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Angaben zur Veröffentlichung / Publication details:

Wagner, Elias, Tatiana Oviedo-Salcedo, Nicola Pelzer, Wolfgang Strube, Isabel Maurus, Stefan Gutwinski, Stefanie Schreiter, et al. 2020. "Effects of smoking status on remission and metabolic and cognitive outcomes in schizophrenia patients treated with clozapine." Pharmacopsychiatry 53 (6): 272–83. https://doi.org/10.1055/a-1208-0045.

Effects of Smoking Status on Remission and Metabolic and Cognitive Outcomes in Schizophrenia Patients Treated with Clozapine

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Key words
Clozapine, Schizophrenia, smoking, remission rates

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Supporting Information for this article is available online at https://doi.org/10.1055/a-1208-0045

ABSTRACT

Background Even though clozapine is the recommended last-resort antipsychotic, many patients fail to respond and show treatment-refractory psychotic symptoms. Smoking has been suggested as a possible risk factor for poor clozapine response, hampering remission and negatively impacting somatic outcomes.

Methods Our aim was to test whether smoking status is associated with remission rates and other symptomatic and somatic outcomes. We therefore assessed remission rates according to The Remission in Schizophrenia Working Group (RSWG) criteria, and metabolic and cognitive outcomes among patients with schizophrenia-spectrum disorders treated with clozapine for at least 6 months. For analyses, we grouped our cohort into 3 groups according to clozapine treatment duration (6 months, 2 years, 5 years).

Results One hundred five patients were included in our analyses and grouped according to their clozapine treatment duration. In the 6-months analyses, patients who smoked were significantly more likely to be younger of age ($p = 0.002$) despite on average shorter duration of clozapine treatment ($p = 0.041$) and significantly more likely to be treated with mood-stabilizing co-medication ($p = 0.030$) compared to non-smokers. Remission rates ($p = 0.490$), as well as a set of metabolic and cognitive variables did not differ between the 2 groups. A related pattern could be observed for the 2- and 5-years analyses.

Conclusions Smoking behavior among clozapine-treated schizophrenia patients might delineate a cohort with an earlier onset of the disease. Nevertheless, most findings comparing disease-specific and clinical outcomes among smokers and nonsmokers were negative. Further research is needed to identify strategies to overcome insufficient remission rates in this patient group.

* Both authors contributed equally.

Introduction

Most patients with schizophrenia respond to antipsychotic treatment, but 20–30 % are estimated to be treatment-resistant, defined as being unresponsive to at least 2 adequate trials of antipsychotic non-clozapine medication [1]. Treatment-resistant schizophrenia (TRS) is presumed to lead to a decrease in patient-related quality of life and an increase in medical costs as well as increased rates of serious comorbidities, adverse events, and suicide risk [2].

For the clinical situation of TRS, the antipsychotic clozapine is presumed to have superior effects on psychotic symptom improvement compared to other antipsychotics [3]. Nonetheless, up to 60 % of patients with TRS are reported to remain symptomatic despite adequate clozapine treatment [4]. In general, symptom severity must be maintained over a period of 6 months in order to be able to evaluate whether remission criteria are fulfilled or not [5–7] and the same period should be assumed for evaluating the effectiveness of clozapine. A possible risk factor for poor clozapine treatment response might be smoking behavior, i. e., smoking more than 1 pack/day [8]. This reasoning may be partially explained by pharmacokinetic mechanisms as smoking decreases clozapine blood levels more than a third by activating enzymes of the Cytochrome P-450 family [9]. Schizophrenia patients treated with clozapine and who smoke (PCS) are likely to receive higher doses of clozapine than nonsmokers [10]. As possible reasons, clozapine/desmethylclozapine ratios are presumed to be significantly decreased in smokers compared to nonsmokers, and it was previously recommended that if a certain dose of clozapine would be administered to smokers, about half of the dose should be administered to nonsmokers [11]. It could be speculated that since smoking decreases antipsychotic blood levels, antipsychotic polypharmacy occurring in up to half of patients treated with clozapine [12] might be more common among smoking compared to nonsmoking schizophrenia patients. Nevertheless, differences in prescription patterns in smokers vs. nonsmokers cannot be exclusively attributed to differences in blood levels. Other factors, e. g., alteration in nicotinergic neurotransmission, that may be implicated in TRS have to be taken into account [13].

Meta-analytic data suggests an average prevalence for smoking of 62 % among patients with schizophrenia [14], which is higher than in the general population [15]. The negative effects of smoking on morbidity and premature mortality in individuals with schizophrenia are well established [16, 17]. Furthermore, prediabetic conditions and metabolic abnormalities are highly prevalent among patients treated with clozapine [18], and presumably higher dosages of clozapine among smokers might be associated with a higher risk of unfavourable metabolic outcomes due to dose-dependent side effects [19, 20].

Moreover, a large-scale prospective cohort study showed that smoking in schizophrenia patients was associated with significantly more frequent self-reported positive symptoms, negative symptoms, and depressive symptoms and lower quality of life compared to nonsmokers [21]. These results were reported to be similar in the sub-analyses for patients treated with clozapine [21] and thus were consistent with earlier research showing unfavourable outcomes in smoking schizophrenia patients compared to nonsmokers with regard to positive symptoms [22–26], depressive symptoms [15], functional outcomes [27, 28], and cognition [28–30]. It may be speculated that PCS are more likely *not* to achieve symptomatic remission according to "Andreasen criteria" [6], as indicated in 1 cross-sectional study of 102 outpatients with schizophrenia [31].

