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Functioning and cognitive characteristics of clozapine users referred to psychosocial rehabilitation centers: A REHABase cohort study

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ABSTRACT

Objectives: To explore whether clozapine users have specific rehabilitation needs compared to users of other antipsychotics.
Methods: The study was performed using the REHABase collecting data on persons referred to a French network of psychosocial rehabilitation centers. It was restricted to persons with schizophrenia spectrum disorder using antipsychotics. Multivariate analyses were used to compare baseline functioning and cognitive characteristics in clozapine users vs. users of other antipsychotics.
Results: Of the 675 patients identified in the REHABase, one out of ten (n = 70) used clozapine. Compared to users of other antipsychotics, clozapine users had been more frequently hospitalized in psychiatry and presented less frequently with psychoactive substance use. Functional measures did not significantly differ between the two groups. Clozapine users had poorer short-term verbal memory performance than users of other antipsychotics and did not differ on executive performance.
Conclusion: Clozapine users may reach a recovery level comparable to that obtained in persons without treatment-resistant schizophrenia. In order to reduce the negative impact of memory deficits on the recovery process of clozapine users, it is necessary to optimize their psychotropic treatment and to promote their access to cognitive remediation programs addressing their specific needs.

1. Introduction

Use of clozapine is essential for the promotion of recovery in persons with treatment-resistant schizophrenia (TRS) owing to its marked effects on psychotic symptoms as well as on global morbidity and mortality (Nielsen et al., 2011, Stroup et al., 2016; Howes et al., 2017, Siskind et al., 2016, Siskind et al., 2017, Wimberley et al., 2017; Vermeulen et al., 2019).

Contrasting with the large body of literature documenting the clinical efficacy of clozapine, few clinical trials have investigated whether clozapine use contributes to functional recovery in persons with TRS. In the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study, no difference was found between clozapine users vs. users of olanzapine, quetiapine or risperidone in Quality of Life Scale change scores at 6 and 12 months (Swartz et al., 2007). A recent meta-analysis of three short-term (3 months) and five long-term

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trials found that change in psychosocial function did not differ between persons with TRS using clozapine vs. other antipsychotics (Olagunju et al., 2018). Nonetheless, observational studies showed that delayed clozapine initiation had a deleterious impact on the likelihood of recovery (Kohler-Forsberg et al., 2017), and that clozapine use had a positive impact on occupational outcome (Kaneda et al., 2010).

Clinical improvement is a necessary but not sufficient condition in the recovery process of persons with severe mental illness, as there is often a marked gap between clinical and functional recovery (Wunderink et al., 2009; Jaaskelainen et al., 2013; Lee et al., 2014; Van Eck et al., 2018). This gap is partly explained by the impact of poor cognitive and metacognitive abilities on psychosocial functioning (Green et al., 2000; Prouteau et al., 2005; Green, 2016; Lysaker et al., 2018). Discrepant findings have been obtained by studies investigating whether clozapine differs from other antipsychotics with respect to effects on cognitive performance (Meltzer and McGurk, 1999; Bellack et al., 2004; Woodward et al., 2005; Han et al., 2015). The crucial role of cognitive deficits in functional outcome is also observed in clozapine users (Kaneda et al., 2010).

The key role of psychosocial rehabilitation programs for enhancing functional outcome of clozapine users was emphasized soon after the reintroduction of clozapine (Rosenheck et al., 1998). However, nearly 30 years after, little is known about the profile of clozapine users participating in rehabilitation programs. This population should be characterized in order to assess whether clozapine users may have specific rehabilitation needs.

The aim of the present study, carried out among persons with psychosis referred to the centers of a French psychosocial rehabilitation network, was to explore whether clozapine users differed from users of other antipsychotics with regard to baseline functioning and cognitive characteristics.

2. Materials and methods

2.1. Population

The REHABase cohort has already been presented (Franck et al., 2019). Briefly, it was implemented in 2016 to collect information on patients with severe mental illness or autism spectrum disorder attending the five centers of a French psychosocial rehabilitation network. Clinically stabilized patients are referred to these centers by public mental health services, private psychiatrists or any other private practitioner, or are self-referred. A functional and cognitive standardized evaluation is performed in order to establish a personalized rehabilitation care plan in collaboration with the patient.

