Acta Psychiatrica Scandinavica

Acta Psychiatr Scand 2020: 142: 456–466

DOI: 10.1111/acps.13228

ACTA PSYCHIATRICA SCANDINAVICA

Systematic Review or Meta-Analysis

Impact of smoking behavior on clozapine blood levels – a systematic review and meta-analysis

E. Wagner[1], L. McMahon[2], P. Falkai[1], A. Hasan[1,3], D. Siskind[2,4]

[1]Department of Psychiatry and Psychotherapy, University Hospital, LMU Munich, Munich, Germany, [2]School of Medicine, University of Queensland, Brisbane, Australia, [3]Department of Psychiatry, Psychotherapy and Psychosomatics of the University Augsburg, Bezirkskrankenhaus Augsburg, Medical Faculty, University of Augsburg, Augsburg, Germany and [4]Metro South Addiction and Mental Health Service, Brisbane, Australia

Wagner E, McMahon L, Falkai P, Hasan A, Siskind D. Impact of smoking behavior on clozapine blood levels – a systematic review and meta-analysis.

Objective: Tobacco smoking significantly impacts clozapine blood levels and has substantial implications on individual efficacy and safety outcomes. By investigating differences in clozapine blood levels in smoking and non-smoking patients on clozapine, we aim to provide guidance for clinicians how to adjust clozapine levels for patients on clozapine who change their smoking habits.
Methods: We conducted a meta-analysis on clozapine blood levels, norclozapine levels, norclozapine/clozapine ratios, and concentration to dose (C/D) ratios in smokers and non-smokers on clozapine. Data were meta-analyzed using a random-effects model with sensitivity analyses on dose, ethnic origin, and study quality.
Results: Data from 23 studies were included in this meta-analysis with 21 investigating differences between clozapine blood levels of smokers and non-smokers. In total, data from 7125 samples were included for the primary outcome (clozapine blood levels in ng/ml) in this meta-analysis. A meta-analysis of all between-subject studies (N = 16) found that clozapine blood levels were significantly lower in smokers compared with non-smokers (Standard Mean Difference (SMD) −0.39, 95% confidence interval (CI) −0.55 to −0.22, $P < 0.001$, I^2 = 80%). With regard to the secondary outcome, C/D ratios (N = 16 studies) were significantly lower in the smoker group (n = 645) compared with the non-smoker group (n = 813; SMD −0.70, 95%CI −0.84 to −0.56, $P < 0.00001$, I^2 = 17%).
Conclusion: Smoking behavior and any change in smoking behavior is associated with a substantial effect on clozapine blood levels. Reductions of clozapine dose of 30% are recommended when a patient on clozapine stops smoking. Reductions should be informed by clozapine steady-state trough levels and a close clinical risk-benefit evaluation.

Key words: Schizophrenia; clozapine; meta-analysis; smoking

Elias Wagner, Department of Psychiatry and Psychotherapy, LMU Munich, Nussbaumstraße 7, Munich D-80336, Germany. E-mail: Elias.Wagner@med.uni-muenchen.de

Accepted for publication August 19, 2020

Summations

- Smoking behavior significantly reduces clozapine blood levels.
- When a patient stops smoking, reductions of clozapine dose of 30% are recommended.

Considerations

- Besides smoking behavior, other factors impacting clozapine blood levels (e.g., age, gender, comedication with clinically relevant CYP1A2-interaction, caffeine intake, Cytochrome P-polymorphisms, ethnic origin) should be accounted for in future studies and, more importantly, measurement of clozapine blood levels has to be implemented in future studies to provide further evidence for a safe and efficacious use of clozapine.

Introduction

Clozapine is the most effective antipsychotic agent for treatment-resistant schizophrenia (TRS) (1,2). Clozapine is one of the few antipsychotics where therapeutic level monitoring is used, with levels above the maximum threshold (1000 ng/ml) being associated with an increased risk of seizures (3). In clinical practice, pseudo-resistance to clozapine may occur as a result of blood levels below the minimum threshold definition (350 ng/ml) and there is an association between clozapine blood levels and response (4). Cytochrome P450 (CYP) 1A2 (CYP1A2) is the major clozapine metabolic enzyme and is responsible for approximately 70% of clozapine's metabolism (5). Clozapine is metabolized to its primary metabolite norclozapine (5). In this regard, polycyclic aromatic hydrocarbons generated by tobacco smoking induce the activity of CYP1A2 (6) which leads to increased clozapine metabolism.

Rates of smoking are up to five times higher among people with schizophrenia compared to the general population, with smoking rates among people with schizophrenia as high as 60% (7). A daily consumption of 7–12 cigarettes may be sufficient for maximum induction of clozapine metabolism (8). Beginning smoking is therefore a clinically relevant risk for relapse and inadequate response to clozapine treatment (9) and smoking cessation among clozapine users can induce severe clozapine intoxication (10). Ethnicity (Asian heritage) (11,12), gender (13), age (13-15), CYP-polymorphisms (16), caffeine (17), and comedication with clinically relevant CYP1A2-interaction (9) can also influence clozapine blood levels through the CYP-450 system. In this context, for example, people of Asian heritage are presumed to need a lesser clozapine dose compared with Caucasian or American populations (12,18) which might be due to a relatively reduced CYP1A2 activity (11). On a similar note, the clinical relevance of CYP1A2 can be observed in smoking patients after transition to electronic cigarettes, where the termination of CYP1A2 induction also induces a clinically relevant increase in clozapine blood levels (19).

Concentration to dose (C/D) ratio is a measure of clozapine clearance and higher ratios—indicating lower clearance—are associated with females, non-smokers, Asians, genetic poor metabolizers, CYP-inhibitors, obesity, inflammation and possibly with renal impairment and pregnancy (18), whereas lower ratios indicate lack of adherence or are associated with males, smokers, non-Asians, and CYP-inducers (18).

In summary, there is a lack of clarity in the available literature as to how great an influence changes in smoking habit can have on clozapine blood levels. To guide clinical care of people treated with clozapine, and to assist in averting sub- or supra-therapeutic clozapine levels and their associated deleterious effects, we conducted a systematic review and meta-analysis of the impact on changes in smoking habit on clozapine blood levels among people on clozapine. Our primary outcome of interest was impact on clozapine blood levels, with secondary outcomes of impact on clozapine to C/D ratios, norclozapine/clozapine ratios, and norclozapine levels. We planned sensitivity analyses and meta-regression analyses on other factors which influence clozapine metabolism including ethnicity, age, and gender, to assist in clarifying the role of potential confounders, if any.

