From the Central Institute for Mental Health
Medical Faculty Mannheim
(Director: Prof. Dr. Andreas Meyer-Lindenberg)

Department for Molecular Neuroimaging
(Chair: Prof. Dr. Gerhard Gründer)

Therapeutic reference range for olanzapine in schizophrenia revised

Inaugural dissertation
for obtaining the doctoral degree in Medicine
at the
Medical Faculty Mannheim
of the Ruprecht Karls University
of
Heidelberg

submitted by
Katja Wesner

from
Elsterwerda
2023

Dean: Prof. Dr. med. Sergij Goerdt
Lector: Prof. Dr. med. Gerhard Gründer

TABLE OF CONTENTS

Page

LIST OF ABBREVIATIONS

ACS	Anticholinergic Side Effects
ADR	Adverse Drug Reaction
AE	Adverse Event
AIMS	Abnormal Involuntary Movement Scale
AM	Acute Mania
AMI	Amisulpride
AP	Antipsychotic
ARI	Aripiprazole
ASS.	Association
BAS	Barnes Akathisia Rating Scale
BARS	Brief Adherence Rating Scale
BD	Bipolar Disorder
BL	Blood Level
BMI	Body-Mass-Index
BPRS	Brief Psychiatric Rating Scale
C	Concentration
C/D	Concentration-to-dose
CES	Concentration/effect study
CGI-I	Clinical Global Impressions scale; Global Improvement
CGI-S	Clinical Global Impressions scale; Severity of illness
CI	Confidence Interval
CLO	Clozapine
corr.	Correlation
COS	Concentration Study
C_{PL}	Plasma concentration
CS	Cohort Study
CSS	Cross-Sectional Study
CYP	Cytochrome P450
DDD	Defined Daily Doses
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
ESRS	Extrapyramidal Symptom Ratings Scale
FEP	First Episode Psychosis
FIG	Figure
HAL	Haloperidol
FLB 457	Benzamide
HPLC	High Performance Liquid Chromatography
HRS-D	Hamilton Rating Scale for Depression
5-HT	5-Hydroxytryptamin, Serotonin
IBZM	Iodobenzamide
ICD	International Statistical Classification of Diseases and Related Health Problems
IQR	Interquartile Range
KW	Katja Wesner
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
NA	Not Available
NF	Not Founde
OLZ	Olanzapine
PANSS	Positive and Negative Syndrome Scale
PD	Pharmacodynamics
PDS	Paranoid-Depressivity Scale
PDSS	Post-injection Delirium/Sedation Syndrome

PET	Positron Emission Tomography
PGP	P-Glycoprotein
p.i.	Post-injection
PK	Pharmacokinetic
QUE	Quetiapine
RCT	Randomized Controlled Trial
RIS	Risperidone
ROC	Receiver Operating Characteristic
RR	Reference Range
SAS	Simpson-Angus Scale
SANS	Scale for the Assessment of Negative Symptoms
SCZ	Schizophrenia
SD	Standard Deviation, Schizoaffective Disorder
SPECT	Single-Photon Emission Computerized Tomography
TDM	Therapeutic Drug Monitoring
TOP	Thematically Organized Psychosis
TRSCZ	Therapy-Resistant Schizophrenia
UGT1A4	UDP Glucuronosyltransferase Family 1 Member A4
UKU	Udvalg for Kliniske Undersøgelser Side Effects Rating Scale
WAIS	Wechsler Adult Intelligence Scale
WFSBP	World Federation of Societies of Biological Psychiatry
XH	Dr.sc.hum. Xenia M. Hart
XL	Xenija Lense
YRMS	Young Mania Rating Scale

1. INTRODUCTION

1.1 Olanzapine

1.1.1 Clinical indications

Olanzapine is a thienobenzodiazepine that was approved by the U.S. Food and Drug Administration (FDA) in 1996 for the treatment of schizophrenia. It has also proven its effectiveness for the treatment of bipolar I disorder (BD), and, combined with fluoxetine, for treatment-resistant depression (Citrome et al., 2019; Lilly, 2021; Samara et al., 2016). It is effective against positive symptoms like hallucinations, delusions or disorganized behavior and speech. Compared to other antipsychotics, olanzapine shows relative benefits in improvement of negative symptoms, including flattened affect, loss of a sense of pleasure, will or drive, and social withdrawal (DGPPN, 2019; Novick et al., 2017; Schultz et al., 2007). Furthermore, patients with first-episode psychosis (FEP) and schizophrenia showed the lowest all-cause discontinuation rate under olanzapine treatment (Citrome et al., 2019; Green et al., 2006; Lieberman et al., 2005).

In daily practice, olanzapine is widely used especially for the treatment of schizophrenia spectrum and other psychotic disorders according to DSM-5, but also for obsessional thinking in patients with eating disorders, and for the induction of weight gain in patients with anorexia nervosa (APA, 2013; Hilbert et al., 2017; Meftah et al., 2020; Muratore & Attia, 2021). Recent data reveal positive effects for olanzapine as an add-on to the prophylaxis of chemotherapy-induced nausea and vomiting in low dose therapy (5 - 10 mg/d olanzapine per day) in patients with highly and moderately emetogenic chemotherapy (Chow et al., 2021; Navari et al., 2016; Sutherland et al., 2018; Yang et al., 2017).

1.1.2 Pharmacokinetics

Olanzapine is metabolized in the liver, mainly via cytochrome p450 (CYP)1A2, but also by CYP2D6, CYP3A4, flavin-containing monooxygenase and glucuronidation. Whereas the CYP1A2-isoenzyme (N-demethylation, formation of 4-N'-desmethyl-olanzapine (DMO)) accounts for approximately up to 60 % of olanzapine metabolism, hydroxylation via CYP2D6 is a minor pathway (Callaghan et al., 1999). Metabolites of olanzapine are less active than the parent compound and negligible for the clinical

effects of olanzapine (Calligaro et al., 1997; Soderberg & Dahl, 2013). After a single dose of olanzapine, the mean peak is achieved after about five hours (Bergemann et al., 2004; Bhana & Perry, 2001). The mean elimination half-life is 33 hours, ranging from 30 to 60 hours, and steady state is reached after approximately seven days (Callaghan et al., 1999; Hiemke et al., 2018). As an effective CYP1A2-inducer, tobacco smoking plays a significant role as an influencing factor on olanzapine plasma levels (Callaghan et al., 1999). Co-administration can result in a reduced olanzapine blood levels (Lucas et al., 1998). Likewise, co-medication with CYP1A2-inhibitors have to be considered in case of increased drug levels (Bigos et al., 2008; Gex-Fabry et al., 2003; Olesen & Linnet, 1999; Patel et al., 2011). Impairment of liver or kidney as well as ethnicity do not seem to have a significant influence on olanzapine blood levels (Callaghan et al., 1999). Significant differences were found in dose-adjusted drug concentrations for women and elderly people (Castberg et al., 2017; Gex-Fabry et al., 2003; Jonsson et al., 2019; Tveito et al., 2018). Possible causes are presumably lower CYP1A2 activity in females as well as pharmacokinetic changes associated with aging (Castberg et al., 2017).

1.1.3 Receptor binding profile

Olanzapine has a broad receptor binding profile and shows a high binding affinity for dopamine- (D_1-, D_2-, D_4-), serotonin- ($5\text{-}HT_{2A}$-, $5\text{-}HT_{2C}$-), α_1-adrenergic, histaminergic (H_1-), and muscarinic (M_1-) receptors (Bymaster et al., 1996; Citrome et al., 2019). At clinically relevant levels of D_2-receptor occupancy (D_2RO), olanzapine does not occupy D_3-receptors (McCormick et al., 2013). Dopamine D_2-receptor binding characterizes the receptor binding profile of all antipsychotics (Mauri et al., 2014). In case of olanzapine, moderate D_2-antagonism seems to be the mechanism of action for the improvement of positive symptoms (Gründer et al., 2009). As a second-generation antipsychotic, it shows a higher temporal cortical dopamine-receptor binding, while striatal binding is lower (Bigliani et al., 2000). This preferential extrastriatal binding and comparatively low occupancy of receptors in the striatum, in conjunction with strong $5\text{-}HT_{2A}$-antagonism, could result in less EPS and possibly other adverse effects (Gründer et al., 2009).

1.1.4 Side effects under olanzapine treatment

While EPS seem to rarely occur under olanzapine treatment**,** patients are at higher risk for metabolic side effects, most frequently weight gain, but also hyperglycemia, dyslipidemia, and hyperprolactinemia (Citrome et al., 2009; De Hert et al., 2011; Huhn et al., 2019; Zhang et al., 2013). Latest data emphasizes that the impact of olanzapine treatment on weight gain and BMI is more severe in drug-naive patients and also dose-dependent (Bobes et al., 2003; Kang et al., 2022). The risk of early weight gain, in contrast, was associated with treatment duration and co-medication (Schoretsanitis et al., 2022). Olanzapine treatment of patients with dementia is associated with an increased risk of cerebrovascular events, myocardial infarction, somnolence, abnormal gait, hip fracture, urinary tract infection, and increased mortality (Farlow & Shamliyan, 2017; Lilly, 2021). As a consequence, olanzapine is officially not approved for the treatment of patients with dementia-related psychosis (Lilly, 2021).

1.1.5 Olanzapine pamoate

While oral antipsychotics are highly effective for the treatment of schizophrenia, poor adherence remains challenging. Up to 50% of patients with schizophrenia do not adhere to their treatment in short term, and over 70% experience recurrent relapse and disability (Citrome et al., 2019; Kaplan et al., 2013). Nonadherence to therapy is one of the major causes for relapse. It can cause symptom exacerbation, associated with an increased risk for impaired mental functioning, emergency treatment, or rehospitalization (Ascher-Svanum et al., 2006; Correll et al., 2021; Lafeuille et al., 2013). Long-acting injectable (LAI) formulations were developed to improve adherence to therapy by ensuring a stable drug plasma concentration. As a consequence, the risk of adverse effects and relapse is reduced (McEvoy, 2006). Treatment with LAI formulations are associated with better functioning, quality of life, and patient satisfaction (Kaplan et al., 2013). LAI's are furthermore advantageous for the treatment of therapy-resistant patients as well as patients with comorbidities including substance use disorders and aggressive and suicidal behavior (Abdel-Baki et al., 2020; Díaz-Fernández et al., 2020; Howes et al., 2017; Schoretsanitis et al., 2021).

Olanzapine pamoate was approved in the European Union in 2008 for the maintenance treatment of schizophrenia in adults with a comparable efficacy to oral olanzapine (Bishara & Taylor, 2008; Di Lorenzo & Brogli, 2010).

It consists of a low-soluble, microcrystalline salt of pamoic acid and olanzapine, which is suspended in an aqueous solution. After intramuscular gluteal injection, the salt slowly dissolves into olanzapine as its free base, pamoic acid, and other acids and bases (Correll et al., 2021; Park et al., 2013; Schoretsanitis et al., 2021). The absorption rate is slower than the elimination rate, resulting in a so called ‘flip-flop’ pharmacokinetics. After the shift into the bloodstream, distribution and elimination of olanzapine pamoate is the same as for oral olanzapine (Correll et al., 2021; Spanarello & La Ferla, 2014). Peak olanzapine plasma concentrations after application of the LAI formulation appear after two to six days. The apparent half-life is 30 days, so steady state is reached in approximately three months, respectively 12 weeks (Correll et al., 2021; Heres et al., 2014; Lilly, 2016). According to the recommendation of the manufacturer, oral supplementation is not required during initiation of olanzapine pamoate (Lilly, 2016). Olanzapine pamoate is available in dosages of 210, 300, and 405 mg for depot injections and dosage schedule comprises 150 - 300 mg every two weeks up to 300 - 405 mg every four weeks.

The safety profile of olanzapine pamoate is comparable to that of oral olanzapine with the exception of a rare and serious adverse drug reaction, called Post-injection Delirium/Sedation Syndrome (PDSS). It occurs in 0.07 % of injections and is consistent with an acute olanzapine overdosing caused by unintentional intravascular injection of olanzapine pamoate due to its relatively high hematic solubility (Di Lorenzo & Brogli, 2010; Kane et al., 2010; Lindenmayer, 2010). When the salt comes into contact with blood, it rapidly dissolves resulting in supratherapeutic olanzapine blood levels (Correll et al., 2021; Detke et al., 2010). PDSS occurs within minutes to hours after injection of olanzapine pamoate with a mean time occurrence of 49 minutes (Luedecke et al., 2015; Novakovic et al., 2013). Symptoms of PDSS appear to be associated with delirium and sedation; such as disorientation, confusion, ataxia, dysarthria, irritability, anxiety, dizziness, somnolence, from mild sedation up to coma (Detke et al., 2010; Luedecke et al., 2015; Meyers et al., 2017). A full recovery within 72 hours was seen in all observed cases. A clinical observation period of three hours after injection is required (Detke et al., 2010; Lilly, 2016).

1.2 TDM and the therapeutic reference range of olanzapine

Therapeutic drug monitoring (TDM) implies the measurement of drug levels in plasma or serum along with a clinical and pharmacological interpretation and aims to optimize individual drug dosing, maximizing clinical efficacy while minimizing toxicity (Pennazio et al., 2022). There are different clinical scenarios where TDM is useful, or even required: Nonadherence to antipsychotic treatment is a main concern in daily clinical practice and a frequent cause to determine plasma drug concentrations. A lack of response, relapse or side effects to drug treatment, as well as drug-drug interactions under polypharmacy can result in the need for a dosage adjustment based on the patient's individual pharmacokinetic and drug concentration. Specific vulnerable groups such as children, elderly patients, pregnant women, forensic patients, or patients with pharmacokinetically relevant comorbidities (such as hepatic or renal dysfunction) are target populations with particular benefit of TDM. Switching from an oral to a long-acting injectable drug formulation also requires an assessment of drug concentration to specify a level that ensures clinical stability (Schoretsanitis et al., 2021; Schoretsanitis et al., 2020). The rationale for TDM is the verification of a relationship between drug level, clinical effects, and toxicity (Hiemke et al., 2018). It is based on a drug concentration range for maximum effectiveness and acceptable safety, the so-called “therapeutic reference range’’. This range is defined as ‘a range of drug concentrations in blood that specify a lower limit below which a drug induced therapeutic response is relatively unlikely to occur and an upper limit above which tolerability decreases or above which it is relatively unlikely that therapeutic improvement may be still enhanced’ (Hiemke et al., 2018). These ranges are population based and not necessarily applicable to all patients. It can be a guide to identify the individual’s required therapeutic concentration when the drug concentration is determined after the envisaged clinical outcome is reached and no significant side effects are present (Hiemke et al., 2018; Pennazio et al., 2022).

Based on the assumption of a direct relationship between clinical and adverse effects of olanzapine on the one hand and receptor occupancy on the other, D_2-receptor occupancy studies via Positron Emission Tomography (PET) are closely related to determination of olanzapine’s pharmacokinetics (Gründer et al., 2011; Hiemke et al., 2018). Early PET studies revealed an optimal clinical response at 65 - 80% D_2-receptor occupancy for first- and second-generation antipsychotic drugs (Farde et al., 1992; Nordström et al., 1993). The occurrence of EPS was evident above 80% D_2-

receptor occupancy, indicating the upper therapeutic threshold (Kapur et al., 2000; Nyberg et al., 1995).

In 2018, an updated guideline for TDM in Neuropsychopharmacology was published with the highest level of recommendation for olanzapine to use TDM. Based on findings from studies in patients with schizophrenia, olanzapine dose titration within a range of 20 to 80 ng/ml, with a laboratory alert level of 100 ng/ml, was proposed (Hiemke et al., 2018). However, evidence emerged that suggested an adaption of olanzapine's reference range towards lower values after oral administration (20 - 40 ng/ml; (Bishara et al., 2013; Olesen & Linnet, 1999)) as well as for olanzapine pamoate (10 - 40 ng/ml; (Schoretsanitis et al., 2021)).

1.2.1 Critics on TDM guidelines and published reference ranges

After the Arbeitsgemeinschaft für Neuropsychopharmakologie und Pharmako-psychiatrie (AGNP) published the updated TDM guidelines in 2017, discussions about the underlying methods of the guidelines emerged, considering the reported therapeutic reference ranges based on inconsistent methodologies as more or less experts' opinions (Hart et al., 2021). It was recommended that therapeutic reference ranges were deduced from well-designed studies and based on standardized methods on how to search and evaluate clinical studies as well as a subsequent rating and discussion of included studies and their methodology (Cooney et al., 2017; Noel, 2019).

1.3 Research objectives

In the first step, a systematic approach was developed and used to determine a therapeutic reference range for olanzapine based on a systematic literature approach, evaluation and grading of available literature. The evidence for a relationship between concentration and clinical effects was subsequently graded into a level. The applicability of the revised range was compared to the previously published range using TDM data from patients at the Central Institute of Mental Health in Mannheim.

