Therapeutic Reference Range for Olanzapine in Schizophrenia:

Systematic Review on Blood Concentrations, Clinical Effects, and Dopamine Receptor Occupancy

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Abstract

Objective: Aiming at revising the therapeutic reference range for olanzapine, the present study highlights the association between blood olanzapine levels, clinical effects, and dopamine D_2–receptor occupancy for oral and long-acting injectable (LAI) formulations.

Data Sources: Databases were systematically searched for randomized controlled trials (RCTs) and uncontrolled trials concerning blood olanzapine levels in relation to clinical outcomes or D_2-receptor occupancy using MEDLINE (PubMed), Web of Science, PsycINFO, and Cochrane Library (March 2021, updated in December 2021). We excluded articles not written in English or German and non-human data. Search terms included *olanzapine*, *blood level*, *drug monitoring*, *PET*, and *SPECT*.

Study Selection: The process of study selection followed a previously published protocol and PRISMA guidelines. A total of 2,824 articles were identified through database search and 1 article via reference list check. Thirty-four studies were suitable for qualitative synthesis, and 13 studies were included in the quantitative analysis.

Data Extraction: Reviewers performed data extraction and quality assessment of the included studies independently following the review protocol.

Results: Evidence for a relationship between blood olanzapine level and efficacy/side effects (constipation) is considered low (Level C). In total, 3 studies of moderate quality consistently showed therapeutic thresholds of around 20 ng/mL for olanzapine 12 hours post-dose. This threshold is in line with findings from positron emission tomography (PET) studies that suggest optimal drug efficacy (65%–80% D_2-receptor occupancy) between 17 and 44 ng/mL.

Conclusions: We suggest a therapeutic reference range of 20–40 ng/mL for olanzapine oral and LAI formulations. In this range, optimal treatment response is expected in patients with schizophrenia and schizophrenia spectrum disorders. Side effects, especially weight gain, may already occur at therapeutic levels. However, higher plasma concentrations are in general well tolerated and should not necessarily require a dose reduction in case of good response and tolerance.

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Following a previously introduced systematic methodology,[1] the current study systematically investigates the relationship between blood levels, clinical effects, and dopamine D_2–receptor occupancy to discuss a therapeutic reference range for olanzapine. The antipsychotic drug olanzapine has been proven effective for the treatment of schizophrenia and bipolar I disorder.[2,3] In clinical practice, olanzapine is furthermore used for the treatment of other psychiatric disorders and symptoms such as delusional, schizophreniform, schizoaffective, and substance-induced psychotic disorders and obsessional thinking in patients with eating disorders.[4,5] While extrapyramidal side effects (EPS) seem to quite rarely occur under olanzapine treatment,[6] patients treated with olanzapine are at higher risk for metabolic side effects compared to those treated with other antipsychotic drugs, most frequently weight gain, but also hyperglycemia, dyslipidemia, and hyperprolactinemia.[6–10] Of note, doses that usually result in mean blood levels around the upper range (beyond the approved dose of 20 mg/d, up to 40 mg/d) have been frequently associated with greater weight gain compared to lower doses.[11] Data from neuroimaging studies reveal that, for most dopamine D_2-antagonists like olanzapine,

Clinical Points

- Optimal treatment effects in schizophrenia/schizophrenia spectrum disorders are reached within a therapeutic reference range of 20–40 ng/mL for oral (12–15 h after intake, 1/d) and long-acting injectable (LAI) olanzapine.
- Dose increase is indicated with blood drug levels below 20 ng/mL in case of insufficient efficacy.
- Dose reduction is not required above 40 ng/mL in case of good clinical efficacy and tolerance.

an optimal treatment response has been associated with a dopamine D_2–receptor occupancy of 65%–80%. Above 80% occupancy, the risk for EPS increases notably.[12–14]

The safety profile of olanzapine pamoate has been shown to be comparable to that of the oral formulation except for a rare and serious adverse drug reaction called post-injection delirium/sedation syndrome (PDSS). The risk for PDSS clinically requires an observation period of 3 hours after each injection.[15–17]

Current recommendations for therapeutic drug monitoring (TDM) of olanzapine oral and long-acting injectable (LAI) predominantly follow findings from studies in patients with schizophrenia[9,18,19] and emphasize the use of TDM for olanzapine dose titration into a range of 20–80 ng/mL (laboratory alert level: 100 ng/mL).[9,20] However, evidence emerged that discusses an adjustment of olanzapine's reference range toward lower values after oral administration (20–40 ng/mL)[11,21] as well as after the injection of the LAI depot formulation olanzapine pamoate (10–40 ng/mL).[22,23] Establishing a clear concentration-effect relationship is a prerequisite to confirm 1 of the 2 diverging ranges that have recently been discussed in the literature.

METHODS

Inclusion Criteria

Randomized controlled trials (RCTs) and uncontrolled trials concerning blood olanzapine levels in relation to clinical outcomes or D_2-receptor occupancy were included. There was no restriction to dose, application form, or diagnoses. The eligibility criteria are presented in the Supplementary Table 1. This systematic review is registered under PROSPERO number CRD42021216182.

Study Selection and Quality Assessment (Study Scores)

The process of study selection and quality assessment followed a previously published review protocol and PRISMA guidelines.[1,24,25] Four electronic databases were systematically searched (last updated December 2021; see Supplementary Table 2 for search strategy). Two reviewers (K.W./X.M.H., K.W./X.M.L.) performed data extraction and quality assessment of the included studies independently. In case of insufficient data, authors of eligible articles were contacted for additional data. Risk of bias (RoB) for RCTs were rated using the Cochrane risk-of-bias tool, and results were visualized using robvis (X.M.H./T.G.R.).[1,26,27]

Qualitative and Quantitative Data Synthesis

Clinical efficacy and side effects should have been reported in a quantitative way using established rating scales. For the inclusion of neuroimaging studies, (mean) D_2-receptor occupancy and blood olanzapine levels have to be accessible. The effective concentration for 50% of maximum receptor occupancy (EC_{50}) value of each study was retrieved to compute effective concentration for 65% (EC_{65}) and 80% (EC_{80}) values. For quantitative synthesis, mean blood olanzapine levels, standard deviations, median concentrations, interquartile ranges (IQRs), and concentration-to-dose (C/D) ratios were calculated. Whenever available, concentration data from patients responding and not responding to olanzapine drug treatment were collected. Data were either extracted from the articles or calculated manually. If more than one concentration measurement was conducted, the latest measurement was included. Additional factors that could possibly influence blood olanzapine levels were considered.

Statistical Analysis

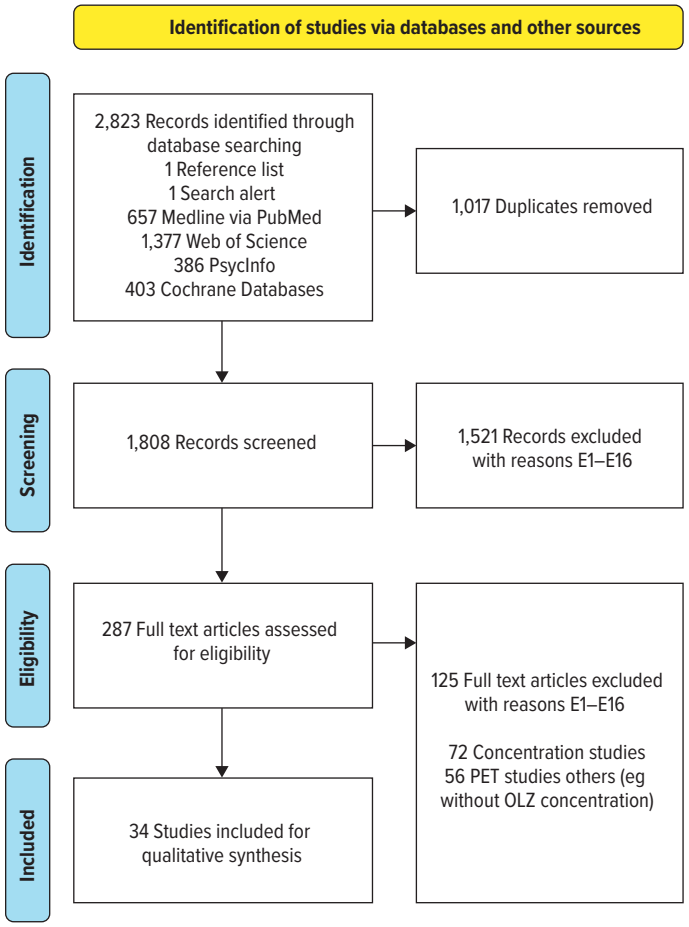
A meta-analysis using random-effect models with mean concentrations and standard deviations was performed with R (version 4.0.3) "metafor" and "meta" packages; for subgroup analysis of nonresponders, Review Manager (RevMan, version 5.4.1) was used. I^2 statistics was performed to evaluate heterogeneity of the included studies, and 95% confidence intervals (CIs) were calculated from mean concentrations. In all tests, $P < .05$ was considered as statistically significant. Linear regression analysis was conducted to test the relationship between olanzapine dose and blood level.

RESULTS

Study Selection

A total of 2,824 articles were identified through database search, and 1 study was manually selected from a reference list. A total of 1,521 records were excluded after the title/abstract screening. Another 125 articles were removed after full text examination. Thirty-four studies met the inclusion criteria and were suitable for a qualitative synthesis. Of these studies, 23 studies reported efficacy measures and blood olanzapine levels for oral olanzapine and 4 for olanzapine LAI (Supplementary Tables 3–5). Seven neuroimaging studies were identified. The PRISMA flow diagram is

Figure 1.
Flow Diagram According to PRISMA[a]



[a]Flow diagram created following the PRISMA 202 statement.[24] See Supplementary Table 1 for more information.
Abbreviations: OLZ = olanzapine, PET = positron emission tomography.

presented in Figure 1. (A list of abbreviations included in this article can be found in Supplementary Appendix 1.)

Quality Assessment of TDM Components (TDM Score)

According to our previously published protocol, general quality criteria for the TDM component were assessed for all studies (Supplementary Table 6 and Supplementary Figure 1).[1] Study type–specific quality assessment for cohort studies, cross-sectional studies, and randomized controlled studies is also presented in detail in Supplementary Tables 7 and 8 and Supplementary Figures 2 and 3. Six studies (18%) did not investigate a representative patient sample in terms of our review outcomes (Q1), eg, comprising (i) emergency cases, (ii) patients who were treatment-resistant, (iii) patients with late-life schizophrenia, (iv) only men, or (v) only children and adolescents. Nearly half of the studies (47%) did not provide a (sub)analysis in case of a heterogeneous sample in terms of diagnoses (16 studies; Q2) or did not report a psychiatric classification system (2 studies; Q2). Twenty-one studies (62%) used pharmacologically active concomitant medication like antipsychotics, antidepressants, and mood stabilizers or did not report information about co-medication (Q3). In total, the most frequently missed criterion was appropriate dose design (Q4) in 24 studies (71%) due to the use of flexible dosing regimens. Forty-one percent of the studies (14 studies) did not provide information about the analytic method that was used for the determination of blood olanzapine levels or did not report a limit of detection (LOD; Q5). In 12 articles (35%), sampling times were not sufficiently reported (to ensure blood level determination at trough level; Q6b) and/or steady state was not reached (respectively, 7 days of constant dosing of oral olanzapine or 3 months for olanzapine LAI; Q6a). Repeated blood samples, at least 2 per patient, should have been drawn during the study period (Q7a), and a sufficiently broad range of blood olanzapine levels covering a sub- and/or supratherapeutic range should have been assessed (Q7b). Twenty studies (59%) did not fulfill Q7a and/or Q7b.

Blood Olanzapine Concentrations and Therapeutic Response (Level of Evidence)

We identified 19 studies that reported blood olanzapine levels and clinical effects (Table 1). Of those, 3 cohort studies reported a positive[19,28,29] and 1 cohort study a negative association[30] between blood olanzapine levels and antipsychotic effects. In addition, 3 studies[31–33] showed better therapeutic effects in patients with higher dose-corrected concentrations/metabolite-to-parent compound ratios.