Subtitle

To investigate the impact of smoking behavior on clozapine blood levels and clozapine concentration to dose ratios in order to provide guidance for clinicians how to manage patients on clozapine who smoke or stop smoking.

Methods

The methods are based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (20). This study was registered with PROSPERO (registration number CRD42020185579), an international database of prospectively registered systematic reviews.

Searches

Systematic searches were conducted of publications indexed in PubMed, EMBASE, and PsycINFO using the search terms (level OR levels OR concentration OR concentrations OR ratio OR ratios) AND (blood OR serum OR plasma) AND (clozapin* OR clozaril OR zaponex OR denzapin* OR clopine OR norclozapine OR desmethylclozapine). The abstracts and titles of articles identified through electronic searches were independently screened by two reviewers (EW, LM). Publications in all languages were considered for inclusion.

Inclusion criteria

Studies were included if they reported information on mean (and SD) of clozapine blood levels OR C/D ratios for people with psychiatric disorders who were smoking and not smoking in cohort studies, case–control studies or randomized or non-randomized controlled trials.

Exclusion criteria

Case reports and case series were excluded.

Assessment of reporting strength

As all studies suitable for inclusion were observational studies, we used a modified Newcastle-Ottawa Quality Assessment Scale (21) for assessment of quality. The maximum score was 5, and studies with score of at least 3 were rated as high-quality studies. We considered the following domains: representativeness of the sample, sample size, comparability between smokers and non-smokers, ascertainment of clozapine blood levels (outcome) and quality of descriptive statistics (quality scores are provided in Table S2, modified Newcastle-Ottawa Quality Assessment Scale is provided in Appendix S1).

Data extraction

Two reviewers (EW, LM) independently extracted the data into an electronic spreadsheet and disagreements were resolved by joint examination of the papers. The following data were extracted:

1. Sample size of subjects on clozapine (smokers and non-smokers)
2. Mean (and SD) clozapine blood levels in both groups (ng/ml)
3. Mean (and SD) clozapine dose in both groups (in mg/day)
4. Type of comparison (within-subject or between-subject comparisons between the two groups)

The following characteristics of each study were recorded where possible and if available, both for male and female participants in both groups separately:

1. Mean age of subjects in both groups
2. Ratio male:female in both groups
3. Clozapine blood levels and clozapine doses for male and female participants
4. Whether data collection was prospective or retrospective
5. Inpatient or outpatient status of subjects
6. Amount of smoking in the smoking group
7. Concentration to dose (C/D) ratio in both groups
8. Norclozapine levels in both groups
9. Norclozapine to clozapine ratios in both groups

Data synthesis and analysis

The primary outcome was the clozapine blood level (in ng/ml) in the smoker and non-smoker group. Where adequate quantitative data were not reported, corresponding authors were contacted to provide means and SDs. Where confidence intervals were reported, these were converted to SD using the Cochrane Handbook formula (17). Included studies were divided into between-subject studies and within-subject studies. Between-subject studies compared data from subjects on clozapine divided into smokers and non-smokers, whereas within-subject studies investigated effects within the same individuals as smokers and then non-smokers. Meta-analyses were conducted using RevMan (version 5.3), and meta-regression analyses were conducted using Comprehensive Meta-Analysis (version 3.3). We assessed heterogeneity using the I^2 statistic, a measure that does not depend on the number of studies in the meta-analysis and hence has greater power to detect heterogeneity when the number of studies is small. I^2 provides an estimate of the percentage of variability due to heterogeneity rather than chance alone. An estimate of 50% or greater indicates possible heterogeneity, and scores of 75–100% indicate considerable heterogeneity. Given the observational nature of primary studies and expected high rates of heterogeneity, a random-effects model was used for all the analyses. A significance level of $\alpha < 0.05$ was applied for all analyses.

Subgroup and sensitivity analyses

Subgroup analyses were undertaken for between-subject studies for high-quality (as defined by ≥3 out of 5 points on the modified Newcastle-Ottawa Scale) vs. low-quality studies, male populations, female populations, and studies with people from Asian origin vs. studies with people not from Asian origin. Meta-regression analyses were performed for between-subject studies for clozapine blood levels and the moderators (i) difference in clozapine dose between smokers and non-smokers (ii) proportion of male smokers and (iii) proportion of male non-smokers (iv) age (smokers) and (v) age (non-smokers).

Publication bias

Where meta-analyses included at least 10 studies, publication bias was tested using funnel plot asymmetry with Kendall's Tau, where low *P*-values suggest publication bias. A threshold of 10 for funnel plots was chosen in accordance with the recommendations from the Cochrane Handbook (22).

Results

In total, 7600 articles were independently screened on title/abstract level and 113 articles on full-text

level by two reviewers. A total of 90 articles were excluded at full-text review (see Table S1 for list of excluded studies with reasons), with 23 articles (8,16,23-43) included in the meta-analysis (see Fig. 1, List of included studies see Table 1). Twenty-one articles (8,16,23-31,34-43) investigated differences between smokers and non-smokers as between-subject analyses and two studies (32,33) compared differences as within-subject analyses change of blood levels among smokers after institutional smoking ban). In total, data from 7125 samples were included for the primary outcome (clozapine blood levels in ng/ml) in this meta-analysis. Of these, 4925 were from smokers and 2185 from non-smokers (N = 21, between-subject analyses) and 15 were smokers and subsequent non-smokers (N = 2, within-subject analyses). 18 out of 23 studies were performed exclusively in schizophrenia-spectrum populations, with the remaining five additionally including (a small amount of) patients with bipolar disorder (26,33), unspecified psychiatric disorders (38,43), and psychiatric disorders except organic disorders (27).

Between-subject analyses

Clozapine blood levels. The 16 studies (8,23,25-31,34,35,37-39,41,42) reported on blood levels for samples of smokers (n = 4925) and non-smokers (n = 2185). Overall, study quality was moderate,

