than in non-aggressive patients. The most frequently administered drug in these patients was Haloperidol (23.91%), with a higher mean daily dosage in violent vs non-violent patients. Our results confirm the well-established relationship between substance abuse and violent behaviors in psychiatric inpatients also within outpatient community services. Observed rates of most frequently prescribed antipsychotics to aggressive patients did not show any preference for newer generation compounds, with clinicians operating in the community setting likely being in need for further evidence and specific training to support their treatment choice.

Keywords Aggressive behavior · Violence · Substance abuse · Pharmacological treatment · Antipsychotics · Outpatients

The impact of worldwide violence, included in the top twenty causes of loss of disability-adjusted living years (DALYs) (Wolf et al., 2014), is projected to increase by 2030 (Mathers et al., 2008). Indeed, psychiatric disorders are considered among the leading causes of violent acts in current literature (Arseneault et al., 2000; Brennan et al., 2000; Elbogen & Johnson, 2009; Li et al., 2020). Different studies indicate that the more severe

✉ Giovanna Cirnigliaro
gio.cirnigliaro@gmail.com

Extended author information available on the last page of the article

the disorder, the more prone to commit violent acts patients seem to be (Fazel et al., 2009a, b; Swanson et al., 2002; Witt et al., 2013). The associated use of alcohol and/or other substances of abuse is a frequent complicating factor in psychiatric patients, resulting in an increased risk of aggressive and violent behaviors, especially in the acute phase of the disorder (Fazel et al., 2009a, b, 2010; Ferns & Cork, 2008; McNaughton Reyes et al., 2014; Reyes et al., 2015).

In Italy, as in many other countries, the public mental health system is largely based on a widespread network of community mental health centers (CMHCs): as a result, the majority of people with mental disorders live in the community and can have access to illicit drugs with relative ease. In spite of the territorial dimension of the Italian mental health services, a very limited number of studies investigated the relationship between outpatients' clinic-therapeutic variables and the occurrence of aggressive/violent behaviors (Pinna et al., 2016). Therefore, to the best of our knowledge, the present study was specifically aimed to investigate the association between aggressive/violent behavior and substance abuse in a sample of psychiatric outpatients attending a community mental health center in Northern Italy.

Clinicians often evaluate aggressive and violent behaviors among psychiatric patients through the Modified Overt Aggression Scale (MOAS) (Foley et al., 2005; He et al., 2017; Yudofsky et al., 1986), which is able to primarily assess aggressive and violent behaviors through four subscales (verbal aggression, aggression against objects, self-aggression, and aggression against others).

As far as the acute management of aggression is concerned, recent guidelines emphasize the importance of specific de-escalation techniques, followed by physical restraint and pharmacotherapy exclusively in the more severe cases. First-line treatments in these situations are antipsychotics and benzodiazepines (Brown et al., 2017; Gillings et al., 2016).

As for the chronic management of persistent aggressive and violent behaviors, no medication has been approved by the American Food and Drug Administration (FDA) or the European Medicines Agency so far. In these contexts, currently used pharmacological interventions often consist of drug combinations on a *trial-and-error* basis that can elicit side effects that further complicate the overall clinical management of aggressive patients. However, neurobiological considerations combined with real-world data can provide a comprehensive framework for systematic medication trials to manage persistently aggressive patients (Meyer et al., 2016). Ultimately, the primary disorder they have been suffering from is an important variable to consider in the treatment choice.

In the case of psychotic patients, ineffective treatment of psychosis often manifests as violent and aggressive behaviors that warrant treatment strategies that are not evidence-based. These include both antipsychotic polypharmacotherapy and high-dose antipsychotic monotherapy (Morrissette & Stahl, 2013). For instance, Haloperidol is frequently used as monotherapy to handle situations of aggression or agitation for psychotic patients. Apart from being widely accessible, in its intramuscular formulation, it may be the only antipsychotic medication available in limited-resource areas (Ostinelli et al., 2017). Where additional drugs with a better tolerability profile are available, the sole use of Haloperidol may be considered controversial, as it might aggravate violent behavior in a subgroup of patients, probably as a consequence of dysphoria associated with neuroleptic treatment (Mizrahi et al., 2007). These problems can be minimized by using the new-generation antipsychotics (Kirsch et al., 2007; van Schalkwyk et al., 2018). Indeed, in a previous review, Paliperidone-extended release appeared to be the agent with the strongest evidence of efficacy for the management of hostility among inpatients with schizophrenia spectrum

disorders (Victoroff et al., 2014). Anti-aggressive effects have been reported with Risperidone as well (Buckley et al., 1997; Ostinelli et al., 2018a).