As early as in 2005, Mauri and colleagues[19] reported a positive curvilinear relationship between blood olanzapine level and improvement in Brief Psychiatric Rating Scale (BPRS), Positive and Negative Syndrome Scale (PANSS), and Hamilton Depression Rating Scale (HDRS) scores in 54 patients with schizophrenia and a preceding exacerbation phase (TDM score: 8/10, study score: 7/10). Clinical effects were assessed at baseline and after 2 weeks of treatment. The authors suggest a range of 20–50 ng/mL for optimal treatment effects.[19] The study by Lin et al[28] is a re-analysis of a 2002 study by Ellingrod et al,[34] with focus on P-glycoprotein polymorphisms and reported a positive correlation between blood olanzapine level and percent change in BPRS score in a sample of 41 patients with schizophrenia (TDM score: 9/10, study score: 9/10). In a prospective cohort study, Laika and colleagues[29] also found a positive concentration-effect relationship

Table 1.

Studies Reporting a Concentration-Effect or Concentration–Side Effect Relationship

Author(s), Year	OLZ-Treated Subjects, n	Indication	Study, Dose Design	PD Comedication (Except BZ)	Clinical Effects	Side Effects	Comments (Study Design/Clinical Effect Relationship)
Mauri et al, 2005[19]	54	SCZ	CS, flexible	N	Positive	NF (HDRS, EPSE)	Positive curvilinear correlation between BL and BPRS, PANSS improvement
Lin et al, 2006[28]	41	SCZ	CS, fixed	N	Positive	NA	BL and positive symptom reduction (BPRS), SANS (NF)
Laika et al, 2010[29]	73	mDx	CS, flexible	Y	Positive	NF (DOTES)	Relationship found for SCZ patients only (PDS, CGI-S)
Zabala et al, 2017[30]	23	mDx, FEP	CS, flexible	Y	Negative	NF (UKU)	Negative curvilinear correlation between BL and PANSS improvement, MADRS (NF)
Lu et al, 2016[31]	151	SCZ	CSS, flexible	N	Partly (C/D)	NA	Positive correlation for C/D ratio and PANSS, not for subgroup of smokers
Carrillo et al, 2003[32]	17	mDx	CS, fixed	N	Partly (C/D)	NF (UKU)	Positive correlation for C/D ratio and % BPRS decrease
Arnaiz et al, 2021[33]	47	FEP	CSS, flexible	Y	Partly (C/D)	NA	Positive correlation for C/D ratio and PANSS, not for OLZ BL
Nozawa et al, 2008[39]	51	SCZ	CS, flexible	NA	Partly	NA	BL and sub scores of BPRS (suspiciousness, hallucinations, blunted affect)
Raposo et al, 2011[40]	18	SCZ	RCT, flexible	N	Partly	NA	BL and PANSS negative syndrome subscore
Bech et al, 2006[41]	20	AM	CS, flexible	Y	Partly	NA	Positive correlation for MAS in a subgroup of 8 females, YMRS (NF)
Perry et al, 2001,[42] **Perry et al, 1997**[18]	84	SCZ	RCT, flexible	N	NF (BPRS)	NF (SAS, AIMS, BARS)	No correlation between BL and BPRS score change (12 h post-dose), CGI (NA)
Kelly et al, 2006[35]	13	TR-SCZ	RCT, fixed	N	NF (BPRS, CGI)	Partly	Higher BL in patients with anticholinergic side effects (significant for constipation); no correlation of BL and weight gain. NA for SAS, BARS
Mauri et al, 2015[43]	25	Chronic SCZ, SD	CS, fixed	N	NF (BPRS, PANSS)	NA	Patients switched to OLZ LAI: less variation of BL OLZ as most predictable factor for clinical benefit
Lane et al, 2002[44]	13	SCZ	RCT, flexible	N	NF (MADRS)	NA	Focus on depressive symptoms
Fellows et al, 2003[37]	53	SCZ	CS, flexible	Y	NA (PANSS)	NF (SAS, AIMS, BARS)	ROC curve identified breakpoint, *P* values not significant
Italiano et al, 2015[45]	25	SCZ	CS, flexible	N	NF (PANSS)	NA	Focus on different formulations (branded/generic)
Veselinović et al, 2019[46]	14	SCZ	RCT, flexible	N	NA (PANSS, CGI)	NA (AIMS, BARS)	Negative correlation of estimated D_2RO and subjective well-being; no correlation between OLZ BL and subjective well-being in OLZ subgroup
Citrome et al, 2009[36]	380	SCZ, SD	RCT, fixed	Y	NF (PANSS)	NF	No correlation of BL and weight gain
Fekete et al, 2017[38]	115	mDx	CSS, flexible	Y	NF	NF	TDM study, children and adolescent, validation of therapeutic reference range, CGI, UKU

Abbreviations: AIMS = Abnormal Involuntary Movement Scale, AM = acute mania, BARS = Barnes Akathisia Rating Scale, BL = blood level, BPRS = Brief Psychiatric Rating Scale, BZ = benzodiazepine, C/D ratio = concentration-to-dose ratio, CGI = Clinical Global Impressions scale, CGI-S = CGI–Severity of Illness scale, CLO = clozapine, CS = cohort study, CSS = cross-sectional study, D_2RO=dopamine D_2 receptor occupancy, DOTES = Dosage Record and Treatment Emergent Symptoms Scale, EPSE = extrapyramidal side effects scale, FEP = first-episode psychosis, HDRS = Hamilton Depression Rating Scale, LAI = long-acting injectable, MADRS = Montgomery-Asberg Depression Rating Scale, mDx = multiple psychiatric diagnoses, N = no, NA = not available, NF = not found, OLZ = olanzapine, PANSS = Positive and Negative Syndrome Scale, PD = pharmacodynamically active, PDS = Paranoid Depression Scale, PDSS = post-injection delirium/sedation syndrome, RCT = randomized controlled trial, ROC = receiver operating characteristic, SAS = Simpson-Angus Scale, SCZ = schizophrenia, SD = schizoaffective disorder, TR-SCZ = therapy-resistant schizophrenia, UKU = Udvalg for Kliniske Undersøgelser scale, Y = yes.

for the subsample of patients with schizophrenia (n = 32, TDM score: 8/10, study score: 9/10). After 4 weeks of treatment, higher blood olanzapine levels were associated with better improvement of paranoid and depressive symptoms (improvement in Paranoid Depression Scale [PDS]) in a self-rating score and better Clinical Global Impressions–Severity of Illness scale (CGI-S) scores.

Two studies reported an association between C/D ratios and treatment effects. A positive relationship between C/D ratios and decrease in BPRS scores was reported in a small sample of 17 patients with schizophrenia spectrum disorders (TDM score: 7/10; study score: 8/10).[32] In this study, the study population was divided into smokers and nonsmokers, who received different doses (10 mg/d for smokers, 7.5 ± 2.5 mg/d for nonsmokers). Clinical assessment was performed at baseline and after 15 days of constant dosing. Another positive correlation between C/D ratios and improvement in PANSS score was shown

Table 2.
Selected Dopamine Receptor Occupancy Studies

Author(s), Year	Subjects, n	Method	Mean Dose (mg/d)	Mean BL OLZ (ng/mL)	EC_{50} (ng/mL)	EC_{65} (ng/mL)	EC_{80} (ng/mL)	Brain Region
Kapur et al, 1998[47]	12	PET	17	46	10.3	19	41	Striatal/cerebellar
Attarbaschi et al, 2007[50]	17	SPECT	15	12	7[a]	17	...	Striatal/frontal
Catafau et al, 2008[49]	12	SPECT	13	32	22.7	42	...	Striatal/occipital
Mamo et al, 2008[53]	14	PET	Oral: 15; IM: 300 mg/4 w	Oral: 37; IM: 20	11.0	20	44	Striatal/cerebellar

[a]Extracted from graphic.
Abbreviations: BL OLZ=vblood olanzapine level, EC_{50}=effective concentration for 50% of maximum receptor occupancy, EC_{65}=effective concentration for 65% of maximum receptor occupancy, EC_{80}=effective concentration for 80% of maximum receptor occupancy, IM=intramuscular, NA=not available, PET=positron emission tomography, SPECT=single-photon emission computerized tomography.

by Arnaiz et al[33] in a cohort of 47 patients with first-episode psychosis after 2 months of treatment (TDM score: 6/10, study score: 5/8). This correlation could not be confirmed for non–dose-corrected blood olanzapine levels. Conflicting results were also reported from a Taiwanese study[31] comprising a large sample of 151 patients with schizophrenia who were on a stable olanzapine dose for at least 3 months (TDM score: 7/10, study score: 4/8). Among patients with higher metabolite-to–parent compound ratios, better PANSS improvement was found. However, a marginally negative correlation was found between blood olanzapine levels and general PANSS scores.

A negative curvilinear relationship between blood olanzapine levels and improvement in PANSS scores was reported in a pilot study[30] that investigated a small sample of patients with first- episode psychosis (schizophrenia, schizophrenia Spectrum Disorders and bipolar I disorder) (TDM score: 7/10, study score: 7/10). All patients showed blood levels above the lower limit of olanzapine's reference range (20 ng/mL). To sum up, a clear relationship between blood olanzapine levels and antipsychotic effects in schizophrenia has been shown by 3 prospective cohort studies that measured blood olanzapine levels within and below the current reference range. All studies are at low to moderate risk for bias. Two studies of moderate risk for bias reported conflicting results. In conclusion, the level of evidence for a concentration effect relationship has to be considered "low" (Level C).[25]

Blood Olanzapine Concentrations and Adverse Drug Reactions (Level of Evidence)

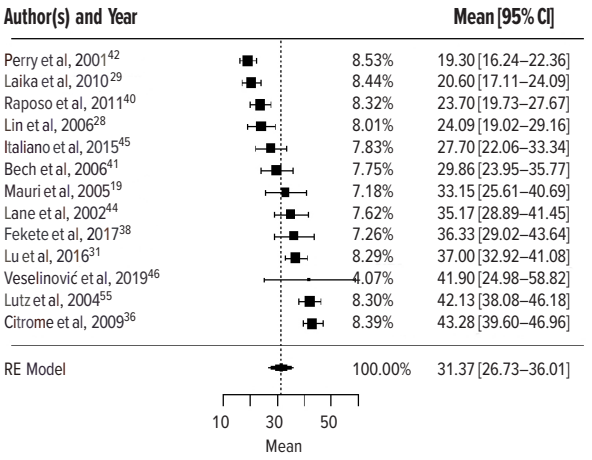
Nine studies assessed side effects for olanzapine-treated patients using established rating scales (Table 1). Higher plasma levels were found in patients experiencing constipation (P=.02) in a double-blind crossover study by Kelly and colleagues[35] that compared patients treated either with high dose olanzapine (50 mg/d) or with clozapine (450 mg/d) (TDM score: 7/10, RoB: high). A similar trend was found for dry mouth and tachycardia in this study that included treatment-resistant patients with schizophrenia. Women in particular had higher blood levels and were generally more affected by anticholinergic side effects. Plasma levels were not found to be related to weight gain. In contrast, none of the patients in the study by Mauri and colleagues[19] experienced an anticholinergic syndrome. The rate of EPS was low at 0.5%. Citrome and colleagues[36] investigated a large sample of 380 patients over 8 weeks of treatment with olanzapine 10, 20 and 40 mg/d. The authors reported a dose-, but not blood level–dependent increase in weight gain. Carillo and colleagues[32] reported a trend toward higher dose-corrected blood levels in patients affected by adverse effects (n=17; not statistically significant). Fellows and colleagues[37] as well as Perry and collaegues[42] could not find a relationship between blood olanzapine levels and various side effect scales (Simpson-Angus Scale [SAS], Abnormal Involuntary Movement Scale [AIMS], Barnes Akathisia Rating Scale [BARS]). Similar results were reported by Laika et al[29] using the Dosage Record and Treatment Emergent Symptoms Scale (DOTES) and by Zabala et al[30] using the Udvalg for Kliniske Undersøgelser scale (UKU). Examining 115 children and adolescent patients in a naturalistic setting, Fekete et al[38] noted a high incidence of side effects (54%) during treatment with olanzapine. Of note, most of the included patients with schizophrenia spectrum disorders were treated with concomitant medication (TDM score: 5/10; study score: 3/8). To conclude, one RCT of high risk for bias[35] reports a correlation between anticholinergic side effects, in particular constipation and blood olanzapine levels, which results in a low level of evidence (Level C).[25]