Nevertheless, a recent 20-year follow-up study in a nationwide cohort of 62 250 people with schizophrenia showed cumulative mortality rates of 46.2 % for no antipsychotic use, 25.7 % for any antipsychotic use, and 15.6 % for clozapine use [32]. Clozapine use was associated with the lowest rates with regard to all-cause, cardiovascular, and suicide mortality compared to other antipsychotics [32]. Whether this is a protective effect of clozapine or a secondary effect due to less frequent psychotic episodes or the continuous clozapine-associated monitoring procedures remains elusive.

While a large prospective cohort study investigated smoking status and disease-related outcomes among schizophrenia patients [21], comprehensive data concerning symptomatic remission rates of patients on clozapine with regard to smoking behavior and duration of clozapine treatment is lacking. We aimed at investigating clozapine response and safety associated with smoking behavior from a multidimensional perspective in a clinically deeply characterized cross-sectional cohort of patients treated with clozapine for at least 6 months. Especially, as 6 months are accepted to be the minimum treatment duration before discussing clozapine-resistance [7], such an investigation is of high clinical relevance. Furthermore, we investigated group differences in these outcomes between patients being treated with clozapine for at least 5 years to investigate group differences in long-term clozapine users based on the definition of late-onset treatment-resistance [5]. Our primary aim was to compare the frequency of remission rates according to Andreasen criteria [6] between smokers and nonsmokers, expecting reduced remission rates among smokers at the aforementioned time periods.

Methods

Recruitment

Between 3 and 4 years ago, from estimated 300 pre-screened in- and outpatients on clozapine, 105 patients were screened for eligibility for this bicentric cross-sectional study at the Department of Psychiatry and Psychotherapy at the University Hospital of Munich (LMU Munich) and at the Department of Psychiatry at the Charité Universitätsklinikum Berlin. Inclusion criteria defined for this publication were: 1) current treatment with clozapine for at least 6 months, 2) diagnosis of schizophrenia, schizophreniform disorder, schizoaffective disorder or psychotic disorder NOS (DSM-IV)/(un)specified schizospectrum or other psychotic disorder (DSM-V), 3) age ≥ 18, 4) fluency in speaking and reading in German and 5) ability to give informed consent. Applying inclusion criteria and after giving informed consent, 105 patients were included in the study (53 smokers, 52 nonsmokers). Smoking status was defined as regular tobacco consumption. The project was approved by the local ethics committees (*Reference number* 458–16).

Outcomes

To investigate symptomatic remission between smokers and nonsmokers, we used the Remission in Schizophrenia Working Group (RSWG) criteria ("Andreasen criteria") [6]. As detailed elsewhere [6, 33, 34], 3 symptom clusters need to be considered: (1) psychoticism/reality distortion (PANSS items: delusions (P1), unusual thought content (G9), and hallucinatory behaviour (P3)), (2) disorganization (PANSS items: conceptual disorganisation (P2) and mannerisms/posturing (G5)), and (3) negative symptoms (PANSS items: blunted affect (N1), social withdrawal (N4), and lack of spontaneity (N6)). According to the Andreasen criteria, the symptomatic criterion states that to achieve symptomatic remission, all above mentioned items must be rated as absent or present only to a mild degree (PANSS value ≤ 3). All assessments were performed by trained study personnel who received PANSS training. We defined duration of clozapine treatment to be at least 6 months to confirm symptomatic remission [5–7]. For subsequent analyses, we investigated within the same cohort outcomes for clozapine treatment duration of 2 years and 5 years respectively.

To compare clinical symptom severity between groups, we investigated the subscales of the Positive and Negative Syndrome Scale (PANSS) [35], the Calgary Depression Scale for Schizophrenia (CDSS) [36], and the Clinical Global Impression Scale (CGI) [37] respectively. To compare functional outcomes, the Global Assessment of Functioning (GAF) [38] was assessed. Furthermore, we measured waist circumference (WC) in smokers and nonsmokers and assessed sex-specific high-risk groups to develop metabolic complications according to World Health Organization (WHO) cutoffs being defined as a WC > 102 cm for men and > 88 cm for women [39].

Cognitive outcomes were investigated with the Trail-Making Tests A and B (TMT-A and TMT-B) [40]. The grade of nicotine dependency in the smoker group was evaluated with the Fagerström test for Nicotine Dependence [41]. For group comparisons regarding somatic parameters, we assessed WC, systolic blood pressure, body mass index (BMI), and heart frequency. For the calculation of the Framingham CVD (Cardiovascular Disease) Risk Prediction Scores [42] (FRPS), age, BMI, antihypertensive treatment, diabetes, systolic blood pressure, and smoking behavior were used. For the calculation of the FRPSs. only patients aged between 30 and 74 years (FRPS defined age range) with complete data on covariates were included due to FRPS specifications. FRPSs for 10-year CVD risk prediction were calculated using available risk score calculators (www.framinghamheartstudy.org). Smoking behavior leads to 4 points in men and 3 points in women, whereas nonsmoking status yields 0 points in the sum calculation of the primary score. A sum score between > 10– < 15 points (men) or between > 12– < 18 points (women) respectively results in the stratification into an intermediate-risk group (FRPS ≥ 10–19 %) for CVD over a 10-year follow-up period. We calculated for each patient an individual FRPS (in %). Scores below or above these sex-specific ranges resulted into a stratification into low-risk and high-risk groups respectively.

