Randomised clinical trial comparing oral versus depot formulations of zuclopenthixol in patients with schizophrenia and previous violence

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Abstract

Purpose. – The aim of this longitudinal study was to determine whether the depot formulation of an antipsychotic reduces violence in outpatients with schizophrenia as compared to oral administration of the same antipsychotic.

Methods. – Forty-six previously violent patients with schizophrenia were randomised to receive treatment with oral or depot zuclopenthixol for 1 year. Clinicians interviewed patients at baseline and every month thereafter to assess treatment adherence. An interviewer blinded to treatment assignments interviewed an informant about any violent behaviour during the previous month.

Results. – Violence during the follow-up year was inversely proportional to treatment adherence, better compliance, and greater reduction of positive symptoms. Lower frequency of violent acts was observed in the depot group. The level of insight at baseline was not significantly associated with violence recidivism. Regardless of route of administration, treatment non-adherence was the best predictor of violence.

Conclusions. – Some patients with schizophrenia and prior violent behaviour may benefit from the depot formulation of antipsychotic medication.

Keywords: Schizophrenia; Violence; Treatment adherence; Depot medication

1. Introduction

Violence associated with schizophrenia has negative repercussions for patients and their families, in addition to rendering difficult the reduction of stigma.

Although most patients with schizophrenia are not violent, several recent longitudinal studies of large cohorts have demonstrated a link between schizophrenia and violence [1,8,10,26,33,36]. The relationship between schizophrenia and violence can be explained in part by sociodemographic factors such as a low socio-economic status and unemployment, as well as alcohol abuse and antisocial personality, all of which are predictors of violence in the general population and over-represented in schizophrenia. These factors are also over-represented among persons with schizophrenia [11].

However, increased rates of violence in schizophrenia cannot be attributed solely to social factors (Monahan 1992 [23]). Actually, clinical symptoms such as certain psychotic manifestations and a lack of insight into illness have also been related to violence in schizophrenia [2,13,30,31]. Medication non-adherence has been related to higher rates of violence among patients with schizophrenia [7,27,29]. The hypothesis has been posed that the violent-behaviour profile of drug treatment-compliant patients with schizophrenia does not differ from that of the general population and that violence in schizophrenia is at least in part due to inadequate treatment [25]. However, more recent studies have shown that, although adherence and lack of positive symptoms are important predictors of violence in schizophrenia, some patients who comply with medication are still violent, especially those with an additional diagnosis of illegal substance abuse, antisocial personality disorder, or brain damage [11,14,20,24]. Many studies propose different strategies to reduce violence...
in schizophrenia, one of those being increasing medication compliance.

In a recent study comparing the effectiveness of different second-generation antipsychotics and conventional antipsychotics in reducing violent behaviour among outpatients with schizophrenia, the greater cumulative effect of second-generation antipsychotics was attributed to consistent compliance [28]. To our knowledge, no previous longitudinal clinical trial has been specifically performed to assess the effect of treatment compliance on violence, nor are we aware of any randomised, controlled trial with oral versus depot medication to evaluate the effect on violence.

The aim of this study was to longitudinally assess the effect of depot and oral medication on treatment compliance, and the effect of treatment compliance on reduction of violence, presumably through reduction of positive symptoms. The initial hypotheses were that:

- Patients receiving depot antipsychotic medication will be more treatment compliant and, therefore, will present lower rates of violent behaviour compared to patients receiving oral antipsychotic medication.
- Patients with schizophrenia who are compliant with antipsychotic medication will present lower rates of violent behaviour compared to non-compliant patients.

Additionally, we were also interested in comparing violent and non-violent patients through follow-up for variables that have been shown to be related to violence in schizophrenia.

2. Material and methods

2.1. Participants, recruitment, and assignment

Participants were recruited from three inpatient hospitals in Madrid over a 24-month period. Two of the inpatient units were located in general hospitals and one in a psychiatric hospital. Inclusion criteria were:

- DSM-IV criteria for schizophrenia (American Psychiatric Association);
- a violent episode in the previous year, with a score of at least 3 on the physical aggression subscale of the Modified Overt Aggression Scale (MOAS);
- a family member living with the patients and willing to collaborate with the researchers;
- informed consent signed by the patient and the informant.

