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Reducing Restraint With Clozapine in Involuntarily Admitted Patients With Schizophrenia

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Background: In the entire world, restraint and seclusion are common interventions in psychiatric inpatient settings because of aggressive behavior.

Study Question: Our objective was to test for the immediate antiaggressive property of clozapine compared with other antipsychotic treatments in an enriched cohort with high rates of restraint during early hospitalization.

Methods: We present a retrospective chart review in all involuntary admissions with schizophrenia during 2011–2014 in Psychiatry and Neurology Hospital, Brasov, Romania. Timing and number of restraints in addition to clinical, demographic, and treatment characteristics were extracted. Based on our earlier observation of clinical efficacy of early, fast titration of clozapine, we tested the hypothesis that clozapine treatment was associated with reduced use of restraint and with longer restraint-free periods.

Results: In 115 consecutive patients with schizophrenia (age = 39.7 ± 11.1 years; male = 59%) involuntarily admitted because of externalized (74.7%) or self-directed violence (25.2%), restraint was used in 89.6%; with a median duration of 3 hours until restraint past admission. Antipsychotics used immediately after hospitalization included haloperidol (70.4%), clozapine (11.3%), olanzapine (10.4%), and other second-generation antipsychotics (7.9%). Comparison of restraint characteristics favored immediate clozapine use with highly reduced rates of restraint (23% vs. 95.6%; $P < 0.001$) and significantly extended hours until restraint [(118, 24, 426 hours) vs. (3, 0.25, 48 hours); median; 25th, 75th percentile; $P < 0.001$] relative to the remaining cohort. These effects remained highly significant after controlling for potential moderators of restraint use in multivariate models.

Conclusions: These retrospective data suggest an early antiaggressive effect of clozapine during the immediate use of clozapine in highly problematic patients.

Keywords: restraint, aggressiveness, clozapine, schizophrenia

INTRODUCTION

In the entire world, restraint and seclusion are common interventions in psychiatric inpatient settings because of aggressive behavior.[1] Since the 1990s, there is a growing interest in the incidence of coercive measures in most European countries.[2] During the last years, there have been a few European studies in which psychiatric hospitals were compared regarding the frequency and duration of coercive measures. These studies are from

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the UK,[3] Switzerland,[4] Finland,[5] and Germany.[6] To date, there is no available data for Romania regarding this topic. Because of possible physical and psychological damage on patients affected by coercive measures,[7] the use of coercive measures can be seen as an indicator of the quality of psychiatric inpatient treatment.

In this study, we assessed antipsychotic (AP) use in involuntarily admitted patients with schizophrenia to (1) test the antiaggressive properties of clozapine by recording time until first use of restraint past admission and (2) to identify risk profiles for early restraint use in this population.

METHODS

Data were collected from charts, covering the period 2011–2014 during routine clinical care in the Psychiatry and Neurology Hospital, Brasov, Romania. This hospital is a public care facility which covers a population of 400,000. The admission ward is a 120-bed facility with 24-hour service of board certified psychiatrists. Data from all subjects with schizophrenia (clinical DSM IV diagnosis), who were admitted involuntarily with the diagnosis of schizophrenia were extracted. Because of our earlier report on fast titration of clozapine,[8] our hospital policy permitted the early use of clozapine as an equal alternative to other first-generation and second-generation antipsychotics (SGA). AP choice during the early admission was however the sole responsibility of the respective psychiatrist on duty in the emergency department/the admission wards. Restraint order was written whenever subjects appeared to be a threat for staff or fellow patients. Because of clinical departmental policy, Positive and Negative Symptoms Scale[9] and Clinical Global Impression[10] were recorded during admission in all subjects. This study was approved by the local ethics committee and with the Helsinki Declaration of 1975/2000.