2. MATERIAL AND METHODS

2.1 Systematic literature search

In March 2021, we conducted a systematic literature search according to the PRISMA statement including a quality control of the publications and grading of available evidence. It was updated in December 2021. This systematic review is registered under PROSPERO number CRD42021216182.

2.1.1 Search strategy

The literature search was conducted via following databases: Medline via PubMed, Web of Science, PsycINFO and Cochrane Database for Systematic Reviews and Trials. The detailed search strategy is shown in Figure 16 and included the key terms ‘olanzapine’, ‘blood level’, ‘therapeutic drug monitoring’ and ‘PET/SPECT scan’. There was no time limit set for the publication date and no filter was used. Search alerts were activated for every search string.

2.1.2 Study eligibility

The inclusion and exclusion criteria are presented in Table 1. Studies investigating oral and olanzapine LAI were included. Reports of olanzapine blood levels in relation to clinical outcomes or dopamine D_2-receptor occupancy (D_2RO) were mandatory. Titles and abstracts of study results were screened by two reviewers (KW and XH). If a concluding decision could not be made based on the abstract, the full paper was examined. Disagreements between reviewers were resolved by discussion. References of included studies were checked for other relevant articles. In addition, one guideline was screened for relevant articles.

2.1.3 Data extraction

Screening of the literature was performed by two independent reviewers. Initially, one reviewer (KW) examined titles and abstracts of references according to the inclusion and exclusion criteria (Table 1). Subsequently, relevant articles were transferred into one combined EndNote library, and duplicates were removed automatically and

manually. All relevant papers were checked for eligibility in full text and screened for relevant details.

Table 1. In- and exclusion criteria for the selection of relevant studies

Inclusion criteria for all studies	**Exclusion criteria for all studies**
I1 The study concerns olanzapine I2 Olanzapine blood levels are measured and reported (mean or median concentration) I3 Publication is written in English or German	E1 Non-human subjects E2 Studies not concerning olanzapine E3 Studies without an abstract E4 Studies not written in English/ German E5 Studies primarily comparing blood analysis techniques E6 Grey literature (e.g. expert opinions, conference papers and abstracts) E7 Case reports and case series E8 Data from simulation studies E9 Reviews and meta-analysis E10 Maternal use during pregnancy or lactation E11 Postmortem studies E12 No olanzapine monotherapy E13 Papers containing the same data E14 Studies that do not report olanzapine concentrations E15 Other reasons
Additional inclusion criteria for	**Additional exclusion criteria for**
<u>Concentration/effect studies</u> I4 Direct clinical outcome measures are reported, using a standardized rating scale (e.g. CGI, BPRS, PANSS, UKU, AIMS)[A] I5 Drug concentration is measured in steady state[B] <u>Neuroimaging studies</u> I6 Dopamine D2-receptor occupancy is measured in the brain	<u>Concentration/effect studies</u> E 16 Drug effects assessed in healthy volunteers

[A] biomarkers (e.g. blood sugar, prolactin levels) are not regarded as a direct clinical outcome measurement

[B] not for studies, in which injectable formulations were administered

AIMS: Abnormal Involuntary Movement Scale; BPRS: Brief Psychiatric Rating Scale; CGI: Clinical Global Impressions scale; PANSS: Positive and Negative Syndrome Scale; UKU: Udvalg for Kliniske Undersøgelser Side Effects Rating Scale

A second reviewer (XH) separately screened titles and abstracts of the references and compared them to the selection criteria. In case a final decision could not be made based on the abstract alone, the full article was reviewed. Studies were identified, which investigated olanzapine in relation to a concentration/effect relationship or D_2RO. Two reviewers (KW, XL) independently extracted the following information from

each study: reference (author, year); study design; study participants (including age, sex, diagnoses, and country); olanzapine dosage and concentration; outcome measures; co-medication; dose design; analytical method with Limit of Detection (LOD); blood sample collection (steady state and time of last drug intake); and concentration design. Finally, we contacted authors of eligible trials for additional data. If any differences between reviewers' choices occurred, a consensus decision had to be reached by discussion.

2.2 Quality assessment of selected studies

Three reviewers (KW, XH, XL) independently rated all included studies according to a self-designed rating instrument to assess the quality of TDM components of the studies and reporting (Hart et al., 2021). To date, there are no standardized quality tools for studies specifically investigating TDM. Therefore, we adapted the quality criteria to a recent review by Kloosterboer et al. on the concentration/effect relationship of psychotropic drugs in minors, which was adapted from a previously published meta-analysis by Ulrich et al. for haloperidol (Kloosterboer et al., 2020; Ulrich et al., 1998). If a study did not report or implement an item to the full extent, that item was rated as insufficient. The TDM quality score ranges from 0 to 10 (selection (scale 0 - 3), comparability (scale 0 - 2), and drug monitoring (scale 0 - 5)). For the quality assessment of cohort studies and cross-sectional studies, an adapted version of the Newcastle-Ottawa Scale (NOS) was used. The quality score ranges from 0 to 10 (selection (scale 0 - 4), comparability (scale 0 - 2), and outcome (scale 0 - 4)) for cohort studies, and from 0 to 8 (selection (scale 0 - 4), comparability (scale 0 - 2), and outcome (scale 0 - 2)) for cross-sectional studies.

Single items of the TDM quality score and quality assessment of cohort and cross-sectional studies are listed in in the following section. Likewise, two reviewers (TR, XH) rated the quality of the relevant efficacy cohort of randomized controlled trials separately using the Cochrane Risk of Bias Tool for randomized trials (RoB 2, Table 2, appendix). Any disagreements were resolved through discussion. Results were visualized using robvis. The level of evidence for a concentration/response relationship and for a concentration/side effects relationship was determined following the recommendations of the WFSBP guidelines for clinical guideline development (Hasan et al., 2019). The overall quality of evidence was recorded as strong, limited, low or no evidence (Table 3, appendix).

General quality criteria for the **TDM component** (Total 10 points)
Items marked with * are rated sufficient

Selection (Maximum 3 points):

1) Representativeness of the patient sample (Q1, Maximum 1 point):
   a) Truly representative of the average patient population in the community (referred to as average Caucasian patient population)*
   b) Somewhat representative of the average patient population in the community*
   c) Selected group of users or user not representative for review outcome
   d) No description of the derivation of the cohort

For b) "Somewhat representative": i) A study population only comprises of patients for whom TDM was requested by the clinician. ii) Patients are drawn from an ethnic group with a different distribution in CYP expression patterns than Caucasians, which are relevant for the metabolism of the administered drug and the main metabolite does not contribute to the pharmacologic action.
For c) "Selected group of users": i) Patients are drawn from an ethnic group with a different distribution in CYP expression patterns than Caucasians, which are relevant for the metabolism of the administered drug and the main metabolite contributes to the pharmacologic action. ii) A study population only comprises of treatment-resistant patients or patients with side effects to another treatment iii) A study population only comprises of patients for whom genotyping has been demanded by the clinician. iii) A study population only comprises of patients 65 years and older or 18 years and younger

2) Diagnosis (Q2, Maximum 2 points):
   a) Patients selected according to psychiatric classifications and associated classification system are reported*
   b) Homogenous sample according to one main diagnosis, healthy controls or: With a heterogeneous sample, a sub-analysis per relevant category should be provided*
   c) no description of the patient classification or heterogeneous sample in regard to diagnosis

Comparability (Maximum 2 points):

3) Co-medication (Q3, Maximum 1 point):
   a) If clinical effects are assessed: No drug that influences the investigated clinical effect (e.g. antidepressant or antipsychotic effect) or metabolism of the drug (clinically relevant) under study is taken simultaneously, or: A sub- analysis/ correction is provided (Medication on demand, e.g. Benzodiazepines or sleep medication, is permitted)*

   b) If no clinical effects are assessed: No drug that influences the metabolism of the drug (clinically relevant) under study is taken simultaneously, or: A sub-analysis/ correction is provided*
   c) No or insufficient information that allows to assess possible influence of administered co-medication is given
4) Dose design (Q4, Maximum 1 point):
   a) Fixed doses were administered*
   b) Flexible dosing was performed
   c) Single doses were administered or no information on dosing strategy

For b) Flexible dosing describes the adaption of doses according to the clinician's decision, in case of side effects or insufficient tolerability.

Drug Monitoring (Maximum 5 points):

5) Analytical method for the assay of drug concentration in serum or plasma (Q5, Maximum 1 point)
   a) Validated analytical method with appropriate LOD*
   b) Not validated analytical method was used
   c) Insufficient description or no validated analytical method used
6) Blood sample collection (Q6, Maximum 2 points)
   a) Plasma or serum concentrations are in the steady state*
   b) Time interval between sampling and drug intake described or sampling at trough*
   c) Insufficient description
   d) Steady state not reached
7) Concentration design (Q7, Maximum 2 points)
   a) A schedule with frequent measurements (at least 2) of blood samples was used*
   b) Sufficiently broad concentration range including sub- and/ or supratherapeutic drug concentrations (in the steady state) according to former recommended reference ranges*
   c) Single concentration measurements
   d) No sufficiently broad concentration range

This scale has been adapted from a published systematic review by Kloosterboer et al. to perform a comparable quality assessment across study types for the systematic review. (Kloosterboer et al., 2020) A comparable rating across studies is needed in order to decide, which studies can be included in the data synthesis.

Study type specific quality assessment - **Cohort studies** (Total 10 points)

Items marked with * are rated sufficient

Selection (Maximum 4 points):

1. Representativeness of the exposed cohort (Maximum 1 point):
   a) Truly representative of the average patient population in the (referred to as average Caucasian patient population)*
   b) Somewhat representative of the average patient population in the community*
   c) Selected group of users or user not representative for review outcome
   d) No description of the derivation of the cohort

For b) "Somewhat representative": i) A study population only comprises of patients for whom TDM was requested by the clinician. ii) Patients are drawn from an ethnic group with a different distribution in CYP expression patterns than Caucasians, which are relevant for the metabolism of the administered drug and the metabolite does not contribute to the pharmacologic action.
For c) "Selected group of users": i) Patients are drawn from an ethnic group with a different distribution in CYP expression patterns than Caucasians, which are relevant for the metabolism of the administered drug and the metabolite does contribute to the pharmacologic action. ii) A study population only comprises of treatment-resistant patients or patients with side effects to another treatment iii) A study population only comprises of patients for whom genotyping has been demanded by the clinician. iii) A study population only comprises of patients 65 years and older or 18 years and younger.

2) Selection of the control cohort (Maximum 1 point):
   a) Drawn from the same community as the exposed cohort*
   b) Drawn from a different source
   c) No description of the derivation of the non-exposed cohort
   d) No control cohort
3) Ascertainment of exposure (drug intake, Maximum 1 point):
   a) Secure record (e.g. adherence problems detected by blood level measurement or pill counting and discussed by the authors)*
   b) Study record (e.g. drug intake documented by study personal)*
   c) Patient self-report (e.g. patient diary)
   d) No description or no record
4) Demonstration that outcome of interest was not present at start of study (Maximum 1 point):
   a) Yes (outcome of most interest according to the authors)*
   b) No
   c) Not applicable

Comparability (Maximum 2 points):

5) Comparability of "exposed" and "non-exposed" individuals or of outcome groups
   a) The study controls for the most important factor*

b) The study controls for any additional factor*

Either exposed and non-exposed individuals must be matched in the design and/ or confounders must be adjusted for in the analysis. Statements of no differences between groups or that differences were not statistically significant are not sufficient for establishing comparability. Note: If the relative risk for the exposure of interest is adjusted for the confounders listed, then the groups will be considered to be comparable on each variable used in the adjustment. There may be multiple ratings for this item for different categories of exposure (e.g. ever vs. never, current vs. previous or never). (Examples for factors controlled by study design: co-medication, premedication and washout-phase. Examples for factors controlled by analysis: Mean doses if flexible design, sex, age and baseline severity of illness).

Outcome (Maximum 4 points):

6) Assessment of outcome (Maximum 1 point):
   a) Independent or blind assessment stated in the article, or confirmation of the outcome by reference to secure records (e.g. receptor occupancy by PET scan)*
   b) Record linkage*
   c) Self-report (i.e. self-rating scales or non-established rating scales)
   d) No description or insufficient information

For some outcomes (e.g. genotypes, blood concentrations) reference to the medical record is sufficient to satisfy the requirement for confirmation. This would not be adequate for clinical efficacy outcomes where a structured rating scale would be required. For neuroimaging studies, which also assess clinical effects, both methods will be evaluated and the lowest rating will be used.

7) Was follow up long enough for outcomes to occur (Maximum 1 point):
   a) Yes (select an adequate follow up period for outcome of interest)*
   b) No
   c) Not applicable
8) Adequacy of follow up of cohorts (Maximum 1 point)
   a) Complete follow up; all subjects accounted for*
   b) Subjects lost to follow up unlikely to introduce bias - small number lost - ≥ 5% follow up, or description provided of those lost indicates no bias (see Cochrane Tool RoB 2.0 Item 3.2, 3.3 and 3.4)*
   c) Follow up rate < 95% and no description of those lost
   d) No statement

9) Statistical test (Maximum 1 point):

a) The statistical test used to analyze the data is clearly described and appropriate, and the measurement of the association is presented, including confidence intervals and the probability level (p-value)*
b) The statistical test is not appropriate, not described or incomplete

This scale has been adapted from the Newcastle- Ottawa Quality Assessment Scale for cohort studies. We have not selected one factor that is the most important for comparability, because the variables are not the same in each study. Thus, the principal factor should be identified for each study. The resulting quality score can be used to compare risk of bias across cohort studies in this review.

Study type specific quality assessment- **Cross-sectional studies** (total 8 points)

Items marked with * are rated sufficient

Selection (Maximum 4 points):

1) Representativeness of the sample (Maximum 1 point):
   a) Truly representative of the average in the target population (referred to average Caucasian patient population)*
   b) Somewhat representative of the average in the target population*
   c) Selected group of users or user not representative for review outcome
   d) No description of the sampling strategy

For b) “Somewhat representative”: i) A study population only comprises of patients for whom TDM was requested by the clinician. ii) Patients are drawn from an ethnic group with a different distribution in CYP expression patterns than Caucasians, which are relevant for the metabolism of the administered drug and the metabolite does not contribute to the pharmacologic action.
For c) “Selected group of users”: i) Patients are drawn from an ethnic group with a different distribution in CYP expression patterns than Caucasians, which are relevant for the metabolism of the administered drug and the metabolite does contribute to the pharmacologic action. ii) A study population only comprises of treatment-resistant patients or patients with side effects to another treatment iii) A study population only comprises of patients for whom genotyping has been demanded by the clinician. iii) A study population only comprises of patients 65 years and older or 18 years and younger

2) Sample size (Maximum 1 point):
   a) A priori sample size calculation justified and satisfactory*
   b) Sample size not justified or not satisfactory
3) Nonrespondents (Maximum 1 point):
   a) Comparability between respondents and nonrespondents characteristics is established, and the response rate is satisfactory (e.g. responders/ nonresponders, genotype groups, co-medication groups)*
   b) The response rate is unsatisfactory, or the comparability between respondents and nonrespondents is unsatisfactory
      No description of the response rate or the characteristics of the responders and the nonresponders

4) Ascertainment of exposure (drug intake) (Maximum 1 point):
   a) Secure record (e.g. adherence problems detected by blood level measurement or pill counting and discussed by the authors)*
   b) Study record (e.g. drug intake documented by study personal)*
   c) Patient self-report (e.g. patient diary)
   d) No description or no record

Comparability (Maximum 2 points):

5) Comparability of outcome groups (Maximum 2 points):
   a) The study controls for the most important factor*
   b) The study control for any additional factor*

The subjects in different outcome groups are comparable, based on the study design or analysis. Confounding factors are controlled. (Examples for factors controlled by study design: co-medication, premedication and washout-phase. Examples for factors controlled by analysis: Mean doses if flexible design, sex, age and baseline severity of illness).

Outcome (Maximum 2 points):

6) Assessment of outcome (Maximum 1 point):
   a) Independent or blind assessment stated in the article, or confirmation of the outcome by reference to secure records (e.g. receptor occupancy by PET scan)*
   b) Record linkage*
   c) Self-report (i.e. self-rating scales or non-established rating scales)
   d) No description or insufficient information

For some outcomes (e.g. genotypes, blood concentrations), reference to the medical record is sufficient to satisfy the requirement for confirmation. This would not be adequate for clinical efficacy outcomes where a structured rating scale would be required. For neuroimaging studies, which also assess clinical effects, both methods will be evaluated, and the lowest rating will be used.