In order to assess whether the inclusion criteria b) were met, both the patients and relatives were interviewed to ascertain whether there had been at least one episode during the previous year that could be rated 2 on the MOAS [17] physical aggression subscale (a score of 2 on this subscale means “strikes, kicks, hair pulls, pushes, attempted scratches, without causing injury,” a score of 3 means “attacks causing mild injury” and a score of 4 means “attacks causing serious injury”). A low baseline rate of severe violence decreases statistical accuracy [34]. We established these inclusion criteria in order to increase the prevalence of violence in our sample, since previous violence has been shown to be the best predictor of future violent behaviour in this patient population [35].

Exclusion criteria were:

- Any other axis I disorders, including alcohol and/or drug abuse or dependence.
- Mental retardation.

2.2. Study design

This was an open-label, prospective, randomised, controlled trial with a 1-year follow-up period. Eligible patients were randomly assigned to oral or depot formulations of zuclopenthixol. The trial administrator randomised the study participants at one of the centres. Patients were stratified according to the following variables: age, gender and severity of previous violence (as defined by a score of 2 or 3–4 in the physical aggression subscale of the MOAS in the previous year).

2.3. Drug information

At the time this study was conducted, zuclopenthixol was the only drug available in both oral and depot formulation in our country. Zuclopenthixol, a conventional antipsychotic, has been proven to be as effective as other conventional antipsychotics, but with fewer side effects [6]. Zuclopenthixol was the only antipsychotic administered throughout the study period. In the event subjects required a different antipsychotic medication, they were withdrawn from the trial. Dosage was flexible. Patients on depot medication received their injections every 14 days. All study participants received biperiden at a minimum dose of 2 mg daily for those on oral medication or one 5 mg ampoule every 14 days for subjects receiving depot medication. Other psychotropics (e.g. benzodiazepines) were permitted during the trial.

2.4. Assessments and measurements

The identified key relative was interviewed by phone every month by an interviewer who was blinded to the study hypotheses and medication status (I.B.). Generally, the informant was a family member, usually the mother (79.1%), but also the spouse (16.7%) or a sibling (4.2%).

The informants were told that they must not disclose which treatment their relative was taking to the telephone interviewer. At baseline, they were instructed to keep a daily paper diary in which they were to make note of any violent incident and all information they could recall about such incidents. The relatives were also asked to elicit information from the patients about any violent episode occurring during the previous month. During every monthly telephone call, the informants were reminded to follow these instructions. If the key relative was not available or if he/she did not have all the relevant information when the call was made, he/she was called on consecutive days.
The MOAS [17], a widely used aggression scale with documented reliability and validity, was used to evaluate violent behaviour. The scale has four categories of aggressive behaviour (verbal aggression, aggression against property, auto-aggression, and physical aggression). Although the four subscales were rated every month, only the fourth category was used in the present study, since aggression toward others appears to be the most clinically relevant category.

Patients met with their clinicians at least once a month. Clinical scales were administered every 3 months. Assessments included a psychopathology scale: the Positive and Negative Symptoms Scale (PANSS) [16] and a side effects scale: UKU [21]. The three clinicians (C.A., T.G.S., and I.G.C.) were trained in the use of the PANSS and rated 10 videotaped patients with a total intraclass correlation (ICC) of 0.93. A trained rater (I.B.) administered an insight scale (SUMD) [3] to the entire sample at the beginning of the follow-up period and assessed 10 patients with an ICC ranging from 0.92 to 0.96 for the different items comprising the scale (awareness of mental disorder, awareness of benefits of medication, awareness of social consequences of mental disorder, awareness of symptoms, and attribution of symptoms to the disorder).

2.5. Adherence

Patients were seen by their own clinician (C.A., T.G.S., I.G.C.) who evaluated adherence to treatment on a monthly basis. Adherence to oral medication was evaluated on the basis of information from the patient and a key relative; depot medication adherence was based on the record of intramuscular (IM) administration. In patients receiving oral medication, adherence was retrospectively assessed by means of the informant’s report during the monthly clinical interview. Relatives were asked if patients had taken their medication 100, 66, 33, or 0% of the time. Monthly and yearly adherence to medication were defined a priori as follows: In a given month, non-adherence was defined as compliance only 0 or 33% of the time for oral administration, or two consecutive missed injections for the depot form. At the 1 year follow-up, the compliance level was rated as high (administration for 10–12 months), intermediate (5–9 months), or low (fewer than 4 months).

