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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

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DISCLAIMER

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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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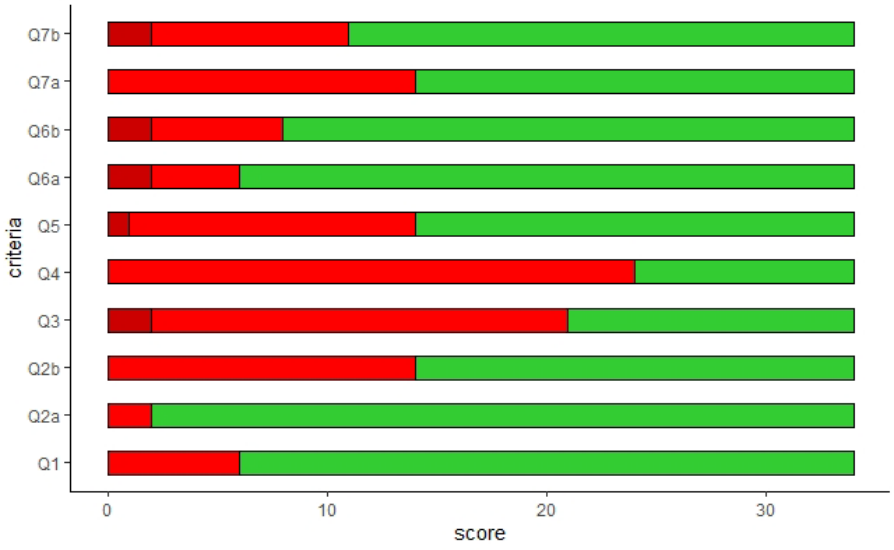
Supplementary Figure 1. Quality assessment results for TDM component



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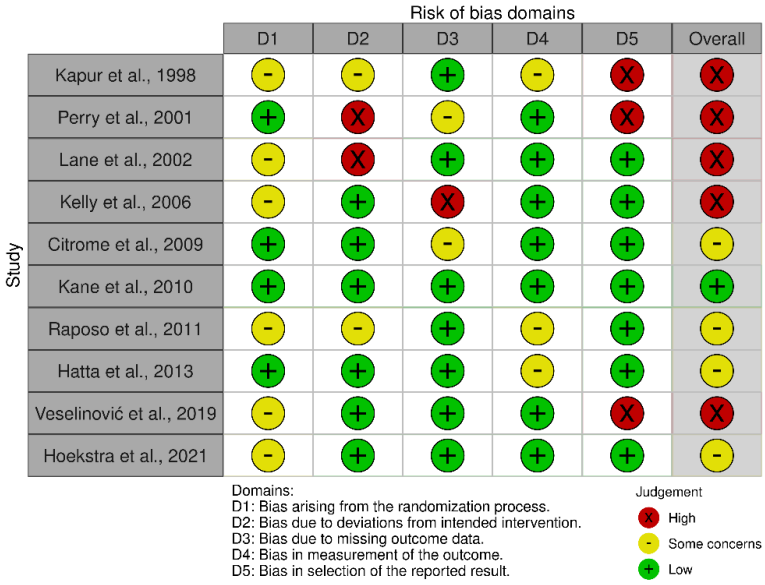
Supplementary Table 8. Study type specific quality assessment - cross-sectional studies [10]

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

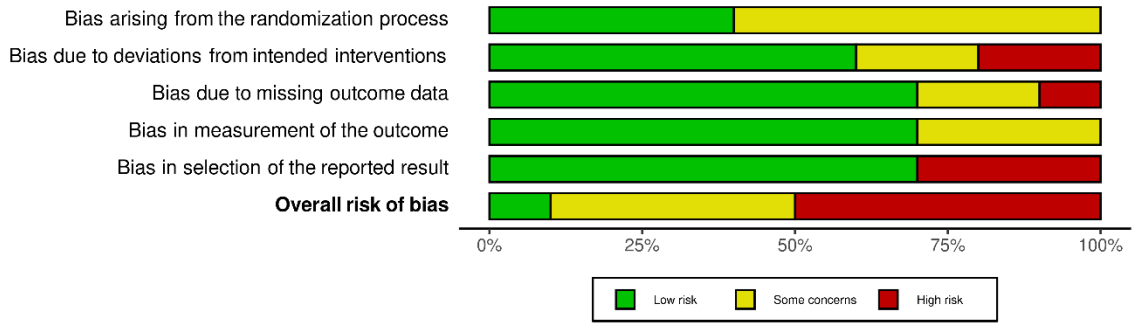
x = sufficient, o = insufficient, ? = no information