D_2 Receptor Occupancy and Blood Olanzapine Level

Five studies were identified that performed positron emission tomography (PET) imaging and 2 studies, that performed single-photon emission computerized tomography (SPECT) imaging using high affinity D_2/D_3 antagonist radiotracers (Table 2; see Supplementary Table 5 for more details). Kapur and colleagues[47] conducted the first study in 1998. The authors included 12 patients with schizophrenia who were randomly allocated to different olanzapine doses (5–40 mg/d) for at least 5 days prior to PET scanning. Sixty-five percent of occupancy was reached at a blood olanzapine level of about 19 ng/mL

(corresponding to a dose of about 7 mg/d). Eighty percent receptor occupancy was reached with 41 ng/mL olanzapine (corresponding to a dose of about 15 mg/d). Moreover, almost complete saturation of serotonin-2 (5-HT_2) receptors was observed, even at low doses (5 mg/d). Clinical effects were assessed at baseline and time of PET scan (PANSS, BPRS, BARS, SAS). The lack of response in 2 patients, who were administered higher olanzapine doses after not responding to their assigned doses, was not due to lack of sufficient D_2-receptor occupancy (both > 80%). One year later, Kapur et al[48] reexamined a part of the study population with a larger olanzapine dose range of up to 60 mg/d using an unconstrained model with a maximum occOne SPECT study (n = 12 patients with schizophrenia)[49] reported considerably higher EC_{50} values compared to PET studies. Clinical efficacy measures, however, indicate therapeutic effects below the (established by PET studies) 65% receptor occupancy. A lower D_2-receptor occupancy (eg, 50%) was suggested as a marker of insufficient antipsychotic efficacy. The relationship between striatal occupancy and EPS was explored in 17 patients with bipolar I disorder by Attarbaschi and colleagues.[50] After at least 2 weeks of constant dosing, a correlation between blood olanzapine levels and D_2-receptor occupancy was demonstrated with an EC_{50} of about 7 ng/mL (approximated EC_{65} = 17 ng/mL). However, EPS did not occur while occupancy levels did not exceed 80%. Arakawa et al[51] assessed D_2-receptor occupancy of olanzapine in extrastriatal regions using PET scanning. Ten patients with schizophrenia were treated with different doses of olanzapine. Blood levels were determined under steady state conditions. Patients with high PANSS score at the time of the PET scan also had higher occupancy. The EC_{50} value of 11 ng/mL was comparable with values measured in striatal regions. Graff-Guerrero et al[52] examined 22 outpatients with late-life schizophrenia (age at time of inclusion: ≥ 50 years; schizophrenia or schizoaffective disorder) in a PET study. The lowest D_2-receptor occupancy associated with clinical stability was 50% (EC_{50} = 7.7 ng/mL), suggesting a lower threshold for patients with late-life schizophrenia. D_2-receptor occupancy was not different between participants with or without EPS. Remarkably, EPS were observed with striatal D_2-receptor occupancy as low as 40% and occupancy of around 80% was reached with blood olanzapine levels beyond 100 ng/mL based on an unconstrained model. Only 1 study[53] included patients with a fixed dose of olanzapine pamoate given every 4 weeks for 6 months. All patients remained stable during the switch from oral administration. The estimated $EC_{65–80}$ range from 14 patients was 20–44 ng/mL. To sum up, 2 PET studies (1 used oral, 1 used LAI formulation) provided sufficient data, measured occupancy in striatal brain regions, and used a constrained model. Relating to 65%–80% receptor occupancy, a quite consistent therapeutic range was estimated with lower values between 19 and 20 ng/mL and upper values between 41 and 44 ng/mL.

Figure 2.
Mean Concentration Across 13 Studies[a]



[a]N = 1,137, Q_{12} = 194, P < .0001, I^2 = 91.7, τ^2 = 63.2, mean dose = 15.4 mg/d.
Abbreviation: RE = random effect.

Olanzapine Dose/Concentration Relationship

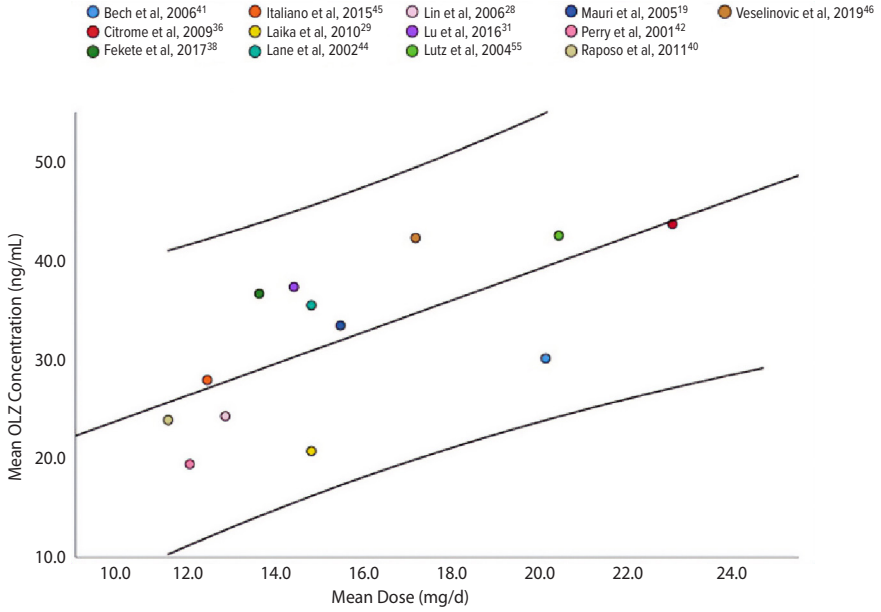
A total of 13 oral olanzapine studies provided sufficient data and were eligible for meta-analysis. Ten studies were excluded due to insufficient data report (7 studies), a non-representative patient sample (2 studies), or the application of high olanzapine doses only (1 study). The mean concentration across all studies was 31.4 ng/mL (95% CI, 26.7–36.0; range: 19.3–43.3 ng/mL) (Q_{12} = 194, P < .0001, I^2 = 91.7, τ^2 = 63.2) with a mean dose of 15.4 mg/d (Figure 2). Interquartile ranges (IQRs) for concentration (IQR 25 and 75) were available from 2 studies: (*i*) 1 study in adult patients with schizophrenia (IQR, 18–35 ng/mL)[19] and (*ii*) 1 study in children and adolescents with multiple psychiatric diagnoses (IQR, 20–53 ng/mL) (Supplementary Figure 4).[38] Linear regression analysis of mean concentrations across 13 studies revealed a strong association between dose and blood olanzapine level (r^2 = 0.467, P = .01; Figure 3). In addition, 13 individual studies reported a positive correlation between oral olanzapine dose and blood level with correlation coefficients ranging from 0.2 to 0.8. Among all, 5 studies provided C/D ratios, which ranged from 1.4–3.4 (ng/mL)/(mg/d). One LAI study reported a median C/D ratio of 2.3 (ng/mL)/(mg/d) that remained stable over the study period.[54]

Suggested Target Level/Ranges for Olanzapine From Previous Clinical Studies

Studies discussing target level or target ranges for olanzapine are listed in Table 3. Five studies were identified that reported blood levels for olanzapine in responders and nonresponders. Two studies reported higher blood levels in nonresponders[30,38] and 3 studies, in responders.[19,37,42] Conflicting results impede the finding

Figure 3.

Linear Regression Analysis of Mean Concentrations Across 13 Studies[a]



[a]r^2 linear = 0.467, P = .01, y = 7.83 + 1.56*x.
Abbreviation: OLZ = olanzapine.

Table 3.

Summary of Previously Suggested Target Level/Ranges for Antipsychotic Effects of Olanzapine

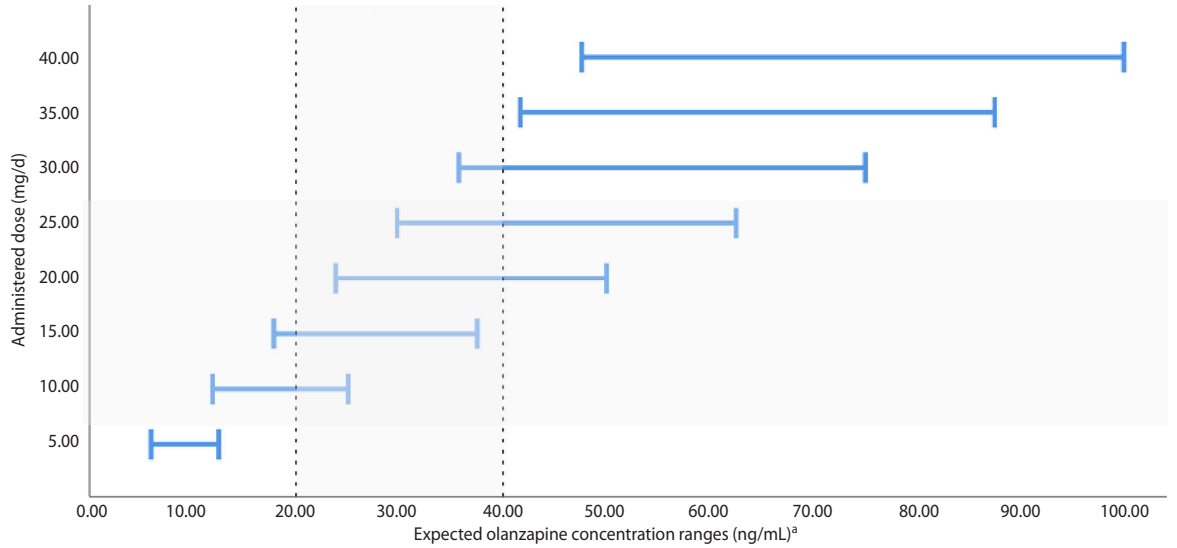
Author(s), Year	Time Post-Dose (h)	Lower Limit Discussed (ng/mL)	Upper Limit Discussed (ng/mL)	Comment
Perry et al, 2001[42]	12	23.2		ROC analysis, response as 20% BPRS reduction
Fellows et al, 2003[37]	12	23–25		ROC analysis, response as 20% PANSS reduction
Lu et al, 2016[31]	12	22.8		ROC analysis, response as PANSS score ≤ 58
Junutula et al, 2021[23]	NA	20	40	TDM study, ADRs observed at a BL OLZ > 80 ng/mL
Mauri et al, 2005[19]	12	20	50	Relationship for positive, negative and affective symptoms
Zabala et al, 2017[30]	12	23	78	Response as 30% PANSS reduction
Olesen and Linnet, 1999[57]	12	8[a]	47[a]	No treatment effect, pharmacokinetically expected range
Xiao et al, 2021[58]	10–23	8	45	TDM study of BL OLZ in elderly patients, no information about diagnoses
Perry et al, 1997[18]	24	9.3		ROC analysis, response as 20% BPRS reduction

[a]Converted from nmol/L.
Abbreviations: ADR = adverse drug reaction, BL OLZ = blood olanzapine level, BPRS = Brief Psychiatric Rating Scale, PANSS = Positive and Negative Syndrome Scale, ROC = receiver operating characteristic, TDM = therapeutic drug monitoring.

of a concentration-effect relationship across studies, as depicted in a concentration-effect meta-analysis across 5 studies (N = 243) (Supplementary Figure 5). Thresholds that divide responders from nonresponders have been discussed in 4 studies that conducted receiver operating characteristic (ROC) analyses. In 1997[18] and 2001,[42] Perry and colleagues shaped a 12-h and 24-h post-dose breakpoint of 9 and 23 ng/mL, respectively, that indicates treatment response, defined as ≥ 20% decrease in BPRS score. Later on, in 2003 and 2016, Fellows et al[37] and Lu et al[31] were able to confirm the threshold of 23 ng/mL. A post hoc analysis from a double-blind trial focused on depressive symptoms in patients with schizophrenia and found a threshold of 36 ng/mL for the improvement in MADRS score.[44] Another study that included a sample of 48 children and adolescents with schizophrenia spectrum disorders (F20–F29 according to *ICD-10* classification) found higher blood levels in nonresponders compared to responders (median = 37 vs 22 ng/mL).[38,56] Treatment effects were assessed by the Clinical Global Impressions–Improvement scale (CGI-I) with a rating as "very much improved" and "much improved" indicating treatment response. A threshold of 27 ng/mL was estimated by ROC analysis that is able to discriminate responders

Figure 4.