Furthermore, as categorial variables, we assessed polypharmacy (defined once as current use of ≥ 3 and once as current use of ≥ 5 different neuroactive and non-neuroactive compounds including clozapine), as well as the use of antidepressant, antipsychotic (other than clozapine), and mood-stabilizing co-medication, among others (see ▶ **Tables 1–3**). The duration of clozapine treatment was calculated in years from the date of clozapine initiation and the date of study visit. If the exact day and month for "date of clozapine initiation" were both unknown, e. g., if patients were treated for several years with clozapine, January 1 of the respective year was defined as starting date. Furthermore, we screened all patient files for their last available clozapine blood levels. Thus, the presented clozapine blood levels (ng/ml) were extracted retrospectively and do not correspond to the reported clozapine doses.

Power analysis and statistical analyses

The likelihood of remission with clozapine is presumed to be around 40 % [4]. Assuming that non-smoking patients have higher remission rates in a mixed cohort as ours, we expected the likelihood to achieve remission in non-smoking patients treated with clozapine is $p = 0.60$ and in smoking patients $p = 0.20$. Thus, a total sample size of 82 is needed to show group differences. Power analysis was calculated with GPower 3.1.9.4 [43].

Analyses were performed using IBM SPSS version 25.0 with a significance level of $\alpha = 0.05$. Distributions of continuous variables were tested for normality with Kolmogorov-Smirnov tests where a normal distribution was defined as $p > 0.05$. If the distribution was normal, independent t-tests were applied. Mann-Whitney U tests were applied in the event of a violation of the normal distribution assumption. Chi-square tests were used to compare differences in categorical variables between groups (smokers vs. nonsmokers; 2-sided Fisher's exact test was applied for cell count < 5 for 2 × 2 tables). To provide a correction for potential center effects, we repeated all analyses using univariate ANOVAs with smoking status and center as fixed factors for all parametric variables (ANCOVA approach). To allow an estimation of center effect for all aforementioned variables, ANCOVA was performed for normally and nonnormally distributed variables as covariate analyses for Mann-Whitney U tests are not possible (see Supplementary ▶ **Tables 1S–6S**). The here presented analyses should be considered exploratory rather than confirmatory. Thus, adjustments for multiple testing were not made.

Results

Description of the cohort

Of the 105 participants, 67 were male and 38 were female; 53 participants were smokers and 52 nonsmokers. Fifty-nine study participants were recruited at the Department of Psychiatry and Psychotherapy at the Charité Universitätsklinikum Berlin, Berlin, Germany, and 46 at the Department of Psychiatry and Psychotherapy at the University Hospital Munich, LMU Munich, Munich, Germany. Eighty-five participants were diagnosed with paranoid schizophrenia (43 smokers, 42 nonsmokers), 19 had a diagnosis of schizoaffective disorder (9 smokers, 10 nonsmokers), and 1 patient was diagnosed with schizophreniform disorder (smoker). Further details are shown in ▶ **Table 1**. Smokers had an average FTDN score of 5.78 ± 2.05 points, fulfilling the cut-off for "moderate nicotine dependence," and were smoking an average of 20.67 ± 10.96 ciga-

▶ **Table 1** Clinical and laboratory parameters of included patients with clozapine-treatment of at least six months.

	Smokers			Nonsmokers			Group comparisons		
	n	**mean**	**SD +/-**	**n**	**mean**	**SD +/-**		**df**	**p**
							t		
Age (years)	53	42.0	11.46	52	48.81	10.4	3.19	103	**0.002**
							χ^2		
Remission (yes:no)	14:39	–	–	16:33	–	–	0.48	1	0.490
Gender (m:f)	38:15	–	–	29:23	–	–	2.88	1	0.089
Center (LMU:Charité)	16:37			30:22			8.07	1	**0.005**
Diagnosis (F20:F25:F23)	43:9:1	–	–	42:10:0	–	–	1.06	2	0.590
Polypharmacy ≥ 3 (yes:no)	41:8	–	–	32:9	–	–	0.46	1	0.497
Polypharmacy ≥ 5 (yes:no)	17:32	–	–	18:23	–	–	0.80	1	0.372
AD (yes:no)	15:34	–	–	17:24	–	–	1.15	1	0.284
AP (non-CLZ, yes:no)	35:14	–	–	27:14	–	–	0.32	1	0.569
MS (yes:no)	17:32	–	–	6:35	–	–	4.72	1	**0.030**
BMI > = 30kg/m² (yes:no)	23:29	–	–	21:29	–	–	0.05	1	0.820
Heart rate >100 bpm (yes:no)	7:46	–	–	11:40	–	–	1.27	1	0.260
WC for men >102 cm (yes:no)	21:16	–	–	11:14	–	–	0.97	1	0.324
WC for women >88 cm (yes:no)	9:6	–	–	12:8	–	–	0.00	1	1.000
Diabetes (yes:no)	9:38	–	–	5:41	–	–	1.25	1	0.264
AH treatment (yes:no)	8:41	–	–	10:31	–	–	0.91	1	0.341
							Z#		
Clozapine treatment (yrs)	53	10.05	8.06	52	13.83	9.93	−2.05	1	**0.041**
Clozapine dose (mg/day)	53	280.19	166.58	50	220.00	120.06	−1.76	1	0.078
Clozapine blood level (ng/ml)	43	317.70	296.23	51	404.05	330.22	−2.24	1	**0.025**
Duration of illness (yrs)	35	18.14	13.43	37	20.38	10.78	−1.06	1	0.289
PANSS positive	53	15.53	5.21	49	14.06	5.22	−1.55	1	0.122
PANSS negative	53	14.85	5.12	49	16.24	5.98	−1.03	1	0.303
PANSS general	53	32.04	8.88	49	32.04	8.76	−0.11	1	0.912
PANSS total	53	62.25	16.28	49	62.37	16.97	−0.05	1	0.957
CDSS	53	4.25	4.59	49	3.76	3.72	−0.18	1	0.858
TMT-A (sec)	49	67.00	119.29	41	57.34	30.54	−0.99	1	0.323
Errors TMT-A	48	0.27	0.57	41	0.17	0.44	−0.80	1	0.423
TMT-B (sec)	40	124.04	63.07	36	160.83	117.37	−1.64	1	0.100
Errors TMT-B	37	0.92	1.06	36	0.89	1.30	−0.58	1	0.562
GAF score	52	51.38	14.31	48	54.38	13.00	−1.14	1	0.254
CGI score	51	4.43	1.12	49	4.24	0.99	−0.86	1	0.391
BP systolic (mmHg)	53	126.51	15.83	49	126.43	13.96	−0.20	1	0.843
Framingham-Score (%)	37	15.44	11.03	32	8.97	6.48	−3.07	1	**0.002**
Fagerström test	51	5.78	2.05	–	–	–	–	–	–
Number of cigarettes/day	50	20.67	10.96	–	–	–	–	–	–
							t		
BMI (kg/m²)	52	29.42	5.01	50	29.07	5.63	−0.34	100	0.738
WC (cm)	53	102.08	14.02	46	101.78	16.27	−0.10	97	0.924
Heart rate (bpm)	53	87.60	13.27	51	87.65	15.88	0.02	102	0.988