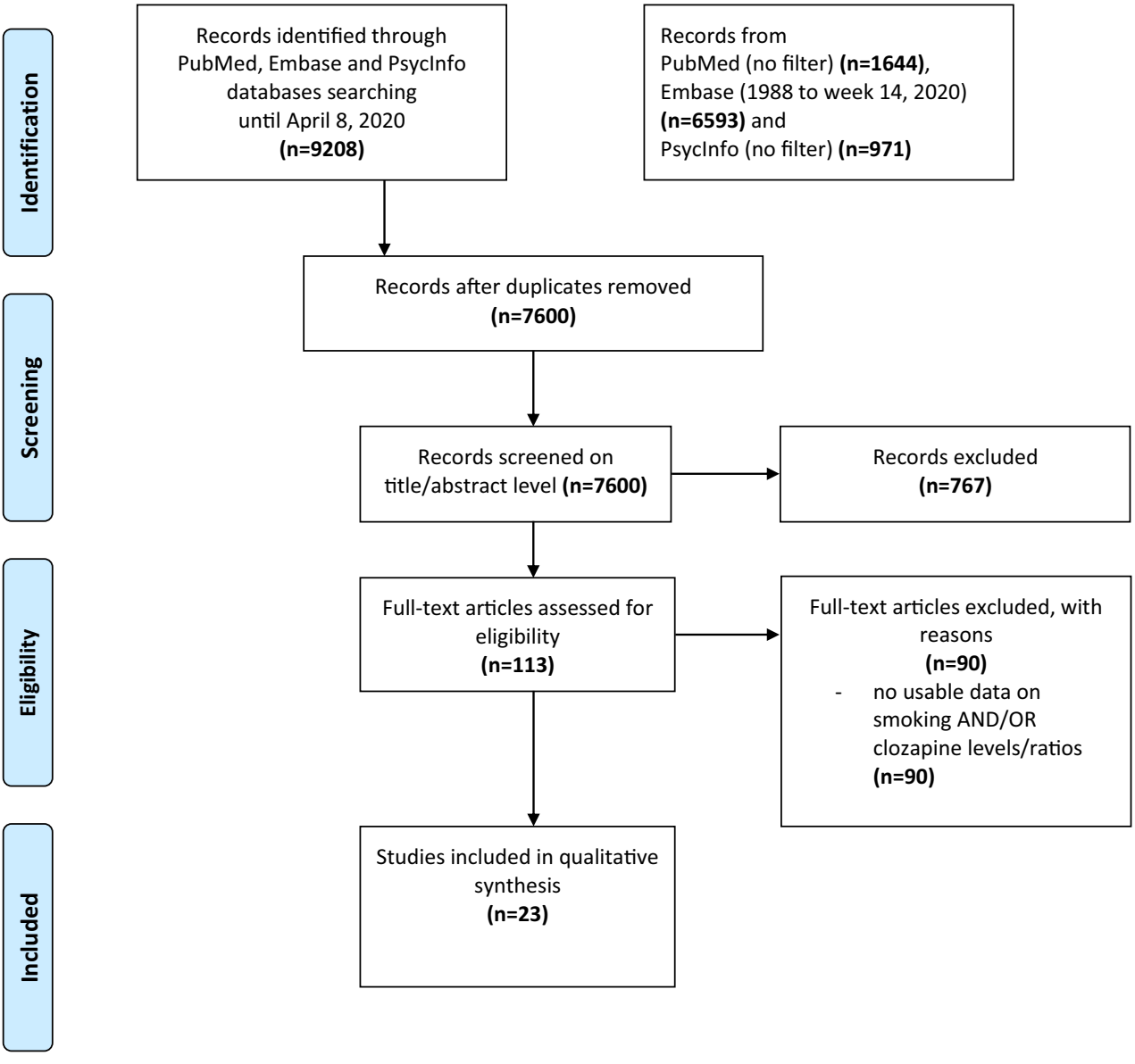

Fig. 1. PRISMA-Flowchart (study selection process). Systematic literature search according to Moher et al. (20). [Colour figure can be viewed at wileyonlinelibrary.com]

Table 1. Description of included studies

Author (year)	Country	CYP-450 comedication excluded in the analysed cohort (y/n)	Proportions smoker vs. non-smoker balanced (y/n), ratio	Setting	Type of study	Diagnosis	Diagnostic tool	Smoking quantity (mean, SD) in smoking group†	Clozapine dose (mean, SD) in smoking group (mg/d)	Clozapine dose (mean, SD) in non-smoking group (mg/d)	Clozapine level (mean, SD) in smoking group (ng/ml)	Clozapine level (mean, SD) in non-smoking group (ng/ml)	Age (mean, SD) in smoking group (yrs)	Age (mean, SD) in non-smoking group (yrs)	M:f ratio in smoking group	M:f ratio in non-smoking group
Augustin (2019)	Germany	y	y, 43:28	Inpatient	Retrospective	Sz	Chart, TDM database	ns	339, 150	286, 123	315, 192	454, 183	40, 13	46, 14	27:16	11:17
Dettling (2000)	Germany	y	n, 25:9	Inpatient + outpatient	Prospective	Sz	DSM-III-R	≥10 cigs/d	ns	ns	ns	ns	ns	ns	ns	ns
González-Esquivel (2011)	Mexico	n	n, 16:53	Inpatient + outpatient	Prospective	Sz	DSM-IV	ns	265, 123	236, 134	329, 274	394, 274	ns	ns	ns	ns
Haring (1990)	Austria	y	y, 81:67	Inpatient	Retrospective	Sz + BD	DSM-III	>5 cigs/d	262, 132	304, 150	141, 114	183, 16	30, 7	32, 11	ns	ns
Haslemo (2006)	Norway	y	n, 28:5	Psychiatric nursing homes	Prospective	Sz	ns	7–>20 cigs/d	495, 1012	415, 228	548, 1586	825, 291	ns	46, 9	18:10	3:2
Kuzin (2019)	Germany	y	n, 326:250	Inpatient + outpatient	Retrospective	mental disorders‡	Chart, TDM database	ns	363, 181	291, 148	294, 209	392, 218	39, 244‡‡	44, 278‡‡	240: 86	145: 105
Lee (2009)§	Korea	y	n, 17:53	clinic	Retrospective	Sz	DSM-IV	>10 cigs/d	384, 132	314, 121	536, 412	632, 372	37, 8	31, 8	ns	ns
Lin (2006)	Taiwan	n	n, 34:68	clinic	Prospective	Sz	ns	ns	295, 95	277, 145	387, 235	549, 329	ns	ns	ns	ns
Lu (2000)	Taiwan	y	y, 10:8	Inpatient	Prospective open-label	TR-Sz	DSM-IV	>10 cigs/d	100, 0	100, 0	154, 99	212, 96	ns	ns	ns	ns
Mayerova (2018)	Czech Republic	n	y, 46:52	Inpatient	Prospective	TR-Sz	ICD-10	24.20 cigs/d, SD = 11.21	363, 122	327, 121	338, 178	607, 388	36, 12	35, 12	38:8	30:22
Meyer (2001)	USA	y	y, 11:11	Inpatient	Prospective within-subject	Sz	ns	ns	568, 123	568, 123	550, 160	993, 713	42, 5	42, 5	8:3	8:3
Murayama (2011)¶	USA	n	y, 4:4	Inpatient	Prospective within-subject	Sz, 1 BD	ns	5.25 cigs/d, SD = 2.06	681, 312	681, 312	570, 188	749, 157	40, 9	40, 9	3:1	3:1
Olmos (2019)	Uruguay	n	y, 46:52	ns	Prospective	Sz	DSM-IV	ns	375, 104	373, 106	382, 269	462, 212	39, 8	38, 10	37:9	39:13
Palego (2002)	Italy	y	y, 22:27	Inpatient + outpatient	Prospective	Psychiatric disorders	DSM-IV	>5 cigs/d	ns	ns	ns	ns	ns	ns	ns	ns
Rostami (2004)	UK, Ireland	Probably not	n, 4139:1360	Inpatient + outpatient	Retrospective	ns	ns	ns	491, 9662 (m), 458, 5878 (f)	428, 5701 (m), 398, 4182 (f)	ns	ns	35, 494 (m), 38, 368 (f)	35, 285 (m), 38, 247 (f)	3021:1118	852: 508
Ruan Beijing 1 (2019)††	China	y	n, 26:100	Inpatient	Retrospective	Sz	ns	ns	271, ns (m), 301, ns (f)	230, ns (m), 202, ns (f)	ns	ns	47, ns (m), 55, ns (f)	37, ns (m), 45, ns (f)	22:5	35:64
Ruan Beijing 2 (2019)	China	y	n, 51:140	Inpatient	Retrospective	Sz	ns	ns	341, ns (m), 313, ns (f)	262, ns (m), 297, ns (f)	ns	ns	41, ns (m), 39, ns (f)	43, ns (m), 47, ns (f)	49:2	65:75
Ruan Taipei (2019)	China	y	n, 25:60	Outpatient	Retrospective	Sz	ns	ns	286, ns (m), 325, ns (f)	300, ns (m), 254, ns (f)	ns	ns	36, ns (m), 36, ns (f)	36, ns (m), 39, ns (f)	22:3	29:31
Ruan Seoul (2019)	China	y	n, 16:51	Outpatient	Retrospective	Sz	ns	ns	378, ns (m), 450, ns (f)	347, ns (m), 282, ns (f)	ns	ns	37, ns (m), 38, ns (f)	31, ns (m), 32, ns (f)	15:1	26:25
Ruan Vellore (2019)	China	y	n, 19:82	Inpatient + outpatient	Retrospective	Sz	ns	ns	401, ns (m), no f	329, ns (m), 323, ns (f)	ns	ns	39, ns (m), no f	34, ns (m), 36, ns (f)	19:0	54:28
Salazar-Pereyra (2011)	Mexico	y	n, 7:18	ns	Prospective	Sz	DSM-IV	>5 cigs/d	314, 175	226, 123	268, 188	384, 261	ns	ns	ns	ns