Olanzapine Oral Doses Needed to Reach Revised Target Range in the Average Patient



[a]Computed from dose-related concentration (DRC) factors in TDM Guidelines.[9]

from nonresponders (Supplementary Figure 6). Above this limit, the probability of response is considerably decreased. Calculation of interquartile concentration ranges for responders and nonresponders from Mauri et al[19] revealed, that 50% of all patients responding to the olanzapine treatment had blood levels between 17 and 39 ng/mL. Assuming recommended therapeutic doses, recently published pharmacokinetic studies suggest an upper limit of around 40–50 ng/mL for olanzapine.[19,57,58]

DISCUSSION

Olanzapine's Therapeutic Reference Range Revised

The present study systematically evaluated the concentration-effect relationship for olanzapine as a basis for the therapeutic reference range. We have shown that evidence is available for an association between blood olanzapine levels and efficacy. Ambiguous findings, however, result in an overall state of evidence for the concentration-effect relationship that has to be considered as "low." In total, 3 studies of moderate quality consistently showed therapeutic thresholds of 23 ng/mL for olanzapine 12 h post dose.[31,37,42] This threshold is in line with findings from PET studies. In the average patient, at least 65% of D_2-receptors are being occupied above this threshold.

Adverse drug reactions have not been discussed by the majority of studies, and only 1 study was able to find a link to anticholinergic side effects (ie, constipation, Level C "low").[25] Moreover, the occurrence of anticholinergic side effects was here assessed after fixed doses of 50 mg/d that resulted in very high olanzapine levels well above the efficacy maximum discussed in this work.

The occurrence of EPS with higher blood levels has been suggested for a D_2-receptor blockade of 80% and higher.[12–14] In the reviewed studies, EPS were generally rare and no correlation with blood olanzapine levels was detectable in the few patients with EPS (Table 1). As a result, the upper limit of olanzapine's reference range might be described by a therapeutic maximum/ceiling rather than by drug safety measures. This threshold can be for example determined by a ROC-analysis (threshold of 27 ng/mL, re-analysis of Fekete et al,[38] Supplementary Figure 6; $P = .007$) or by a visual inspection of a concentration/effect curve (maximum effect at about 40 ng/mL).[19] PET studies report a 80% D_2 receptor occupancy around 41–44 ng/mL (Table 2). We suggest a therapeutic target range of 20–40 ng/mL for olanzapine oral formulations. The lower threshold is based on a ROC analysis of blood levels of patients with schizophrenia, but our results reveal a transferability of the therapeutic reference range to schizophrenia spectrum disorders.

Blood olanzapine levels after LAI administration reached the current reference range for oral olanzapine. None of the LAI studies intended to investigate a therapeutic reference range for olanzapine LAI, and recommendations to narrow down olanzapine's range for the LAI formulation are based on pharmacokinetic findings. They are supported in 1 prospective pharmacokinetic study that included 21 antipsychotic-naive patients with schizophrenia treated with 210, 300, or 405 mg every 4 weeks (not steady state).[22,59] A trough level < 20 ng/mL was observed in 70% of the patients who received 210 mg compared to 57% each for the 300/405 mg group. The PET study by Mamo

et al[53] justifies a range of 20–40 ng/mL for olanzapine pamoate. Patients with levels below 20 ng/mL in many cases experienced a worsening of their symptoms.[45]

Limitations

Mean concentrations across studies varied widely, from 19 to 43 ng/mL. Despite a proven linearity of olanzapine's dose/concentration relationship, a high interindividual variability results in unpredictable blood levels from given doses. A simulation pharmacokinetic study[60] showed that a dose of 10 mg given once daily results in a predicted concentration of 9–37 ng/mL (4-fold variation), whereas a dose of 5 mg given twice daily leads to 12–40 ng/mL (3-fold variation). Estimations from current guidelines are more conservative. Figure 4 presents expected olanzapine concentrations (12-h sampling time) from 5–40 mg/d oral doses in the average patient. Notably, tobacco smoke and comedication influencing cytochrome P450 1A2 (CYP1A2) have a well-known influence on blood olanzapine levels, but sex and age do as well.[61] Strong pharmacokinetic variability gives a special indication to perform TDM-guided dosing. Of note, specific patient groups (ie, women) seem to be more sensitive to developing certain side effects (ie, anticholinergic effects). Besides the infrequent rate of side effects during olanzapine treatment, they can occur at therapeutic drug levels[52,62] and doses.[3] This holds especially true for the frequently discussed weight gain.[36,63] New drug formulations, such as the combined formulation of olanzapine-samidorphan, introduced in 2021, address this problem by a pharmacodynamic interaction without influencing blood olanzapine levels.[64] Future research is needed to assess whether the proposed target ranges are adaptable to the new formulation.

A therapeutic reference range is strongly limited by the quality of the underlying study design. The study quality, rated by established quality items, did not considerably increase or decrease over time (1998–2021; see Supplementary Figure 7). The presented information was mostly extracted from non-controlled studies since information from large (sponsored) randomized clinical trials is rare. Dose/efficacy assumptions lie beyond the scope of this study. Of note, former dose-response reviews and meta-analyses for antipsychotic drugs have discussed an efficacy of lower doses in maintenance treatment compared to acute therapy, presenting indefinite findings.[10,65,66] Clinical studies have been included in the present work irrespective of former treatment duration, which may affect the clinical transferability of the suggested reference range.

Findings from neuroimaging studies were solely evaluated in regard to $D_{2/3}$ receptor antagonism as it is still considered the major mechanism of antipsychotics. Of note, other receptor systems such as 5-HT_2 might also play a role in olanzapine's drug action.[48] Incomplete reporting of study method such as missing information and differences in analytic methods represents another limitation. The majority of studies have measured olanzapine in plasma, and some studies have measured serum blood levels. While olanzapine is stable in ethylenediaminetetraacetic acid (EDTA) plasma probes, it is in general unstable in whole blood and in serum. Nevertheless, we did not exclude studies that measured olanzapine concentration in serum.[29,38,45] All of these studies have used a validated analytic method for the assessment of olanzapine in serum. The analytic procedure described in each study was furthermore rated in our quality assessment. This rating revealed that 41% of all studies have not reported at least a detection limit of the applied method. Inadequate study designs in the past have led to artificial outcomes resulting in a systematic underestimation of the clinical relevance of TDM. We discuss several study-specific risk factors that may conceal a concentration-effect relationship in the following sections.

Blood Sampling Strategy

One of the most obvious prerequisites when collecting drug samples is the compliance to steady-state conditions, which for olanzapine are presumed after at least 7 days of constant dosing (respectively, 3 months for olanzapine LAI).[9] Most studies have complied with these standards. However, 3 studies took blood samples before day 7 (see TDM rating Q6a, Supplementary Table 6[1,19,47,48]). These studies are at risk of underestimating drug effects, which may in clinical practice result in an overdosing of the medication.[67] In addition, a drug intake control is recommended to ensure adherence to medication. Not even half of studies using a cohort or cross-sectional design have measured, reported, and/or discussed drug adherence in their patient sample apart from TDM (Q4, study score).[1] Due to olanzapine's half-life of around 33 hours, the determined blood olanzapine levels vary up to 1.62-fold when sampling 12 h compared to 24 h post-dose.[9,60] Twelve of 23 studies specified a 12- to 15-h post-dose interval (TDM score: Q6b), which does not represent trough level. Moreover, in daily practice, olanzapine is often administered twice daily. As an example, Raposo et al[40] demonstrated only a correlation between blood olanzapine levels and PANSS negative symptom improvement. With a focus on metabolic outcomes of olanzapine treatment, a small patient sample (N = 18 on olanzapine) consisting of only men and a lack of data about steady-state conditions, dose to sampling time, and blood olanzapine level range, evaluation of the influence of blood olanzapine levels on clinical response could be impeded.

Assessment of Response

A relatively rapid improvement of psychotic symptoms is usually seen within the first 2 weeks, which slows down over the following 4 weeks.[68] Hence, 2 weeks can be regarded adequate to identify responders from nonresponders (study score: Q7 for cohort studies). A major challenge is still posed by placebo response and

nonresponse to antipsychotic drug treatment when measuring antipsychotic drug efficacy. Both aspects may perplex the unraveling of concentration-effect relationships or even result in a falsely negative correlation.[69] To address these challenges, recommended study designs use a placebo lead-in phase followed by a fixed dosing schedule of the investigated drug.[67] Placebo lead-in phases are uncommon, and most studies still use flexible-dose regimens to "maximize" treatment effects. In our review, 19 of 23 oral concentration-effect studies used flexible dosing (TDM score: Q4). In a population of patients with chronic schizophrenia, whose symptoms were not controlled under previous antipsychotic treatment, clinical effects could have been underestimated due to a higher nonresponse rate.[39] In addition, the assessed outcomes in the reviewed psychiatric trials are highly heterogeneous. Rating scales represent multifactorial surrogate markers in concentration-effect studies that (i) examine antipsychotic effects (PANSS, BPRS), (ii) examine particular (depressive) symptoms (MADRS,[44] PDS, mania scales[41]), (iii) assess disease severity (CGI-S), or (iv) assess general improvement under current treatment (CGI-I).[29] As a consequence, the results are not comparable. Self-rating scales should be confirmed by a professional rating (see Laika et al[29]). Global rating scales like the PANSS or BPRS have been proven valid in antipsychotic drug trials. Furthermore, studies should provide sufficient information about and control for interrater reliability (study score: Q6, RoB: D4).[67] One LAI study[43] examined a cohort of chronically ill patients with schizophrenia and schizoaffective disorder. Proof of a concentration-effect relationship cannot be expected, as patients were previously stabilized on oral olanzapine. Hospitalization or discontinuation rate were considered as alternative clinical efficacy parameters.

Pharmacodynamic Interactions

Administration of pharmacodynamically interacting medication like prior antipsychotics, antidepressants, or mood stabilizers can lead to an overestimation of clinical improvement.[70] Coadministration of antiparkinsonian medication can lead to underestimation of EPS occurrence or furthermore cause anticholinergic side effects itself.[71] For the TDM quality rating (Q3), administration of these substances was considered. In daily practice, comedication with potential pharmacodynamic interaction is not only common, but sometimes even intended. This is reflected in the study results: 22 of 34 study protocols allowed a coadministration of the aforementioned drugs.

CONCLUSION

On the basis of the findings in the present study, we suggest a correction of the therapeutic reference range to 20–40 ng/mL for the olanzapine oral and LAI formulations in schizophrenia and schizophrenia spectrum disorders. The highest response rate (defined by a minimum decrease of 20% in PANSS score and constant dosing for 1 to 6 weeks; Table 3) is expected within the suggested reference range.

As olanzapine is well tolerated with blood levels exceeding 40 ng/mL, serum concentrations above the upper threshold do not require dose reduction in case of good clinical response and tolerance. The therapeutic reference range refers to a 12- to 15-h sampling timepoint after once daily dosing, which does not reflect trough level conditions. Concentrations that are 1.6-fold lower are expected when sampling 24 h post-dose. Sufficient data to determine a 24-h post dose therapeutic reference range are still scarce.

Research with focus on the therapeutic reference range for olanzapine in elderly and minor patients as well as olanzapine LAI is needed.