7) Statistical test (Maximum 1 point):
   a) The statistical test used to analyze the data is clearly described and appropriate, and the measurement of the association is presented, including confidence intervals and the probability level (p-value)*
   b) The statistical test is not appropriate, not described or incomplete (e.g. results from all rating scales performed should be described)

This scale has been adapted from the Newcastle-Ottawa Quality Assessment Scale for cohort studies to perform a quality assessment for cross-sectional studies for the systematic review. We have not selected one factor that is the most important for comparability, because the variables are not the same in each study. Thus, the principal factor should be identified for each study. The resulting quality score can be used to compare risk of bias across cross-sectional studies in this review.

TDM quality score and quality assessment of cohort and cross-sectional studies are retrieved from Hart et al.; a protocol for systematic reviews (Hart et al., 2021).

2.2.1 Risk of bias rating for TDM components

For the study results to be applied in a generalized manner, a representative sample is important that reflects the target population for the investigated drug and its resulting reference range. A study population only comprising of men, treatment-resistant patients or patients with side effects to another treatment may not reflect the general patient population and a resulting range might not be transferable. Likewise, a study population drawn from patients who were admitted to the hospital involuntarily and needed an emergency treatment will not reflect the target population. Patients 65 years and older or 18 years and younger should be further evaluated for comparability with the average adult population. For some psychoactive drugs, ethnic variation in distribution in CYP expression patterns are relevant for the metabolism of the administered drug. This is important if the main metabolite of the drug contributes to the pharmacologic action, which is not relevant for olanzapine.

Investigated diagnoses should be assigned according to psychiatric classifications as Diagnostic and Statistical Manual of Mental Disorders (DSM; (APA, 2013)) or International Statistical Classification of Diseases and Related Health Problems (ICD; (WHO, 2019)). A homogenous patient sample according to one main diagnosis is included, or, with a heterogeneous sample, a sub-analysis per relevant category should be provided.

To avoid drug interactions and associated clinical effect bias, no drugs that affect the pharmacodynamic of olanzapine, e.g. antipsychotics, antidepressants and mood stabilizers, should have been taken concomitantly during the study. If detailed information on co-medication was not provided, this was considered as insufficient. The use of on-demand medication such as benzodiazepines or sleep medication was rated as adequate. Premedication was registered as study characteristic and was not scored. In case of possibly interfering co-medication, the item was not fulfilled.

The clinical status of a subject may determine the amount of dose administered and thus the drug concentration. To avoid a possible reversal of a causal relationship resulting from such an effect, a study design with a fixed dose should be preferred over a design with a flexible dose. Therefore, flexible dosing was judged to be insufficient.

An analytical method is considered valid if it is accurate, precise, selective, sensitive, reproducible, with stable measurements of the substance's concentration. In general, chromatographic methods, such as high-performance liquid chromatography (HPLC) and liquid chromatography-mass spectrometry (LC-MS), are selective and sensitive methods. Immunoassays are considered low specific. The LOD of the chosen analytical method should allow drug concentration measurements below the lower limit of currently recommended therapeutic reference ranges. Double measurements of samples are preferred but not performed in clinical routine practice.

Since the time of sample collection affects olanzapine blood levels, the sample should be collected at steady state and preferably at trough level. If the information on the sampling time was missing, this was considered insufficient. Olanzapine reaches steady state after a constant drug intake of seven days. A steady state level of olanzapine LAI is achieved in approximately three months when switching from oral olanzapine. The sampling schedule should include repeated sampling of one patient.

Analysis of only the current blood level with actual response is problematic because of the known time lag between use and antipsychotic onset of clinical effect. Since the study period usually extends over several weeks, a schedule of multiple measurements of blood samples is rated sufficient. Intraindividual measurements at different olanzapine doses would be best. However, this is not generally done, all studies in which a minimum of two measurements were made, were judged to be sufficient. A second requirement for the concentration design is a sufficiently wide concentration range with sufficient data of sub- and/or supratherapeutic blood levels.

2.2.2 Level of evidence

In order to assess, whether available data support a concentration/response relationship, grading of the revealed evidence into Levels of Evidence (LoE) should be performed following a systematic approach according to a modification of the WFSPB guidelines. The WFSPB guidelines also provide guidance on how to assess the risk of bias and the quality of clinical trials. The authors have explored specific demands of randomized controlled trials in the field of psychiatry including validity, control group, uncontrolled studies, randomization, study conditions, blinding, sample sizes, intent-to-treat analysis, endpoints, statistics, sponsor and allegiance effects. Levels of Evidence relating to the published literature are documented in Table 3 (appendix).

2.3 Qualitative and quantitative data synthesis

Clinical efficacy or side effects should be reported in a quantitative way using established rating scales. Factors influencing olanzapine blood levels like daily dose, smoking status, sex, tobacco consumption, co-medication or CYP1A2 genotype were extracted. For the inclusion of neuroimaging studies, determination of D_2-receptor occupancy in relation to olanzapine blood levels was required. Half maximal effective concentration which induces a D_2-receptor occupancy of 50% (EC_{50}) of any study was of special interest in order to calculate EC_{65} and EC_{80} values. For a quantitative synthesis, mean olanzapine plasma concentrations, standard deviations, median concentrations, interquartile ranges and C/D ratios were assessed. Data were either extracted from the study paper or calculated manually whenever all numbers were available. Unpublished information was accordingly indicated. In case of more than one concentration measurement, the latest value was included.

2.4 Evaluation of in-house TDM data

Patient samples for TDM, collected at the Central Institute of Mental Health in Mannheim, were provided by the SYNLAB Laboratory in Heidelberg, Germany. Blood samples were taken from in- and outpatients during the time period from 01/2014 to 12/2018. Indications for blood sampling were the following: i) routine TDM in outpatients, ii) inpatient admission, iii) control of drug adherence, iv) blood level determination after initiation or dose adjustment of olanzapine, v) nonresponse to current antipsychotic treatment, vi) before and after switching from oral to injectable olanzapine formulation. For inclusion of blood levels into the analysis, steady state had to be reached. Therefore, documentation of constant olanzapine dose intake was required (for oral olanzapine: seven days; for LAI: three months of regular injections). Steady state could be considered for outpatients, if there was no information about noncompliance, acute deterioration or drug adherence and assurance of capability of understanding the importance of regular drug intake was documented. The following information were collected from patients' clinical records: i) age, ii) sex, iii) last change of olanzapine dose (date), iv) start of olanzapine (date or year), v) olanzapine dose and dose regimen, vi) co-medication, vii) diagnoses (ICD-10 codes), viii) patient setting (in- or outpatient, semi-inpatient: day clinic patient), ix) smoking status, x) discharge medication, xi) days of constant olanzapine dose.

2.5 Statistical analyses

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 non-/responders 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.

Statistical analyses of patient data retrieved from the Central Institute of Mental Health were performed with IBM SPSS Statistics, Version 25 (IBM SPSS Statistics for Macintosh, Armonk, NY: IBM Corp). Multiple regression analyses were carried out for the influence of age, sex, and cigarette smoking on olanzapine doses, blood concentrations, and C/D ratios with Analysis of Variance (ANOVA). Sub-analyses concerning discharge medication, main diagnoses, and elderly patients were performed by Mann-Whitney U Test (independent samples). The Kruskal-Wallis-Test was used for comparison of olanzapine doses, concentrations, and C/D ratios in patients with main psychiatric diagnosis except from paranoid schizophrenia.

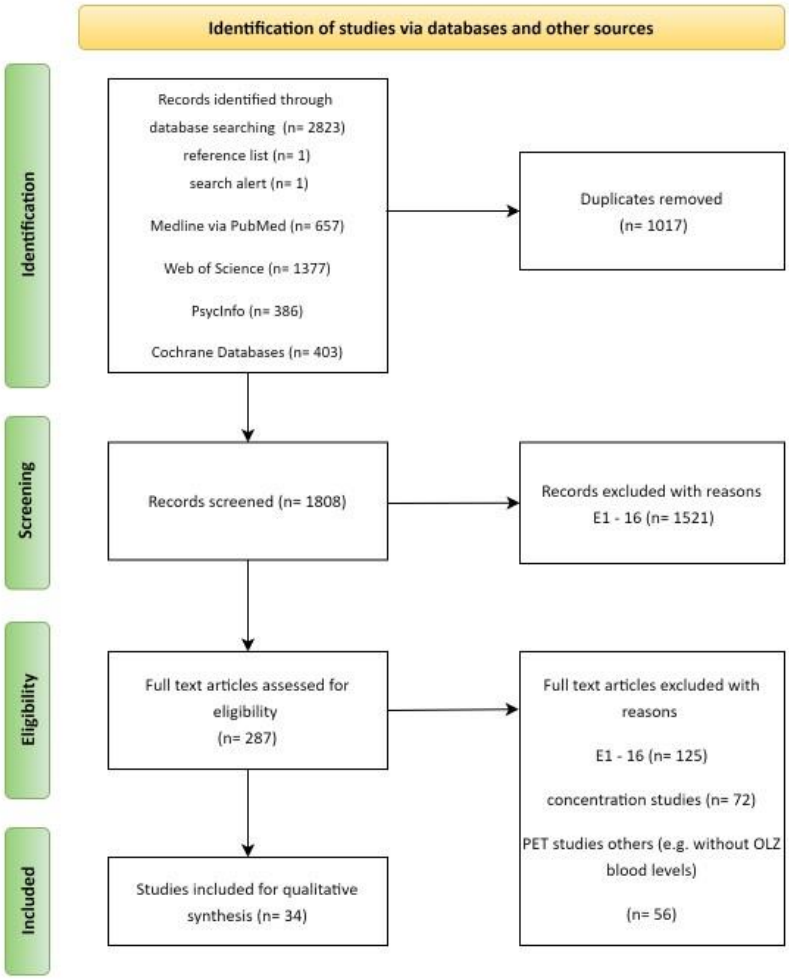
In all tests, $p < 0.05$ was considered as statistically significant. Linear regression analysis was conducted to test the relationship between olanzapine dose and blood level.

3. RESULTS

3.1 Study selection

A total of 2824 articles were identified through data base search and one study was manually selected from a reference list. 1521 records were excluded with reasons listed in Table 1 and another 126 articles were removed after full text examination. A total of 34 studies met the inclusion criteria and were used for a qualitative synthesis. Of these studies, 23 studies reported efficacy measures in relation to olanzapine blood levels for oral and four for olanzapine injectable formulation. Seven neuroimaging studies were identified. The PRISMA flow diagram is presented in Figure 1.

Figure 1. Flow diagram according to PRISMA



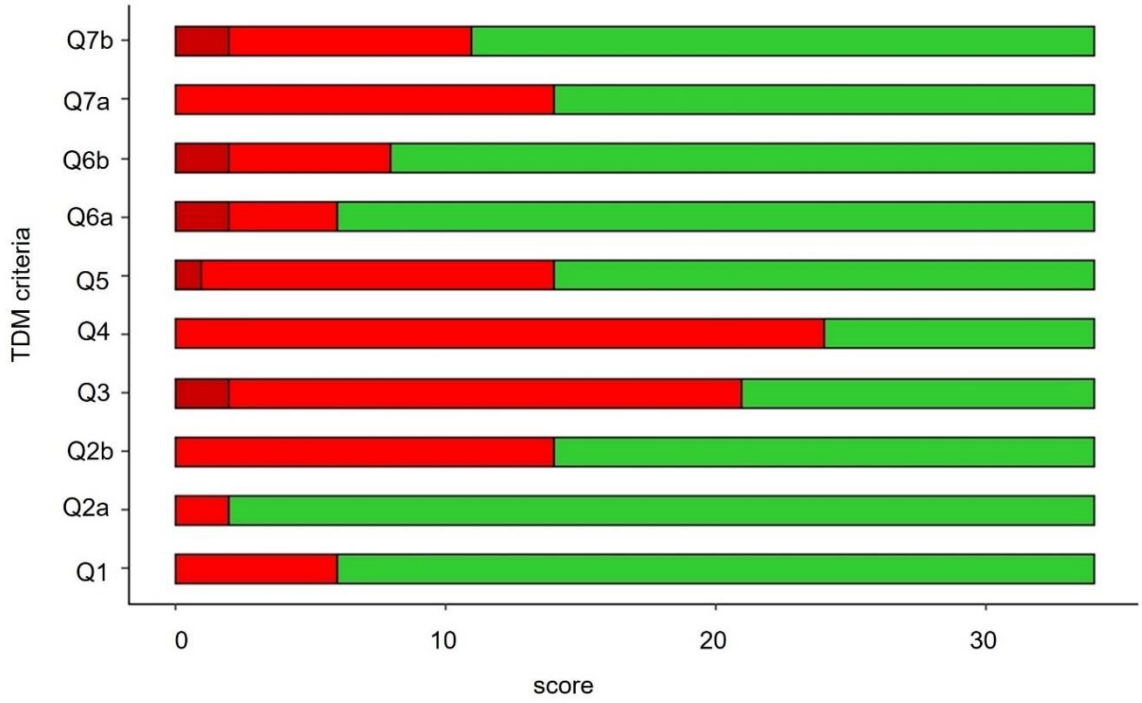
From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021; 372:n71. doi: 10.1136/bmj.n71. For more information, visit: http://www.prisma-statement.org/

OLZ: olanzapine; PET: Position Emission Tomography

3.2 Quality assessment of TDM components (TDM score)

According to the general quality criteria listed under the section 2.2 and a previously published protocol, TDM components were assessed for all studies as shown in Table 7 (appendix) and Figure 2 (Hart et al., 2021). Study type specific quality assessment for cohort studies, cross-sectional studies and randomized controlled studies (study scores) are presented in Tables 8 - 9 (appendix) and Figures 3 - 4.

Figure 2. Quality assessment results for TDM components



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

TDM: Therapeutic Drug Monitoring; Q: General quality criterion

Q1: Representativeness of the patient sample; Q2: Diagnosis (a: classification system, b: homogenous sample); Q3: Co-medication; Q4: Dose design; Q5: Analytical method; Q6: Blood sampling (a: steady state, b: sampling time); Q7: Concentration design (a: frequent measurement, b: concentration range)

Figure 3. Study type specific quality assessment – randomized controlled trials

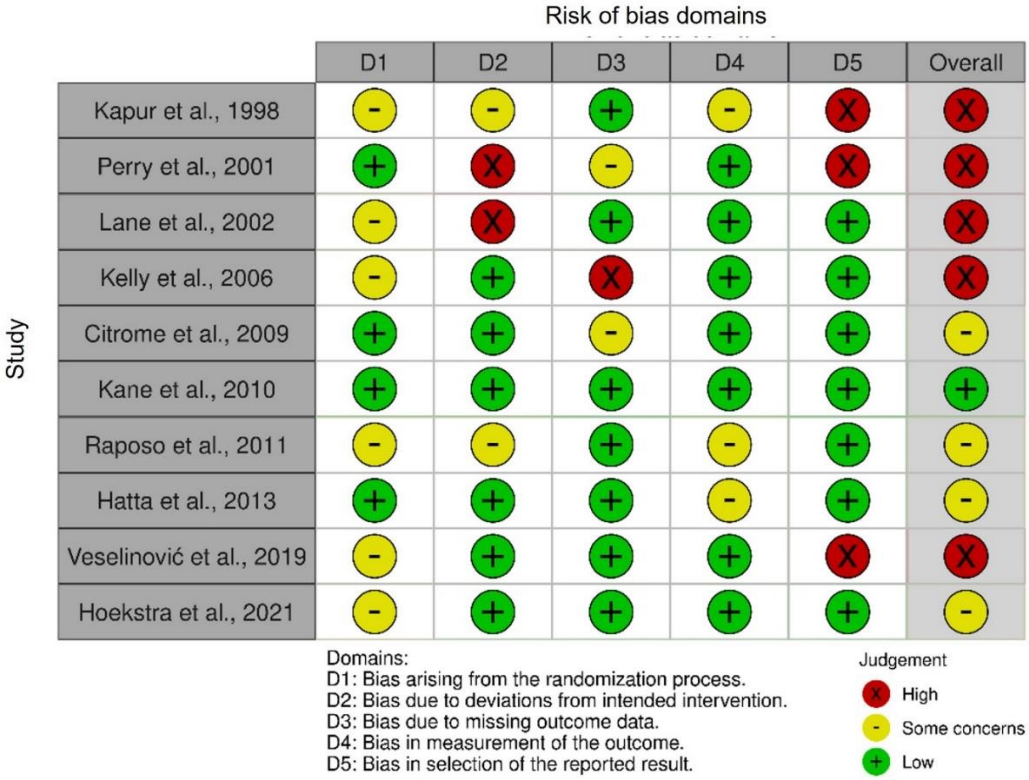
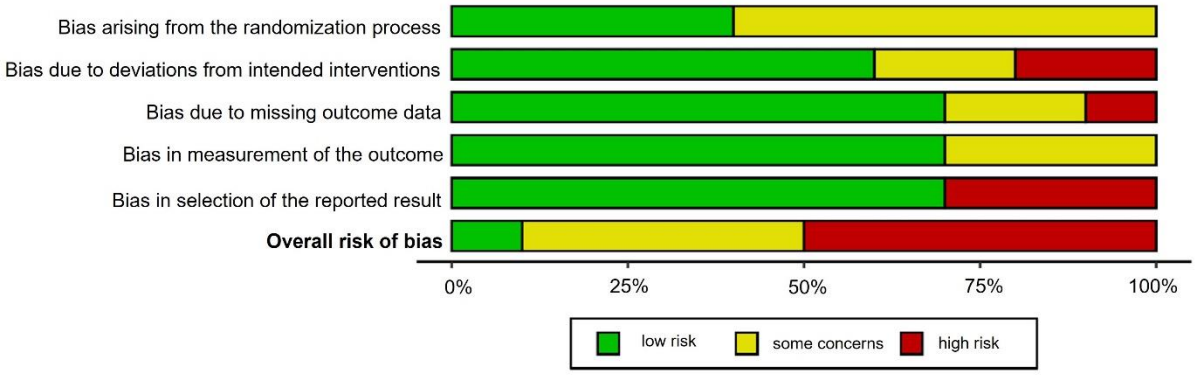


Figure 4. Risk of bias in randomized controlled trials



Six studies (18 %) did not investigate a representative patient sample (Q1). Cohorts comprising patients, who needed emergency treatment, with therapy resistant conditions, late-life schizophrenia (LLS), only minors (≤ 18 years), or only men did not represent an average target population. In 47% of the studies, a classification system for the investigated psychiatric diagnoses was not reported (N = 2; Q2a) or a sub-analysis was not performed (N = 16, Q2b). 21 studies (62 %) used pharmacodynamically active co-medication like antipsychotics, antidepressants and mood stabilizers or co-medication was not reported. The most frequently missed

criterion was dose design (Q4) in 24 studies (71%) due to flexible dosing regimens. 41% of the studies (N = 14) did not provide information about the analytical method used or no lower limit of detection (LOD) of this method was reported (Q5). In 12 articles (35%), steady state was not reached (Q6a), or information about sampling time (Q6b) was not sufficiently reported. 20 studies (59%) missed criterion Q7 (Q7a and/or Q7b), comprising repeated blood sampling (Q7a) and a sufficiently broad range of blood levels (Q7b).