According to a more recent review, Clozapine might be more effective than other drugs in reducing aggressive behaviors (Patchan et al., 2018), and its anti-aggressive effect seems to be distinct from its antipsychotic and sedative action (Buckley et al., 1995; Krakowski et al., 2006).

Consensus on the efficacy of other second-generation antipsychotics (SGAs) in treating patients' aggressiveness is still lacking (Penzner et al., 2009), although studies reported that Olanzapine, Quetiapine, and Aripiprazole showed some effectiveness (Arango & Bernardo, 2005; Lindenmayer & Kanellopoulou, 2009) with no significant difference among them (Mauri et al., 2011). Interestingly, a recent meta-analysis found that antipsychotics were broadly effective for the treatment of aggression, but with effect sizes similar to those of non-pharmacologic interventions. Furthermore, no differences were found in relation to the type of pharmacological agent or the underlying diagnosis, while a small but significant dose effect was identified (van Schalkwyk et al., 2018).

The lack of consensus on the long-term management of aggressiveness in psychiatric patients arouses the need to further investigate the use of specific pharmacological treatments in these individuals, particularly in the outpatient setting, where most individuals are taken care overtime. In a previous report of our group on this specific topic, we observed that diagnosis of personality disorders and specific sociodemographic factors, including employment status, represented major determinants of aggressive and violent behaviors among psychiatric outpatients (Mauri et al., 2019).

In continuity with the abovementioned report (Mauri et al., 2019), the present study focused on the prevalence of substance abuse in violent/aggressive psychiatric patients with different diagnoses attending a territorial service in Milan, Italy. In addition, we analyzed types and dosages of antipsychotic drugs prescribed in the real world to aggressive versus non-aggressive patients, and compared the use of these specific psychotropics.

Methods

Patients attending the territorial psychiatric service of zone 1—“*Centro Psicosociale*” (CPS)—Department of Psychiatry, Ospedale Maggiore Policlinico of Milan, Italy, were assessed over a 3-year period. The service is a public CMHC that provides assistance to post-acute psychiatric outpatients in need of pharmacological, psychological, and social support.

For the purpose of the present study, all psychiatric patients attending the facility were assessed. Inclusion criteria consisted of the occurrence of at least one psychiatric visit for each patient. There was no exclusion in relation to psychiatric diagnosis, psychiatric nor medical comorbidity.

Clinical, socio-demographic, and therapeutic data were collected from patients' medical records. Diagnoses were formulated by two expert psychiatrists on the basis of the International Classification of Disease, 10th Edition (ICD-10) (World Health Organization, 1993) criteria. We considered as alcohol and substance abuse all those conditions that, according to the ICD-10, are included in “Mental and behavioural disorders due to psychoactive substance use”: acute intoxication, harmful use, dependence syndrome, and withdrawal state.

The Modified Overt Aggression Scale (MOAS) (Foley et al., 2005; He et al., 2017; Yudofsky et al., 1986) was administered to each patient during the follow-up visit at the

CPS. Any aggressive or violent behavior occurring in the week before the contact with the members of the CPS team was retrospectively recorded through the MOAS. A member of the medical staff, who was blind in relation to the clinical diagnosis, quantified the MOAS scores, on the basis of his/her direct observation or the information given by relatives or caregivers that were aware of any clinically relevant information regarding patient's behavior.

MOAS is a semi-structured interview that evaluates 4 clusters of aggressive behavior: verbal aggression, aggression against objects, self-aggression, and aggression against others. Each subscale score ranges from 0 (no aggression) to 4 (maximum score). The subscales were weighted, as previously reported (Kay et al., 1988). The total MOAS score is the sum of the weighted scores. The prevalence of violent behaviors was calculated considering the presence of a score > 0 in one MOAS subscale other than verbal aggression (e.g., aggression against objects, self-aggression, aggression against others), as done in previous investigation (Foley et al., 2005). In this study, we used the Italian version of MOAS that has been validated in terms of inter-rater reliability and internal consistency by Margari and colleagues (Margari et al., 2005). Additional details on the CPS1 structure and the MOAS have been provided elsewhere (Mauri et al., 2019).

Information regarding psychopharmacological treatments, taken during the period when the visit and the MOAS administration occurred, was collected from medical records and subdivided into the following classes: antipsychotics (oral and long-acting), antidepressants, mood stabilizers, benzodiazepines, and psychotherapy or group therapy.