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Supplementary Material

Article Title: Therapeutic Reference Range for Olanzapine in Schizophrenia: Systematic Review on Blood Concentrations, Clinical Effects, and Dopamine Receptor Occupancy

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LIST OF SUPPLEMENTARY MATERIAL FOR THE ARTICLE

1. **Table 1** Inclusion and exclusion criteria for study eligibility
2. **Table 2** Full database search string
3. **Table 3** Detailed information on all included trials for oral OLZ
4. **Table 4** Detailed information on all included trials for OLZ LAI
5. **Table 5** Neuroimaging studies reporting D_2RO and OLZ blood concentrations
6. **Table 6** Rating result of general quality criteria for the therapeutic drug monitoring component for all studies (TDM score)
7. **Figure 1** Quality assessment results for TDM component
8. **Table 7** Study type specific quality assessment - cohort studies
9. **Table 8** Study type specific quality assessment - cross-sectional studies
10. **Figure 2** Study type specific quality assessment – randomized controlled trials
11. **Figure 3** Risk of bias in randomized controlled trials
12. **Figure 4** Target ranges for OLZ
13. **Figure 5** Metaanalysis of mean olanzapine concentration differences of Responders vs. Nonresponders across five studies (N = 243)

The Journal of Clinical Psychiatry

14. **Figure 6** ROC analysis Fekete et al., 2017 (AUC 0.743 (95 % CI: 0.597 - 0.889), p = 0.007, responders N = 19, nonresponders N = 24)

15. **Figure 7** Study Scores over time from 1998 – 2021

16. **Appendix 1** Abbreviations

17. **References**

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Supplementary Table 1. Inclusion and exclusion criteria for study eligibility

Inclusion criteria for all studies	Exclusion criteria for all studies	No. of excluded studies
I1 The study concerns olanzapine	E1 Non-human subjects	119
I2 Drug BLs are measured and reported (mean or median concentration)	E2 Studies not concerning olanzapine	562
	E3 Studies without an abstract	36
	E4 Studies not written in English/German	8
I3 Publication is written in English or German	E5 Studies primarily comparing blood analysis techniques	69
	E6 Grey literature (e.g. expert opinions, conference papers and abstracts)	98
	E7 Case reports and case series	88
	E8 Data from simulation studies	9
	E9 Reviews and meta-analysis	188
	E10 Maternal use during pregnancy or lactation	5
	E11 Postmortem studies	5
	E12 No olanzapine monotherapy	34
	E13 Papers containing the same data	22
	E14 Studies that do not report olanzapine concentrations	299
	E15 Other reasons	49
Additional inclusion criteria for	**Additional exclusion criteria for**	
Concentration-effect studies	Concentration-effect studies	
I4 Direct clinical outcome measures are reported, using a standardized rating scale (e.g. CGI, BPRS, PANSS, UKU, AIMS)[A]	E16 Drug effects assessed in healthy volunteers	55
I5 Drug concentration is measured in the steady-state (7d)[B]		
Neuroimaging studies		
I6 Dopamine receptor occupancy is measured in the brain		

A biomarkers (e.g. ECG, EEG) are not regarded as a direct clinical outcome measurement

B not for studies, in which injectable formulations were administered

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Supplementary Table 2. Full database search string

PubMed

(("serum level*"[Text Word] OR "plasma level*"[Text Word] OR "blood level*"[Text Word] OR "drug level*"[Text Word] OR "serum concentration*"[Text Word] OR "plasma concentration*"[Text Word] OR "blood concentration*"[Text Word] OR "drug concentration*"[Text Word] OR ("Drug Monitoring"[MeSH Terms] OR "drug monitor*"[Text Word]) OR ("positron emission tomography"[MeSH Terms] OR "positron emission tomogra*"[Text Word] OR "pet scan*"[Text Word] OR "tomography, emission computed, single photon"[MeSH Terms] OR "single photon emission*"[Text Word] OR "SPECT"[Text Word] OR "CAT Scan"[Text Word] OR "single photon emission computed tomography computed tomography"[MeSH Terms])) NOT ("Animals"[MeSH Terms] NOT "humans"[MeSH Terms])) AND ("Olanzapine"[MeSH Terms] OR "olanzapin*"[Text Word] OR "Zolafren"[Text Word] OR "olanzapine pamoate"[Text Word] OR "Zyprexa"[Text Word] OR "ly 170053"[Text Word])

Web of Science

TS=(olanzapine) OR TS=(LY170053) OR TS= (Zyprexa) OR TS=(Zolafren) OR TS=(Olanzapine NEAR/1 Pamoate) AND TS=(drug NEAR/1 monitor*) OR
TS=(serum NEAR/1 level*) OR TS=(plasma NEAR/1 level*) OR TS=(blood NEAR/1 level*) OR TS=(drug NEAR/1 level*) OR TS=(serum NEAR/1 concentration*) OR TS=(plasma NEAR/1 concentration*) OR TS=(blood NEAR/1 concentration*) OR TS=(drug NEAR/1 concentration*) OR
TS=(positron NEAR/1 emission NEAR/1 tomogra*) OR TS=(PET NEAR/1 scan*) OR TS=(single NEAR/1 photon NEAR/1 emission*) OR TS=(SPECT) OR TS=(CAT NEAR/1 scan)

PsycINFO

MA „Olanzapine" OR "olanzapin*" OR "Zyprexa" OR "Olanzapine Pamoate" AND MA "positron emission tomography" OR "positron emission tomogra*" OR "PET scan*" OR MA "tomography, emission computed, single photon" OR "single photon emission*" OR "SPECT" OR "CAT Scan" OR MA "Drug Monitoring" OR "Drug Monitoring" OR "serum level*" OR "plasma level*" OR "blood level*" OR "drug level*" OR "serum concentration*" OR "plasma concentration*" OR "blood concentration*" OR "drug concentration*") NOT (MA "Animals" NOT MA "humans")

Cochrane library databases

(mh „Olanzapine" OR "olanzapin*" OR "LY 170052" OR "LY 170053" OR "Zyprexa" OR "Zolafren" OR "Olanzapine Pamoate") AND ([mh "positron emission tomography"] OR [mh "Tomography, Emission-Computed, Single-Photon"] OR [mh "single photon emission computed tomography computed tomography"] OR (positron NEAR/1 emission NEAR/1 tomogra*) OR (PET NEAR/1 scan*) OR (tomography, emission NEAR/1 computed, single NEAR/1 photon) OR (single NEAR/1 photon NEAR/1 emission*) OR SPECT OR (CAT NEAR/1 Scan) OR (single NEAR/1 photon NEAR/1 emission) OR (single NEAR/1 photon NEAR/1 emission NEAR/1 computed NEAR/1 tomography NEAR/1 computed NEAR/1 tomograph*):ti,ab,kw OR (drug NEAR/1 monitor*):ti,ab,kw OR (serum NEAR/1 level*) OR (plasma NEAR/1 level*) OR (blood NEAR/1 level*) OR (drug NEAR/1 level*) OR (serum NEAR/1 concentration*) OR (plasma NEAR/1 concentration*) OR (blood NEAR/1 concentration*) OR (drug NEAR/1 concentration*)):ti,ab,kw

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Supplementary Table 3. Detailed information on all included trials for oral OLZ

Author, year	Country	Design	Subjects	Mean Dose (range) [mg/day]	Mean OLZ Conc. (range) [ng/ml]	Comment	TDM score	Study score
Perry et al., 2001 (1997)	USA	RCT, data for analysis were extracted from the multicenter efficacy trial that compared olanzapine with haloperidol and placebo in the treatment of acutely ill patients with schizophrenia (**Beasley** 1996)	N = 84, SCZ, 85% males, mean age 36.8 ± 10.2 y (18-60)	11.8 ± 4.3	19.3 ± 14.3	ROC analysis identified threshold of 23.2 ng/ml (12h post dose) for improvement of negative symptoms, no upper threshold, Perry 1997: 9.3 ng/ml (24h post dose) for improvement of BPRS and PANSS scores	8/10	high
Lane et al., 2002	China	RCT, post hoc analysis derived from a double-blind trial that compared olanzapine and haloperidol	N = 13, SCZ, 69.2 % males, mean age:39.1 ± 8.4 y (18-65)	14.6 ± 4.8 (week 6)	35.2 ± 11.6 **	positive corr. between BL and mood improvements (MADRS); which was unrelated with changes in positive, negative, or motor symptoms, threshold 36 ng/ml (ROC) for depressive symptoms	8/10	high
Carrillo et al., 2003	Spain	prospective CS, investigation of the influence on smoking inducible CYP1A2 and polymorphic CYP2D6 on the metabolism of OLZ and its clinical effects	N = 17, SCZ (N = 10), SD (N = 5), delusional disorder (N = 2), 53 % males, mean age: 37 ± 16y (18-70)	9*	NA	Mean C/D ratio: 3.42 (ng/ml)/(mg/d), percentage decrease in BPRS total score was consistently correlated with the steady-state BL, measure of drug effectiveness was higher in non-smokers, OLZ BLs were lower than 20ng/ml in nonresponders, C/D ratio was higher in this group of patients (N = 9) that experienced side effects	7/10	8/10
Fellows et al., 2003	Australia	prospective CS, naturalistic setting, flexible dosing, interacting co-medication allowed	N = 53, SCZ, 75.5 % males, age: 32 ± 11 (18-65)	median: 15 (5-30)	32 (2-122)	breakpoint: 23-25 ng/ml (ROC), no significant corr. between side effects scores and OLZ BLs at 6 weeks, smoking was a significant determinant of C/D ratio	7/10	7/10
Lutz et al., 2004 [1]	Germany	CSS, TDM study on OLZ, clinical improvement and side-effects	N = 216, multiple psychiatric Dx (73% SCZ), 61.6 % males, age: 39.6 ± 15.3 y	20.3 ± 7.4 (2.5-40)	42.1 ± 30.4 (10-192)	70 % no side effects, response rate 53 %	5/10	3/8
Mauri et al., 2005	Italy	prospective, open label CS on inpatients with acute SCZ, 2 weeks duration	N = 54, SCZ, 70.4 % males, mean age: 35.6 ± 12.4y (18-75)	15.3 ± 5.5	33.2 ± 28.3 (5-120)	significant curvilinear correlation between OLZ BLs and clinical improvement, no evidence of corr. between OLZ BLs and EPS or anticholingeric syndrome	8/10	7/10
Bech et al., 2006	Switzer-land	re-analysis of a prospective CS [2], 2 weeks fixed, then flexible dosing, co-medication (incl. AP) allowed	N = 20, acute mania, 25 % males, mean age:41.9 ± 10.6y (18-65)	20	29.9 ± 13,5 (11.8-55.0) **	overall response rate: 87.5 %, positive correlation for OLZ BLs and MAS improvement in a subgroup of 8 female, not for YMRS	4/10	5/10
Kelly et al., 2006	USA	RCT, double blind 16 - weeks crossover study of OLZ compared to CLO, fixed dose	N = 13, treatment- resistant SCZ, 61.5 % males, mean age:37.6 ± 9.0 y	50	185*	no significant findings for BL in relation to total BPRS/ CGI change, or response rates, anticholinergic effects seen at greater frequency with higher OLZ BLs (SAS, BARS)	7/10	high
Lin et al., 2006	USA	re-analysis from Ellingrod et al., 6 weeks prospective, open-label CS investigating relationship of PGP polymorphisms and response to OLZ	N = 41, SCZ, 80.5 % males, mean age: 35.7 ± 8.8 y (18-65)	12.6 ± 3.2 (7.5- 20)	24.1 ± 16.6	Threshold of 9.3 ng/ml was used for dose adjustment, percent change in BPRS score was associated with OLZ BLs, positive corr. for OLZ BLs and positive symptom reduction, OLZ BL no predictor of change in SANS	9/10	9/10
Nozawa et al., 2008	Japan	prospective CS on clinical factors and polymorphisms of UGT1A4, CYP1A2, CYP2D6 on OLZ BLs, chronic schizophrenic patients, flexible doses	N = 51, SCZ, 66.7 % males, mean age: 32.6 ± 9.60 y	15.7 ± 5.3 (5-20)	NA	improvement of individual BPRS scores (suspiciousness, hallucinations, blunted affect) was significantly correlated with OLZ BLs, but not total BPRS score, OLZ BLs were not affected by CYP1A2 polymorphism but only by smoking, C/D ratios (SD): smoker: 2.2 (1.2), non-smoker: 3.8 (1.8) (ng/ml)/(mg/d)	6/10	6/10
Citrome et al.,2009	USA	data derived from Kinon et al. [3], RCT, patients allocated to OLZ 10, 20, or 40 mg/d for 8 weeks	N = 599 (N = 380 with BL), SCZ, SD, 69.7 % males, age: 42 ± 11 y (18-60)	23*	43*	Non-treatment resistant pat. responded to all three doses, no differences between dose groups for treatment-emergent EPS, higher OLZ BLs in 40 mg group	7/10	some concerns
Laika et al., 2010	Germany	prospective CS, co-medication allowed, flexible doses	N = 124 (N = 73 with BL), multiple psychiatric Dx, 49 % males, mean age: 41.7 ± 14.7 y (19-76)	14,6 ± 7,5 (2.5-30)	20.6 ± 15.2	mean C/D ratio (SD): 1.39 (0.68) (ng/ml)/(mg/d), higher OLZ BLs correlated with better improvement of paranoid and depressive symptoms in schizophrenic disorders, no correlation of OLZ BLs with improvement of depressive symptoms in pat. with other F-diagnosis	8/10	9/10
Raposo et al., 2011	Brazil	9 months randomized naturalistic study, only male patients under OLZ or HAL monotherapy, flexible dosing	N = 18, SCZ, 100 % male, mean age: 35 ± 12 y (18-60)	11.3 ± 4.3 (5-20)	23,7 ± 8,6	positive corr. of OLZ BLs with negative symptoms	5/10	some concerns
Hatta et al., 2013 [4]	Japan	RCT, newly admitted emergency cases including involuntary admissions, co-medication allowed, flexible doses	N = 22 (N = 5 with BL), SCZ, SD, schizophreniform disorder, 40 % males, 18-64 y	23.0 ± 10.2	47.9 ± 21.6[A]	non-responding was not associated with a low OLZ BLs (all were > 30 ng/ml)	4/10	some concerns
Batail et al., 2014	France	CSS, pharmacokinetics of high dose OLZ (up to 80 mg/d) compared to conventional doses, anticholinergic co-medication allowed, flexible dosing	N = 50, SCZ, SD, 60 % males, mean age: 35.4 ± 1.5 y	31.3	70.1 ± 50.2**	mean C/D ratio: 2.34 (ng/ml)/(mg/d), response rate 68 %, very few side effects, negative influence of tobacco and coffee/tea consumption on OLZ BLs, no gender effect	5/10	3/8
Italiano et al., 2015	Italy	prospective CS, comparison of branded (BF) and generic (GF) formulation of OLZ, flexible doses	N = 25, SCZ, 48 % males, mean age: 41.2 ± 12.8y	12.2 ± 5.4 (5-20)	BF: 27.7 ± 14.4; GF: 22.6 ± 12.3	only responders, no relapse, no new side affects	8/10	8/10