Abbrev: AH: antihypertensive, BP: blood pressure, bpm: beats per minute, CDSS: Calgary Depression Scale for Schizophrenia, CGI: Clinical Global Impressions Scale, χ^2: Pearson's Chi-Square test, df: degrees of freedom, f: female, F20: paranoid schizophrenia, F23: schizophreniform disorder, F25: schizoaffective disorder, GAF: Global Assessment of Functioning, m: male, PANSS: Positive and Negative Syndrome Scale, SD: standard deviation, sec: seconds, t: t-value, TMT-A: Trail-Making-Test A, TMT-B: Trail-Making-Test B, WC: waist circumference, thresholds according to WHO definitions, yrs: years, Z: z-value. #if not normally distributed according to Kolmogorov-Smirnov test, Mann Whitney U was applied with a 2-sided significance level.

rettes per day. Significantly more PCS were recruited at the study site Charité Universitätsklinikum Berlin for clozapine treatment duration of at least 6 months, 2 years, and 5 years compared to the study site LMU Munich ($p = 0.005$, $p = 0.004$ and $p = 0.002$ respectively) (see ▶ **Tables 1–3**).

Comparisons between smokers and nonsmokers according to treatment duration

≥ 6 months clozapine treatment (n = 105)

No differences in remission rates could be observed between groups ($X^2_{(1)} = 0.48$, $p = 0.490$). Smokers were significantly younger of age ($t_{(103)} = 3.19$, $p = 0.002$), had a significantly longer duration of clozapine treatment ($Z_{(1)} = -2.05$, $p = 0.041$) despite a similar duration of illness in the 2 groups ($Z_{(1)} = -1.06$, $p = 0.289$), and were significantly more likely to be treated with mood-stabilizing co-medication ($X^2_{(1)} = 4.72$, $p = 0.030$) compared to nonsmokers. A nonsignificant numeric difference could be observed for higher clozapine dosages in the smoker group ($Z_{(1)} = -1.76$, $p = 0.078$). Smokers had significantly lower clozapine blood levels (last available clinical data) compared to nonsmokers ($Z_{(1)} = -2.24$, $p = 0.025$). FRPSs were significantly higher in the smokers group ($Z_{(1)} = -3.07$, $p = 0.002$). All other outcome variables showed no significant differences between groups (see ▶ **Table 1** and ▶ **Supplementary Table 1S**). An exploratory analysis comparing patients with or without co-prescribed mood-stabilizers irrespective from the smoking status showed no significant difference in FRPSs scores ($t_{(67)} = -0.83$, $p = 0.407$, $n = 67$).

≥ 2 years clozapine treatment (n = 93)

Again, no differences between groups regarding remission rates could be observed ($X^2_{(1)} = 0.31$, $p = 0.581$). Smokers were significantly younger of age ($Z_{(1)} = -2.27$, $p = 0.023$) but were not significantly more likely to be treated with mood-stabilizing co-medication ($X^2_{(1)} = 3.77$, $p = 0.052$). Smokers did not receive significantly different clozapine dosages ($Z_{(1)} = -1.75$, $p = 0.080$) and did not show significantly different clozapine blood levels ($Z_{(1)} = -1.67$, $p = 0.096$) compared to nonsmokers. FRPSs were significantly higher in the smoker group ($Z_{(1)} = -2.83$, $p = 0.005$). All other variables showed no significant group differences (see ▶ **Table 2** and ▶ **Supplementary Table 2S**).

≥ 5 years clozapine treatment (n = 75)

As described for 6 months and 2 years, the 5-years analyses also did not show a difference in remission rates between groups ($X^2_{(1)} = 0.01$, $p = 0.927$). Smokers were significantly younger of age ($t_{(73)} = 2.02$, $p = 0.047$) and were treated with significantly higher clozapine dosages ($t_{(71)} = -2.31$, $p = 0.024$). FRPSs were significantly higher in the smoker group ($Z_{(1)} = -3.35$, $p = 0.001$). All other variables showed no significant differences between the 2 groups (see ▶ **Table 3** and ▶ **Supplementary Table 3S**).