3.3 Olanzapine blood levels and therapeutic response (Level of Evidence)

We identified 19 studies that reported olanzapine blood levels and clinical effects (Table 10, appendix). Of those, three cohort studies reported a positive and one cohort study a negative association between olanzapine blood levels and antipsychotic effects (Laika et al., 2010; Lin et al., 2006; Mauri et al., 2005; Zabala et al., 2017). In addition, three studies showed better therapeutic effects in patients with higher concentration-to-dose (C/D) ratios or metabolite-to-parent compound ratio (Arnaiz et al., 2021; Carrillo et al., 2003; Lu et al., 2016).

In 2005, Mauri and colleagues reported a positive curvilinear relationship between olanzapine blood levels and improvement of BPRS, PANSS and HRS-D scores in 54 patients with schizophrenia after a preceding exacerbation phase (TDM score: 8/10, study score: 7/10). Clinical effects were assessed at baseline and after two weeks of treatment. The authors suggested a range of 20 - 50 ng/ml for estimation of clinical effects (Mauri et al., 2005). Lin et al. is a re-analysis of Ellingrod et al., 2002, with focus on P-glycoprotein polymorphisms, an efflux transporter located on the blood-brain barrier. The authors stated a positive correlation between olanzapine blood levels and percentage decrease in BPRS in a sample of 41 patients with schizophrenia (TDM score: 9/10, study score: 9/10; (Ellingrod et al., 2002; Lin et al., 2006)). A threshold of 9.3 ng/ml was determined for adjustment of the olanzapine dose. Doses were increased if the olanzapine blood level was lower than this threshold. In case the olanzapine blood level was higher, clinical judgment guided dosage changes. In a prospective cohort study, Laika and colleagues also found a positive concentration/effect relationship for the subsample of patients with schizophrenia (N = 32, TDM score: 8/10, study score: 9/10). After four weeks of treatment, higher olanzapine blood levels were associated with better improvement of paranoid and

depressive symptoms in a self-rating score (PDS) and CGI-S score (Laika et al., 2010). 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). In here, 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). In addition, the influence of CYP1A2 and CYP2D6 activity on olanzapine blood levels was examined. Clinical assessment was performed at baseline and after 15 days of constant dosing (Carrillo et al., 2003). A positive relationship between C/D ratios and improvement in PANSS score was also shown by Arnaiz et al. in a cohort of 47 patients with first episode psychosis (FEP) after two months of treatment (TDM score: 6/10, study score: 5/8). Presentation of psychotic symptoms (positive symptoms or disorganization) of at least one week duration in the last 12 months was prerequisite for the diagnosis of FEP. A correlation could not be confirmed for not dose-corrected olanzapine blood levels and improvement of PANSS score (Arnaiz et al., 2021). Conflicting results were also reported from a Taiwanese study comprising 151 patients with schizophrenia, who were on a stable dose of olanzapine for at least three months (TDM score: 7/10, study score: 4/8). Metabolite-to-parent compound ratio (C_{OLZ}/ C_{DMO}) was positively correlated with improvement in PANSS score. This could not be confirmed for olanzapine plasma concentrations, except for the general psychopathology score in PANSS and individual BPRS scores like suspiciousness, hallucinations, and blunted affect (Lu et al., 2016).

A negative curvilinear relationship between olanzapine blood levels and improvement in PANSS score was reported by Zabala et al. in a pilot study that investigated a small sample of FEP patients with schizophrenia, schizophrenia spectrum or bipolar disorders (TDM score: 7/10, study score: 7/10). Patients were recruited within the first year after the onset of positive symptoms. All patients showed blood levels above the lower limit of olanzapine's reference range (≥ 20 ng/ml). A concentration range of 23 - 78 ng/ml for response to psychotic symptoms was suggested (Zabala et al., 2017).

To sum up, a concentration/effect relationship for antipsychotic effects in schizophrenia has been shown by three prospective cohort studies that measured olanzapine blood 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 according to (Hart et al., 2021)).

3.4 Olanzapine blood levels and side effects (Level of Evidence)

Nine studies assessed side effects under treatment with olanzapine using established rating scales (Table 10, appendix). The authors of a double-blind crossover study found a greater frequency of anticholinergic side effects with increasing olanzapine blood levels in a sample of treatment-resistant patients with schizophrenia (TDM score: 7/10, RoB: high). Treatment resistance was defined as persisting positive symptoms, prior failure on two different antipsychotics for at least six weeks of treatment at doses of 600 mg/d clozapine equivalents, and the absence of good social or occupational functioning in the past five years. Nonsmokers and women had significantly higher olanzapine blood levels. Furthermore, women were more affected by anticholinergic effects (Kelly et al., 2006). In the study of Mauri et al., none of the patients experienced an anticholinergic syndrome. The overall rate of EPS was with 0.5% low (TDM score: 8/10, study score: 7/10; (Mauri et al., 2005)). Carrillo et al. reported a trend towards higher C/D ratios in patients affected by adverse effects (N = 17; TDM score: 7/10; study score: 8/10; (Carrillo et al., 2003)). In contrast, Fellows and colleagues could not find a correlation between olanzapine blood levels at week six and adverse effects assessed by various side effect scales (TDM score: 7/10, study score: 7/10; (Fellows et al., 2003)). A TDM study reported a proportion of 54% in children and adolescent patients that experienced adverse drug reactions, mostly classified as ‘mild’ or ‘moderate’. There was no correlation between olanzapine blood levels and the occurrence of side effects. The majority of the included patients were treated with concomitant medication, but the influence on the occurrence of adverse drug reactions could not be verified (TDM score: 5/10; study score: 3/8; (Fekete et al., 2017)).

To conclude, one RCT of high risk for bias (RoB) reports a correlation between anticholinergic effects and olanzapine blood levels (Kelly et al., 2006). No negative studies exist. A classification of the evidence is justified as ‘low’ (Level C according to (Hart et al., 2021)) for a relationship between olanzapine blood levels and anticholinergic side effects.

3.4.1 Post-injection Delirium/Sedation Syndrome (PDSS)

Two studies examined events of PDSS under the treatment with olanzapine pamoate. None of them provided blood levels related to PDSS. Kane et al. reported an overall rate of treatment-emergent adverse drug reactions in 35% of the patient population. Two cases of PDSS occurred in a total sample of 1062 patients (0.2%; (Kane et al., 2010)). In a multicenter, open label study that investigated long-term safety of olanzapine pamoate, 35 patients developed symptoms of PDSS. One patient experienced two events (0.08% of all injections). All cases of PDSS fully resolved within 72 hours post-injection (McDonnell et al., 2014). In a phase IB study, safety and tolerability of single and multiple olanzapine LAI injections were investigated in 281 patients with schizophrenia. 78% of patients with multiple injections experienced at least one treatment-emergent adverse drug reaction. No PDSS was reported (Mitchell et al., 2013). A smaller sample of 25 outpatients with chronic schizophrenia or schizoaffective disorder was investigated by Mauri and colleagues. No PDSS and no new hospitalization were observed. Adverse events were reported in 19% of the patients (Mauri et al., 2015).

3.5 D_2-receptor occupancy and olanzapine blood levels

In Table 6 (appendix), neuroimaging studies identified for this review, are listed. Five studies performed PET and two studies performed Single-Photon Emission Computerized Tomography (SPECT) imaging using high affinity $D_{2/3}$-antagonist radiotracers.

In 1998, Kapur et al. included 12 patients with schizophrenia, who were randomly allocated to different olanzapine doses (5 - 40 mg/d) for at least five days prior to PET scanning. 65% of D_2-receptor occupancy was reached at olanzapine blood levels of about 19 ng/ml (corresponding dose of about 7 mg/d). 80% D_2-receptor occupancy was reached with a blood level of 41 ng/ml (corresponding to a dose of about 15 mg/d). Moreover, almost complete saturation of the serotonin 5-HT_2-receptors was observed at all doses. Clinical effects were assessed at baseline and time of the PET scan (via PANSS, BPRS, BARS, and SAS scores). The lack of response in two patients, who were administered higher doses of olanzapine after nonresponding to their assigned doses, was not due to lack of sufficient D_2-receptor occupancy (both > 80%; (Kapur et al., 1998)). Kapur et al. re-examined a part of the study population with a larger

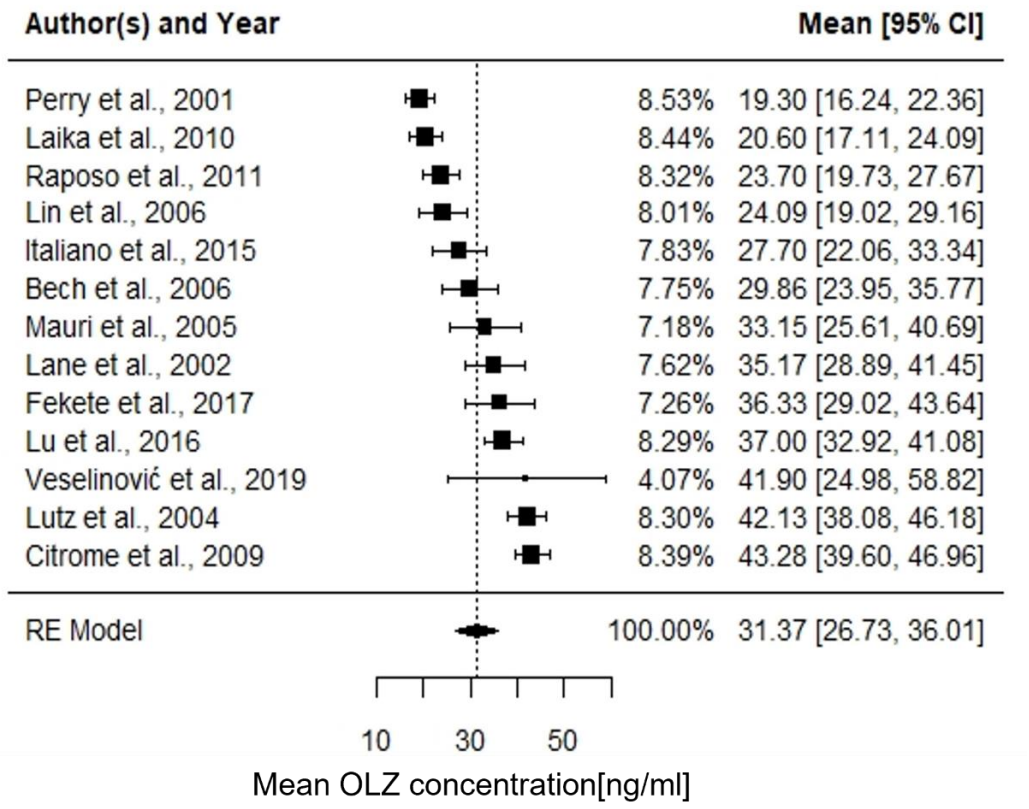
olanzapine dose range of up to 60 mg/d in 1999, using an unconstrained model with a maximum D_2-receptor occupancy of 92% (Kapur et al., 1999). One SPECT study reported considerably higher effective concentration values, that lead to 50% D_2-receptor occupancy (EC_{50}) compared to PET studies. 12 patients with schizophrenia, schizophreniform or schizoaffective disorders on their clinical required dose of olanzapine were examined. A SPECT scan was performed at one time during inter-dose interval and blood samples were taken during SPECT scanning under steady state conditions. Clinical efficacy measures (PANSS, CGI, and ESRS scores) indicated therapeutic effects below the 65% D_2-receptor occupancy, which were established by PET studies. A lower D_2-receptor occupancy (e.g. 50%) was suggested as a marker for antipsychotic efficacy (Catafau et al., 2008). The relationship between striatal D_2-receptor occupancy and EPS was explored in 17 patients with bipolar disorder by Attarbaschi and colleagues in 2007. After at least two weeks of constant dosing, a correlation between olanzapine blood levels and D_2-receptor occupancy, determined via SPECT scan, was demonstrated with an EC_{50} of about 7 ng/ml (approximated EC_{65} 17 ng/ml). EPS did not occur while D_2-receptor occupancy levels did not exceed 80%. These findings were comparable with those of patients with schizophrenia (Attarbaschi et al., 2007). Arakawa et al. assessed D_2-receptor occupancy of olanzapine via PET scan in the temporal cortex, an extrastriatal brain region. Ten patients with schizophrenia were treated with different doses of olanzapine (5 - 20 mg/d). Blood levels were determined under steady state conditions. A positive correlation between D_2-receptor occupancy and total PANSS score was demonstrated. An EC_{50} value of 11 ng/ml was comparable with values measured in striatal brain regions (Arakawa et al., 2010). Graff-Guerrero et al. (2015) assessed 22 outpatients with late-life schizophrenia (age at time of inclusion: ≥ 50 years; patients with schizophrenia or schizoaffective disorder) in their study using a PET scan. Patients were examined at baseline and after a dose reduction up to 40% (≥ 7.5 mg/d). The second PET scan was performed at least two weeks after attaining the final target dose. The lowest $D_{2/3}$-receptor occupancy associated with clinical stability was 50% (EC_{50} = 7.7 ng/ml). A lower therapeutic window of 50 - 60 % $D_{2/3}$-receptor occupancy for patients with late-life schizophrenia was proposed. EPS were observed with striatal D_2-receptor occupancy as low as 40% and an occupancy of around 80% was reached with olanzapine blood levels beyond 100 ng/ml based on an unconstrained model. $D_{2/3}$-receptor occupancies were not different between participants with or without EPS

(Graff-Guerrero et al., 2015). Only one PET study included patients with a fixed dose of olanzapine pamoate given every four weeks for six months. 14 patients with schizophrenia and schizoaffective disorder were previously stabilized on oral olanzapine. All patients remained stable during the switch from oral to injectable formulation. Estimated EC_{65-80} ranged from 20 to 44 ng/ml (Mamo et al., 2008).
To sum up, two PET studies (one used oral, one used LAI formulation) provided sufficient data, measured D_2 -receptor 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 of 19 - 20 ng/ml and upper values around 41 - 44 ng/ml.

3.6 Olanzapine dose/concentration relationship

A total of 13 oral olanzapine studies provided sufficient data and were eligible for a combined analysis. Ten studies were excluded due to insufficient data report (N = 7), a non-representative patient sample (N = 2), or the application of high olanzapine doses (N = 1). The mean concentration across all studies (N = 1137) was 31.4 ng/ml [CI: 26.7, 36.0, range: 19.3 - 43.3 ng/ml] ($Q = 194$, $df = 12$, $p < 0.0001$, $I^2 = 91.7$, $T^2 = 63.2$) with a mean dose of 15.4 mg/d (Figure 5).