Patients attending the centers are included in the REHABase if their Global Assessment of Functioning (GAF) (American Psychiatric Association, 2000) score is < 61, according to the cut-off for social recovery identified by a meta-analysis (Jaaskelainen et al., 2013). The present study was restricted to patients fulfilling the following inclusion criteria: (i) DSM-5 (American Psychiatric Association, 2013) diagnosis of schizophrenia spectrum disorder (schizophrenia, schizoaffective disorder, schizophreniform disorder, delusional disorder, unspecified psychotic disorder) based upon clinical interview performed by a psychiatrist; (ii) antipsychotics use at baseline assessment, in order to compare clozapine users to users of other antipsychotics.

The study obtained the authorizations required under French legislation (French National Advisory Committee for the Treatment of Information in Health Research, 16.060bis), including information processing (French National Computing and Freedom Committee, DR-2017-268).

2.2. Baseline assessment

In all centers of the network, the baseline assessment is performed by a multidisciplinary team specialized in psychosocial rehabilitation including psychiatrists, nurses, neuropsychologists and social workers. Demographic, clinical, functioning and cognitive data are collected by using a standardized electronic case report form. Regular group meetings are held to select the instruments used for the clinical and cognitive evaluations, monitor quality control, and ensure good inter-rater reliability (Franck et al., 2019).

2.3. Clinical and functioning measures

We used data collected in the REHABase on the following scales:

(i) GAF scale (American Psychiatric Association, 2000): clinician-rated global measure of psychological, social, and occupational functioning (score 1–100, high score indicates better functioning).
(ii) Clinical Global Impression severity (CGI-S) scale (Guy, 1976): clinician-rated severity of illness (score 1–7; high score indicates greater severity).
(iii) STage Of Recovery Instrument (STORI) (Andresen et al., 2006), French version by Golay & Favrod (unpublished): 50-item self-administered questionnaire assessing the stage of recovery for 10 groups of 5 items (Moratorium, Awareness, Preparation, Rebuilding, Growth). The stage with the highest total is rated as the person's stage of recovery (score 1–5; high score indicates better recovery).
(iv) Schizophrenia Quality of Life-18 (S-QoL18) (Boyer et al., 2010): 18-item self-administered questionnaire (score 0–100; high score indicates better QoL).
(v) Warwick-Edinburgh Mental Well-Being Scale (WEMWEBS) (Tennant et al., 2007), French version (Trousselard et al., 2016): 14-item self-administered questionnaire assessing individual's state of mental well-being (score 14–70; high score indicates better well-being).
(vi) Internalized Stigma of Mental Illness (ISMI) scale (Ritsher et al., 2003), French version (Brohan et al., 2011): 29-item self-administered questionnaire (score 1–4; high score indicates more severe stigma).
(vii) Rosenberg Self-Esteem scale (RSE) (Rosenberg, 1965), French version (Vallieres and Vallerand, 1990): 10-item self- administered questionnaire (score −70 to 70, high score indicates better self-esteem).
(viii) Birchwood Insight Scale (BIS) (Birchwood et al., 1994), French Version by Linder & Favrod (unpublished): 12-item self-administered questionnaire (score 0–12, high score indicates better insight).
(ix) Medication Adherence Rating Scale (MARS) (Thompson et al., 2000), French version (Misdrahi et al., 2004): 10-item self- administered questionnaire (score 0–10, high score indicates better adherence).

2.4. Cognitive measures

We used data collected in the REHABase on the following cognitive measures:

(i) The digit span of the Wechsler Adult Intelligence scale 3rd edition (WAIS-III) (Wechsler, 1997) was used to measure verbal short-term memory and verbal working memory. The participant hears a sequence of digits (numbers) of increasing length and is asked to recall each sequence in the correct order (forward digit recall) for verbal short-term memory and in reverse order (backward digit recall) for verbal working memory (score 1–19, high score indicates better memory performance).
(ii) The Multiple Errands Test (Martin, 1972) modified version (Fournier et al., 2015) was used to assess executive abilities in everyday functioning through a number of real-world tasks. Using a

neighborhood map, the participant is asked to find a route for shopping by respecting instructions and rules regarding transport (using logical routes to save time, for instance) and schedules of the places to visit. Two scores are obtained: "completion time" assessing the time (mn) taken to complete the itinerary; "total error score" assessing the numbers of errors (logical errors, useless detour and schedule respect).

2.5. Statistical analyses

The demographic and clinical characteristics of clozapine users vs. users of other antipsychotics, as well as of patients with and without missing data on functional and cognitive measures, were compared using univariate analyses (Chi square test and Student's *t*-test). Multiple linear regression analyses giving adjusted regression coefficients (β) were used to explore the associations between functional and cognitive characteristics and type of antipsychotic use (clozapine vs. other), after adjustment for the following *a priori* defined potential confounding factors: age, gender, educational level (<12 vs. ≥ 12 ys), duration of illness (<5, 5–10, >10 ys), number of psychiatric hospitalizations (<2, 2–3, >3) (categorizations based upon the distribution of the characteristics in the sample). The analyses were performed using STATA® 13.