Table 1. (Continued)

Author (year)	Country	CYP-450 comedication excluded in the analysed cohort (y/n)	Proportions smoker vs. non-smoker balanced (y/n), ratio	Setting	Type of study	Diagnosis	Diagnostic tool	Smoking quantity (mean, SD) in smoking group†	Clozapine dose (mean, SD) in smoking group (mg/d)	Clozapine dose (mean, SD) in non-smoking group (mg/d)	Clozapine level (mean, SD) in smoking group (ng/ml)	Clozapine level (mean, SD) in non-smoking group (ng/ml)	Age (mean, SD) in smoking group (yrs)	Age (mean, SD) in non-smoking group (yrs)	M:f ratio in smoking group	M:f ratio in non-smoking group
Scherf-Clavel (2018)	Germany	Probably not	n, 34:72	Inpatient + outpatient	Prospective	any psychiatric disorder	ns	ns	319, 187	252, 117	296, 171	397, 214	39, 11	45, 14	34:11	32:29
Seppala (1999)	Finland	y	n, 34:10	Inpatient	Prospective	Sz	clinical diagnosis	18 cigs/d, ns	184, 97	298, 127	184, 97	298, 127	39, 12	37, 7	26:8	5:5
Spina (2000a)	Italy	y	y, 18:27	Hospital + community	Prospective	TR-Sz	DSM-IV	>10 cigs/d	ns	ns	ns	ns	ns	ns	ns	ns
Tang (2006)	China	y	y, 50:66	Inpatient	Retrospective TDM analysis	Sz	DSM-IV	ns	339, 135	264, 113	432, 355	351, 206	41, 9	43, 13	55:0	66:0
Van der Weide (2003)	Netherlands	n	y, 45:35	ns	Prospective	Sz	ns	≥15 cigs/d	382, 147	197, 138	ns	ns	ns	ns	ns	ns
Yue (2005)[§§]	China	n	y, 16:21	Inpatient	Prospective	Sz	ICD-10	ns	239, 88	250, 84	273, 121	501, 198	ns	ns	ns	ns

Values of age, clozapine dose, and clozapine blood levels were rounded to whole numbers.

In the publication from Rostami et al., TDM sample cases were reported instead of number of patients.

BD, bipolar disorder; cigs, cigarettes; d, day, DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, 4th Edition; DSM-III, Diagnostic and Statistical Manual of Mental Disorders, 3rd Edition; DSM-III-R, Diagnostic and Statistical Manual of Mental Disorders, 3rd Edition, Text Revision; f, female; ICD-10, International Classification of Diseases, 10th Revision; m, male; m:f, male to female ratio; mg/d, milligram per day; n, no; ns, not specified; SD, standard deviation; Sz, schizophrenia; TDM, therapeutic drug monitoring; TR-Sz, treatment-resistant schizophrenia; y, yes; yrs, years.

[†]Mean cigarettes per day (and SD) in smoking group.

[‡]Except organic mental disorders.

[§]During the treatment period (46.2 ± 25.4 months), the medication dose was adjusted by physicians based on therapeutic response and adverse effects (. . .) When the clozapine dose was changed, the steady-state serum concentration was measured after at least 7 days of constant dosing"(28).

[¶]From $n = 14$, those excluded where dose pre–post not stable or who were caught smoking after the ban ($n = 10$), age mea $n = 39.75$ yrs, SD = 9.11, 3 men, 1 woman.

[††]Multiple samples/patient.

[‡‡]SD calculated from 95%CIs: smokers 38.8 years 95%CI (19.0–72.0), non-smokers 44.32 years 95%CI (19–88).

[§§]Levels in week 8 were taken for analyses.

with 6/16 rated as high-quality (23,26,31,35,39,41) and 10 as low/moderate-quality according to modified Newcastle-Ottawa Rating Scale (see Appendix S1). Four studies were retrospective (23,26,27,41) and 12 prospective (8,25,28-31,34,37-39,42). All except three studies (26,27,38) were exclusively covering people with schizophrenia-spectrum disorders. From these 16 studies, four (28-30,41) were restricted to people of Asian origin.