Lu et al., 2016	Taiwan	CSS, TDM study analyzing C_{OLZ} and Desmethyl- OLZ concentration (C_{DMO})	N = 151, SCZ, 47 % males, mean age: 41.3 ± 12.1 y (18-60)	14.2 ± 5.4	37.0 ± 25.6	threshold: 22.8 ng/ml (ROC), mean C/D ratio (SD): 2.9 (2.3) (ng/ml)/(mg/d), no corr. between PANSS and OLZ BLs	7/10	4/8
Fekete et al., 2017	Germany	CSS, TDM study at departments of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy, 72 % psychotropic co-medication	N = 115, multiple psychiatric Dx, 40.9 % males, mean age: 15.9 ± 1.8 y	11.6 ± 5.8	35.7 ± 23.9	majority of pat. were in reference range (20-80 ng/ml), no upper limit could be calculated, no difference between the OLZ BLs of "responders" and "non-responders" (psychotic and eating disorders), no association between OLZ BLs and occurrence of ADRs	5/10	3/8
Steen et al., 2017 [5]	Norway	prospective CSS on cognitive function (TOP study); flexible doses, control groups: QUE, ARI, RIS	N = 222, multiple Dx; 55.2 % males, median age 28 y	NA	NA	Attention (WAIS) was positively ass. with OLZ BLs, negative ass. between long term delayed recall and OLZ BLs, negative ass. for verbal memory and OLZ BLs (SCZ subsample), negative ass. between processing speed and OLZ BLs (BD subsample)	6/10	6/8
Zabala et al., 2017	Spain	prospective CS on FEP patients, antidepressant co-medication allowed, flexible doses	N = 23, SCZ, SD, other schizophrenia spectrum disorders, 56.5 % males, mean age: 29.5 ± 8.7y (18-50)	13.8 ± 5.7 (5-30)	44.9 ± 33.8	22.6-77,9 ng/ml for psychotic symptoms, curvilinear relationship between OLZ BLs and percentage of clinical improvement, no corr. between OLZ BLs and ADRs	7/10	7/10
Veselinović et al., 2019	Germany	cohort nested in RCT (NeSSy trial) comparing conventional and atypical AP, flexible design	N = 14, SCZ, 62 % males, mean age 34.6 ± 12.9 y (18-65)	17.0 ± 3.5	41.9 ± 32.3	No corr. of OLZ BLs (and consequently D_2RO) and subjective well-being	8/10	high
Arnaiz et al., 2020	Spain	CSS on FEP patients, co-medication allowed, flexible dosing	N = 47, 68.1 % males, mean age: 26.2 ± 5.1y (17-36)	NA	NA	Positive corr. between C/D ratio with the percentage response according to total PANSS scores (no corr. for OLZ BLs found), C/D ratio > 2.12 (ng/ml)/(mg/d) as a positive predictor of a good response (ROC)	6/10	5/8
Hoekstra et al., 2021 [6]	Norway	data derived from BeSt InTro study [7], semi RCT, efficacy and side effects compared to ARI and AMI, AP co-med. Allowed, flexible doses	N = 52, 37 % males, SCZ spectrum disorders, mean age: 32.2 ± 13.3 y	12.3 ± 3.8 (2.5-20)	Norway: 30.1 ± 17.0; Austria: 17.7 ± 7.2	No differences in efficacy or neurologic symptoms (UKU) between men and women, men had more increase in BMI and glucose level and more sexual side effects (UKU), women had a higher prolactin level	3/10	some concerns

*pooled data, **additional data provided by the authors, ***values calculated by the given numbers A) Blood samples taken from patients with 20 mg (N = 5)

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Supplementary Table 4. Detailed information on all included trials for OLZ LAI

Author, year	Country	Design	Subjects (* = estimated from original data)	Mean dose +/-SD (range)	Oral supplementation (except benzos and sleep medication)	Mean OLZ Conc. (range) [ng/ml]	Comment	TDM score	Study score
Kane et al., 2010 [8]	26 diff.	RCT on efficacy and tolerability of OLZ LAI	N = 1062, SCZ, 65.2 % males, mean age: 38.9 y (18-75)	Oral: 10,15, 20 mg/d, 150 mg/ 2 weeks; 405 mg/ 4 weeks; 300 mg/ 2 weeks; 45 mg/ 4 weeks	No	NA	Stability rate: 95 % high- dose group, 69 % very low-dose group	9/10	low
McDonnell et al., 2014	25 diff.	prospective CS, 6 years duration, single-arm, open label, flexible doses and intervals based on clinical judgment, concomitant psychotropic medication allowed	N = 931, SCZ, SD, 66.7 % males, mean age: 39.3 ± 11.7 y (18-75)	45-300 mg every 2/3/4 weeks (1.6 mg/d), 315-405 mg every 4 weeks (28.9 mg/d max.)	oral OLZ up to 20 mg/d	NA	mean C/D ratio: 2.25 (ng/ml)/(mg/d), CGI-S remained stable, study discontinuation rate: 57.8 %, hospitalization rate: 23.8 %, N = 36 PDSS,41 % weight gain	3/10	6/10
Mitchell et al., 2013 [9]	Belgium, Croatia, Spain, USA	prospective CS, phase IB study, 24 weeks, pat. prior stabilized on oral OLZ for 4 weeks, multiple doses and dose intervals, single and multiple dose groups, fixed doses	N = 34, SCZ, single injection; N = 247 multiple dose inj., 70.1 % males, mean age: 38.5 ± 9.09 y	2 weeks injection interval: 100 mg 150 mg 160 mg 210 mg 300 mg 4 weeks injection interval: 200 mg 255 mg 300 mg 405 mg	oral OLZ up to 20 mg/d	2 weeks injection interval: 10.5 ± 46.7 22.4 ± 26.2 20.4 ± 51.0 31.0 ± 46.2 37.0 ± 46.5 4 weeks injection interval: 13.6 ± 44.7 18.4 ± 51.5 28.1 ± 44.0 35.2 ± 50.0	77.7% of pat. with multiple doses experienced at least one treatment-emergent AEs	9/10	9/10
Mauri et al., 2015	Italy	prospective CS on chronic outpatients on tolerability of OLZ LAI and relation of OLZ BLs and clinical outcome	N = 25 (N = 11 for 36 weeks), chronic SCZ and SD, 57.1 % males, mean age: 35.4 y (20-55)	oral dose: 19.5 ± 11.3 injection: 334.7 ± 60.9	NA	20.6 ± 14.7 (4.0- 78.9)	No positive corr. between OLZ dose and BL; steady state at fourth injection, no PDSS	8/10	9/10

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Supplementary Table 5. Neuroimaging studies reporting D_2RO and OLZ blood concentrations

Author, year	Country	PET tracer	Design	Subjects	Mean Dose (range) [mg/day]	Mean OLZ Conc. (range) [ng/ml]	Mean receptor occupancy (%) (range)	EC_{50} [ng/mL]	EC_{65} (estimated from EC_{50}) [ng/ml]	EC_{80} (estimated from EC_{50}) [ng/ml]	Comment	TDM score	Study score
Kapur et al.,1998	Canada	[11C] raclopride	RCT, PET scan at steady state 12 h post dose, fixed, multiple doses until scan	N = 12, SCZ, 73.3 % males, mean age: 27 y (19-44)	17* (5-40)	46* (9.2-181.4)	73* (43-88)	ED 50 (4,5 mg): 10.3	19***	41***	lack of response at the higher dose was not due to lack of sufficient D_2RO	6/10	high
Kapur et al., 1999	Canada	[11C] raclopride	CSS, PET scan 12-13 h post dose. control groups: RIS, CLO, overlap with pat. sample from Kapur et al.,1998	N = 17, SCZ and atypical psychosis 76.5 % males, median age: 26.8 y (19-44)	18,8* (5-60)	43* (8,5-181,5) *** [B]	74* (43-89)	ED50 (3.2 mg): 6.4	-	-	even lowest doses of OLZ led to more than 95 % occupancy of frontal $5HT_2$- receptors	4/10	4/8
Attarbaschi et al., 2007	Austria	[123] I-IBZM	prospective CS on the relationship between striatal D_2RO and EPS in patients with BD, SPECT after 10 days of drug intake, 12-14 h post dose	N = 17, BD, 64.7 % males, mean age: 33.4 y ± 9.8 (21-57)	15* (5-45)	11.8 ± 9.3	55.4 ± 13.9	Ca. 7[C]	17***	-	pos. corr. between OLZ BLs and D_2RO, pat. did not exhibit EPS at D_2RO levels of 28-80 % (D_2RO levels > 80 % not reached)	5/10	7/10
Catafau et al., 2008	Spain, Italy	[123] I-IBZM	prospective CS, sparse-sampling design, SPECT scan at one time during inter dose interval, OLZ compared to RIS, CLO, QUE	N = 12, SCZ and schizophreniform disorder, 58.3 % males, age: 28 ± 7 y	12.9 ± 6.8	(8.6-89.5)	(22-84)	22.7	42***	-	low inter-subject variability in potency (individual EC_{50}), no corr. between efficacy and D_2RO, corr. between OLZ BLs and D_2RO	7/10	8/10
Mamo et al., 2008	Canada, USA	[11C] raclopride	prospective CS, baseline and 4 follow-up PET scans, pat. were switched to OLZ LAI after being stabilized on oral OLZ, no oral OLZ supplementation during injection cycle with PET scan	N= 14, SCZ, SD, 64.3% males, mean age: 34.7±9,8y (18-50)	oral: 15.2±4.8 (5–20) LAI: 300 mg/4 w	oral: 37.4±31.2; p.i.: 20.3±11,2	oral: 69.1±15.2%, LAI: 50% (steady state), ≥60% (after 6 months)	11.0±1.3	20***	44***	D_2RO and OLZ BLs were pos. corr. (curvilinear asymptotic curve), D_2RO reached levels consistent with antipsychotic efficacy, both the D_2RO attained and tolerability profile of OLZ LAI were consistent with those found for oral OLZ	7/10	6/10
Arakawa et al., 2010	Japan	[11C] FLB457	CSS, D_2RO was determined in temporal cortex, PET scan 2-20 h after last dose	N = 10, SCZ, 70 % males, mean age: 36.2 ± 9 y (23-47)	11* (5-20)	42* (16.4- 88.2)[D]	72* (66.9-82.7)	10.5	-	-	positive corr. between D_2RO and OLZ BLs and total PANSS scores, but not daily dose, no corr. between age and D_2RO	8/10	5/8
Graff-Guerrero et al., 2015	Canada	[11C] raclopride	prospective CS on AP reduction in patients with LLS (aged ≥ 50 y), control group: RIS, PET scan at baseline and ≥ 2 weeks after final target dose and 14-16 h post dose	N = 22	baseline: 20.8 ± 6.6 (12.5-35); follow-up: 13.5 ± 4.4	baseline: 57.4 ± 33.8; follow-up: 40.8 ± 30.4	whole striatum baseline: 70.4 ± 12.2 (40.6-88.8) follow- up: 64.5 ± 12.3 (40.0-84.7)	7.7	14***	31***	lowest D_2RO ass. with clinical stability 50 %, threshold for antipsychotic clinical effect is lower in pat. with LLS, no difference in D_2RO between participants with vs. those without EPS, no sufficient data about calculation of EC_{50} ('unconstrained model')	5/10	7/10