3. Results

3.1. Population

Of the 1828 persons included in the REHABase in March 2019, 713 (39%) presented with a diagnosis of schizophrenia spectrum disorder, of whom 675 (94.4%) used antipsychotics at baseline assessment, constituting the sample under study. The demographic and clinical characteristics of clozapine users (n = 70, 10.4%) and of users of other antipsychotics are described in Table 1. Regarding demographic characteristics, the two groups were comparable: most patients were males, single and unemployed. Regarding clinical characteristics, clozapine users had a higher number of psychiatric hospitalizations and less frequently used nicotine, cannabis or alcohol. The two groups were comparable with respect to use of other psychotropic drugs and antipsychotic polytherapy.

3.2. Clinical, functioning and cognitive measures

Clinical, functioning and cognitive measures were not systematically entered in the REHABase for all patients attending the rehabilitation centers, mostly for logistic reasons. In the sample under survey, data for at least one of the measures listed in Table 2 was available in the database for 476 (70.5%). Patients with missing data for all measures did not significantly differ from those without with regard to all the characteristics listed in Table 1 (data not shown). The proportion of patients without missing data was higher in clozapine users (n = 56, 80%) than in users of other antipsychotics (n = 420, 69.4%). The numbers of patients without missing data for each measure are given in Table 2.

The findings of the multivariate analyses comparing the functional and cognitive measures in clozapine users vs. users of other antipsychotics are reported in Table 2. The two groups did not significantly differ with regard to functioning measures. Clozapine users had poorer verbal short-term memory performance and did not differ from users of other antipsychotics regarding other cognitive tests.

The association between poor short-term memory performance and clozapine use was not modified after further adjustment for use of other psychotropic drugs (antidepressants, conventional mood stabilizers, anxiolytics/hypnotics, anticholinergic drugs) (β= −0.98, 95%CI −1.94; −0.02, p = 0.046). The association was also unchanged when the group of users of other antipsychotics was restricted to users of second-generation antipsychotics (SGAs) (n = 468, 77.4%) (β= −0.97, 95%CI −1.92; −0.02, p = 0.046).

4. Discussion

4.1. Main findings

Of the 675 patients with schizophrenia spectrum disorder attending a French national network of psychosocial rehabilitation centers, one out of ten used clozapine. Compared to users of other antipsychotics, clozapine users had been more frequently hospitalized in psychiatry and presented less frequently with psychoactive substance use. Functional measures did not differ between the two groups. Regarding cognitive measures, clozapine users had poorer short-term verbal memory performance than users of other antipsychotics and did not differ on executive performance.

4.2. Limitations

The findings should be interpreted in the light of potential limitations. First, patients referred to the psychosocial rehabilitation centers are not representative of the whole population of persons with schizophrenia spectrum disorders presenting with rehabilitation needs, as referral is highly dependent of the commitment of the patient and of his/her mental health team in a psychosocial rehabilitation project. Second, this selection bias may also differentially operate between clozapine users vs. users of other antipsychotics. Patients with less severe forms of TRS may be preferentially referred, as suggested by the relatively low (300 mg) mean dosage of clozapine. Such a bias may have contributed to reducing the differences between the two groups. Third, TRS criteria were not assessed, so patients with TRS not treated by clozapine may have been included in the group of users of other antipsychotics, also contributing to reducing the differences between the two groups. Lastly, the sample size of clozapine users was small for most cognitive and functioning measures. Consequently, only two cognitive measures could be used, and type 2 errors cannot be excluded for other measures.

4.3. Interpretation of findings

Considering the very low prevalence of clozapine use in France (Verdoux and Pambrun, 2014; Bachmann et al., 2017), the frequency of clozapine use was higher than anticipated in this population. It is likely that a lower prevalence would be found in the whole population of schizophrenia patients with rehabilitation needs, as mental health teams referring patients to the centers may be more aware of recommendations regarding the adequate treatment of schizophrenia. However, since up to 20–30% of schizophrenia patients present with TRS (Kennedy et al., 2014), the expected prevalence of clozapine use should be higher than 10% in patients referred for psychosocial rehabilitation, demonstrating the need to implement interventions promoting access to clozapine use (Bogers et al., 2016; Carruthers et al., 2016; Verdoux et al., 2018).