We divided the patients in 2 groups. The clozapine group (CLZ-group) included all cases treated with clozapine during admission. In the nonclozapine group (non-CLZ), we entered all patients treated with other AP (haloperidol, olanzapine, quetiapine, risperidone, amisulpride, and aripiprazole). The primary aim of the study was to identify the index incident of restraint and the duration until restraint past admission. Demographic data included sex, age, duration of illness, and age of onset. We also collected data regarding reason for admission, number of restraints, length of stay, previous involuntary admissions, and history of violence.

Group comparisons were performed using Fisher exact test or Wilcoxon rank-sum tests as per data type and distribution, as well as nominal logistic fits, and a Kaplan–Meier survival analysis. Two-sided tests with alpha = 0.05 were used without correction for multiple comparisons because of the purely descriptive nature of the study. Statistical calculations used JMP 5.0.1, 1989–2003, SAS Institute Inc, Cary, NC.

RESULTS

We collected data from 115 consecutive patients with schizophrenia (51.3% male, 39.6 ± 11.05 years; mean/SD), who were admitted involuntarily to Psychiatry and Neurology Hospital, Brasov, Romania during January 01, 2011 and December 31, 2014. Based on clinical decisions of their treating psychiatrists, subjects were started on the following AP: haloperidol (n = 81; 70.4%), clozapine (n = 13; 11.3%), olanzapine (n = 12; 10.4%), or other SGAs (7.9%; including amisulpride: n = 3, quetiapine: n = 3, aripiprazole: n = 2, risperidone: n = 1). Clinical and demographic characteristics of the full cohort and the clozapine subgroups are provided in Table 1.

To test the immediate effect of early clozapine use, restraint characteristics were contrasted for subjects receiving clozapine as the first AP during this hospitalization. Moreover, these analyses were repeated for the CLZ-group and for the non-CLZ group. Accordingly, clinical and demographic characteristics were analyzed and compared for these respective subgroups (Table 1). In addition to the 13 subjects, who received clozapine as the first AP immediately after hospitalization (and receipt of white blood count), 11 subjects received clozapine as the second intention. The median duration until clozapine was started as a second option was 11.1 ± 4.1 days. The median duration of clozapine treatment was 19.5 (11.2; 23) days; clozapine was up-titrated during 5 ± 2.2 days, to a mean maximal dose of 437.5 ± 132.1 mg.

Because of the naturalistic nature of the study, demographic, clinical, and treatment characteristics of subgroups differed slightly (Table 1). In particular, the subgroup of subjects, in whom clozapine was used as the first AP (CLZ-first) included a significantly higher proportion of subjects, who were admitted involuntarily because of self-destructive behavior (53.8%) compared with the remaining cohort (21.5%; $P = 0.002$), whereas the externally targeted violence was the main reason for involuntary admission in the remaining cohort (Table 1). Moreover, the CLZ-group included more subjects with a longer hospitalization-free period prior the current admission (median period past prior hospitalization 220 days vs. 90 days; $P = 0.005$; Table 1). Nevertheless, all other clinical

Table 1. Demographic, illness and treatment characteristics in involuntarily admitted subjects with schizophrenia.