A meta-analysis of all between-subject studies ($N = 16$) found that clozapine blood levels were statistically significantly lower by more than a third in smokers compared with non-smokers (Standard Mean Difference (SMD) −0.39, 95% confidence interval (CI) −0.55 to −0.22, $P < 0.00001$, $I^2 = 80\%$; see Figure 2). On sensitivity analyses, when restricted to the six high-quality studies ($n = 4393$ samples in the smoker group and $n = 1583$ samples in the non-smoker group), results remained significant (SMD −0.29, 95%CI −0.51 to −0.07, $P < 0.009$; see Figure S1). Neither the difference between clozapine dose for smokers or non-smokers ($Q = 0.04$, $df = 1$, $P = 0.848$) nor age of smokers or non-smokers significantly impacted the effect size in a meta-regression ($Q = 0.36$, $df = 2$, $P = 0.834$).

Nevertheless, a higher proportion of male participants among smokers and non-smokers had increased the effect size ($Q = 18$, $df = 2$, $P = 0.0001$). Scatterplots for moderator variables are displayed in the Figures S19-S25. There was no evidence of publication bias ($\tau = -0.05$, $P = 0.77$, see Table S3).

When restricted to the five studies conducted among people with Asian origin, results were not significant (SMD −0.43, 95% CI −0.97 to 0.11, $P = 0.12$). However, there was one outlier study (41) from Asia where levels in the smoker group were reported to be higher than in the non-smoker group (see Figure S2). When this study was removed ($N = 4$ studies, 75 smokers vs. 127 non-smokers), results were significant (SMD −0.63, 95%CI −1.05 to −0.21, $P = 0.003$). When the analysis was restricted to non-Asian studies, results were also significant (SMD −0.39, 95%CI −0.58 to −0.21, $P < 0.0001$; see Figure S3).

There was insufficient relevant data to conduct sensitivity analysis or meta-regression for gender.

Clozapine Dose. Sixteen studies reported on associated clozapine doses (in mg per day) for samples of smokers ($n = 4925$) and non-smokers ($n = 2185$). Doses were significantly higher in the smoker group compared to the non-smoker group (SMD 0.22, 95%CI 0.07 to 0.36, $P < 0.003$) with high between-sample heterogeneity ($P < 0.00001$, $I^2 = 71\%$; see Figure S4). When analyses were restricted to the six high-quality studies, results were not significant (SMD 0.14, 95%CI −0.03 to 0.31, $P = 0.11$) between samples of smokers ($n = 4393$) and non-smokers ($n = 1583$; see Figure S5). When restricted to studies among people with Asian origin ($N = 4$), doses were significantly higher in smokers ($n = 125$) compared to non-smokers ($n = 218$; SMD 0.33, 95%CI 0.01 to 0.65, $P = 0.04$; see Figure S6). When restricted to non-Asian studies, results were similar for associated doses between samples of smokers ($n = 4800$) and non-smokers ($n = 1967$; SMD 0.18, 95%CI 0.03 to 0.33, $P = 0.02$; see Figure S7). There were not enough data for additional analyses (e.g., male vs. female comparisons).

Norclozapine/Clozapine Ratio. Five studies (23,24,28,30,35) reported on norclozapine/clozapine ratios for samples of smokers ($n = 4232$) and non-smokers ($n = 1460$), with no significant difference in norclozapine/clozapine ratios between the two groups (SMD −0.00, 95%CI −2.04 to 2.03, $P = 1.00$; see Figure S8). There were not enough data for additional analyses.

Norclozapine blood levels. Seven studies (23,28-30,34,35,38) reported on norclozapine blood levels for samples of smokers ($n = 4321$) and non-smokers ($n = 1643$). There was no significant difference between the two groups (SMD −0.08, 95%CI −0.19 to 0.04, $P = 0.18$) with low/moderate heterogeneity ($P = 0.12$, $I^2 = 39\%$; see Figure S9). When restricted to five non-Asian studies, results remained non-significant between samples of smokers ($n = 4263$) and non-smokers ($n = 1512$; SMD −0.05, 95%CI −0.16 to 0.07, $P = 0.44$; see Figure S10). There were not enough data for additional analyses.

C/D ratio. Eight studies (8,16,23,24,27,36,40,43) reported on C/D ratios for smokers ($n = 645$) and non-smokers ($n = 813$). C/D ratios were statistically significantly lower in the smoker group (SMD −0.70, 95%CI −0.84 to −0.56, $P < 0.00001$) with low between-sample heterogeneity ($P = 0.28$, $I^2 = 17\%$; see Figure S11). In a sensitivity analysis restricted to four high-quality samples, results remained significant between smokers ($n = 140$) and non-smokers ($n = 349$; SMD −0.58, 95%CI −0.83 to −0.34, $P < 0.00001$; see Figure S12). In a sensitivity, analysis restricted to five samples of people from Asian origin from one study (36) with $n = 138$ smokers and $n = 432$ non-smokers, results remained significant (SMD

−0.59, 95%CI −0.79 to −0.39, $P < 0.00001$) with low between-sample heterogeneity ($P = 0.39$, $I^2 = 2\%$; see Figure S13). When restricted to seven non-Asian studies, results remained significant between smokers ($n = 507$) and non-smokers ($n = 381$; SMD −0.78, 95%CI −0.97 to −0.59, $P < 0.00001$; see Figure S14). There were not enough data for additional analyses (e.g., male vs. female comparisons).

Within-subject analyses

Clozapine blood levels. A meta-analysis of two within-subject studies (32,33) found significantly increased levels after transition from smoking status ($n = 15$) to non-smoking status ($n = 15$; SMD −0.84, 95%CI −1.60 to −0.08, $P = 0.03$; see Figure S15). There were insufficient data for further analyses.

Discussion

This meta-analysis from a total of $n = 23$ studies comprising more than 7000 subjects with psychiatric disorders represents the most comprehensive analysis on the relationship of clozapine levels/ratios and smoking to date. We found that clozapine blood levels are reduced by around a third in smokers compared with non-smokers. Our analysis is the first to comprehensively combine and quantify published data on the impact of smoking on clozapine levels. For patients on clozapine who smoke and subsequently quit smoking, dosages should be decreased by 30% and clozapine blood level analyses should be performed. It is important to note that the CYP1A2 activity decrease may be a gradual process over the first three to four days after smoking cessation (44). Conversely, if patients start to smoke clozapine blood levels may fall by 30% resulting in the need to increase the dose and to monitor blood levels. In this regard, clinical signs of clozapine underdosing, such as anxiety, restlessness, and sleep disturbances must be monitored in patients who commence smoking.