The few clinical characteristics differentiating the two groups are concordant with the clinical profile of clozapine users, who present with a more severe course of illness (proxied by a higher number of psychiatric admissions) and a lower prevalence of psychoactive substance use (Arranz et al., 2018). Despite having a more severe form of illness, clozapine users did not differ from users of other antipsychotics with regard to multidimensional measures of functioning. Although the differences were not significant, clozapine users had even better functioning scores than users of other antipsychotics for measures of quality of life, insight and self-esteem. This finding is reassuring, as it demonstrates that once clozapine is initiated, persons with TRS may reach a recovery level comparable to that obtained with other antipsychotics in persons without TRS.

Table 1
Characteristics of patients with and without clozapine use.

	Clozapine n = 70 (10.4%)	Other antipsychotics n = 605 (89.6%)	
Demographic characteristics[1]			*Student's t-test (df)*
Age (mean, SD)	32.8 (1.2)	33.1 (0.4)	0.26 (673) p = 0.80
			Chi2 (df)
Gender, male	54 (77.1%)	451 (74.6%)	0.22 (1) p = 0.64
Education level ≥ 12 ys	38 (56.7%)	303 (51.2%)	0.75 (1) p = 0.39
Always single	62 (91.2%)	500 (84.0%)	2.41 (1) p = 0.12
Living independently[2]	27 (39.7%)	255 (43.1%)	0.28 (1) p = 0.60
Currently employed	4 (5.9%)	46 (7.8%)	0.33 (1) p = 0.57
Clinical characteristics[1]			
Illness duration			0.94 (2) p = 0.62
< 5 ys	11 (19.0%)	132 (24.7%)	
5–10 ys	15 (25.9%)	125 (23.4%)	
> 10 ys	32 (55.2%)	278 (52.0%)	
Number of hospitalizations			11.52 (2) p = 0.003
< 2	5 (8.9%)	163 (30.2%)	
2–3	25 (44.6%)	196 (36.3%)	
> 3	26 (46.4%)	181 (32.5%)	
Lifetime history of suicide attempt	16 (25%)	151 (26.3%)	0.05 (1) p = 0.83
Current nicotine use[3]	22 (33.9%)	294 (51.2%)	7.05 (1) p = 0.008
Current cannabis use[3]	5 (7.8%)	12 (19.1%)	4.51 (1) p = 0.03
Current alcohol use[3]	6 (9.4%)	103 (18.0%)	4.22 (1) p = 0.04
Psychotropic treatment			
Clozapine dosage (mean, SD)	300.2 (139.6)		
Antipsychotics			0.08 (2) p = 0.96
2 antipsychotics	20 (28.6%)	169 (27.9%)	
3 antipsychotics	2 (2.9%)	21 (3.5%)	
Antidepressants	19 (27.1%)	143 (23.6%)	0.42 (1) p = 0.51
Conventional mood stabilizers[4]	9 (12.9%)	62 (10.3%)	0.45 (1) p = 0.50
Anxiolytics/hypnotics[5]	22 (31.4%)	217 (35.9%)	0.54 (1) p = 0.46
Anticholinergic drugs[6]	6 (8.6%)	69 (11.4%)	0.51 (1) p = 0.48

[1] Numbers lower than total number of subjects are due to missing data;.
[2] Living alone or in couple in his/her own residence vs. 'other' (with family or with another person; hostel, sheltered housing, homeless);.
[3] Any current use of the substance as the assessment of substance use disorder criteria was not standardized;.
[4] Anticholinergic drugs (Trihexyphenidyl, Biperiden and Tropatepine);.
[5] Lithium and anticonvulsants with marketing authorization for mood disorders: carbamazepine, divalproate sodium, valpromide, lamotrigine);.
[6] benzodiazepines and hydroxyzine.

Contrasting findings are reported by studies exploring the impact of clozapine on cognitive performance. Improvement of cognitive abilities has been observed after clozapine initiation, especially verbal fluency and attention, which are likely to be linked to withdrawal of first-generation antipsychotics (FGA) rather than to a direct positive effect of clozapine (Meltzer and McGurk, 1999; Woodward et al., 2005; Kaneda et al., 2010). Studies comparing the cognitive impact of clozapine vs. other SGA showed that vigilance and selective attention were more impaired in clozapine users, while verbal fluency was less impaired (Woodward et al., 2005). With regard to memory abilities, early studies reported no effect of clozapine initiation on verbal memory (Meltzer and McGurk, 1999). A meta-analysis found that delayed recall was less improved in clozapine users than in users of other SGA (Woodward et al., 2005), and worse immediate and delayed recall memory performance was also observed in clozapine users vs. FGA users (Han et al., 2015). Although these findings cannot be directly compared to those obtained in the present study due to methodological dissimilarities, they consistently suggest that clozapine users may have more impaired memory performance than users of other antipsychotics. Irrespective of the underlying mechanisms, i.e. a direct impact of

Table 2
Functioning and cognitive characteristics of patients with and without clozapine: multiple regression analyses.