Center effects

To facilitate comparability and to provide the basis for covariate analyses to adjust for possible center effects, exploratory independent t-tests were performed for all continuous variables (see ▶ **Supplementary Tables 4S–6S**). These tests showed for the 6-months analyses compared to the primary Mann-Whitney-U tests differences in the clozapine dose ($p = 0.037$ vs. $p = 0.078$), and also for the 2-years analyses differences in clozapine dose ($p = 0.045$ vs. $p = 0.080$). ANCOVAs showed that compared to the independent t-tests and Mann-Whitney-U tests, the following changes in significances could be observed:

Clozapine treatment duration ≥ 6 months

Compared to the primary analyses (see ▶ **Table 1**), ANCOVAs showed now nonsignificant differences in duration of clozapine treatment ($p = 0.052$; primary analysis: $p = 0.041$) and clozapine blood levels ($p = 0.199$; primary analysis: $p = 0.025$), whereas differences in age ($p = 0.007$; primary analysis: $p = 0.002$) and FRPSs ($p = 0.032$; primary analysis: $p = 0.002$) remained significant (see ▶ **Supplementary Table 1S** for ANCOVA results).

Clozapine treatment duration ≥ 2 years

Compared to the primary analyses (see ▶ **Table 2**), ANCOVAs showed now nonsignificant differences in age ($p = 0.056$, primary analysis: $p = 0.002$) and FRPSs ($p = 0.058$, primary analysis: $p = 0.002$) between the 2 groups (see ▶ **Supplementary Table 2S** for ANCOVA results).

Clozapine treatment duration ≥ 5 years

Compared to the primary analyses (see ▶ **Table 3**), ANCOVAs showed now nonsignificant differences in age ($p = 0.086$, primary analysis: $p = 0.047$) and FRPSs ($p = 0.066$, primary analysis, $p = 0.001$) between the 2 groups, whereas differences in clozapine dose ($p = 0.043$, primary analysis: $p = 0.024$) remained significant (see ▶ **Supplementary Table 3S** for ANCOVA results).

Dichotomous variables in group analyses for clozapine treatment duration ≥ 6 months, ≥ 2 years, and ≥ 5 years

Apart from the variable mood-stabilizer in the 6-months analyses, all dichotomous variables did not show any group differences in all the analyses (6 months, 2 and 5 years). Thus, these variables were not adjusted for center effects.

Discussion

To the best of our knowledge, our cross-sectional study is the first to investigate the possible impact of smoking on likelihood for remission according to RSWG criteria in schizophrenia and schizophrenia spectrum disorder in relation to the duration of clozapine treatment. However, we could not establish group differences in the likelihood to fulfill the RSWG remission criteria after 6 months, 2 or 5 years of clozapine treatment. It has to be noted that the rate of remitters for patients treated with clozapine was only 29.4 %, which is lower than expected [4]. Smokers had on average a higher daily dosage of clozapine with significantly higher doses in the cohort of patients being treated with clozapine for at least 5 years ($p = 0.024$). However, this group had no increased risk to be more severely affected with regard to e. g., psychotic symptoms than nonsmokers, which is inconsistent with the hypothesis that smoking schizophrenia patients represent a biological subsample that is more severely affected [21]. On the other hand, it is remarkable that the smoker-group was on average significantly younger than the nonsmoker group despite nonsignificant differences in terms

▶ **Table 2** Clinical and laboratory parameters of included patients with clozapine treatment of at least two years.