In our analyses, clozapine blood levels were significantly lower in smokers. However, there may be unaccounted for confounding factors. Co-occurring caffeine intake might have increased clozapine blood levels due to CYP1A2 inhibition as previously observed in the literature (17). Smoking and caffeine use may co-occur among people with schizophrenia (45). Thus, differences in blood levels between smokers and non-smokers might have been underestimated since none of the included studies controlled for caffeine consumption. We were not able to conduct sensitivity analyses for caffeine as these data were not reported. We were only able to include information on other reported relevant CYP-450 interacting comedication.

C/D ratios were significantly lower in smokers in our analyses and our results remained significant when analyses were restricted to high-quality studies or studies from Asian origin. This allows for adjustment for certain factors associated with CYP activity such as Asian genetic heritage. However, impact of other factors associated with influence on C/D ratios (e.g., gender, poor metabolizer, obesity, and inflammation) was not able to be controlled for in our analyses. Furthermore, we were able to undertake meta-regressions examining the impact of dose, age, and gender on clozapine blood levels between smokers and non-smokers. Our findings regarding the influence of gender on clozapine blood levels with smoking should be treated with caution, since only three studies reported blood levels (33,35,39), one reported C/D ratios (36) between smokers and non-smokers for male and female populations separately and one study only included only one gender (41). In one of the studies which disaggregated data by gender and smoking status, only 14% of men were non-smokers (35), which may have skewed the results. Between-subject analyses may be biased since the included studies, with the exception of Lu et al. (30), were not fixed-dose studies and doses in smokers might have been increased by the treating clinicians. Thus, the true difference induced by smoking might be bigger than estimated, as suggested by within-subject analyses based on limited subject numbers. Furthermore, one study from Rostami et al. reported samples of smokers and non-smokers, and thus various samples might be derived from the same patients increasing the risk of bias.

Our analyses had a high degree of heterogeneity, and as such our results should be viewed with caution. We were able to conduct sensitivity analyses and meta-regression on dose, gender, ethnicity, and age. There were insufficient data to permit meta-regression for comedications, smoking quantity, genetics for fast metabolizer, caffeine use or body weight, since none of the included studies reported these confounders for smokers and non-smokers homogenously allowing for meta-analyses. Nevertheless, comedication was considered as an item in our assessment of reporting strength and thus high-quality studies excluded clinically relevant CYP1A2 interacting comedication. Furthermore, seven out of our included studies were retrospective analyses which may be more prone to bias than prospective approaches, especially since data may not be available on medication

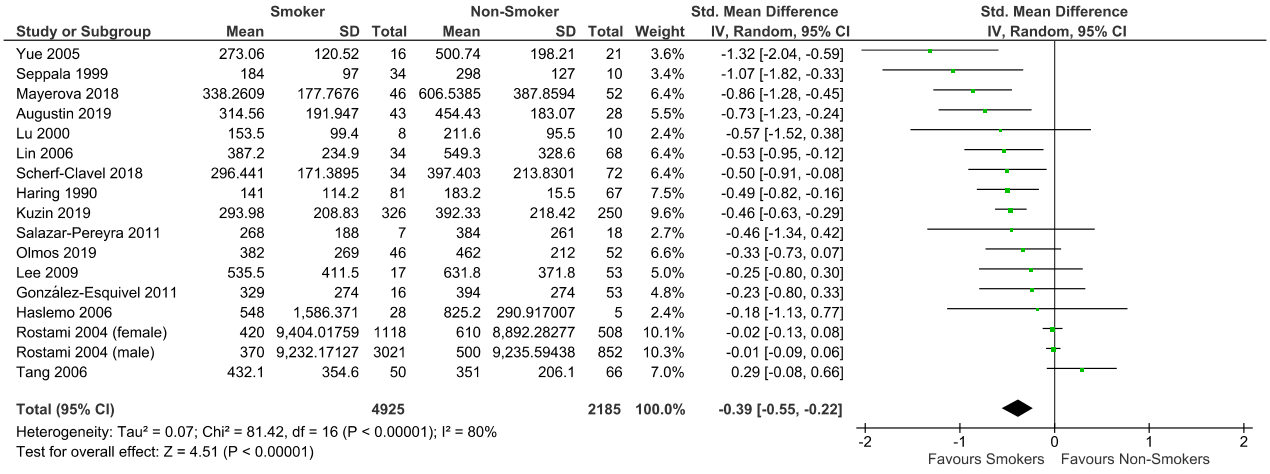

Fig. 2. Clozapine blood levels (ng/ml) in between-subject comparisons of smokers vs. non-smokers. [Colour figure can be viewed at wileyonlinelibrary.com]

adherence and ascertainment of smoking behavior is less certain. We attempted to address this through our sensitivity analysis of study quality.

Ours is the largest meta-analysis on clozapine blood levels and C/D ratios from a total of four studies (46). In contrast to the work from Tsuda et al., we included studies of patients of Asian heritage, assessed risk of bias and conducted sensitivity analyses and meta-regression analyses, if possible. Based on their meta-analysis on C/D ratios, Tsuda et al. estimated that if 200 and 400 mg per day of clozapine would be administered to smokers, about 100 and 200 mg per day, respectively, should be administered to non-smokers, based on a SMD C/D ratio of 1.1 (46). In our analyses, SMD of C/D ratio between smokers and non-smokers (0.7 ng/ml per mg/day) was lower than in the one from Tsuda et al. suggesting an estimated 30% reduction of dose after a patient stops smoking.

Conclusion

Our meta-analysis confirms that smoking behavior and any change in smoking behavior is associated with substantial clinical implications for patients on clozapine and extends the current knowledge by providing an evidence-based quantification of these effects. According to our analyses, reductions of clozapine dose by 30% are recommended when a patient on clozapine stops smoking. Nevertheless, reductions have to be performed with TDM of clozapine steady-state trough levels and a clinical risk-benefit evaluation since high variability between individuals (95% CI in the range of −0.55 to −0.22 in our analyses) has to be expected. Dose reductions should be combined with instruction of patient and nurses (for signs of intoxication and relapse) and a close monitoring of clozapine blood levels.

Acknowledgements

Open access funding enabled and organized by Projekt DEAL.

Contributors

EW, DS, AH, and PF conceptualized the present analysis. EW and LM conducted the literature search with validation by DS and AH. The analyses were conducted by AH and DS. EW and DS wrote the first draft of the manuscript. All authors have contributed to editing subsequent drafts and have approved the final manuscript.

Funding

None.