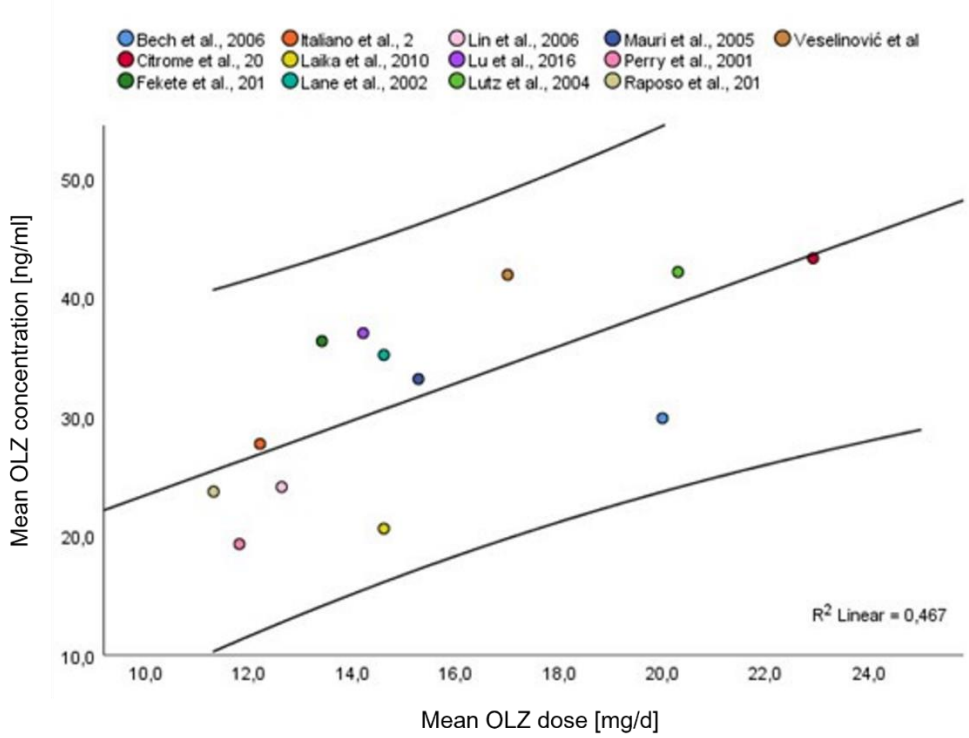
Figure 5. Mean olanzapine concentration (Q = 193.98, df = 12, p < 0.0001; I^2 = 91.7 %, τ^2 = 63.18)



CI: confidence interval; OLZ: olanzapine; RE: random effects

Interquartile concentration ranges (IQR 25 and IQR 75) were available from two studies: one study in adult patients with schizophrenia (IQR 18 - 35 ng/ml), and one study in children and adolescents with multiple psychiatric diagnoses (IQR 20 - 53 ng/ml; data not shown) (Fekete et al., 2017; Mauri et al., 2005). Linear regression analysis of mean concentrations across 13 studies revealed a strong association between dose and blood levels (Figure 6; r^2 = 0.467, p = 0.01, y = 7.83 + 1.56 * x). In addition, 13 individual studies reported a positive correlation between oral olanzapine dose and blood levels with correlation coefficients ranging from 0.2 to 0.8. Five 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 (McDonnell et al., 2014).

Figure 6. Linear regression analysis of mean olanzapine dose and concentration (β-coefficient = 7.830 (-9.656 - 25.315), r^2 = 0.467, p = 0.01, y = 7.83 + 1.56 * x)



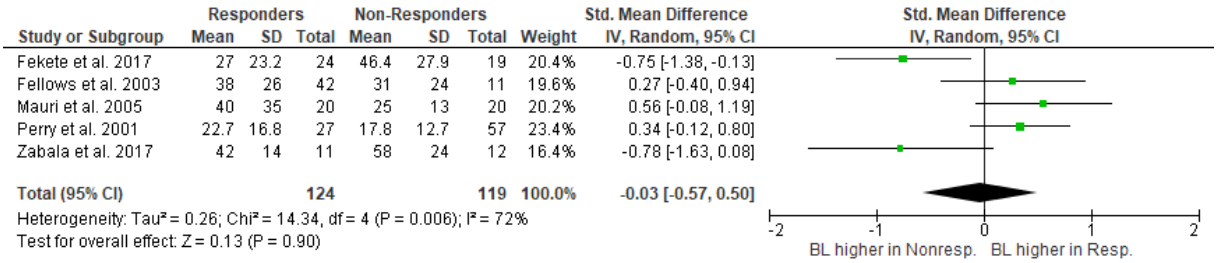
OLZ: olanzapine

3.7 Therapeutic reference range for olanzapine

3.7.1 Therapeutic thresholds

Five studies were identified that reported blood levels for olanzapine in responders and nonresponders. Two studies reported higher blood levels in nonresponders (Fekete et al., 2017; Zabala et al., 2017), three studies for responders (Fellows et al., 2003; Mauri et al., 2005; Perry et al., 2001). Conflicting results complicate the finding of a concentration/effect relationship across studies (Figure 7).

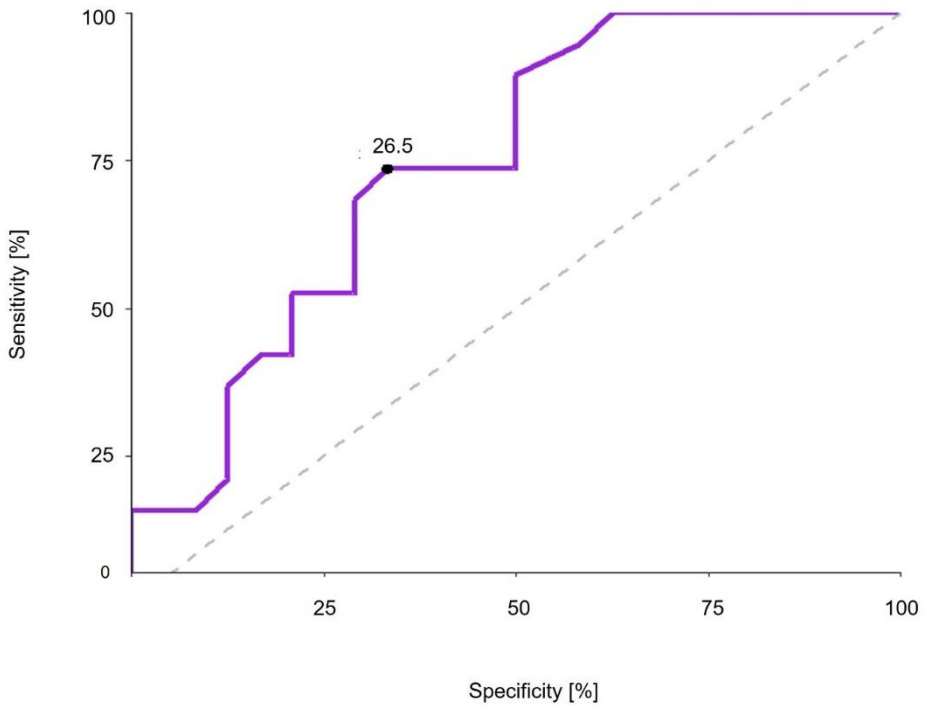
Figure 7. Meta-analysis of mean olanzapine blood level differences of responders vs. nonresponders across five studies



BL: blood level, CI: confidence interval, SD: standard deviation

Four individual studies conducted ROC-analyses that provided thresholds dividing responders from nonresponders. In 1997 and 2001, Perry and colleagues specified a 12h- and 24h- post dose breakpoint of 9 and 23 ng/ml that indicates treatment response, defined as ≥ 20% decrease in BPRS score (Table 11, appendix; (Perry et al., 2001; Perry et al., 1997). Later on, in 2003 and 2016, Fellows et al. and Lu et al. were able to confirm the threshold of 23 ng/ml (Fellows et al., 2003; Lu et al., 2016). A post hoc analysis from a double-blind trial with focus on depressive symptoms in patients with schizophrenia found a threshold of 36 ng/ml for the improvement of MADRS score (Lane et al., 2002). Another study that included a sample of 48 children and adolescents with schizophrenia spectrum disorders (F20 - 29; ICD-10; (WHO, 2019)), found higher olanzapine blood levels in nonresponders compared with responders (median: 37 vs. 22 ng/ml; data not shown). Treatment effects were assessed by CGI-I with a rating “very much improved” and “much improved” indicating treatment response. A threshold of 27 ng/ml was estimated by ROC-analysis for the differentiation of responders and nonresponders (Figure 8). Above this limit, the probability of response is considerably decreased (Fekete et al., 2017).

Figure 8. ROC-analysis of Fekete et al., 2017 (AUC 0.743 (95% CI: 0.597 - 0.889), p = 0.007, responders N = 19, nonresponders N = 24)



AUC: area under the curve; CI: confidence interval; ROC**:** Receiver Operating Characteristic

Interquartile ranges for responders and nonresponders from Mauri et al. were calculated (re-analysis by the authors; data not shown) and revealed that 50% of all patients, who responded to olanzapine treatment, had blood levels between 17 and 39 ng/ml (Mauri et al., 2005).

3.7.2 Suggestion for a therapeutic reference range

Three studies of moderate quality consistently proposed therapeutic thresholds of 23 ng/ml for olanzapine 12h post dose (Table 11, appendix; (Fellows et al., 2003; Lu et al., 2016; Perry et al., 2001)). This threshold is in line with findings from PET studies with a miminum D_2-receptor occupancy of 65% above this threshold (Table 6, appendix). The upper limit of olanzapine's reference range can be specified by maximum treatment efficacy or the occurrence of a specific side effect, namely EPS. Maximum treatment effects above a certain concentration may lead to increasing nonresponse. It can be determined by ROC-analysis (Figure 8) or by a visual inspection of a concentration/effect curve (maximum effect at about 40 ng/ml; (Fekete

et al., 2017; Mauri et al., 2005)). The occurrence of EPS at higher olanzapine blood levels has been theoretically discussed for concentrations that occupy more than 80% of D_2-receptors (Farde et al., 1997; Farde et al., 1992; Kapur et al., 2000). PET studies report EC_{80} values around 41 - 44 ng/ml (Table 6, appendix). Recently published pharmacokinetic studies confirm an upper limit of around 40 ng/ml for olanzapine (Table 11, appendix). Olesen et al. already discussed a lower reference range back in 1999. 80% of the investigated patients had olanzapine blood levels of 8 - 47 ng/ml (12h post dose) under clinical routine conditions (Olesen & Linnet, 1999). In 2021, an adaption of the current range for older patients (≥ 65 years) to 8 - 45 ng/ml was proposed (10 - 23h post dose; (Xiao et al., 2021)).

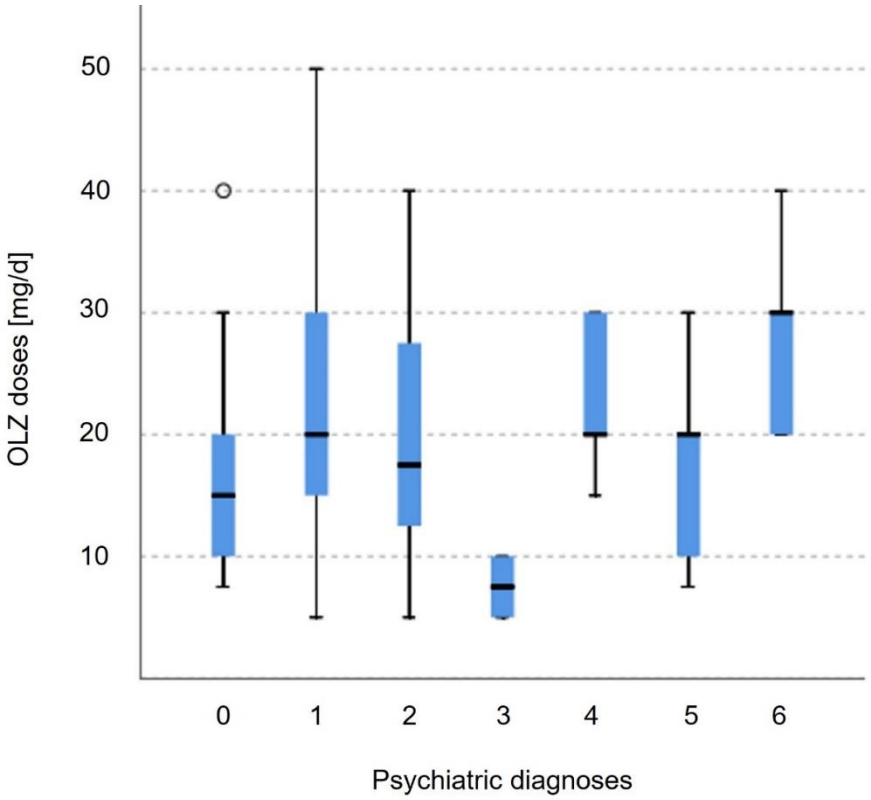
None of the studies that investigated olanzapine pamoate intended to examine a therapeutic reference range for olanzapine LAI. Most of the olanzapine blood levels determined after LAI administration fell into the current therapeutic reference range for the oral formulation. Recommendations for a reduction of the current olanzapine reference range for the LAI formulation are based on pharmacokinetic findings and supported in one retrospective TDM study that included 21 antipsychotic naive patients with schizophrenia treated with 210, 300, or 405 mg olanzapine pamoate every four weeks (not steady state). Noteworthy, a trough level < 20 ng/ml was observed in 70% of the patients who received 210 mg compared to 57% for the 300 and 405 mg group (Baldelli et al., 2018; Schoretsanitis et al., 2021). The PET study by Mamo et al. likewise justified a range of 20 - 40 ng/ml for olanzapine pamoate (Mamo et al., 2008).

3.8 Evaluation of TDM data from the Central Institute of Mental Health

1588 blood samples from 508 patients were measured between 2014 and 2018. If multiple data points were available, the last data point was used for evaluation. Plasma levels from patients treated with olanzapine pamoate (N = 3) were excluded, as were patients, who underwent an electroconvulsive therapy (N = 12). The resulting efficacy sample comprised 219 patients. The mean age was 41 ± 16.6 years, ranging from 14 to 83 years. 57.5% were male (N = 126); 87.2% were inpatients, treated stationary, and in day clinic setting. Psychiatric main diagnoses (N = 231) were the following (according to ICD-10; (WHO, 2019)), listed in the order of frequency: i) paranoid schizophrenia (50.2%); ii) bipolar affective disorder (17.7%); iii) other specified psychiatric diagnoses; iv) schizoaffective disorder (6.1%); v) schizotypal, delusional, acute schizophrenia-like psychotic disorder, and other nonorganic psychotic disorders

(5.2%); vi) mental disorders due to brain damage and dysfunction and to physical diseases (2.6%); vii) emotionally unstable personality disorder (0.9%) (Figure 9).
In 57.1% of cases, blood sampling was performed in the morning after olanzapine dosing in the evening; 10% were blood levels taken in the morning before once daily dose in the morning. In 32.9% of cases, no information about sampling time and/or dose regime were available.