	Smokers			Nonsmokers			Group comparisons		
	n	**mean**	**SD +/-**	***n***	**mean**	**SD +/-**		**df**	***p***
							Z#		
Age (years)	55	44.11	10.818	49	49.14	10.430	−2.27	1	**0.023**
							χ^2		
Remission (yes:no)	12:32	–	–	15:31	–	–	0.31	1	0.581
Gender (m:f)	31:13	–	–	28:21	–	–	1.77	1	0.183
Center (LMU:Charité)	13:31			29:20			8.22	1	**0.004**
Diagnosis (F20:F25:F23)	37:6:1	–	–	40:9:0	–	–	1.45	2	0.484
Polypharmacy ≥3 (yes:no)	34:6	–	–	31:7	–	–	0.16	1	0.685
Polypharmacy ≥5 (yes:no)	14:26	–	–	18:20	–	–	1.23	1	0.267
AD (yes:no)	11:29	–	–	15:23	–	–	1.26	1	0.262
AP (non-CLZ, yes:no)	29:11	–	–	26:12	–	–	0.16	1	0.693
MS (yes:no)	14:26	–	–	6:32	–	–	3.77	1	0.052
BMI ≥30kg/m² (yes:no)	21:22	–	–	21:26	–	–	0.16	1	0.693
Heart rate >100 bpm (yes:no)	7:37	–	–	11:37	–	–	0.71	1	0.397
WC for men >102 cm (yes:no)	19:11	–	–	11:14	–	–	2.06	1	0.152
WC for women >88 cm (yes:no)	8:5	–	–	11:7	–	–	0.00	1	0.981
Diabetes (yes:no)	8:31	–	–	5:39	–	–	1.31	1	0.252
AH treatment (yes:no)	8:32	–	–	9:29	–	–	0.16	1	0.694
							Z#		
Clozapine treatment (yrs)	44	11.86	7.67	49	14.60	9.70	-1.27	1	0.206
Clozapine dose (mg/day)	44	284.09	168.53	47	220.74	123.61	−1.75	1	0.080
Clozapine blood level (ng/ml)	35	343.09	317.02	48	403.65	338.82	−1.67	1	0.096
							T		
Duration of illness (yrs)	27	22.41	12.30	34	21.0	10.60	−0.48	59	0.633
							Z#		
PANSS positive	44	15.84	5.50	46	13.83	5.28	−1.83	1	0.067
PANSS negative	44	14.61	5.13	46	16.15	5.85	−1.14	1	0.256
							t		
PANSS general	44	32.05	8.97	46	31.46	8.67	−0.32	88	0.752
							Z#		
PANSS total	44	62.30	16.69	46	61.46	16.89	−0.33	1	0.744
CDSS	44	4.07	4.74	46	3.35	3.27	−0.17	1	0.867
TMT-A (sec)	42	72.42	128.13	39	57.79	31.22	−0.39	1	0.698
Errors TMT-A	41	0.24	0.58	39	0.18	0.45	−0.29	1	0.775
TMT-B (sec)	33	126.71	58.83	34	159.71	120.62	−1.03	1	0.304
Errors TMT-B	30	0.87	1.01	34	0.82	1.29	−0.72	1	0.475
GAF score	44	50.39	13.94	45	55.11	12.92	−1.58	1	0.113
CGI score	43	4.47	1.14	46	4.17	0.97	−1.29	1	0.196
BP systolic (mmHg)	44	128.07	16.45	46	127.57	13.08	−0.07	1	0.948
Framingham-Score (kg/m²)	33	15.92	11.52	30	9.24	6.54	−2.83	1	**0.005**
Fagerström test	43	5.86	2.07	–	–	–	–	–	–
Number of cigarettes/day	43	21.96	10.84	–	–	–	–	–	–
							t		
BMI (kg/m²)	43	29.71	5.19	47	29.32	5.69	−0.32	88	0.749
WC (cm)	44	103.89	14.05	44	103.36	16.40	−0.47	86	0.641
Heart rate (bpm)	44	87.57	13.88	48	87.94	15.80	0.12	90	0.906

Abbrev: AH: antihypertensive, BP: blood pressure, bpm: beats per minute, CDSS: Calgary Depression Scale for Schizophrenia, CGI: Clinical Global Impressions Scale, $\chi 2$: Pearson's Chi-Square test, df: degrees of freedom, f: female, F20: paranoid schizophrenia, F23: schizophreniform disorder, F25: schizoaffective disorder, GAF: Global Assessment of Functioning, m: male, PANSS: Positive and Negative Syndrome Scale, SD: standard deviation, sec: seconds, t: t-value, TMT-A: Trail-Making-Test A, TMT-B: Trail-Making-Test B, WC: waist circumference, thresholds according to WHO definitions, yrs: years, Z: z-value. #if not normally distributed according to Kolmogorov-Smirnov test, Mann Whitney U was applied with a 2-sided significance level.

▶ **Table 3** Clinical and laboratory parameters of included patients with clozapine treatment of at least five years.

	Smokers			Nonsmokers			Group comparisons		
	n	**mean**	**SD +/-**	***n***	**mean**	**SD +/-**		**df**	***p***
							t		
Age (years)	35	45.43	10.35	40	50.25	10.30	2.02	73	**0.047**
							χ^2		
Remission (yes:no)	11:24	–	–	12:25	–	–	0.01	1	0.927
Gender (m:f)	24:11	–	–	24:16	–	–	0.60	1	0.440
Center (LMU:Charité)	10:25			26:14			9.92	1	**0.002**
Diagnosis (F20:F25)	30:5	–	–	34:6	–	–	0.01	1	0.930
Polypharmacy ≥ 3 (yes:no)##	26:5	–	–	28:3	–	–	–	1	0.707
Polypharmacy ≥ 5 (yes:no)	10:21	–	–	16:15	–	–	2.39	1	0.123
AD (yes:no)	7:24	–	–	13:18	–	–	2.66	1	0.103
AP (non-CLZ, yes:no)	22:9	–	–	22:9	–	–	0.00	1	1.000
MS (yes:no)	10:21	–	–	6:25	–	–	1.35	1	0.246
BMI ≥30kg/m² (yes:no)	18:16	–	–	15:23	–	–	1.31	1	0.252
Heart rate >100 bpm (yes:no)	4:31	–	–	8:31	–	–	1.12	1	0.290
WC for men >102 cm (yes:no)	16:7	–	–	9:12	–	–	3.19	1	0.074
WC for women >88 cm (yes:no)##	7:4	–	–	10:5	–	–	–	1	1.000
Diabetes (yes:no)	7:25	–	–	3:32	–	–	2.33	1	0.127
AH treatment (yes:no)	5:26	–	–	7:24	–	–	0.41	1	0.520
							Z#		
Clozapine treatment (yrs)	35	13.947	7.23	40	17.01	9.12	−1.47	1	0.141
							t		
Clozapine dose (mg/day)	35	297.14	173.92	38	215.13	127.94	−2.31	71	**0.024**
Clozapine blood level (ng/ml)	27	373.41	350.70	39	370.06	297.89	−0.04	64	0.967
Duration of illness (yrs)	21	25.10	11.68	27	22.82	9.87	−0.52	67	0.603
							Z#		
PANSS positive	35	16.0	5.916	37	14.0	5.52	−1.466	1	0.143
PANSS negative	35	14.54	4.895	37	16.05	6.18	−0.836	1	0.403
							t		
PANSS general	35	32.29	9.70	37	31.46	9.40	−0.37	70	0.715
PANSS total	35	62.57	17.51	37	61.49	17.92	−0.26	70	0.796
							Z#		
CDSS	35	3.31	4.25	38	3.32	3.43	−0.30	1	0.763
TMT-A (sec)	33	78.17	144.16	30	57.70	30.71	−0.41	1	0.680
Errors TMT-A	33	0.27	0.63	30	0.17	0.46	−0.59	1	0.559
TMT-B (sec)	25	126.02	58.78	26	166.54	132.76	−1.05	1	0.296
Errors TMT-B	23	0.91	1.08	26	0.77	1.18	−0.74	1	0.459
GAF score	35	49.69	14.52	37	54.92	13.75	−1.48	1	0.139
CGI score	34	4.47	1.21	38	4.24	1.03	−0.88	1	0.380
BP systolic (mmHg)	35	128.29	15.92	37	126.60	11.78	0.66	1	0.664
Framingham-Score (kg/m²)	27	17.59	12.07	23	8.92	6.29	−3.35	1	**0.001**
Fagerström test	34	5.94	2.22	–	–	–	–	–	–
Number of cigarettes/day	34	22.97	11.51	–	–	–	–	–	–
							t		
BMI (kg/m²)	34	30.27	4.98	38	28.68	4.98	−1.31	70	0.194
							Z#		
WC (cm)	35	105.29	14.45	36	101.5	15.05	−1.39	1	0.164
Heart rate (bpm)	35	87.37	13.24	39	87.92	15.81	−0.21	1	0.837