2.6. Ethical issues

All patients signed an informed consent before enrolment in the study. At least one relative was informed and concurred. The study was approved by the Ethics Committee of the three hospitals that participated in the study.

2.7. Statistical analysis

An outcome analysis was performed on an intention-to-treat basis with all available participants included in the analysis.

Patients receiving depot medication were compared to participants taking the oral formulation on the basis of at least one violent episode during follow-up (defined as an incident scoring 2 or more on the MOAS physical aggression subscale), severity of the violent episode, frequency of violence (none, low – one to eight violent episodes, or high – more than eight violent episodes), and number of violent episodes. Given that not all patients completed the 12 months follow-up period, the variable number of violent episodes was converted into a number of violent episodes per month by dividing the total number of violent episodes during follow-up by the months the patient remained in the study.

In all comparisons, a t-test was used for quantitative normally-distributed variables, a Kruskal–Wallis test for quantitative non-normally-distributed variables, and a Chi-square for categorical variables. The number of violent episodes was compared among the three adherence categories by means of a one-way ANOVA with Scheffe post-hoc analysis.

Logistics and linear regression analyses were performed using the entire sample, where the dependent variables were presence or absence of violence and number of violent episodes during follow-up, respectively. The following independent variables were used in the analysis: severity of violence during the previous year, positive symptoms during follow-up, insight into symptoms at baseline, number of months during which the patient adhered to medication, and type of treatment (oral or depot).

Composite PANSS scores were obtained by adding all the scales available for each patient (a maximum of 5 scales for each patient) divided by the number of times the scale was administered.

3. Results

Of the original sample of 46 subjects who met the inclusion criteria and signed an informed consent, five subjects dropped out of the study during the follow-up period: four subjects (two in the depot subgroup and two in the oral subgroup) dropped out of the study at the end of the first trimester. The fifth drop-out, from the oral subgroup, withdrew from the study at the end of the fourth month of follow-up. The reasons for discontinuation were: loss to follow-up (one patient in the depot group and two patients in the oral group), lack of efficacy (one patient in the oral group and one in the depot group had to be converted to a different antipsychotic). The drop-out rate was not statistically different between the two experimental subgroups ($x^2 = 2.94$; d.f. = 3; $P = 0.4$). The mean dose of zuclopenthixol for patients randomised to oral medication was 35 mg/day throughout the study. The mean dose of IM zuclopenthixol was 233 mg every 14 days. The number of patients who received benzodiazepines at least once during the study was similar for both groups (40% in the oral group and 31% in the depot group). One subject in the depot group was treated with venlafaxine and another with lithium. One patient in the oral group was treated with propanolol.
Of the entire sample, 41.7% \((N = 20)\) presented at least one violent episode during the follow-up period, as defined by a score of 3 or more on the physical aggression subscale of the MOAS. The average number of violent episodes in this group of patients was 12.80; S.D. = 4.70 (range 1–45). The remaining subjects in the sample (54.2%; \(N = 26\)) did not present any episode of physical aggression with a score of at least 2 on the MOAS physical aggression subscale during follow-up.

As seen in Table 1, participants randomised to oral or depot medication did not differ in terms of level of education, PANSS negative score, PANSS general psychopathology score, or insight into illness, medication, or symptoms. Patients randomised to depot did, however, have higher positive PANSS scores on enrolment in the study \((P = 0.005)\).