The protocol was approved by the local Ethics Committee and a written informed consent was obtained from patients or their relatives after receiving a full study description.

Statistical analyses were conducted by means of descriptive methods, analysis of variance (ANOVA), chi-squared test, multifactor analysis of variance (Tukey's test), and regression analysis (simple regression), using the Statgraphic Centurion version 2018 (2018 Statpoint, Inc. USA, <http://www.statgraphics.com>).

Results

The study included 400 patients whose mean clinical variables are shown in Table 1.

Violent behaviors were significantly higher in patients with alcohol abuse ($p < 0.01$), cocaine abuse ($p < 0.001$), and cannabis abuse ($p < 0.001$), compared with non-abusers (Fig. 1). No significant difference in subjects with heroine abuse compared with non-abusers emerged in terms of violent behaviors.

The most relevant therapeutic variables, including psychotherapy and group therapy, of the total sample are summarized in Table 2. Mean weighted MOAS scores (MWMOASs) were significantly higher in patients taking antipsychotic drugs ($p < 0.005$), while they were significantly lower in those taking antidepressants ($p < 0.001$). No significant correlation with regard to long-acting therapy, mood stabilizers, or anxiolytics was observed (Table 2). No statistically significant difference in MWMOASs was found among patients taking different antipsychotics compared to those taking monotherapies.

MWMOASs were significantly higher in patients who were not currently receiving psychotherapy (2.63 ± 5.52) than in patients who were receiving it (1.26 ± 3.48) ($p < 0.05$) (Table 2). No significant correlation in regard to group therapy was observed.

Figure 2 shows the different types of antipsychotics utilized in the CPS and how often they were administered in non-aggressive and aggressive patients. The frequency

Table 1 Clinical variables of the total sample

Clinical variables	Values
Age	(49.7 ± 14.72)
<i>Gender:</i>	
Male	52.75%
Female	47.25%
<i>Diagnosis:</i>	
Schizophrenia (SCH)	23.31%
Personality disorder (PD)	13.53%
Bipolar disorder (BD)	17.04%
Anxiety disorder (AD)	20.3%
Major depression (MD)	8.77%
Mental retardation (MR)	3.76%
Substance-induced psychosis (SIP)	4.51%
Obsessive–compulsive disorder (OCD)	1.75%
Eating disorder (ED)	0.75%
Senile dementia (DEM)	2.01%
Delusional disorder (DD)	4.26%
<i>Substance abuse:</i>	
Cannabis	15.75%
Cocaine	8.75%
Heroin	3.75%
Alcohol	15.75%
Age at onset	(33.74 ± 15.2)
Duration of illness	(15.93 ± 12.25)
<i>Number of hospitalizations:</i>	
0	40%
1–5	40.5%
6–9	6%
≥ 10	13.75%
<i>Number of compulsory admissions:</i>	
0	83%
> 0	17%
<i>Number of attempted suicide:</i>	
0	82.25%
1–3	16.75%
4–6	1%
MWMOAS ^a	2.19 ± 5
MOAS score > 0	21.50%

^aMWMOASs (mean weighted MOAS score); values for categorical and continuous variables are expressed as percentage (%) and mean ± SD, respectively

of Haloperidol, Zuclopenthixol, Clozapine, and Paliperidone administration was higher in aggressive vs non-aggressive patients. In the aggressive population, the most frequently administered drugs were Haloperidol (23.91%), Olanzapine (17.39%), Quetiapine (13.04%), and Zuclopenthixol (10.87%). As shown in Table 2, the mean dosages of