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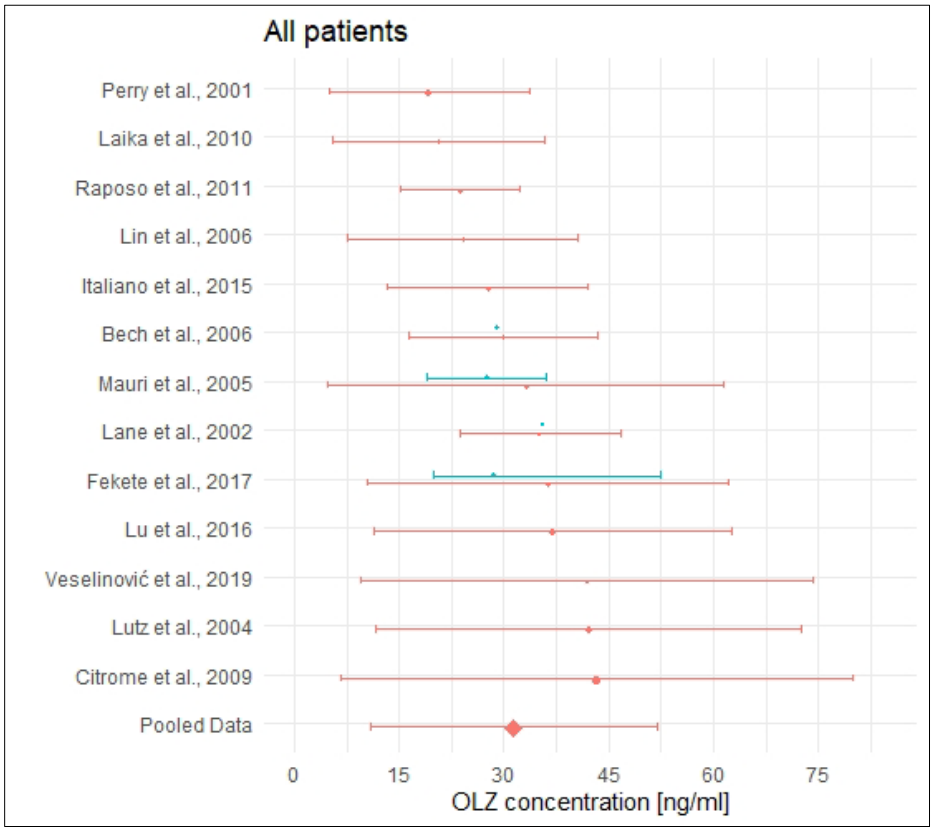
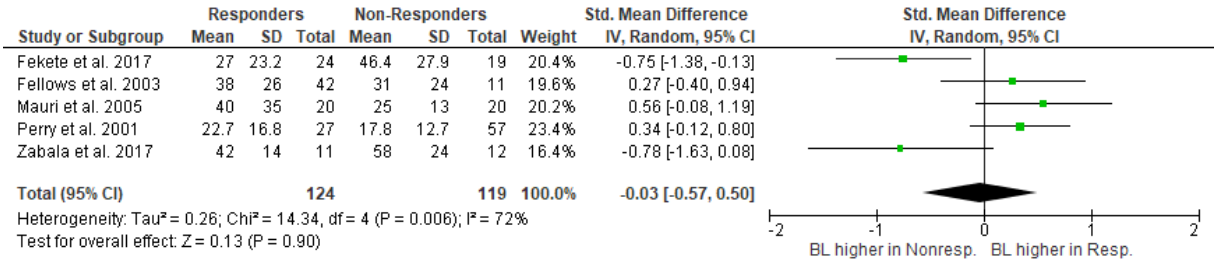
Supplementary Figure 4. Target ranges for OLZ (pooled range mean ± SD; pooled range median concentration; IQ 25 - 75)



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



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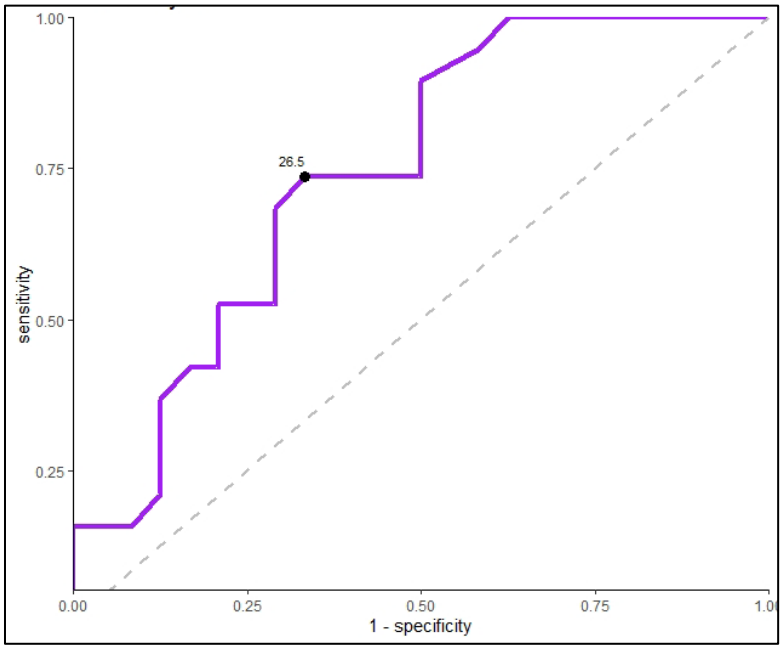
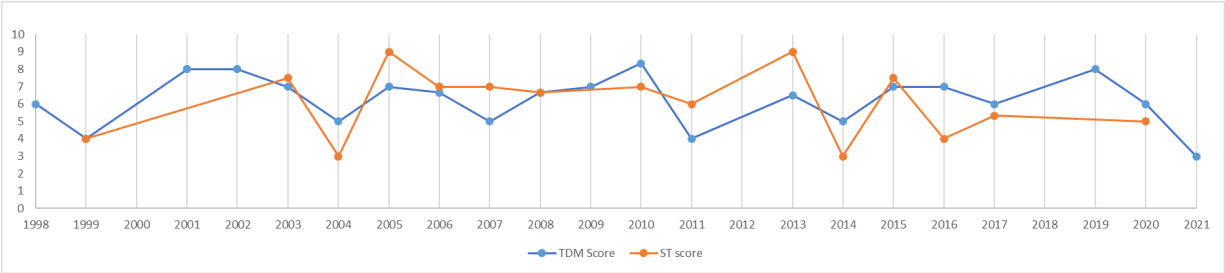
Supplementary Figure 6. ROC analysis Fekete et al., 2017 (AUC 0.743 (95 % CI: 0.597 - 0.889), p = 0.007, responders N = 19, nonresponders N = 24)



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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