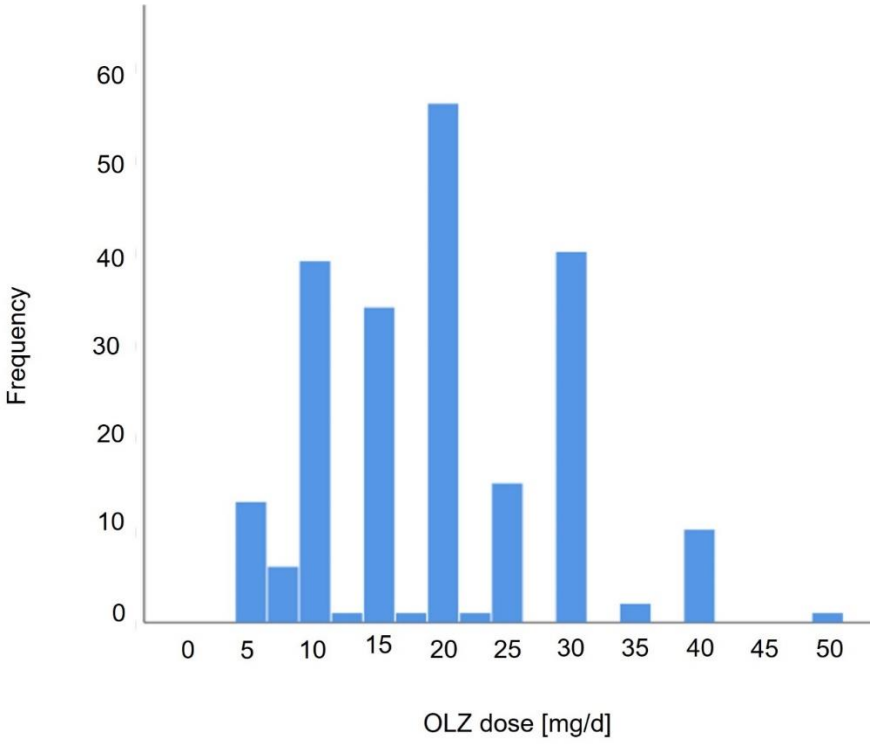
Figure 9. Independent-samples Kruskal-Wallis Test on mean doses among psychiatric main diagnoses (N = 231)



0: other psychiatric diagnoses; 1: paranoid schizophrenia; 2: bipolar affective disorder; 3: emotionally unstable personality disorder; 4: schizoaffective disorder; 5: schizotypal disorder, delusional disorder, acute schizophrenia-like psychotic disorder, other nonorganic psychotic disorders; 6: mental disorders due to brain damage and dysfunction and to physical diseases
OLZ: olanzapine

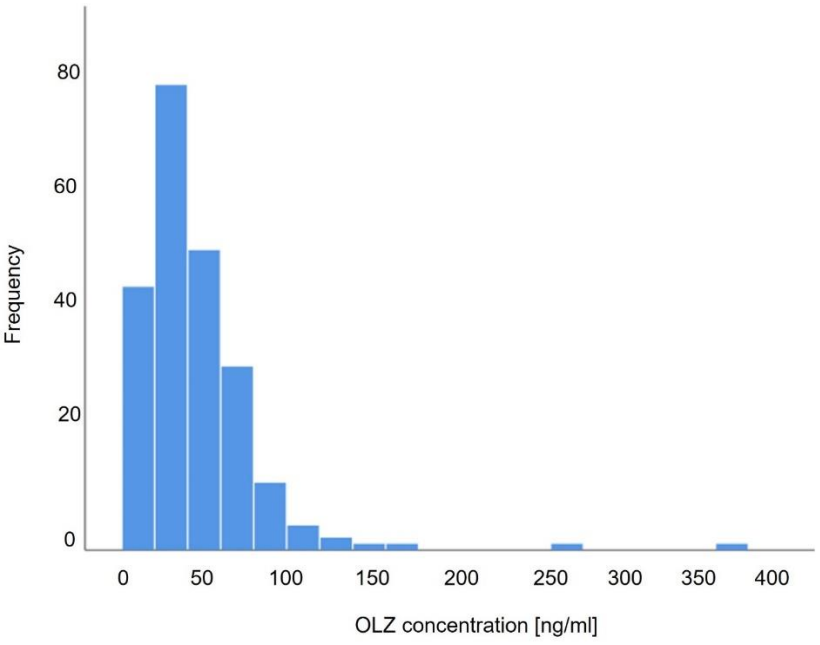
Mean dose of all included patients (N = 219) was 19.5 ± 9.2 mg/d, ranging from 5 to 50 mg/d resulting in a mean concentration of 45.7 ± 38.8 ng/ml (2.5 - 378.0 ng/ml) (Figure 10 - 11). The median plasma concentration was 35.0 ng/ml, and interquartile ranges revealed that 50% of the samples fell into a concentration range of 22.7 - 58.1 ng/ml (data not shown).

Figure 10. Distribution of olanzapine doses among patients (N = 219; mean dose: 19.5 ± 9.2 mg/d)



OLZ: olanzapine

Figure 11. Distribution of olanzapine plasma concentrations under steady state conditions (N = 219; mean concentration: 45.7 ± 38.8 ng/ml)

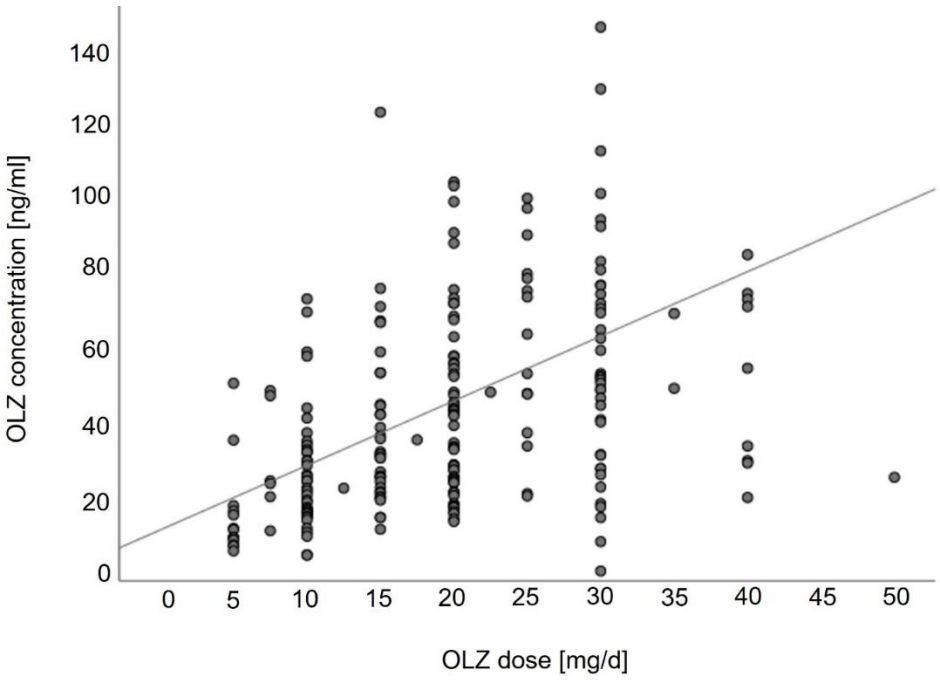


OLZ: olanzapine

C/D ratios showed a large range from 0.1 to 10.2 (ng/ml) / (mg/d) with a mean of 2.5 ± 1.7 (ng/ml) / (mg/d). There were no differences in mean doses between individual main diagnoses, except emotionally unstable personality disorder (Figure 9). This particular sample cannot be considered as representative, as it consisted of only two patients (data not shown).

Olanzapine blood levels and C/D ratios differ not significantly among the investigated diagnoses apart from paranoid schizophrenia ($p = 0.327$ for olanzapine blood level, and $p = 0.416$ for olanzapine C/D ratio). A significant positive correlation was found between administered the olanzapine dose and resulting plasma concentration (Figure 12; $p < 0.001$).

Figure 12. Linear regression analysis of mean olanzapine dose and concentration (β-coefficient = 1.668 (1.149 - 2.187), $r^2 = 0.156$, $p < 0.001$)



OLZ: olanzapine

Response to olanzapine treatment was defined as hospital discharge with olanzapine as discharge medication. Response rate based on discharge medication was 80.2%. No differences in distribution of olanzapine concentrations in responders and nonresponders were found (data not shown).

3.8.1 Patients with schizophrenia

The administered olanzapine doses for patients with schizophrenia (N = 116) ranged from 15 to 30 mg/d with a mean dose of 20.5 ± 9.0 mg/d. The mean plasma concentration was 47.7 ± 31.0 ng/ml with a median of 41.0 ng/ml. IQR 25 - 75 ranged from 23.5 to 70.1 ng/ml. Mean C/D ratio was 2.5 ± 1.5 (ng/ml) / (mg/d) with a median of 2.2 (ng/ml) / (mg/d). No significant differences in mean or median olanzapine doses ($p = 0.078$), plasma concentrations ($p = 0.066$) or C/D ratios ($p = 0.405$) were found between patients with main diagnosis of paranoid schizophrenia or patients treated for other psychiatric diagnoses mentioned under section 3.8.

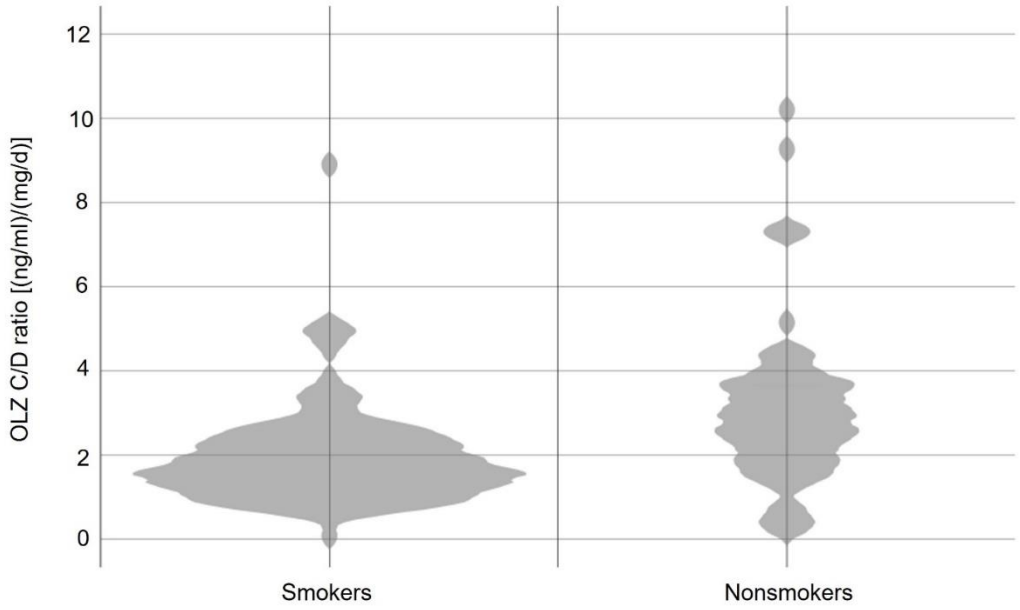
3.8.2 Adverse drug reactions under olanzapine treatment

Side effects under olanzapine treatment were experienced by 32 patients (14 %). Most common were sleepiness (N = 15, 6%), followed by EPS like akathisia, parkinsonism, dyskinesia (N = 12, 5%), and weight gain (N = 12, 5%). A significant increase of blood sugar or diabetes was seen in only two patients (1%). The highest olanzapine concentration associated with side effects was 103 ng/ml and the lowest was 13 ng/ml. Both patients experienced sleepiness. Doses ranged from 5 to 50 mg/d, resulting in blood levels of 14 ng/ml and 27 ng/ml. No correlation between olanzapine blood levels and occurrence of side effects could be identified.

3.8.3 Factors influencing olanzapine pharmacokinetics

Linear regression analysis including covariates age, sex, smoking status, and Body-Mass-Index (BMI), as well as binary logistic regression analysis revealed only smoking status as a significant factor influencing C/D ratios (Figure 13; $p < 0.001$, $r^2 = 0.203$). Smokers had a mean olanzapine plasma concentration of 41.4 ± 27.9 ng/ml (median: 32.6 ng/ml) compared to nonsmokers with 52.7 ± 40.1 ng/ml (median: 46.1 ng/ml). Olanzapine doses were significantly higher for smokers (21.7 ± 8.2 mg/d) than for nonsmokers (17.5 ± 8.5 mg/d; $p = 0.007$).

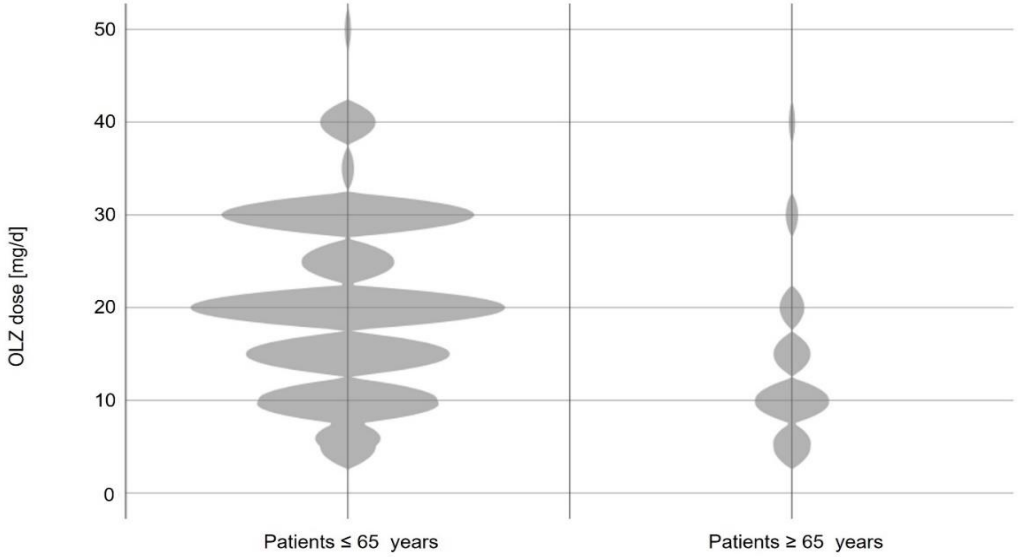
Figure 13. Violinplot on the distribution of C/D ratios in dependence of smoking status (N = 172; p < 0.001)



C/D: Concentration-to-dose; OLZ: olanzapine

Although a higher age (≥ 65 years) was not a factor influencing C/D ratios (p = 0.088), the administered doses differed significantly between younger (N = 198; mean dose: 20.4 ± 9.00 mg/d, median: 20 mg/d) and older patients (N = 32; mean dose: 13.2 ± 8.2 mg/d, median: 10 mg/d; p < 0.001; Figure 14).

Figure 14. Violonplot on administered mean olanzapine doses depending on age (N = 230; p < 0.001)



OLZ: olanzapine

3.8.4 Factors influencing olanzapine pharmacokdynamics

Response to olanzapine treatment was defined as continuation of olanzapine as discharge medication. Of these patients (N = 88), 65% received pharmacodynamically active co-medication like antipsychotic, antidepressant, anticonvulsive, anticholinergic medication, or other agents acting on the central nervous system. 26% of the responding patients received at least one antipsychotic besides olanzapine.

Co-administration of more than two pharmacodynamically active substances was recorded in 27% of the responder sample. The most commonly co-prescribed antipsychotics were amisulpride (N = 16), aripiprazole (N = 14), and risperidone (N = 6). Sertraline was the most frequently co-administered antidepressant in six patients. Anticholinergic co-medication was documented in four patients, indicating a low rate of EPS under olanzapine treatment.

4. DISCUSSION

The review of the current literature demonstrates a wide use of olanzapine in daily psychiatric practice. Previous data suggested a predictable therapeutic response with drug concentration within the therapeutic reference range. Finding a concentration/effect relationship for olanzapine is a prerequisite for a therapeutic reference range (Hiemke, 2019). In this meta-analysis such a relationship, for clinical efficacy and side effects, was systematically evaluated. It was shown that there is available evidence for an association between olanzapine blood levels and efficacy. Notably, the study quality remained quite consistent over time (Figure 15; Table 4, appendix) Ambiguous findings, however, result in a level of evidence for the concentration/effect relationship that has to be considered as 'low' (Hart et al., 2021).

Figure 15. Study scores over time from 1998 – 2021

TDM score= Therapeutic Drug Monitoring Score; ST score= study score according to (Hart et al., 2021)

Since adverse drug reactions have not been discussed by the majority of studies, and only one study was able to find a link to anticholinergic side effects, the level for this concentration/side effect relationship is also considered 'low' (Hart et al., 2021). Besides the infrequent rate of adverse drug reactions under olanzapine treatment, adverse events apparently occur at therapeutic drug levels (Batail et al., 2014; Graff-Guerrero et al., 2015). EPS were generally rare, and no correlation with olanzapine blood levels was detectable in the few patients who experienced EPS (Table 10, appendix).

Despite a proven linearity of olanzapine's dose/concentration relationship (Figure 12), a high interindividual variability leads to unpredictable olanzapine drug concentrations (Callaghan et al., 1999). A simulation pharmacokinetic study 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 (Korell et al., 2018)).

Drug-specific pharmacokinetic factors like co-medication influencing CYP1A2 activity play an important role and should therefore be identified and taken into account (Callaghan et al., 1999). Tobacco smoke is a proven CYP1A2 inducer and the most important factor influencing olanzapine blood levels, which was supported by multiple regression analysis of patient data (Figure 13).

Inadequate study designs in the past have led to artificial outcomes resulting in a systematic underestimation of the clinical relevance of Therapeutic Drug Monitoring. In the following sections we are going to discuss several study-specific risk factors that may conceal a concentration/effect relationship.

4.1 Blood sampling strategy

One of the most important prerequisites when collecting drug samples is the compliance to steady state conditions, which for oral olanzapine are presumed after at least seven days of constant dosing, respectively three months for olanzapine pamoate (Hiemke et al., 2018). Most studies have complied with these standards. However, three studies took blood samples before day seven, and two studies missed providing information about steady state conditions (see TDM rating Q6a, Table 7; (Hart et al., 2021; Hoekstra et al., 2021; Kapur et al., 1999; Kapur et al., 1998; Mauri et al., 2005; Raposo et al., 2011)). These studies are at risk of underestimating drug effects, which may result in an overdosing of the medication (Zernig & Hiemke, 2020).