Abbrev: AH: antihypertensive, BP: blood pressure, bpm: beats per minute, CDSS: Calgary Depression Scale for Schizophrenia, CGI: Clinical Global Impressions Scale, $\chi 2$: Pearson's Chi-Square test, df: degrees of freedom, f: female, F20: paranoid schizophrenia, F23: schizophreniform disorder, F25: schizoaffective disorder, GAF: Global Assessment of Functioning, m: male, PANSS: Positive and Negative Syndrome Scale, SD: standard deviation, sec: seconds, t: t-value, TMT-A: Trail-Making-Test A, TMT-B: Trail-Making-Test B, WC: waist circumference, thresholds according to WHO definitions, yrs: years, Z: z-value. #if not normally distributed according to Kolmogorov-Smirnov test, Mann Whitney U was applied with a 2-sided significance level. ## two-sided Fisher's exact test was applied for cell count <5 in a 2×2 table.

of duration of illness. Smoking and younger age is not presumed to be associated in the general population [44], and therefore the effects might be disease-related. Smoking schizophrenia patients might be at risk of an earlier onset of treatment-resistance and thus, are likely to receive clozapine at an earlier time point. In general, several theories that were developed from the clinical observation of increased smoking rates among people with schizophrenia, e. g., compensatory strategy to ameliorate cognitive deficits [45], relieve symptoms (self-medication hypothesis), or reduce drug-levels to improve the burden of side-effects but also neurobiological effects of nicotine, must be considered [46]. For example, 1 rodent study showed that the administration of nicotine effectively reversed acute clozapine-induced memory impairments while this effect was not present for antipsychotics with a higher D_2-blockade (risperidone, haloperidol) [47]. Thus, with regard to our findings of a younger age in smoking clozapine users, one could speculate that despite having a potentially more severe disease course compared to nonsmokers, the expected deficits are ameliorated by the smoking behavior *x* clozapine interaction.

Furthermore, smoking patients with a duration of clozapine treatment of at least 6 months were more likely to be treated with mood-stabilizing co-medication. However, differences were not significant when clozapine-treatment duration was adjusted to 2 years. In patients with schizophrenia, mood stabilizers are common adjuncts to antipsychotics and are presumed to be co-prescribed in around 50 % [48]. For patients treated with high-dose clozapine regimens, mood stabilizers are used to prevent seizures and for mood control in schizoaffective disorder [49]. Nevertheless, evidence for the effectiveness of clozapine augmentation with a mood stabilizer remains sparse [50]. Previous studies showed a significant relationship between younger age and mood-stabilizing medication among patients with schizophrenia [51–53]. It can be speculated that smoking patients are on average younger patients and are more likely to exhibit aggressive or impulsive behavior and thus are treated more often with mood-stabilizing co-medication. Interestingly, in our cohort smokers did not have significantly higher PANSS positive scores and were not more likely to be symptomatic nonremitters according to Andreasen criteria [6] compared to nonsmokers. Previous results regarding psychopathological symptom severity in smoking vs. nonsmoking schizophrenia patients are still inconsistent [15, 22–26, 30, 54–61], but our results show that PANSS positive scores remain nonsignificantly higher among smokers when compared to nonsmokers regardless of clozapine treatment duration. This finding suggests either a higher load of psychotic symptoms in the smoker group despite throughout and partially significantly higher clozapine doses per day or a hampered clozapine response as a consequence of insufficient clozapine blood levels in the smoker group. CDSS scores to measure depressive symptoms among our cohort of patients treated with clozapine were not significantly higher among smokers, which is inconsistent with previous results [21].