*pooled data, **additional data provided by the authors, ***values calculated by the given numbers; B) Mean concentration without sample of pat. with 60 mg dose (N = 1), C) Estimated from graphics given in study paper, D) Mean concentration without sample of pat. with 15 mg dose (N = 1)

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Supplementary Table 6. Rating result of general quality criteria for the therapeutic drug monitoring component for all studies (TDM score) [10]

Concentration-effect studies for oral OLZ									
No	Reference	Q1	Q2	Q3	Q4	Q5	Q6	Q7	TDM Score (X/10)
1	Perry et al.,2001	x	xx	x	o	x	xx	xo	8/10
2	Lane et al., 2002	x	xx	x	o	o	xx	xx	8/10
3	Carrillo et al., 2003	x	xo	x	x	x	xx	o?	7/10
4	Fellows et al., 2003	x	xx	o	o	x	xx	ox	7/10
5	Lutz et al., 2004	x	xo	?	o	o	xx	ox	5/10
6	Mauri et al., 2005	x	xx	x	o	x	ox	ox	7/10
7	Bech et al., 2006	x	xx	o	o	o	xo	oo	4/10
8	Kelly et al., 2006	o	xx	x	x	o	xx	xo	7/10
9	Lin et al., 2006	x	xx	x	x	x	xo	xx	9/10
10	Nozawa et al., 2008	o	xx	?	o	x	xx	xo	6/10
11	Citrome et al., 2009	x	xo	o	x	x	xo	xx	7/10
12	Laika et al., 2010	x	xx	o	o	x	xx	xx	8/10
13	Raposo et al., 2011	o	xx	x	o	x	??	xo	5/10
14	Hatta et al., 2013	o	xo	o	o	x	xx	oo	4/10
15	Batail et al., 2014	x	xo	o	o	o	xx	xo	5/10
16	Italiano et al., 2015	x	ox	x	o	x	xx	xx	8/10
17	Lu et al., 2016	x	ox	x	o	x	xx	ox	7/10
18	Fekete et al., 2017	o	xo	o	o	x	xx	ox	5/10
19	Steen et al., 2017	x	xx	o	o	x	xx	oo	6/10
20	Zabala et al., 2017	x	xo	o	o	x	xx	xx	7/10
21	Veselinović et al., 2019	x	xx	x	o	x	xx	xx	8/10
22	Arnaiz et al., 2020	x	xx	o	o	x	ox	ox	6/10
23	Hoekstra et al., 2021	x	xo	o	o	?	??	ox	3/10
Concentration-effect studies OLZ LAI									
No	Reference	Q1	Q2	Q3	Q4	Q5	Q6	Q7	TDM Score (X/10)
24	Kane et al., 2010	x	xx	x	x	o	xx	xx	9/10
25	McDonnell et al., 2011	x	xo	o	o	o	oo	x?	3/10
26	Mitchell et al., 2013	x	xx	o	x	x	xx	xx	9/10
27	Mauri et al., 2015	x	xo	x	x	o	xx	xx	8/10
Neuroimaging studies									
No	Reference	Q1	Q2	Q3	Q4	Q5	Q6	Q7	TDM Score (X/10)
28	Kapur et al.,1998	x	xx	o	x	o	ox	ox	6/10
29	Kapur et al., 1999	x	xo	o	o	o	ox	ox	4/10
30	Attarbaschi et al.,2007	x	xx	o	o	x	xo	oo	5/10
31	Catafau et al., 2008	x	xo	x	o	x	xo	xx	7/10
32	Mamo et al.,2008	x	xo	o	x	o	xx	xx	7/10
33	Arakawa et al., 2010	x	xx	o	x	o	xx	xx	8/10
34	Graff-Guerrero et al., 2015	o	xo	o	o	o	xx	xx	5/10

x = sufficient, o = insufficient, ? = no information

Abbreviations: Q1: Representativeness of the patient sample, Q2: Diagnosis, Q3: Comedication, Q4: Dose design, Q5: Analytical method for the assay of drug concentration in serum or plasma, Q6: Blood sample collection, Q7: Concentrations design

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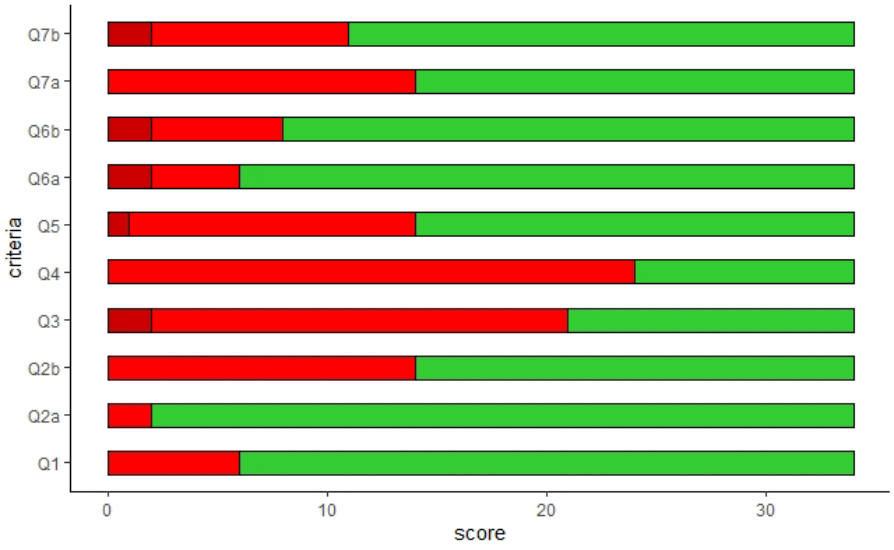
Supplementary Figure 1. Quality assessment results for TDM component



dark red = unclear; red = insufficient; green = sufficient

Supplementary Table 7. Study type specific quality assessment - cohort studies [10]

No	Study	Selection (Max. 4 p):				Comparability (Max. 2p)	Outcome (Max. 4p)				Total score
		Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	(x/10)
1	Carrillo et al., 2003	x	x	x	x	xo	o	x	x	x	8/10
2	Fellows et al., 2003	x	o	x	x	oo	x	x	x	x	7/10
3	Mauri et al., 2005	x	o	o	x	xo	x	x	x	x	7/10
4	Bech et al., 2006	x	o	o	x	oo	x	x	o	x	5/10
5	Lin et al., 2006	x	x	o	x	xx	x	x	x	x	9/10
6	Attarbaschi et al., 2007	x	x	x	o	oo	x	x	x	x	7/10
7	Catafau et al., 2008	x	x	o	o	xx	x	x	x	x	8/10
8	Mamo et al., 2008	x	o	o	x	oo	x	x	x	x	6/10
9	Nozawa et al., 2008	o	x	o	x	oo	x	x	x	x	6/10
10	Laika et al., 2010	x	x	x	x	xx	o	x	x	x	9/10
11	Mc Donnell et al., 2011	x	o	x	x	oo	o	x	x	x	6/10
12	Mitchell et al., 2013	x	x	x	x	xx	o	x	x	x	9/10
13	Graff-Guerrero et al., 2015	o	x	o	x	xo	x	x	x	x	7/10
14	Italiano et al., 2015	x	x	o	x	xx	x	x	o	x	8/10
15	Mauri et al., 2015	x	o	x	x	xx	x	x	x	x	9/10
16	Zabala et al., 2017	x	o	x	x	xo	x	x	o	x	7/10

x = sufficient, o = insufficient, ? = no information

Abbreviations: Q1: Representativeness of the exposed cohort, Q2: Selection of the control, Q3: Ascertainment of exposure (drug intake), Q4: Demonstration that outcome of interest was not present at start of study, Q5; Comparability of 'exposed' and 'non- exposed' individuals or of outcome groups, Q6: Assessment of outcome, Q7: Was follow- up long enough for outcomes to occur, Q8: Adequacy of follow-up of cohorts, Q9: Statistical tests

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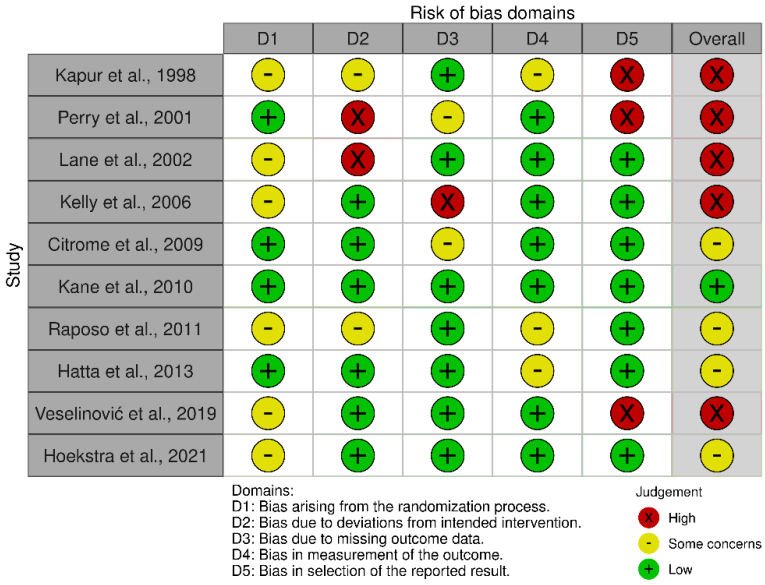
Supplementary Table 8. Study type specific quality assessment - cross-sectional studies [10]