Declaration of interest

E. Wagner reports no conflicts of interest. L. McMahon 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. 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 member of Roche, Otsuka, Lundbeck, and Janssen-Cilag advisory boards. D. Siskind reports no conflict of interest.

Peer Review

The peer review history for this article is available at https://publons.com/publon/10.1111/acps.13228.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

References

1. Siskind D, McCartney L, Goldschlager R, Kisely S. Clozapine v. first-and second-generation antipsychotics in treatment-refractory schizophrenia: systematic review and meta-analysis. Br J Psychiat 2016;**209**:385–392.
2. Land R, Siskind D, McArdle P, Kisely S, Winckel K, Hollingworth SA. The impact of clozapine on hospital use: a systematic review and meta-analysis. Acta Psychiatr Scand 2017;**135**:296–309.
3. Varma S, Bishara D, Besag FMC, Taylor D. Clozapine-related EEG changes and seizures: dose and plasma-level relationships. Therapeutic Adv Psychopharmacol 2011;**1**:47–66.
4. Howes OD, McCutcheon R, Agid O et al. Treatment-resistant schizophrenia: treatment response and resistance in psychosis (TRRIP) Working Group Consensus Guidelines on Diagnosis and Terminology. Am J Psychiat 2017;**1**: 216–229.
5. Bertilsson L, Carrillo JA, Dahl Ml et al. Clozapine disposition covaries with CYP1A2 activity determined by a caffeine test. Br J Clin Pharmacol 1994;**38**:471–473.
6. Hukkanen J, Jacob P 3rd, Peng M, Dempsey D, Benowitz NL. Effect of nicotine on cytochrome P450 1A2 activity. Br J Clin Pharmacol 2011;**72**:836–838.
7. de Leon J, Diaz FJ. A meta-analysis of worldwide studies demonstrates an association between schizophrenia and tobacco smoking behaviors. Schizophrenia Res 2005;**15**:135–157.
8. Haslemo T, Eikeseth PH, Tanum L, Molden E, Refsum H. The effect of variable cigarette consumption on the interaction with clozapine and olanzapine. Eur J Clin Pharmacol 2006;**62**:1049–1053.
9. Rajkumar AP, Poonkuzhali B, Kuruvilla A, Jacob M, Jacob KS. Clinical predictors of serum clozapine levels in patients with treatment-resistant schizophrenia. Int Clin Psychopharmacol 2013;**28**:50–56.
10. Cormac I, Brown A, Creasey S, Ferriter M, Huckstep B. A retrospective evaluation of the impact of total smoking cessation on psychiatric inpatients taking clozapine. Acta Psychiatr Scand 2010;**121**:393–397.
11. Ghotbi R, Christensen M, Roh H-K, Ingelman-Sundberg M, Aklillu E, Bertilsson L. Comparisons of CYP1A2 genetic polymorphisms, enzyme activity and the genotype-phenotype relationship in Swedes and Koreans. Eur J Clin Pharmacol 2007;**63**:537–546.
12. Suhas S, Kumar V, Damodharan D et al. Do Indian patients with schizophrenia need half the recommended clozapine dose to achieve therapeutic serum level? An exploratory study. Schizophrenia Res 2020:S0920-9964 (20) 30337-6.
13. Lane HY, Chang YC, Chang WH, Lin SK, Tseng YT, Jann MW. Effects of gender and age on plasma levels of clozapine and its metabolites: analyzed by critical statistics. J Clin Psychiat 1999;**60**:36–40.
14. Ulrich S, Baumann B, Wolf R et al. Therapeutic drug monitoring of clozapine and relapse–a retrospective study of routine clinical data. Int J Clin Pharmacol Therapeut 2003;**41**:3–13.
15. Bowskill S, Couchman L, Maccabe JH, Flanagan RJ. Plasma clozapine and norclozapine in relation to prescribed dose and other factors in patients aged 65 years and over: data from a therapeutic drug monitoring service, 1996–2010. Human Psychopharmacol 2012;**27**:277–283.
16. van der Weide J, Steijns LSW, van Weelden MJM. The effect of smoking and cytochrome P450 CYP1A2 genetic polymorphism on clozapine clearance and dose requirement. Pharmacogenetics 2003;**13**:169–172.
17. Raaska K, Raitasuo V, Laitila J, Neuvonen PJ. Effect of caffeine-containing versus decaffeinated coffee on serum clozapine concentrations in hospitalised patients. Basic Clin Pharmacol Toxicol 2004;**94**:13–18.
18. de Leon J, Ruan CJ, Schoretsanitis G, De Las Cuevas C. A Rational use of clozapine based on adverse drug reactions. Pharmacokinetics, and Clinical Pharmacopsychology. Psychother Psychosomat 2020;**14**:1–15.
19. Khorassani F, Kaufman M, Lopez LV. Supatherapeutic serum clozapine concentration after transition from traditional to electronic cigarettes. J Clin Psychopharmacol 2018;**38**:391–392.
20. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. J Clin Epidemiol 2009;**62**:1006–1012.
21. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol 2010;**25**:603–605.
22. Higgins JPTTJ, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (Editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.0 (updated July 2019). Cochrane; 2011.
23. Augustin M, Schoretsanitis G, Pfeifer P, Grunder G, Liebe C, Paulzen M. Effect of fluvoxamine augmentation and smoking on clozapine serum concentrations. Schizophrenia Res 2019;**210**:143–148.
24. Dettling M, Sachse C, Brockmoller J et al. Long-term therapeutic drug monitoring of clozapine and metabolites in psychiatric in- and outpatients. Psychopharmacology 2000;**152**:80–86.
25. Gonzalez-Esquivel DF, Castro N, Ramirez-Bermudez J et al. Plasma levels of clozapine and norclozapine in Mexican schizophrenia patients. Arzneimittelforschung 2011;**61**:335–339.
26. Haring C, Fleischhacker W, Schett P, Humpel C, Barnas C, Saria A. Influence of patient-related variables on clozapine plasma levels. Am J Psychiat 1990;**147**:1471–1475.
27. Kuzin M, Schoretsanitis G, Haen E et al. The effects of coprescription of pantoprazole on the clozapine metabolism. Pharmacopsychiatry 2020;**53**:65–70.
28. Lee S-T, Ryu S, Nam HJ, Lee S-Y, Hong KS. Determination of pharmacokinetic properties of clozapine and norclozapine in Korean schizophrenia patients. Int Clin Psychopharmacol 2009;**24**:139–144.
29. Lin SK, Su SF, Pan CH. Higher plasma drug concentration in clozapine-treated schizophrenic patients with side effects of obsessive/compulsive symptoms. Ther Drug Monit 2006;**28**:303–307.
30. Lu ML, Lane HY, Chen KP, Jann MW, Su MH, Chang WH. Fluvoxamine reduces the clozapine dosage needed in refractory schizophrenic patients. J Clin Psychiat 2000;**61**: 594–599.
31. Mayerova M, Ustohal L, Jarkovsky J, Pivnicka J, Kasparek T, Ceskova E. Influence of dose, gender, and cigarette smoking on clozapine plasma concentrations. Neuropsychiatr Dis Treat 2018;**14**:1535–1543.
32. Meyer JM. Individual changes in clozapine levels after smoking cessation: results and a predictive model. J Clin Psychopharmacol 2002;**21**:569–574.
33. Murayama-Sung L, Ahmed I, Goebert D, Alaimalo E, Sung H. The impact of hospital smoking ban on clozapine and norclozapine levels. J Clin Psychopharmacol 2011;**31**: 124–126.