	Total (n = 115)	Clozapine (n = 24, 19.30%)	Subgroup: CLZ-first AP (n = 13, 11.3%)	Non-CLZ (n = 91)	*P*, CLZ versus non-CLZ	*P*, CLZ-first versus others
Age, yrs, mean ± SD	39.67 ± 11.05	36.92 ± 8.42	37.15 ± 8.59	40.40 ± 11.57	0.17	0.37
Sex, male, n (%)	59 (51.30)	15 (62.5)	10 (76.92)	44 (48.3)	0.25	0.08
Age at onset, yrs, median (25th; 75th percentile)	25.0 (22.0; 30.0)	18.25 (22.5; 24.75)	23 (21; 24.5)	26 (22; 33)	0.002	0.07
Illness duration, yrs, median (25th; 75th percentile)	12 (3; 20)	11 (6; 22)	11 (9; 16)	9 (3; 20)	0.22	0.30
Reason for involuntary admission, n (%)					0.06	0.02
Threat for/violence against others/objects	86 (74.78)	14 (58.33)	6 (46.15)	72 (79.12)		
Threat for/violence against self	29 (25.22)	10 (41.67)	7 (53.85)	19 (20.88)		
MOAS total, mean ± SD	11.25 ± 1.67	11.23 ± 1.56	11.61 ± 1.66	11.23 ± 1.70	0.92	0.46
MOAS verbal aggression, mean ± SD	3.19 ± 0.67	3.41 ± 0.65	3.38 ± 0.65	3.13 ± 0.70	0.06	0.27
MOAS aggression against property, mean ± SD	2.53 ± 0.98	2.60 ± 0.97	2.69 ± 0.27	2.51 ± 1.00	0.50	0.54
MOAS physical aggression, mean ± SD	3.04 ± 0.67	2.80 ± 1.02	2.92 ± 0.28	3.07 ± 1.01	0.18	0.76
MOAS autoaggression, mean ± SD	2.49 ± 0.87	2.50 ± 0.93	2.61 ± 0.77	2.8 ± 0.65	0.90	0.53
PANSS at admission, median (25th; 75th percentile)	100 (98; 104)	102.7 (99; 106.5)	101 (98.5; 106)	100 (98; 104)	0.43	0.58
PANSS hostility, median (25th; 75th percentile)	5 (5; 6)	6 (5; 6)	6 (5; 6.5)	5 (5; 6)	0.14	0.28
CGI at admission, median (25th; 75th percentile; range)	6 (6; 6; 5–7)	6 (6; 6; 5–7)	6 (6; 6; 6–7)	6 (6; 6; 5–7)	0.47	0.40
History of violence, n (%)*	66 (57.90)	21 (91.30)	10 (83.33)	45 (49.45)	0.0003	0.07
History of involuntary admission, n (%)	21 (18.26)	11 (45.83)	7 (53.85)	10 (10.99)	0.0003	0.002
No. previous hospitalizations within prior 12 months, median (25th; 75th percentile; range)	1 (0; 1; 0–5)	1 (0; 1; 0–3)	0 (0; 1; 0–3)	1 (0; 2; 0–5)	0.94	0.31
Days since prior hospitalization, median (25th; 75th percentile)†	120 (60; 240)	210 (121; 300)	220 (104.75; 300)	90 (45; 217)	0.005	0.14
Length of stay, mean ± SD	27.33 ± 9.14	26.3 ± 9.77	24.23 ± 9.61	27.5 ± 9.02	0.46	0.06

*Based on n = 114; missing information for 1 subject.
†For subjects with at least 1 hospitalization within last year.
CGI, Clinical Global Impression; MOAS, Modified Overt Aggressiveness Scale; PANSS, Positive and Negative Symptoms Scale.

and demographic parameters, in particular those characterizing disease severity and aggressive potential, did not differ between AP treatment groups (Table 1).

Restraint was used in the vast majority (n = 103; 89.5%) of the cohort anytime during the hospitalization. Mostly, restraint was used very early during the admission (median time until restraint: 3 hours; 25th; 75th percentile: 0.25; 48 hours). These parameters were strikingly lowered in the CLZ-first group; in which only 3 subjects (23%) experienced restraint ($P > 0.0001$ relative to the remaining cohort), with a median time until restraint of 408 hours (25th; 75th percentile: 48; 540; $P > 0.0001$; Table 2). In the non-CLZ group, the proportion of restraint was significantly higher (n = 87, 95.6%). Similarly, restraint reduction and delay of restraint

Table 2. Use of restraint in involuntarily admitted subjects with schizophrenia.