	Clozapine n = 70 (10.4%) (mean, SD)	Other antipsychotics n = 605 (89.6%) (mean, SD)	Statistical test β (95%CI)[1]
Functional measures[2]			
Global Assessment of Functioning	55.5 (14.4) n = *44*	55.4 (13.0) n = *362*	−0.02 (−4.21; 4.18) p = 0.99
Clinical Global Impression-Severity Scale	4.16 (1.10) n = *45*	4.19 (1.05) n = *361*	−0.05 (−0.37; 0.28) p = 0.79
Stages of Recovery Instrument	3.3 (1.5) n = *32*	3.5 (1.5) n = *246*	−0.26 (−0.83; 0.30) p = 0.36
Schizophrenia Quality of Life 18	56.5 (18.1) n = *34*	53.2 (18.1) n = *256*	3.46 (−2.95; 9.88) p = 0.29
Warwick-Edinburgh Mental Well-Being Scale	43.4 (8.8) n = *39*	43.9 (9.5) n = *297*	−0.59 (−3.75; 2.58) p = 0.72
Internalized Stigma of Mental Illness	2.2 (0.5) n = *33*	2.2 (0.4) n = *279*	0.07 (−0.09; 0.23) p = 0.38
Rosenberg Self-Esteem scale	9.1 (20.1) n = *28*	5.2 (19.8) n = *255*	3.8 (−4.14; 11.68) p = 0.35
Birchwood Insight Scale	9.3 (2.5) n = *37*	8.6 (2.5) n = *281*	0.53 (−0.31; 1.38) p = 0.22
Medication Adherence Rating Scale	6.6 (1.5) n = *28*	6.9 (2.1) n = *256*	−0.32 (−1.11; 0.46) p = 0.42
Cognitive measures[2]			
Multiple errands test: completion time	8.21 (3.96) n = *29*	7.24 (3.73) n = *246*	0.99 (−0.47; 2.46) p = 0.18
Multiple errands test: total error score	2.97 (2.03) n = *29*	2.88 (1.85) n = *246*	0.14 (−0.58; 0.86) p = 0.70
Digit span: verbal short-term memory	8.11 (2.05) n = *37*	8.94 (2.89) n = *272*	−0.97 (−1.92; −0.02) p = 0.046
Digit span: verbal working memory	7.97 (8.35) n = *37*	8.36 (2.80) n = *271*	−0.48 (−1.40; 0.44) p = 0.30

[1] Regression coefficient (95% confidence interval) adjusted on age, gender, education level, illness duration, number of psychiatric hospitalizations.
[2] For each scale, mean scores are calculated for the subsamples without missing data on the variables of interest (including adjustment variables).

clozapine or a characteristic of TRS, the memory deficits of clozapine users should be considered in the psychosocial rehabilitation plan. Indeed, a study found that verbal working memory and attention were the strongest determinants of work outcome 12 months after initiation of clozapine (Kaneda et al., 2010).

First, it is essential to optimize psychotropic treatment in clozapine users in order to reduce polytherapy with other drugs affecting memory performance. In the present sample, 31% and 9% of clozapine users were also prescribed anxiolytics/hypnotics or anticholinergic drugs, respectively. Considering the negligible extra-pyramidal impact of clozapine, it is striking that the prevalence of anticholinergic use was not significantly lower in clozapine users than in users of other antipsychotics. These coprescriptions increase the risk not only of memory and attentional disturbances but also of a range of possibly lethal adverse drug reactions by potentialization of the effects of clozapine on sedation and gastro-intestinal hypomotility (Cohen, 2017; Cicala et al., 2019). Diffusion of clozapine guidelines and educational interventions are necessary to increase knowledge about clozapine prescribing (Bogers et al., 2016; Carruthers et al., 2016; Verdoux et al., 2018)

Second, although the benefits of cognitive remediation in persons with psychosis are well-demonstrated (Wykes et al., 2011; Bowie et al., 2012; Franck et al., 2013), very few studies have explored the efficacy of cognitive remediation in clozapine users (Quinn and Kolla, 2017). This issue should be further addressed to promote the access of clozapine users to cognition remediation programs addressing their specific needs.

Declaration of competing interest

The authors declare that there are no conflicts of interest in relation to the subject of this study.

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Supplementary materials

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