The proportion of recidivistic patients receiving oral medication (40%) did not differ from that of patients receiving IM medication (46%) (see Table 2). The severity of the episode or the frequency of violent episodes did not differ between groups either. In contrast, of those participants who presented at least one violent episode, the number of violent episodes per month was significantly lower in patients treated with the depot formulation \((P = 0.034)\). The number of months between baseline and first violent episode was significantly longer for patients receiving depot medication \((mean = 4.71; S.D. = 1.73)\) than for patients receiving oral medication \((mean = 2.83; S.D. = 1.75)\) \((\chi^2 = 6.26; d.f. = 1; P = 0.012)\). Patients receiving depot medication also had more months of compliance \((P = 0.011)\) and more of these patients were classified as having a “high rate of adherence” \((P = 0.001)\) (see Table 2). Insofar as hospitalisation during follow-up was concerned, six patients in the oral group and 10 patients in the depot group were admitted to hospital at least once \((\chi^2 = 0.36; d.f. = 1; P = 0.55)\). The difference in number of hospitalisations was not significant between the two groups \((t = 0.02, d.f. = 24, P = 0.98)\). Subjects taking depot and oral medication did not differ in terms of PANSS-evaluated positive symptomatology throughout the follow-up period \((P = 0.417)\).

When patients were divided into the three adherence categories described in Section 2, the one-way ANOVA analysis showed that low-adherence patients presented higher rates of violent episodes than both medium- and high-adherence patients \((F = 36.11; d.f. = 2, 45; P < 0.001)\).

There were no differences between violent and non-violent patients in terms of gender, years of education, PANSS negative or the PANSS general psychopathology composite score during follow-up, MOAS score during the prior year, or the three SUMD scores at baseline. Violent patients pre-

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**Table 1**

<table>
<thead>
<tr>
<th>Oral vs. Depot—baseline sociodemographic and clinical variables</th>
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<tr>
<td></td>
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<tr>
<td>Gender* (male/female)</td>
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<tr>
<td>Age*</td>
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<tr>
<td>MOAS previous year* 2/3–4</td>
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<td>HHSES*</td>
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<tr>
<td>Years of education</td>
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<tr>
<td>PANSS positive</td>
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<td>PANSS negative</td>
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<tr>
<td>PANSS general psychopathology</td>
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<tr>
<td>SUMD</td>
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<tr>
<td>Awareness of disorder awareness of benefits of medication</td>
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<tr>
<td>Awareness of symptoms</td>
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* These three variables were used for the stratified randomisation.
* MOAS in the previous year for the physical aggression subscore.
* Head of household socio-economic status (HHSES) measure.

**Table 2**

<table>
<thead>
<tr>
<th>Oral vs. Depot—violence and adherence variables</th>
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<tbody>
<tr>
<td></td>
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<tr>
<td>Violence during follow-up: Yes/No</td>
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<tr>
<td>Severity of violence non/mild/severe*</td>
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<tr>
<td>Frequency of violence: absent/low/medium</td>
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<tr>
<td>Number of violent episodes per month during the study (MOAS ≥ 2)*</td>
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<td>Number of months from baseline to first violent episode</td>
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<tr>
<td>Number of months of adherence to medication*</td>
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<tr>
<td>Classification of adherence: high/medium/low*</td>
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<tr>
<td>Follow-up PANSS positive</td>
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</tbody>
</table>

* Mild = MOAS score = 2; severe = MOAS score = 3 or 4. * Mean violent episodes per month as measured by the MOAS physical aggression subscale in those patients who scored at least 3 during follow-up \((N = 8\) for oral and \(n = 12\) for depot). \(\chi^2\) from Kruskal–Wallis. * Months in which more than 1/3 of the prescribed oral medication was taken or the depot injection was administered at least once. \(\chi^2\) from Kruskal–Wallis. * High = 10–12 months adherent to medication; medium = 5–9 months adherent to medication; low = 1–4 months adherent to medication.
sent fewer months of adherence to medication \((P = 0.001)\) and a lower rate of adherence during follow-up \((P = 0.001)\), as well as more positive symptoms \((P = 0.029)\) (see Table 3).

To further address the role of positive symptoms in violence, we used a Kruskal–Wallis test to compare the number of violent episodes among patients who were admitted at least once during follow-up versus those who were not admitted. Patients with at least one admission had a significantly higher number of violent episodes \((\chi^2 = 18.85; \text{d.f.} = 1; \ P < 0.001)\). In the regression analyses, only the “number of months adherent to medication” variable was entered into the equations and explained 21 and 31% of the variance in presence/absence and number of violent episodes, respectively (see Table 4).