No	Study	Selection (Max 4 p):				Comparability (Max 2 p):	Outcome (Max 2 p)		Total score (x/8)
		Q1	Q2	Q3	Q4	Q5	Q6	Q7	
1	Kapur et al., 1999	x	o	o	o	ox	x	x	4/8
2	Lutz et al.,2004	x	o	x	o	oo	x	o	3/8
3	Arakawa et al., 2010	x	o	o	o	xx	x	x	5/8
4	Batail et al., 2014	x	o	o	o	o	x	x	3/8
5	Lu et al., 2016	x	o	o	o	xx	o	x	4/8
6	Fekete et al., 2017	o	o	x	o	ox	o	x	3/8
7	Steen et al., 2017	x	o	o	o	xo	o	x	6/8
8	Arnaiz et al., 2020	x	o	x	o	xx	o	x	5/8

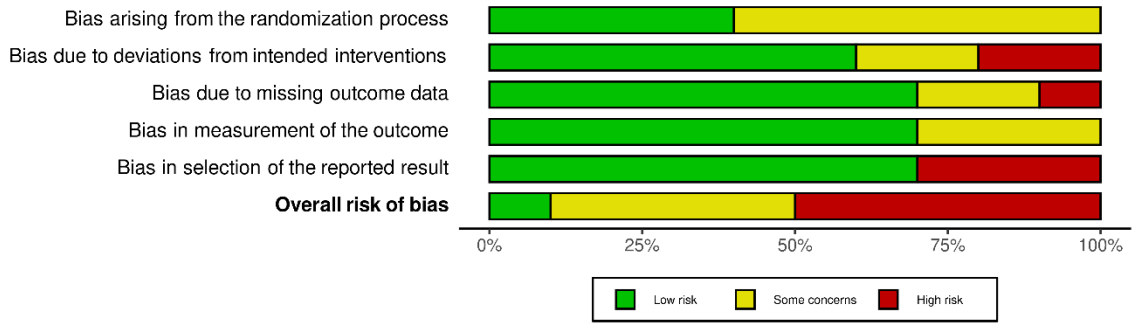
x = sufficient, o = insufficient, ? = no information

Abbreviations: Q1: Representativeness of the sample, Q2: Sample size, Q3:Nonresponders, Q4: Ascertainment of exposure (drug intake), Q5; Comparability of outcome groups, Q6: Assessment of outcome, Q7: Statistical tests

Supplementary Figure 2. Study type specific quality assessment – randomized controlled



Supplementary Figure 3. Risk of bias in randomized controlled trials



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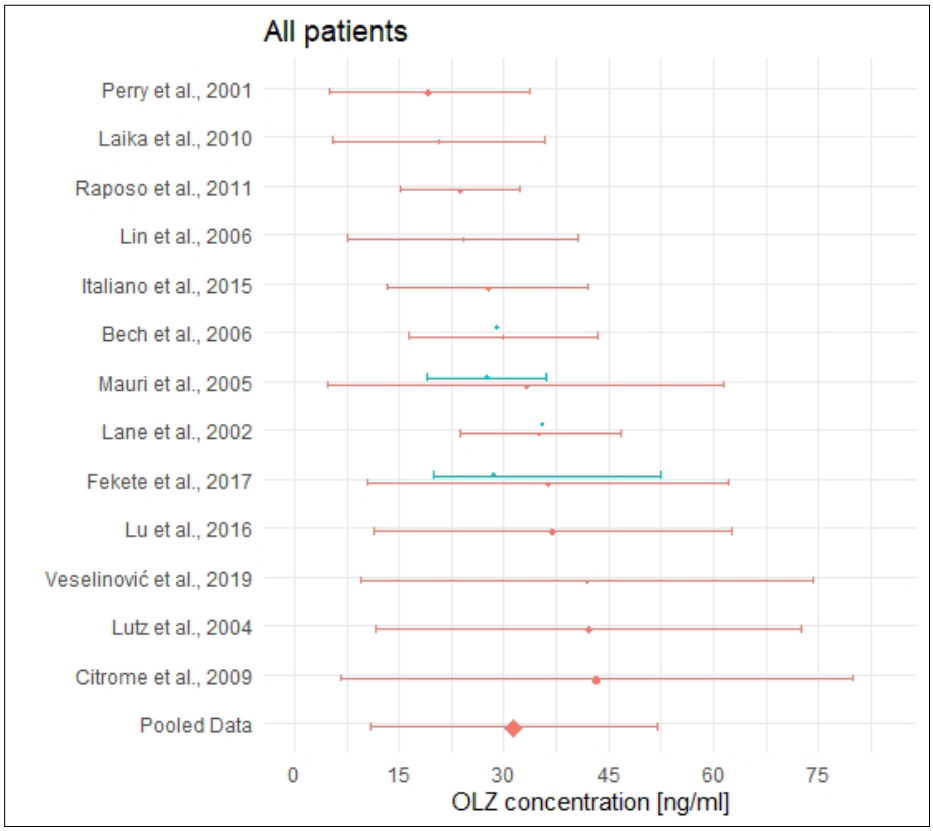
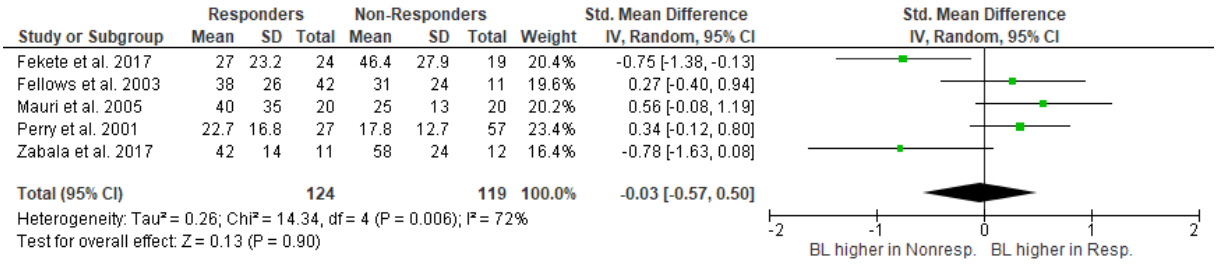
Supplementary Figure 4. Target ranges for OLZ (pooled range mean ± SD; pooled range median concentration; IQ 25 - 75)



Supplementary Figure 5. Metaanalysis of mean olanzapine concentration differences of Responders vs. Nonresponders across five studies (N = 243)



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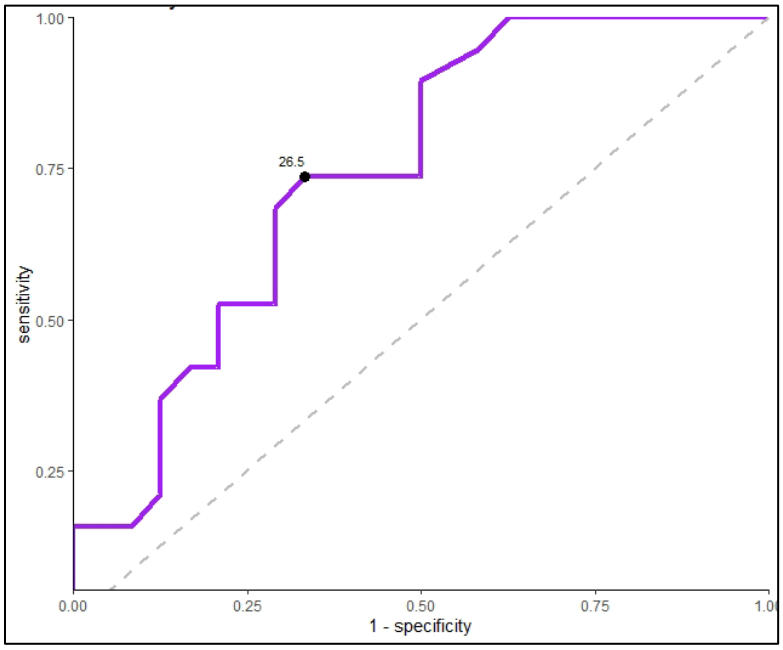
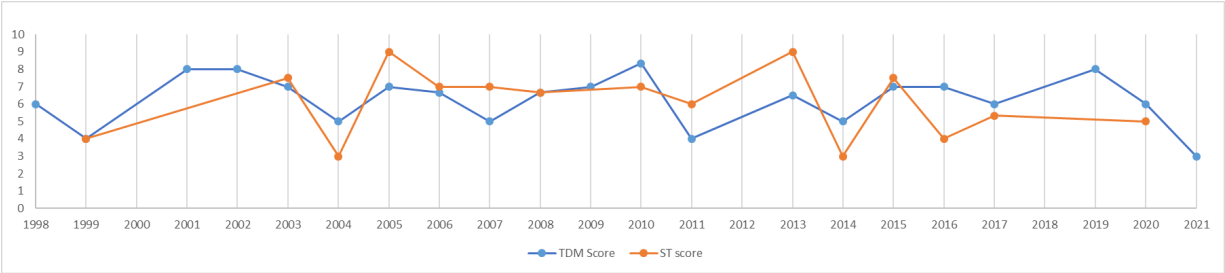
Supplementary Figure 6. ROC analysis Fekete et al., 2017 (AUC 0.743 (95 % CI: 0.597 - 0.889), p = 0.007, responders N = 19, nonresponders N = 24)



Supplementary Figure 7. Study Scores over time from 1998 - 2021



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Appendix 1. Abbreviations

ACE	Anticholinergic Effect
ADR	Adverse Drug Reaction
AIMS	Abnormal Involuntary Movement Scale
AMI	Amisulpride
AP	Antipsychotic
ARI	Aripiprazole
BARS	Barnes Akathisia Rating Scale
BD	Bipolar Disorder
BL	Blood Level
BPRS	Brief Psychiatric Rating Scale
C	Concentration
C/D	Concentration/Dose (ratio)
CGI-I	Clinical Global Impressions scale; Global Improvement
CGI-S	Clinical Global Impressions scale; Severity of illness
CI	Confidence Interval
CLO	Clozapine
C_{PL}	Plasma concentration
CS	Cohort Study
CSS	Cross-Sectional Study
CYP	Cytochrome P450
DOTES	Dosage Record Treatment Emergent Symptom Scale
DSM	Diagnostic and Statistical Manual of Mental Disorders
D_2R	D_2- like dopamine receptor
D_2RO	D_2- receptor occupancy
EC	Effective Concentration
ED	Effective Dose
EPS	Extrapyramidal Symptoms
EPSE	Rating Scale for Extrapyramidal Side Effects
FEP	First Episode Psychosis
FGA	First-Generation Antipsychotics
HAL	Haloperidol
HPLC	High Performance Liquid Chromatography
HRS-D	Hamilton Rating Scale for Depression
5-HT	5- Hydroxytryptamin, Serotonin
ICD	International Statistical Classification of Diseases and Related Health Problems
IQR	Interquartile Range
LAI	Long- Acting Injectable
LC-MS/MS	Liquid Chromatography/ Tandem Mass Spectrometry
LLS	Late- Life Schizophrenia
LOD	Limit of Detection
MADRS	Montgomery- Åsberg Depression Rating Scale
MAS	Bech- Rafaelsen Mania Scale
mDx	Multiple Diagnoses
MPR	Metabolite-to-Parent Compound Ratio
NA	Not Available
NeSSy	Neuroleptic Strategy Study
NF	Not Found
OLZ	Olanzapine
PANSS	Positive and Negative Syndrome Scale

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PD	Pharmacodynamically(active)
PDS	Paranoid- Depressivity Scale
PDSS	Post-injection Delirium/ Sedation Syndrome
PET	Positron Emission Tomography
PK	Pharmacokinetic
QUE	Quetiapine
RCT	Randomized Controlled Trial
RIS	Risperidone
RR	Reference Range
SAS	Simpson- Angus Scale
SANS	Scale for the Assessment of Negative Symptoms
SCZ	Schizophrenia
SD	Standard Deviation, Schizoaffective Disorder
SGA	Second- Generation Antipsychotics
SPECT	Single- Photon Emission Computerized Tomography
TDM	Therapeutic Drug Monitoring
TRSCZ	Therapy Resistant Schizophrenia
UGT1A4	UDP Glucuronosyltransferase Family 1 Member A4
UKU	Udvalg for Kliniske Undersøgelser
WAIS	Wechsler Adult Intelligence Scale
WFSBP	World Federation of Societies of Biological Psychiatry
YRMS	Young Mania Rating Scale

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