To obtain significance of a concentration/effect relationship, the patient sample should be sufficiently large and patient adherence should be high (Hiemke, 2019). A patient sample of at least 10 patients was required for every study to be included in this review. Unfortunately, not half of studies using a cohort or cross-sectional design have measured, reported and/or discussed drug adherence in their patient sample (Q4, study score; (Hart et al., 2021)). Due to its half-life of around 33 hours, the determined olanzapine blood levels vary up to 1.62- fold when sampling 12 h compared to 24 h post dose (Korell et al., 2018). Blood samples should therefore be drawn at the end of the longest dosing interval (trough level) to minimize this source of variability. 12 of 23 studies specified a 12 - 15 hours post dose interval (TDM score: Q6b) which does not represent trough level (Hiemke, 2019). Moreover, in daily practice, olanzapine is often administered twice daily. Different analytical methods with variable precision and

reliability used for quantification of olanzapine blood levels is another confounding factor. This is important as olanzapine is only stable for a few days in EDTA plasma, but unstable in whole blood and in serum (Fisher et al., 2013). In some studies included in the review, olanzapine blood levels were measured in serum (Fekete et al., 2017; Italiano et al., 2015; Laika et al., 2010; Steen et al., 2017). These studies used validated analytical methods like HPLC and LC-MS/MS. Each method has its intra- and inter-day precision. Therefore, a duplication of measurement is recommended, and the LOD should be specified (TDM score: Q5, Q7a; (Hiemke, 2019)).

As an example, Raposo et al. demonstrated only a correlation between olanzapine blood 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 olanzapine blood level range, evaluation of the influence of olanzapine blood levels on clinical response could be impeded (Raposo et al., 2011).

4.2 Assessment of response

A relatively rapid improvement of psychotic symptoms is usually seen within the first two weeks which slows down over the following four weeks (Agid et al., 2013). Hence, two weeks can be regarded adequate to separate responders from nonresponders (study score: Q7 for cohort studies; (Hart et al., 2021)). A shorter treatment length can lead to a possible underestimation of medication efficacy.

A major challenge is still posed by placebo response and nonresponse to antipsychotic drug treatment when measuring antipsychotic drug efficacy. Both aspects may complicate the unravelling of a concentration/effect relationship or even result in a falsely negative correlation (Hiemke, 2019). To address these challenges, recommended study designs use a placebo lead-in phase followed by a fixed dosing schedule (Zernig & Hiemke, 2020). Placebo lead-in phases are uncommon, and most studies still use flexible dose regimens in order to “maximize” treatment effects. In our review, 19 of 23 oral concentration/effect studies used flexible dosing (TDM score: Q4; (Hart et al., 2021)). Clinical effects could have been underestimated due to a higher nonresponse rate in a population of patients with chronic schizophrenia, whose symptoms were not controlled under previous antipsychotic treatment (Nozawa et al., 2008).

The assessed outcomes in the reviewed psychiatric trials are highly heterogeneous. Global psychiatric rating scales like PANSS or BPRS have been proven valid in antipsychotic drug trials. Rating scales represented in concentration/effect studies examined multiple surrogate markers: i) antipsychotic effects (PANSS, BPRS), ii) (particular) depressive symptoms: Montgomery-Åsberg Depression Rating Scale (MADRS; (Lane et al., 2002)), Paranoid-Depressivity Scale (PDS), mania scales (Young Mania Rating Scale (YMRS); Bech-Rafaelsen Mania Scale (MAS; (Bech et al., 2006)), iii) assess disease severity (CGI-S), or iv) general improvement under current treatment (CGI-I; (Laika et al., 2010)). Consequently, the results are not comparable. Self-rating scales should be confirmed by a professional rating (PDS self-rating scale, and CGI by the treating psychiatrist, see (Laika et al., 2010)). In addition, different definitions for improvements based on the applied rating scales were made. In studies for paranoid schizophrenia, a reduction of 20% in BPRS (Perry et al., 2001; Perry et al., 1997) or PANSS score (Fellows et al., 2003) were sufficient for verification of clinical improvement, whereas Zabala et al. defined 30% reduction of PANSS score as clinical response (Table 11, appendix; (Zabala et al., 2017)). For improvement of depressive symptoms in patients with schizophrenia, Lane et al. required 50% reduction in MADRS score for sufficient symptom improvement (Lane et al., 2002).
Furthermore, studies should provide information about and control for inter-rater reliability (study score: Q6, RoB: D4; (Hart et al., 2021; Zernig & Hiemke, 2020)). One study on olanzapine pamoate 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 (Mauri et al., 2015).

4.3 Pharmacodynamic interactions

Administration of pharmacodynamically interacting medication like antipsychotics, antidepressants or mood stabilizers can lead to an overestimation of clinical improvement. Co-administration of antiparkinsonian medication can lead to underestimation of EPS occurrence or furthermore cause anticholinergic side effects itself (Bezchlibnyk-Butler & Remington, 1994). For TDM rating (Q3), administration of these substances was taken into account (Hart et al., 2021). In daily practice, co-medication with potential pharmacodynamic interaction is not only common, but

sometimes intended. This is reflected in the study results. 22 of 34 study protocols allowed co-administration of forementioned drugs.

4.4 Applicability of the therapeutic reference range on routine TDM data

The available data from the patient sample of the Central Institute of Mental health have several limitations. They are not suitable to verify a concentration/effect relationship due to previously mentioned factors. No clinical rating scales were used to determine severity or improvement of clinical symptoms. For this reason, olanzapine as discharge medication was specified as clinical response. Co-medication with pharmacodynamically interacting drugs was common and blood sampling was done only once after dosage change or under the current treatment.

It is noteworthy, that mean doses were at the upper limit of approved, safety-proven doses resulting in blood levels above the therapeutic reference range identified in this review (Lilly, 2021). Nonetheless, 50% of steady state blood levels of responders fell into the current therapeutic reference range.

The clinical routine data demonstrated that indications for the use of olanzapine are broad and extend beyond schizophrenia and bipolar disorder. Olanzapine is well tolerated, even with high plasma concentrations. Adverse drug reactions could not be associated exclusively to the use of olanzapine, as antipsychotic co-medication was commonly used.

4.5 Conclusion

Based on the findings of our meta-analysis, supported by neuroimaging studies, recent TDM, and pharmacokinetic studies, we suggest a correction of the therapeutic reference range to 20 - 40 ng/ml for the olanzapine oral and LAI formulations in patients with schizophrenia. The highest response rate (defined by a minimum decrease of 20% of PANSS score and constant dosing for one to six weeks is expected within the proposed reference range (Table 11, appendix). As olanzapine is well tolerated with blood levels exceeding 40 ng/ml, blood levels above the upper threshold do not require dose reduction in case of good clinical response and tolerance. The range refers to a 12 - This does not reflect trough level. 1.6-fold lower concentrations are expected when sampling 24 h post dose (Korell et al., 2018). Sufficient data to determine a 24 h post dose therapeutic reference range are still scarce. Research with

focus on the influence of the investigated diagnoses besides schizophrenia and the required olanzapine blood levels are recommended. There still is a need for investigations on the therapeutic reference range for elderly and minor patients and further research of olanzapine pamoate.

5. ABSTRACT

Therapeutic Drug Monitoring (TDM) is highly recommended for the antipsychotic drug olanzapine, with a proposed therapeutic reference range of 20 - 80 ng/ml. An adjustment towards lower ranges has already been suggested for the oral and long-acting drug formulations.

Based on a self-designed systematic methodology on how to perform a systematic review and evaluate the evidence for a therapeutic reference range on psychotropic drugs, the relevant literature was systematically searched and reviewed for olanzapine oral and long-acting injectable formulations. Eligible studies were evaluated, and population-based concentration ranges were calculated. Clinical routine TDM data from the Central Institute of Mental Health in Mannheim from 2014 to 2018 were analyzed and compared to the findings of the reviewed data.

The association between olanzapine blood levels, clinical effects, and dopamine D_2-receptor occupancy was investigated. 34 studies were detected for qualitative analysis. Of these, 23 studies reported efficacy measures in relation to olanzapine blood levels for oral olanzapine and four for olanzapine pamoate. Seven neuroimaging studies were identified. Based on these studies, conflicting evidence for a relationship between concentration, efficacy or side effects was found (assigned level of evidence low, according to (Hart et al., 2021)). Effective concentrations for 65% and 80% D_2-receptor occupancy of suitable neuroimaging studies ranged from 17 - 44 ng/ml. According to our analyses, we suggest a correction of the therapeutic reference range towards a lower range of 20 - 40 ng/ml for olanzapine oral and long-acting injectable formulations. In this range, optimal treatment response is expected in patients with schizophrenia. Higher olanzapine blood levels are well tolerated and should not necessarily require dose reduction in case of good response and tolerance.

The evaluation of the in-house TDM data revealed higher olanzapine mean blood levels of 45.7 ± 38.8 ng/ml and a mean dose of 19.5 ± 9.2 mg/d with a high interindividual variability. Interquartile ranges revealed that 50 % of the samples fell into a concentration range of 23 - 58 ng/ml. Pharmacodynamically active co-medication was common. Side effects were seen in 14% of the patients, and no correlation between olanzapine blood levels and the occurrence of side effects could be found.

6. REFERENCE LIST

Abdel-Baki, A., Thibault, D., Medrano, S., Stip, E., Ladouceur, M., Tahir, R., & Potvin, S. (2020). Long-acting antipsychotic medication as first-line treatment of first-episode psychosis with comorbid substance use disorder. *Early Interv Psychiatry, 14*(1), 69-79. https://doi.org/10.1111/eip.12826

Agid, O., Siu, C. O., Pappadopulos, E., Vanderburg, D., & Remington, G. (2013). Early prediction of clinical and functional outcome in schizophrenia. *Eur Neuropsychopharmacol, 23*(8), 842-851. https://doi.org/10.1016/j.euroneuro.2012.10.005

APA. (2013). *Diagnostic and statistical manual of mental disorders: DSM-5™* (A. P. Association, Ed. 5th ed.). American Psychiatric Publishing, Inc. https://doi.org/https://doi.org/10.1176/appi.books.9780890425596

Arakawa, R., Ito, H., Okumura, M., Takano, A., Takahashi, H., Takano, H., Okubo, Y., & Suhara, T. (2010). Extrastriatal dopamine D(2) receptor occupancy in olanzapine-treated patients with schizophrenia. *Eur Arch Psychiatry Clin Neurosci, 260*(4), 345-350. https://doi.org/10.1007/s00406-009-0082-5

Arnaiz, J. A., Rodrigues-Silva, C., Mezquida, G., Amoretti, S., Cuesta, M. J., Fraguas, D., Lobo, A., Gonzalez-Pinto, A., Diaz-Caneja, M. C., Corripio, I., Vieta, E., Baeza, I., Mane, A., Garcia-Rizo, C., Bioque, M., Saiz, J., Bernardo, M., Mas, S., & Grp, P. E. (2021). The usefulness of Olanzapine plasma concentrations in monitoring treatment efficacy and metabolic disturbances in first-episode psychosis. *Psychopharmacology, 238*(3), 665-676. https://doi.org/10.1007/s00213-020-05715-5

Ascher-Svanum, H., Faries, D. E., Zhu, B., Ernst, F. R., Swartz, M. S., & Swanson, J. W. (2006). Medication adherence and long-term functional outcomes in the treatment of schizophrenia in usual care. *J Clin Psychiatry, 67*(3), 453-460. https://doi.org/10.4088/jcp.v67n0317

Attarbaschi, T., Sacher, J., Geiss-Granadia, T., Klein, N., Mossaheb, N., Lanzenberger, R., Asenbaum, S., Dudczak, R., Kasper, S., & Tauscher, J. (2007). Striatal D(2) receptor occupancy in bipolar patients treated with olanzapine. *Eur Neuropsychopharmacol, 17*(2), 102-107. https://doi.org/10.1016/j.euroneuro.2006.07.001

Baldelli, S., Mauri, M. C., Di Pace, C., Paletta, S., Reggiori, A., Rovera, C., Clementi, E., & Cattaneo, D. (2018). Intraindividual and Interindividual Variability of Olanzapine Trough Concentrations in Patients Treated With the Long-Acting Injectable Formulation. *Journal of clinical psychopharmacology, 38*(4), 365-369. https://doi.org/10.1097/jcp.0000000000000913

Batail, J. M., Langree, B., Robert, G., Bleher, S., Verdier, M. C., Bellissant, E., Millet, B., & Drapier, D. (2014). Use of very-high-dose olanzapine in treatment-

resistant schizophrenia. *Schizophrenia research, 159*(2-3), 411-414. https://doi.org/10.1016/j.schres.2014.09.020

Beasley, C. M., Jr., Sanger, T., Satterlee, W., Tollefson, G., Tran, P., & Hamilton, S. (1996). Olanzapine versus placebo: results of a double-blind, fixed-dose olanzapine trial. *Psychopharmacology (Berl), 124*(1-2), 159-167. https://doi.org/10.1007/BF02245617

Bech, P., Gex-Fabry, M., Aubry, J. M., Favre, S., & Bertschy, G. (2006). Olanzapine plasma level in relation to antimanic effect in the acute therapy of manic states. *Nordic journal of psychiatry, 60*(2), 181-182. https://doi.org/10.1080/08039480600601282

Bergemann, N., Frick, A., Parzer, P., & Kopitz, J. (2004). Olanzapine plasma concentration, average daily dose, and interaction with co-medication in schizophrenic patients. *Pharmacopsychiatry, 37*(2), 63-68.

Bezchlibnyk-Butler, K. Z., & Remington, G. J. (1994). Antiparkinsonian drugs in the treatment of neuroleptic-induced extrapyramidal symptoms. *Can J Psychiatry, 39*(2), 74-84. https://doi.org/10.1177/070674379403900203

Bhana, N., & Perry, C. M. (2001). Olanzapine - A review of its use in the treatment of bipolar I disorder. *CNS drugs, 15*(11), 871-904. https://doi.org/10.2165/00023210-200115110-00005

Bigliani, V., Mulligan, R. S., Acton, P. D., Ohlsen, R. I., Pike, V. W., Ell, P. J., Gacinovic, S., Kerwin, R. W., & Pilowsky, L. S. (2000). Striatal and temporal cortical D2/D3 receptor occupancy by olanzapine and sertindole in vivo: a [123I]epidepride single photon emission tomography (SPET) study. *Psychopharmacology (Berl), 150*(2), 132-140. https://doi.org/10.1007/s002130000435

Bigos, K. L., Pollock, B. G., Coley, K. C., Miller, D. D., Marder, S. R., Aravagiri, M., Kirshner, M. A., Schneider, L. S., & Bies, R. R. (2008). Sex, race, and smoking impact olanzapine exposure. *Journal of clinical pharmacology, 48*(2), 157-165. https://doi.org/10.1177/0091270007310385

Bishara, D., Olofinjana, O., Sparshatt, A., Kapur, S., Taylor, D., & Patel, M. X. (2013). Olanzapine: A Systematic Review and Meta-Regression of the Relationships Between Dose, Plasma Concentration, Receptor Occupancy, and Response. *Journal of clinical psychopharmacology, 33*(3), 329-335. https://doi.org/10.1097/JCP.0b013e31828b28d5

Bishara, D., & Taylor, D. (2008). Upcoming Agents for the Treatment of Schizophrenia Mechanism of Action, Efficacy and Tolerability. *Drugs, 68*(16), 2269-2292. https://doi.org/10.2165/0003495-200868160-00002

Bobes, J., Rejas, J., Garcia-Garcia, M., Rico-Villademoros, F., García-Portilla, M. P., Fernández, I., & Hernández, G. (2003). Weight gain in patients with schizophrenia treated with risperidone, olanzapine, quetiapine or haloperidol: results of the EIRE study. *Schizophr Res, 62*(1-2), 77-88. https://doi.org/10.1016/s0920-9964(02)00431-0

Bymaster, F. P., Calligaro, D. O., Falcone, J. F., Marsh, R. D., Moore, N. A., Tye, N. C., Seeman, P., & Wong, D. T. (1996). Radioreceptor binding profile of the atypical antipsychotic olanzapine. *Neuropsychopharmacology, 14*(2), 87-96. https://doi.org/10.1016/0893-133X(94)00129-N

Callaghan, J. T., Bergstrom, R. F., Ptak, L. R., & Beasley, C. M. (1999). Olanzapine. Pharmacokinetic and pharmacodynamic profile. *Clin Pharmacokinet, 37*(3), 177-193. https://doi.org/10.2165/00003088-199937030-00001

Calligaro, D. O., Fairhurst, J., Hotten, T. M., Moore, N. A., & Tupper, D. E. (1997). The synthesis and biological activity of some known and putative metabolites of the atypical antipsychotic agent olanzapine (LY170053). *Bioorganic & Medicinal Chemistry Letters, 7*(1), 25-30. https://doi.org/https://doi.org/10.1016/S0960-894X(96)00567-7