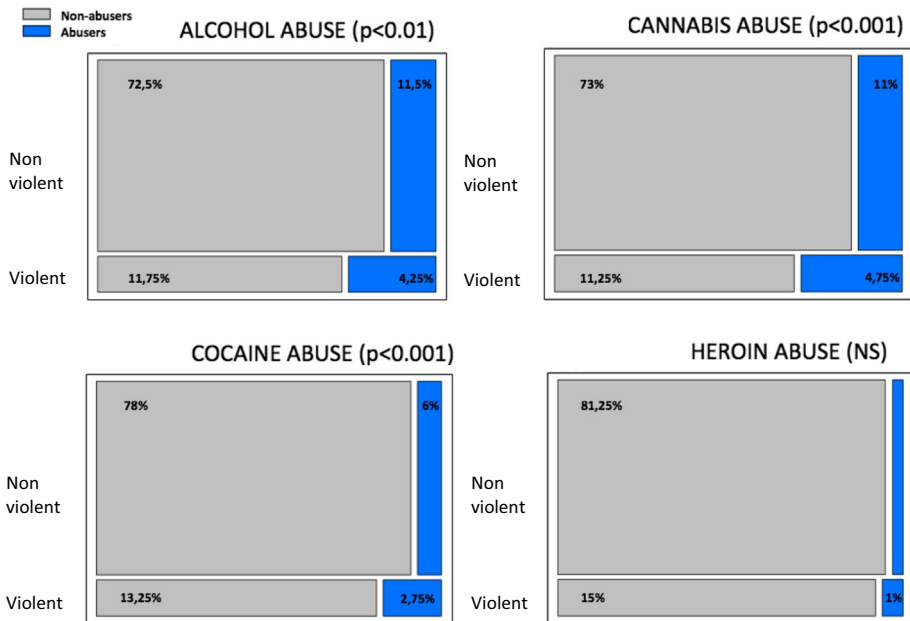


Fig. 1 Frequency of violent behaviours in patients with vs without substance abuse. Alcohol, cannabis, and cocaine abusers were more frequently violent than non-abusers ($p < 0.01$). Heroin abusers were not significantly (NS) more violent than non-abusers

Haloperidol and Zuclopenthixol prescribed in violent patients were higher than those prescribed in non-violent patients.

Discussion

Several studies investigated the presence of aggressive and violent behaviors among inpatients of psychiatric wards (Amore et al., 2008; Ballerini et al., 2007; Biancosino et al., 2009; Colasanti et al., 2008; Cornaggia et al., 2011; Dack et al., 2013; Szabo et al., 2015), while studies with outpatients are limited (Amore et al., 2013; Choe et al., 2008; Folgo & Iennaco, 2020; Pinna et al., 2016).

Our study evaluated aggressive and violent behaviors in psychiatric outpatients attending an Italian CMHC of the central area of Milan, focusing on substance abuse and therapeutic variables.

An important variable in aggressive behaviors is, in fact, substance abuse (Fazel et al., 2009a, b, 2010), particularly alcohol (Renwick et al., 2016). In this perspective, a significant relationship between substance and alcohol abuse and violent behavior was observed. In particular, we found a statistically significant correlation for alcohol abuse, cannabinoid and cocaine abuse, and violence, likely related to the activating effects of these substances, as reported in literature (Boles & Miotto, 2003; Fazel et al., 2014; Phillips, 2000). Conversely, heroin abuse did not correlate with violent behaviors. Most data on heroin abusers, in fact, show that violent acts typically occur during abstinence and not during active use (Gerra et al., 2004). When occurring in heroin-addicted patients, moreover, aggressive

Table 2 Therapeutic variables in relation to the mean weighted MOAS score in the total sample (top part); different mean dosage of the most used oral antipsychotics in violent and non-violent patients (bottom part)

Therapeutic variables <i>N</i> = 400	Prevalence %		MWMOAS ^a ± SD		<i>p</i> value
	No	Yes	No	Yes	
Pharmacotherapy					
Antipsychotics (oral)	48%	52%	1.46 ± 4.2	2.86 ± 5.59	0.005
Antipsychotics (long-acting)	91%	9%	2.15 ± 5.1	2.54 ± 4.2	
Antidepressants	70%	30%	2.71 ± 5.5	0.99 ± 3.2	0.001
Anticonvulsants	72%	28%	1.91 ± 4.6	2.90 ± 5.8	
Anxiolytics	53%	47%	2.45 ± 5.3	1.93 ± 4.7	
Psychotherapy, current	31.75%	68.25%	2.63 ± 5.5	1.25 ± 3.4	0.05
Group therapy, current	18.50%	81.50%	1.98 ± 4.8	3.12 ± 5.8	
	Non-violent patients		Violent patients		
Antipsychotics (oral)	Mean dosage (mg/day) ± SD		Mean dosage (mg/day) ± SD		
Haloperidol	6.68 ± 12		8.91 ± 14		
Zuclopentixol	22.5 ± 13		59 ± 80		

^aMWMOAS (mean weighted MOAS score)