### 4. Discussion

Most subjects failed to satisfy the criteria for violence during the 1-year follow-up, despite the fact that all were recruited precisely because they had been violent in the year prior to enrolment in the study. We were unable to prove that the proportion of patients with at least one violent episode was lower in patients receiving depot medication than in those receiving oral medication. However, of those patients who were violent, subjects treated with the depot formulation had significantly fewer violent episodes. We proved that adherence to antipsychotic medication was related to fewer episodes of violence (regardless of assigned treatment).

Previous studies have shown that adherence to medication reduces the risk of violent behaviour in patients with schizophrenia. In a retrospective study, Bartels et al. [7] found that lack of adherence to medication was significantly related to violence in outpatients with schizophrenia. In 331 severely mentally ill outpatients, most of whom (60%) had schizophrenia or schizoaffective disorder, the combination of medication non-compliance and substance abuse was a significant predictor of violence [29]. In a recent 2 years longitudinal study, Swanson et al. [28] compared the effectiveness of conventional versus second-generation antipsychotics in reducing violent behaviour among schizophrenia outpatients. The authors report that the reduction in violence rates was attributable to consistent compliance with second-generation antipsychotics. Reduction in psychotic symptoms, substance abuse, and medication side effects were found to mediate the association between adherence to second-generation antipsychotics and risk of violence.

Use of long-acting parenteral antipsychotics helps to ensure adherence, hence leading to fewer relapses and rehospitalisations [15]. We therefore postulated that patients treated with depot medication would be more compliant and would present fewer episodes of violence. Adherence was the best predictor of violence during this 1-year longitudinal study. Treatment adherence may reduce violence by decreasing positive symptoms. Despite the fact that subjects receiving depot medication did not differ from those receiving oral medication with respect to presence and severity of positive symptoms \((P = 0.417)\), non-violent patients did present significantly fewer positive symptoms than violent patients during follow-up \((13.86 \text{ vs. } 18.17, \ P = 0.0029)\). These results support our hypothesis by pointing to treatment adherence as the key to reducing violence by decreasing psychotic symptomatology. There were no differences between the two groups with respect to the PANSS negative or general psychopathology subscores. We were not able to demonstrate a significant reduction in violence in the depot-treated patients versus patients treated with the oral antipsychotic. One reason for this is low statistical power due to the small sample size.

### Table 3

<table>
<thead>
<tr>
<th>Differences between violent and non-violent patients</th>
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<tbody>
<tr>
<td>Violent during follow-up ((N = 20))</td>
</tr>
<tr>
<td>Gender (female/male)</td>
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<tr>
<td>Years of education</td>
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<tr>
<td>Number of months adherent to medication</td>
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<tr>
<td>Classification of adherence: high/medium/low*</td>
</tr>
<tr>
<td>Follow-up PANSS positive*b</td>
</tr>
<tr>
<td>Follow-up PANSS negative</td>
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<tr>
<td>Follow-up PANSS general psychopathology</td>
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<tr>
<td>MOAS previous year</td>
</tr>
<tr>
<td>Awareness of disorder</td>
</tr>
<tr>
<td>Awareness of beneficial effects of medication</td>
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<td>Awareness of symptoms</td>
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</tbody>
</table>

*High = 10–12 months adherent to medication; medium = 5–9 months adherent to medication; low = 1–4 months adherent to medication. \(b\) \(\chi^2\) from Kruskal–Wallis.

### Table 4

Regression analysis with violence during follow-up as the dependent variable

<table>
<thead>
<tr>
<th>Variables entered into the equation</th>
<th>Presence/absence of violence</th>
<th>Number of violent episodes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment adherence*</td>
<td>(-3.59, \text{d.f.} = 44, \ P = 0.001, \ R^2 = 0.209)</td>
<td>(-4.56, \text{d.f.} = 44, \ P &lt; 0.001, \ R^2 = 0.306)</td>
</tr>
</tbody>
</table>

*Number of months adherent to the antipsychotic medication.
Previous violence has been proven to be the best predictor of future violence [35]. Because all of the participants in the present study had already demonstrated violent behaviour, it was impossible to evaluate this variable. However, the severity of the most serious prior episode of physical violence was not predictive of violence during follow-up.