34. Olmos I, Ibarra M, Vazquez M, Maldonado C, Fagiolino P, Giachetto G. Population pharmacokinetics of clozapine and norclozapine and switchability assessment between brands in uruguayan patients with schizophrenia. Biomed Res Int 2019;**2019**:3163502.
35. Rostami-Hodjegan A, Amin AM, Spencer EP, Lennard MS, Tucker GT, Flanagan RJ. Influence of dose, cigarette smoking, age, sex, and metabolic activity on plasma clozapine concentrations: a predictive model and nomograms to aid clozapine dose adjustment and to assess compliance in individual patients. J Clin Psychopharmacol 2004;**24**:70–78.
36. Ruan C-J, Wang C-Y, Tang Y-L et al. Exploring the prevalence of clozapine phenotypic poor metabolizers in 4 Asian samples: They ranged between 2% and 13%. J Clin Psychopharmacol 2019;**2019**:644–648.
37. Salazar-Pereyra A, Tome ISR, Ramirez-Bermudez J, Castro-Roman R, Castro-Torres NN, Jung-Cook H. Monitoring of plasma clozapine concentrations in patients with schizophrenia. [Spanish]. Archivos de Neurociencias 2011;**16**:4–7.
38. Scherf-Clavel M, Samanski L, Hommers LG, Deckert J, Menke A, Unterecker S. Analysis of smoking behavior on the pharmacokinetics of antidepressants and antipsychotics: evidence for the role of alternative pathways apart from CYP1A2. Int Clin Psychopharmacol 2019; **34**:93–100.
39. Seppala NH, Leinonen EV, Lehtonen ML, Kivisto KT. Clozapine serum concentrations are lower in smoking than in non-smoking schizophrenic patients. Pharmacol Toxicol 1999;**85**:244–246.
40. Spina E, Avenoso A, Facciola G et al. Relationship between plasma concentrations of clozapine and norclozapine and therapeutic response in patients with schizophrenia resistant to conventional neuroleptics. Psychopharmacology 2000;**148**:83–89.
41. Tang YL, Mao P, Li FM et al. Gender, age, smoking behaviour and plasma clozapine concentrations in 193 Chinese inpatients with schizophrenia. Br J Clin Pharmacol 2007;**64**:49–56.
42. Yue Y, Xu YF, Song LS, Yi ZH, Lu WH. Association of smoking with the therapeutic effects of the drug, side effects and plasma level of drug in patients with schizophrenia. [Chinese]. Chinese J Clin Rehabilit 2005;**9**:44–45.
43. Palego L, Biondi L, Giannaccini G et al. Clozapine, norclozapine plasma levels, their sum and ratio in 50 psychotic patients: influence of patient-related variables. Progress Neuro-psychopharmacol Biol Psychiat 2002;**26**:473–480.
44. Faber MS, Fuhr U. Time response of cytochrome P450 1A2 activity on cessation of heavy smoking. Clin Pharmacol Therapeut 2004;**76**:178–184.
45. Williams JM, Gandhi KK. Use of caffeine and nicotine in people with schizophrenia. Curr Drug Abuse Rev 2008;**1**: 155–161.
46. Tsuda Y, Saruwatari J, Yasui-Furukori N. Meta-analysis: the effects of smoking on the disposition of two commonly used antipsychotic agents, olanzapine and clozapine. BMJ Open 2014;**4**:e004216.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. List of excluded studies (with reason for exclusion).
Table S2. Rating of included studies according to modified Newcastle-Ottawa Scale.
Table S3. Kendall's tau with continuity correction for outcome clozapine blood levels smoker vs. non-smoker.
Figure S1. Clozapine blood levels (ng/ml), between-subject analyses, only high-quality studies.
Figure S2. Clozapine blood levels (ng/ml), between-subject analyses, Asian studies.
Figure S3. Clozapine blood levels (ng/ml), between-subject analyses, only non-Asian studies.
Figure S4. Clozapine dose (mg/day), between-subject analyses, all studies.
Figure S5. Clozapine dose (mg/day), between-subject analyses, only high-quality studies.
Figure S6. Clozapine dose (mg/day), between-subject analyses, only Asian studies.
Figure S7. Clozapine dose (mg/day), between-subject analyses, only non-Asian studies.
Figure S8. Norclozapine/clozapine ratio, between-subject analyses, all studies.
Figure S9. Norclozapine levels, between-subject analyses, all studies.
Figure S10. Norclozapine levels, between-subject analyses, non-Asian studies.
Figure S11. C/D ratio, between-subject analyses, all studies.
Figure S12. C/D ratio, between-subject analyses, only high-quality studies.
Figure S13. C/D ratio, between-subject analyses, only Asian studies.
Figure S14. C/D ratio, between-subject analyses, only non-Asian studies.
Figure S15. clozapine blood levels, within-subject analyses, all studies.
Figure S16. clozapine blood levels, between-subject analyses, only male populations.
Figure S17. clozapine blood levels, between-subject analyses, only female populations.
Figure S18. Age (years), between-subject analyses, all studies.
Figure S19. Scatterplot meta-regression (mean clozapine dose non-smoker on clozapine levels).
Figure S20. Scatterplot meta-regression (proportion male smokers X clozapine levels).
Figure S22. Scatterplot meta-regression (proportion male non-smokers X clozapine levels).
Figure S23. Scatterplot meta-regression (mean age smokers X clozapine levels).
Figure S24. Scatterplot meta-regression (mean age non-smokers X clozapine levels).
Figure S25. Scatterplot meta-regression (difference in clozapine dose smokers minus non-smokers X clozapine levels).
Appendix S1. Modified Newcastle-Ottawa scoring guide.
Appendix S2. PRISMA 2009 checklist.