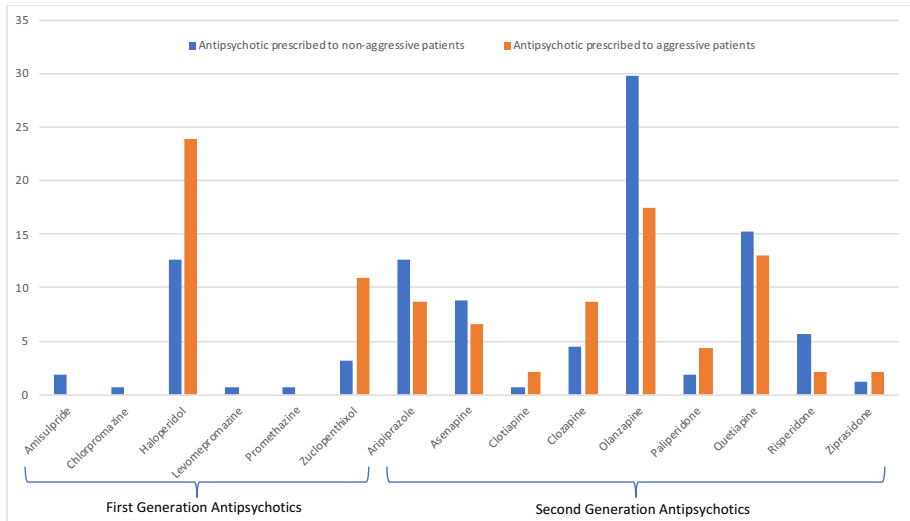


Fig. 2 Distribution of antipsychotics prescription in non-aggressive vs aggressive patients. Values are expressed as percentage

behaviors seem to be mostly correlated with comorbid psychiatric diagnoses (Maremmani et al., 2014). Nevertheless, it needs to be noted that most addicted patients had been taken over by CPS because of their psychiatric comorbidity. Therefore, the potential role played by the psychopathological component or by drug addiction per se on aggression and violence is difficult to understand. Moreover, it is not clear whether these patients had been successfully treated by specific services dedicated to substance addicts (named “Servizi per le dipendenze” [SERD]) and whether patients followed by such services, in comparison to those who were not, had an improvement in relation to aggressive behaviors.

From a pharmacological point of view, in patients with aggressive/violent behaviors, the evidence from RCTs (randomized controlled trials) for the use of benzodiazepines as monotherapy is not solid, while their use in augmentation does not seem to confer a clear advantage and can bring potential adverse effects (Zaman et al., 2017). On the other hand, the efficacy of antiepileptic drugs in reducing aggression and associated impulsivity is very limited (Huband et al., 2014). For these reasons, we focused our analysis to the prescription of antipsychotics rather than benzodiazepines and/or anticonvulsants.

Data on the antipsychotics efficacy in aggressive patients are mixed. Evidence for use of second-generation antipsychotics (SGAs) is mainly supported by very recent literature (Currel et al., 2017; Faay et al., 2018; Ostinelli et al., 2018a, b; Powney et al., 2012). In our sample, Haloperidol and Zuclopenthixol were more frequently prescribed in aggressive than in non-aggressive patients. In addition, the average dose of Haloperidol and Zuclopenthixol prescribed for violent patients was higher than non-violent ones. This might indirectly indicate a greater effectiveness of first-generation antipsychotics (FGAs), when used at higher doses, on aggressive behaviors, also in light of previous literature data (Powney et al., 2012). We can speculate that, in the psychiatric service examined in the present study, Haloperidol was likely considered to be the most effective compound for aggression as well as the most frequently used, despite its known side effects, including tardive dyskinesias (Carbon et al., 2018).

Regarding the treatment of aggressive behaviors in patients with personality disorders, it needs to be taken into account that antipsychotics are indicated only for aggressive behaviors associated with psychotic disorders, as activation of dopamine receptor may lead to defensive aggression (Tsiouris, 2009). Indeed, there is no evidence that antipsychotics are effective in controlling aggression in patients suffering from personality disorders. On the other hand, Quetiapine was shown to be effective in the treatment of aggression, impulsivity, and irritability and has proved to be an effective medication in patients with antisocial personality disorder. In addition, its better tolerability profile may determine a major therapeutic compliance (Walker et al., 2013). Consistently, in our sample, the third most used antipsychotic for aggressive patients was Quetiapine.

Among SGAs, strong evidence supports the use of Clozapine for treating psychotic aggression in refractory patients and for impulsive violence (Mauri et al., 2003; Meyer et al., 2016). In our sample, the frequency of Clozapine use was higher in violent than in nonviolent patients. In terms of effectiveness for aggression, in a previous study, Clozapine was followed by Olanzapine (Citrome & Volavka, 2014) which was the second most administered drug in our sample, after Haloperidol.