	Total (n = 115)	Clozapine (n = 24)	Subgroup: CLZ-first AP (n = 13)	Non-CLZ (n = 91)	*P*, CLZ versus non-CLZ	*P*, CLZ-first versus others
Restraint anytime during hospitalization, n (%)	103 (89.5)	16 (66.6)	3 (23.0)	87 (95.6)	0.0003	<0.0001
Hours until restraint,* median (25th; 75th percentile; range)	3 (0.25; 48)	118 (24; 426)	408 (48; 540)	1.1 (0.2; 24)	<0.0001	<0.0001
Restraint during first 24 h, n (%)	71 (61.7)	5 (20.8)	1 (7.6)	66 (72.5)	<0.0001	<0.0001

*For subjects without any restraint, the length of stay is substituted as restraint-free period.

was observed for the CLZ-group (Table 2). Moreover, the rate of restraint was 23% for clozapine compared with 95% for haloperidol and 100% for another SGAs (risperidone, olanzapine, amisulpride, aripiprazole, and quetiapine).

We performed a secondary survival analysis for the first week of hospitalization for all subjects, who had not needed restraint within the first hour past admission. This analysis involved 69 (60%) of the initial 115 subject and included the CLZ-first subgroup in total (18.8% of this 1-hour restraint-free group) as well as the 56 (81.1%) non-CLZ subjects, who were restraint-free past 1 hour. A significant group separation was noticeable during the first 24 hours and persisted throughout the observation period (Log-rank χ^2 = 9.96; P = 0.0018).

To exclude the possibility that the delay of restraint was primarily mediated by clinical factors but treatment characteristics, we used stepwise forward regression including subgroup CLZ-first, age, sex, and reason for admission as potentially predictive factors. Of these, only CLZ-first and the reason for admission entered the final significant model, and CLZ-first was the sole significant factor within the model.

DISCUSSION

Within the limiting framework of a retrospective observation of naturalistic treatment, this study suggests the possibility that the antiaggressive properties of clozapine can be clinically efficiently used in a highly problematic cohort of involuntarily admitted subjects with schizophrenia.

Therapeutic strategies to reduce violence in patients with schizophrenia suffer from a lack of guiding information from randomized studies and prospective studies are methodologically highly limited because of an inherent selection bias related to informed consent in a predominantly uncooperative study group.[11] Thus, our naturalistic small cohort is thought to contribute to existing clinical expertise despite the limitation of a nonrandomized retrospective study design.

Coercive treatment includes both, physical restraints and involuntary medication; however, rarely can involuntary medication be replaced by physical restraint, whereas the reverse is realistically achievable. Both of these measures are unfortunately frequent during involuntary admissions.[12] Because of the high medical risks including death associated with restraint[13] and because of the traumatic experience associated with restraint,[7] these numbers sorely need to decrease.

Based on our earlier observation of fast clozapine titration,[8] our hospital policies permitted the use of clozapine as an emergency medication without written consent from the patient; we were thus in the exceptional position to make use of the well-established antiaggressive properties of clozapine[14] during early hospitalization. Our data showed a striking reduction of restraint rates with clozapine use, relative to the predominantly haloperidol treated remaining subjects. Importantly, despite the naturalistic study design, clinical and demographic factors did not significantly influence the restraint-free period; the use of clozapine as the first AP was the sole characteristic significantly associated with delayed restraint. These results are in line with earlier studies on the effects of clozapine on restraint frequencies chronic schizophrenia,[15,16] but our results are novel in that clozapine was used as first-line medication.

First limitation of the study is the relative small number of patients treated with clozapine. The second limitation is the retrospective chart review character of the study. Despite those, the clinical meaning of the findings is very important for psychiatrists. Further studies are necessary to validate our results.

CONCLUSIONS

These retrospective data suggest an early antiaggressive effect of clozapine during the immediate use of clozapine in highly problematic patients. Further randomized and controlled studies are necessary to validate our results. Reducing stress and stigma of patients with schizophrenia must be the core objective of professionals in this field alongside with achieving remission.

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