Since there is some evidence that nicotine might improve cognitive deficits in patients with schizophrenia [62, 63], we compared cognitive performance between smokers and nonsmokers using TMT-A and TMT-B scores, which are commonly used as an instrument to measure speed of cognitive processing and executive functioning. Our results could not show significant differences in TMT-A and TMT-B scores between smokers and nonsmokers.

With regard to somatic outcomes, smokers and nonsmokers in both cohorts for at least 6 months and 2 years clozapine treatment were on average pre-obese according to WHO definitions without significant differences between the 2 groups. The smokers in the cohort of patients treated with clozapine for at least 5 years fulfilled obesity criteria with an average BMI score of 30.27 kg/m^2. Even though the group of nonsmokers with average BMI scores of 28.68 kg/m^2 could still be defined as pre-obese, differences were not significant between the 2 groups (see ▶ **Table 3**). This finding is consistent with a recent meta-analysis showing that 51.9 % of patients with schizophrenia treated with clozapine were suffering from metabolic syndrome [64]. Our results show that smoking behavior among patients treated with clozapine significantly increases cardiovascular risk scores and adds further impact to the unfavorable cardiovascular profile of clozapine.

With regard to the FRPSs, our results showed significantly higher risk scores among smokers regardless of clozapine treatment duration. The 1.5- to 2-fold increased CVD risk of smokers compared to nonsmokers can only be partially explained by the fact that smoking itself is a covariate within the calculation of the FRPS since, e. g., diabetes was nonsignificantly more often diagnosed among smokers in the current data. Irrespective of smoking status, co-prescription of mood-stabilizers did not significantly influence FRPSs. In general, our findings show that clozapine-treated patients with smoking behavior can be characterized as a CVD intermediate-risk population, whereas nonsmokers can be characterized as a CVD low-risk population. These findings highlight the need for tobacco cessation treatment in smoking schizophrenia patients treated with clozapine.

Even though our cross-sectional naturalistic study comprises a clinically well characterized cohort of patients on a minimum duration of 6 months clozapine treatment and our findings might appear generalizable to a certain extent, our study has several limitations. First, clozapine blood levels were assessed from last available data in the patient files and mostly did not correspond to the scheduled study visits. Thus, results have to be interpreted with caution. Second, we did not perform follow-up visits. Third, we did not systematically assess clozapine's efficacy, the individual course of symptoms, and whether the criteria for treatment-resistance were fulfilled. Moreover, we cannot specify whether some of our patients might have been treated with clozapine for the management of e. g., suicidal ideation symptoms, the management of motor abnormalities, or to treat a previous episode of catatonia [65]. Fourth, raters of our study were not blinded in the cognitive and PANSS assessments regarding smoking status. Furthermore, the distribution of smokers and nonsmokers differed between both study sites, and even though we used an ANCOVA approach to correct for center effects, some of our findings might be prone to selection bias given a cross-sectional study design with only 2 centers for tertiary care hospitals. Thus, our findings are not fully comparable with a real-world setting as analyzed in population-based studies such as in the study from Taipale et al. [32]. Finally, we did not assess reasons for concomitant medication and did not include metabolic data concerning triglycerides, HDL-cholesterine, and fasting glucose levels to evaluate the prevalence of metabolic syndrome. Nev-

ertheless, our study represents the largest study on a broad variety of clinically highly relevant outcomes among a severely-ill cohort of patients treated with clozapine. Furthermore, our study contributes to the discussion of clozapine's cardiovascular safety [66] with regard to its efficacy in terms of a risk-benefit evaluation. Given the presumed shared underlying neurobiology of schizophrenia and nicotine use [67–69], our smoking clozapine patients might define an ultra-treatment-resistant subgroup with an early onset of the disease requiring further research.

Conclusion

In our study with a large cohort of patients treated with clozapine, we were able to show that PCS patients might receive clozapine treatment earlier when compared to nonsmokers. Overall, our findings comparing disease-specific and clinical outcomes between smokers and nonsmokers were mostly negative.

Nevertheless, PCS patients had a 1.5- to 2-fold increased CVD risk compared to nonsmokers and represented a CVD intermediate-risk population. Further research is needed to disentangle the relationship between smoking behaviour and the development of treatment-resistance among people with schizophrenia.

Acknowledgments

This publication is part of the MD thesis of NP.

Conflict of Interest

E. Wagner reports no conflicts of interest. T. Oviedo-Salcedo reports no conflict of interest. I. Maurus reports no conflict of interest. N. Pelzer reports no conflict of interest. W. Strube received speakership reimbursement by Mag and More. S. Gutwinski reports no conflict of interest. S. Schreiter reports no conflict of interest. P. Kleymann reports no conflict of interest. C.L. Morgenroth reports no conflict of interest. C. Okhuijsen-Pfeifer reports no conflicts of interest. J. Luykx reports no conflict of interest. P. Falkai was honorary speaker for Janssen-Cilag, Astra-Zeneca, Eli Lilly, Bristol Myers-Squibb, Lundbeck, Pfizer, Bayer Vital, SmithKline Beecham, Wyeth, and Essex. During the last 5 years he was a member of the advisory boards of Janssen-Cilag, AstraZeneca, Eli Lilly, and Lundbeck. Presently, he is a member of the advisory boards of Richter Pharma, Abbot, and Otsuka, T. Schneider-Axmann reports no conflict of interest. A. Hasan has been invited to scientific meetings by Lundbeck, Janssen-Cilag, and Pfizer, and he received paid speakerships from Desitin, Janssen-Cilag, Otsuka, and Lundbeck. He was a member of Roche, Otsuka, Lundbeck, and Janssen-Cilag advisory boards.

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