Finally, the evidence for non-pharmacological interventions in reducing aggression and violence in psychiatric disorders is not conclusive, since high-quality RCTs are lacking (Rampling et al., 2016). In our sample, patients who were not currently on psychotherapy were found to be more aggressive than patients who were receiving it. Actually, some cognitive impairment was shown to be involved in the genesis and maintenance of violent behaviors in individuals with schizophrenia (Darmedru et al., 2017). Therefore, its effective management should contemplate new therapeutic perspectives such as cognitive remediation (which is still rarely used for this purpose) to complement the action of pharmacotherapy (Darmedru et al., 2018).

Additional data concerning sociodemographic factors has been discussed elsewhere (Mauri et al., 2019).

The following methodological limitations should be considered when interpreting the abovementioned findings. First of all, the nature of the study was observational, although the raters were blinded to study aim and to the administered drugs. Moreover, the present investigation did not include any measure of efficacy. Thus, we cannot conclude that the efficacy of Haloperidol is greater than that of any other specific antipsychotic for the treatment of aggressiveness. In addition, we could not control bias or confounding factors, as a RCT would allow. On the other hand, it has been postulated that an observational design may be more suitable in evaluating a population of patients that is often difficult to engage with and unlikely to participate in RCTs. Furthermore, the study should continue involving other psychiatric services, including SERD and CPS located in other areas of the city as also economic, cultural, and other factors related to the catchment area may have played a role in the reported results.

Conclusion

Our results confirm the well-established relationship between substance abuse and violent behavior in outpatients with psychiatric disorders attending psychosocial community centers (Fig. 1). The pharmacological approach psychiatrists considered clinically more appropriate in treating aggressive behaviors was analyzed in terms of most widely used treatments in aggressive versus non-aggressive outpatients. In particular, the frequency

and dosages of Haloperidol and Zuclopenthixol administration were higher in aggressive versus non-aggressive patients. Among SGAs, Clozapine was found to be preferred in the treatment of aggressive patients. These results do not necessarily mean that FGAs are more effective than SGAs in the treatment of aggressive outpatients. As Clozapine, despite being a SGA, is the oldest SGA, reported results seem to suggest that mental health professionals working in psychosocial community centers need to be educated and trained about most effective treatments—not necessarily antipsychotic monotherapies—for mitigating violent behaviors. In this regard, in fact, more recent literature data seem to suggest a wider use of newer SGAs, such as Risperidone, Paliperidone, and Quetiapine, also in light of a better tolerability profile (Currel et al., 2017; Faay et al., 2018; Ostinelli et al., 2018a, b; Victoroff et al., 2014; Walker et al., 2013).

Ultimately, the effectiveness of psychotropic drugs on aggressive behaviors still remains unclear with further studies needed in the area of outpatients. Reported real-world findings on this topic may help clinicians to reach a more conscious drug choice, while further studies in the field are warranted.

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Author Contribution All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by Massimo C. Mauri, Giovanna Cirnigliaro, and Bernardo Dell’Osso. The first draft of the manuscript was written by Giovanna Cirnigliaro and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Declarations

Ethics Approval All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000 (5).

Informed Consent Informed consent was obtained from all patients for being included in the study.

Conflict of Interest Prof. Dell’Osso has received speaker fees from Lundbeck, Angelini, Janssen, Livanova, Arcapharma, and Neuraxpharm. The other authors have no relevant financial or non-financial interests to disclose.

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Authors and Affiliations

Massimo Carlo Mauri¹ · Giovanna Cirnigliaro²  · Eleonora Piccoli² · Matteo Vismara² · Vera De Carlo² · Nicolaja Girone² · Bernardo Dell'Osso^{2,3,4,5}

¹ Department of Neuroscience and Mental Health, Clinical Psychopharmacology Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, via F. Sforza 35, 20122 Milan, Italy

² Department of Mental Health, Department of Biomedical and Clinical Sciences Luigi Sacco, ASST Sacco-Fatebenefratelli, University of Milan, Via G.B. Grassi, 74, 20157 Milan, Italy

³ Department of Psychiatry and Behavioral Sciences, Bipolar Disorders Clinic, Stanford University, Stanford, CA, USA

⁴ Aldo Ravelli" Center for Neurotechnology and Brain Therapeutic, University of Milan, Milan, Italy

⁵ "Centro per lo studio dei meccanismi molecolari alla base delle patologie neuro-psico-geriatriche", University of Milan, Milan, Italy