In an epidemiological study of more than 600 subjects including outpatients, inpatients, and healthy controls, the authors found that the difference in violence among the different groups disappeared after controlling for psychotic symptoms [22]. The presence of psychotic symptoms not only predicted violence in patients, but also in the control group. The presence of positive symptoms has also been the best predictor of violence in prospective studies with schizophrenia outpatients [12,18,20]. In a previous prospective study of inpatients with schizophrenia, we proved that positive symptoms and lack of insight into these symptoms predicted violence in an acute context [2]. However, not all studies have shown that positive symptoms, such as delusions, predict violent behaviour [5]. In the present study, patients with at least one episode of violence during follow-up had more positive symptoms, measured as a composite score of scales administered every 3 months. Moreover, patients who were admitted to hospital at least once, which may be an indirect measurement of severity of positive symptoms, had more violent episodes. Despite the fact that positive symptoms measured longitudinally did not predict violence in the regression analysis, this may be due to the fact that most patients were stable (less variance) and violence could occur during exacerbations of positive symptomatology in between scores; a relationship would therefore be more difficult to demonstrate, since psychopathology scales were administered every 3 months at predetermined times. At baseline, there was more severe violence, although this difference failed to reach a level of statistical significance, and more positive symptomatology in patients randomised to depot medication. This would work to the detriment of the depot arm. Had the positive symptomatology and severity of previous violence been the same in both groups, the differences might have been greater than those found in this study. Different types of violence have been described in schizophrenia, one related to more positive symptoms, characterised by episodic and severe violence episodes; and the other related to disorganised symptoms, characterised by continuous and low severity violence [19]. The first type of violence would benefit more from continuous treatment. Because our depot group had higher scores for positive symptoms and severity of previous violence at baseline, we can not rule out that the differences between groups was due to a symptom-related type of violence in the depot group rather than the route of administration of the drug.

Given that non-adherence is often a consequence of lack of insight [4] and that we have previously shown that lack of insight is a predictor of violence, at least in hospitalised patients [2] and others, and also that it is also a predictor of violence in schizophrenia patients in prison or forensic psychiatric clinics [9], we were also interested in assessing the interaction between insight, treatment adherence, and violence. In this study, insight into illness, medication and symptoms were unrelated to violence. The difference with respect to our previous study was that the patients participating in this study were stable outpatients with lower PANSS scores and that, in a 1-year follow-up study, insight was assessed at only baseline. Therefore, as insight may be considered a variable state and changes during a 1-year follow-up, we cannot be certain about insight before the violent acts took place.

Some limitations of the study were that the sample size was small and that more patients were randomised to depot medication. This may have been due to the stratification of the randomisation. Another limitation was that adherence was measured retrospectively, by the relative who served as an informant. Similarly, insight was measured at only baseline. This being a longitudinal study and given the fact that insight is a state-dependent variable, it may have varied through the follow-up period. Hence, it would have been better to measure it longitudinally. There was also a lack of temporal proximity between the violence assessment and the PANSS, which was administered every 3 months. We did not provide the medication to the patients nor did we collect the leftover medication, as is common practice in some clinical trials, nor did we evaluate adherence by measuring plasma levels.

5. Conclusions

Although most patients with mental illness do not demonstrate physical aggression toward others, there is a subgroup that makes it particularly difficult to reduce the stigma associated with mental illness. Understanding the factors associated with violence in mental illness is the first step toward prevention through effective therapeutic approaches. Although antipsychotics have not been traditionally seen as a treatment for violence per se, it is possible to reduce violence indirectly by means of clinical programs, such as antipsychotic depot clinics, aimed at increasing treatment adherence. One way of decreasing exacerbations of psychopathology in a group of patients previously characterised by poor adherence would be to promote adherence through close clinical monitoring and administration of depot drugs. This finding would have significant implications for mental health service policy decision-making and for forensic or committed patients, for whom treatment compliance is a prerequisite for community living [32]. Mechanisms for monitoring adherence should be put in place for the specific population of high-risk patients who become violent when they fail to comply with their prescribed medication.

Acknowledgements

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References