Carrillo, J. A., Herraiz, A. G., Ramos, S. I., Gervasini, G., Vizcaino, S., & Benitez, J. (2003). Role of the smoking-induced cytochrome P450 (CYP)1A2 and polymorphic CYP2D6 in steady-state concentration of olanzapine. *Journal of clinical psychopharmacology, 23*(2), 119-127. https://doi.org/10.1097/00004714-200304000-00003

Castberg, I., Westin, A. A., Skogvoll, E., & Spigset, O. (2017). Effects of age and gender on the serum levels of clozapine, olanzapine, risperidone, and quetiapine. *Acta psychiatrica scandinavica, 136*(5), 455-464. https://doi.org/10.1111/acps.12794

Catafau, A. M., Penengo, M. M., Nucci, G., Bullich, S., Corripio, I., Parellada, E., García-Ribera, C., Gomeni, R., & Merlo-Pich, E. (2008). Pharmacokinetics and time-course of D(2) receptor occupancy induced by atypical antipsychotics in stabilized schizophrenic patients. *J Psychopharmacol, 22*(8), 882-894. https://doi.org/10.1177/0269881107083810

Chow, R., Herrstedt, J., Aapro, M., Chiu, L., Lam, H., Prsic, E., Lock, M., DeAngelis, C., & Navari, R. M. (2021). Olanzapine for the prophylaxis and rescue of chemotherapy-induced nausea and vomiting: a systematic review, meta-analysis, cumulative meta-analysis and fragility assessment of the literature. *Support Care Cancer, 29*(7), 3439-3459. https://doi.org/10.1007/s00520-020-05935-7

Citrome, L., McEvoy, J. P., Todtenkopf, M. S., McDonnell, D., & Weiden, P. J. (2019). A commentary on the efficacy of olanzapine for the treatment of schizophrenia: the past, present, and future. *Neuropsychiatr Dis Treat, 15*, 2559-2569. https://doi.org/10.2147/NDT.S209284

Citrome, L., Stauffer, V. L., Chen, L., Kinon, B. J., Kurtz, D. L., Jacobson, J. G., & Bergstrom, R. F. (2009). Olanzapine Plasma Concentrations After Treatment With 10, 20, and 40 mg/d in Patients With Schizophrenia An Analysis of Correlations With Efficacy, Weight Gain, and Prolactin Concentration. *Journal of clinical psychopharmacology, 29*(3), 278-283. https://doi.org/10.1097/JCP.0b013e3181a289cb

Cochrane (2008): *Risk of Bias 2 (RoB 2) tool*. https://methods.cochrane.org/risk-bias-2. Retrieved 2023/02/05.

Cooney, L., Loke, Y. K., Golder, S., Kirkham, J., Jorgensen, A., Sinha, I., & Hawcutt, D. (2017). Overview of systematic reviews of therapeutic ranges: methodologies and recommendations for practice. *BMC Med Res Methodol, 17*(1), 84. https://doi.org/10.1186/s12874-017-0363-z

Correll, C. U., Kim, E., Sliwa, J. K., Hamm, W., Gopal, S., Mathews, M., Venkatasubramanian, R., & Saklad, S. R. (2021). Pharmacokinetic Characteristics of Long-Acting Injectable Antipsychotics for Schizophrenia: An Overview. *CNS drugs, 35*(1), 39-59. https://doi.org/10.1007/s40263-020-00779-5

De Hert, M., Detraux, J., van Winkel, R., Yu, W., & Correll, C. U. (2011). Metabolic and cardiovascular adverse effects associated with antipsychotic drugs. *Nat Rev Endocrinol, 8*(2), 114-126. https://doi.org/10.1038/nrendo.2011.156

Detke, H. C., McDonnell, D. P., Brunner, E., Zhao, F., Sorsaburu, S., Stefaniak, V. J., & Corya, S. A. (2010). Post-injection delirium/sedation syndrome in patients with schizophrenia treated with olanzapine long-acting injection, I: analysis of cases. *BMC psychiatry, 10*, 43. https://doi.org/10.1186/1471-244x-10-43

DGPPN, e. V. (2019): *S3-Leitlinie Schizophrenie. Langfassung*, 038-009. https://register.awmf.org/assets/guidelines/038-009l_S3_Schizophrenie_2019-03.pdf. Retrieved 2023/01/29.

Di Lorenzo, R., & Brogli, A. (2010). Profile of olanzapine long-acting injection for the maintenance treatment of adult patients with schizophrenia. *Neuropsychiatr Dis Treat, 6*, 573-581. https://doi.org/10.2147/ndt.S5463

Díaz-Fernández, S., Frías-Ortiz, D. F., & Fernández-Miranda, J. J. (2020). Suicide attempts in people with schizophrenia before and after participating in an intensive case managed community program: A 20-year follow-up. *Psychiatry Res, 287*, 112479. https://doi.org/10.1016/j.psychres.2019.112479

Ellingrod, V. L., Perry, P. J., Lund, B. C., Bever-Stille, K., Fleming, F., Holman, T. L., & Miller, D. (2002). 5HT2A and 5HT2C receptor polymorphisms and predicting clinical response to olanzapine in schizophrenia. *J Clin Psychopharmacol, 22*(6), 622-624. https://doi.org/10.1097/00004714-200212000-00014

Farde, L., Mack, R. J., Nyberg, S., & Halldin, C. (1997). D-2 occupancy, extrapyramidal side effects and antipsychotic drug treatment: A pilot study with sertindole in healthy subjects. *International clinical psychopharmacology, 12*, S3-S7. https://doi.org/10.1097/00004850-199702001-00002

Farde, L., Nordström, A.-L., Wiesel, F.-A., Pauli, S., Halldin, C., & Sedvall, G. (1992). Positron Emission Tomographic Analysis of Central D1 and D2 Dopamine Receptor Occupancy in Patients Treated With Classical Neuroleptics and Clozapine: Relation to Extrapyramidal Side Effects. *Archives of general*

psychiatry, *49*(7), 538-544. https://doi.org/10.1001/archpsyc.1992.01820070032005

Farlow, M. R., & Shamliyan, T. A. (2017). Benefits and harms of atypical antipsychotics for agitation in adults with dementia. *Eur Neuropsychopharmacol, 27*(3), 217-231. https://doi.org/10.1016/j.euroneuro.2017.01.002

Fekete, S., Wewetzer, C., Mehler-Wex, C., Holtkamp, K., Burger, R., Reichert, S., Taurines, R., Romanos, M., Gerlach, M., & Egberts, K. (2017). Therapeutic Drug Monitoring in Children and Adolescents Under Pharmacotherapy With Olanzapine in Daily Clinical Practice. *Therapeutic Drug Monitoring, 39*(3), 273-281. https://doi.org/10.1097/ftd.0000000000000398

Fellows, L., Ahmad, F., Castle, D. J., Dusci, L. J., Bulsara, M. K., & Ilett, K. F. (2003). Investigation of target plasma concentration-effect relationships for olanzapine in schizophrenia. *Therapeutic Drug Monitoring, 25*(6), 682-689. https://doi.org/10.1097/00007691-200312000-00006

Fisher, D. S., Partridge, S. J., Handley, S. A., & Flanagan, R. J. (2013). Stability of some atypical antipsychotics in human plasma, haemolysed whole blood, oral fluid, human serum and calf serum. *Forensic Sci Int, 229*(1-3), 151-156. https://doi.org/10.1016/j.forsciint.2013.03.021

Gex-Fabry, M., Balant-Gorgia, A. E., & Balant, L. P. (2003). Therapeutic drug monitoring of olanzapine: The combined effect of age, gender, smoking, and comedication. *Therapeutic Drug Monitoring, 25*(1), 46-53. https://doi.org/10.1097/00007691-200302000-00007

Graff-Guerrero, A., Rajji, T. K., Mulsant, B. H., Nakajima, S., Caravaggio, F., Suzuki, T., Uchida, H., Gerretsen, P., Mar, W., Pollock, B. G., & Mamo, D. C. (2015). Evaluation of Antipsychotic Dose Reduction in Late-Life Schizophrenia: A Prospective Dopamine D2/3 Receptor Occupancy Study. *JAMA psychiatry, 72*(9), 927-934. https://doi.org/10.1001/jamapsychiatry.2015.0891

Green, A. I., Lieberman, J. A., Hamer, R. M., Glick, I. D., Gur, R. E., Kahn, R. S., McEvoy, J. P., Perkins, D. O., Rothschild, A. J., Sharma, T., & et al. (2006). Olanzapine and haloperidol in first episode psychosis: two-year data [Comparative Study; Evaluation Study; Journal Article; Multicenter Study; Randomized Controlled Trial; Research Support, N.I.H., Extramural; Research Support, Non-U.S. Gov't]. *Schizophrenia research, 86*(1-3), 234-243. https://doi.org/10.1016/j.schres.2006.06.021

Gründer, G., Hiemke, C., Paulzen, M., Veselinovic, T., & Vernaleken, I. (2011). Therapeutic plasma concentrations of antidepressants and antipsychotics: lessons from PET imaging. *Pharmacopsychiatry, 44*(6), 236-248. https://doi.org/10.1055/s-0031-1286282

Gründer, G., Hippius, H., & Carlsson, A. (2009). The 'atypicality' of antipsychotics: a concept re-examined and re-defined. *Nat Rev Drug Discov, 8*(3), 197-202. https://doi.org/10.1038/nrd2806

Hart, X. M., Eichentopf, L., Lense, X., Riemer, T., Wesner, K., Hiemke, C., & Grunder, G. (2021). Therapeutic Reference Ranges for Psychotropic Drugs: A Protocol for Systematic Reviews. *Front Psychiatry, 12*, 787043. https://doi.org/10.3389/fpsyt.2021.787043

Hasan, A., Bandelow, B., Yatham, L. N., Berk, M., Falkai, P., Möller, H. J., & Kasper, S. (2019). WFSBP guidelines on how to grade treatment evidence for clinical guideline development. *World J Biol Psychiatry, 20*(1), 2-16. https://doi.org/10.1080/15622975.2018.1557346

Hatta, K., Takebayashi, H., Sudo, Y., Katayama, S., Kasuya, M., Shirai, Y., Morikawa, F., Nakase, R., Nakamura, M., Ito, S., Kuga, H., Nakamura, M., Ohnuma, T., Usui, C., Nakamura, H., Hirata, T., Sawa, Y., & Grp, J. S. (2013). The possibility that requiring high-dose olanzapine cannot be explained by pharmacokinetics in the treatment of acute-phase schizophrenia. *Psychiatry research, 210*(2), 396-401. https://doi.org/10.1016/j.psychres.2013.07.005

Heres, S., Kraemer, S., Bergstrom, R. F., & Detke, H. C. (2014). Pharmacokinetics of olanzapine long-acting injection: the clinical perspective. *Int Clin Psychopharmacol, 29*(6), 299-312. https://doi.org/10.1097/YIC.0000000000000040

Hiemke, C. (2019). Concentration-Effect Relationships of Psychoactive Drugs and the Problem to Calculate Therapeutic Reference Ranges. *Ther Drug Monit, 41*(2), 174-179. https://doi.org/10.1097/FTD.0000000000000582

Hiemke, C., Bergemann, N., Clement, H. W., Conca, A., Deckert, J., Domschke, K., Eckermann, G., Egberts, K., Gerlach, M., Greiner, C., Grunder, G., Haen, E., Havemann-Reinecke, U., Hefner, G., Helmer, R., Janssen, G., Jaquenoud, E., Laux, G., Messer, T., Mossner, R., Muller, M. J., Paulzen, M., Pfuhlmann, B., Riederer, P., Saria, A., Schoppek, B., Schoretsanitis, G., Schwarz, M., Gracia, M. S., Stegmann, B., Steimer, W., Stingl, J. C., Uhr, M., Ulrich, S., Unterecker, S., Waschgler, R., Zernig, G., Zurek, G., & Baumann, P. (2018). Consensus Guidelines for Therapeutic Drug Monitoring in Neuropsychopharmacology: Update 2017. *Pharmacopsychiatry, 51*(1-02), e1. https://doi.org/10.1055/s-0037-1600991

Hilbert, A., Hoek, H. W., & Schmidt, R. (2017). Evidence-based clinical guidelines for eating disorders: international comparison. *Curr Opin Psychiatry, 30*(6), 423-437. https://doi.org/10.1097/yco.0000000000000360

Hoekstra, S., Bartz-Johannessen, C., Sinkeviciute, I., Reitan, S. K., Kroken, R. A., Løberg, E. M., Larsen, T. K., Rettenbacher, M., Johnsen, E., & Sommer, I. E. (2021). Sex differences in antipsychotic efficacy and side effects in schizophrenia spectrum disorder: results from the BeSt InTro study. *NPJ Schizophr, 7*(1), 39. https://doi.org/10.1038/s41537-021-00170-3

Howes, O. D., McCutcheon, R., Agid, O., de Bartolomeis, A., van Beveren, N. J., Birnbaum, M. L., Bloomfield, M. A., Bressan, R. A., Buchanan, R. W., Carpenter, W. T., Castle, D. J., Citrome, L., Daskalakis, Z. J., Davidson, M., Drake, R. J., Dursun, S., Ebdrup, B. H., Elkis, H., Falkai, P., Fleischacker, W. W., Gadelha,

A., Gaughran, F., Glenthoj, B. Y., Graff-Guerrero, A., Hallak, J. E., Honer, W. G., Kennedy, J., Kinon, B. J., Lawrie, S. M., Lee, J., Leweke, F. M., MacCabe, J. H., McNabb, C. B., Meltzer, H., Moller, H. J., Nakajima, S., Pantelis, C., Reis Marques, T., Remington, G., Rossell, S. L., Russell, B. R., Siu, C. O., Suzuki, T., Sommer, I. E., Taylor, D., Thomas, N., Ucok, A., Umbricht, D., Walters, J. T., Kane, J., & Correll, C. U. (2017). Treatment-Resistant Schizophrenia: Treatment Response and Resistance in Psychosis (TRRIP) Working Group Consensus Guidelines on Diagnosis and Terminology. *Am J Psychiatry, 174*(3), 216-229. https://doi.org/10.1176/appi.ajp.2016.16050503

Huhn, M., Nikolakopoulou, A., Schneider-Thoma, J., Krause, M., Samara, M., Peter, N., Arndt, T., Bäckers, L., Rothe, P., Cipriani, A., Davis, J., Salanti, G., & Leucht, S. (2019). Comparative efficacy and tolerability of 32 oral antipsychotics for the acute treatment of adults with multi-episode schizophrenia: a systematic review and network meta-analysis. *Lancet, 394*(10202), 939-951. https://doi.org/10.1016/s0140-6736(19)31135-3

Italiano, D., Bruno, A., Santoro, V., Lanza, G., Muscatello, M. R., Zoccali, R., & Spina, E. (2015). Generic Olanzapine Substitution in Patients With Schizophrenia: Assessment of Serum Concentrations and Therapeutic Response After Switching. *Therapeutic Drug Monitoring, 37*(6), 827-830. https://doi.org/10.1097/ftd.0000000000000211

Johnsen, E., Kroken, R. A., Løberg, E. M., Rettenbacher, M., Joa, I., Larsen, T. K., Reitan, S. K., Walla, B., Alisauskiene, R., Anda, L. G., & et al. (2020). Amisulpride, aripiprazole, and olanzapine in patients with schizophrenia-spectrum disorders (BeSt InTro): a pragmatic, rater-blind, semi-randomised trial [Comparative Study; Journal Article; Multicenter Study; Pragmatic Clinical Trial; Research Support, Non-U.S. Gov't]. *The lancet. Psychiatry, 7*(11), 945-954. https://doi.org/10.1016/S2215-0366(20)30341-2

Jonsson, A. K., Spigset, O., & Reis, M. (2019). A Compilation of Serum Concentrations of 12 Antipsychotic Drugs in a Therapeutic Drug Monitoring Setting. *Therapeutic Drug Monitoring, 41*(3), 348-356. https://doi.org/10.1097/ftd.0000000000000585

Junutula, S. P., Dubasi, S. K., Reddy Padide, S. G., Miryala, G. K., Koppolu, M. S., Bandaru Sheshagiri, S. B., & Eggadi, V. (2021). Therapeutic drug monitoring of olanzapine: Easy and reliable method for clinical correlation. *Indian J Pharmacol, 53*(1), 2-5. https://doi.org/10.4103/ijp.IJP_114_20

Kane, J. M., Detke, H. C., Naber, D., Sethuraman, G., Lin, D. Y., Bergstrom, R. F., & McDonnell, D. (2010). Olanzapine long-acting injection: a 24-week, randomized, double-blind trial of maintenance treatment in patients with schizophrenia. *Am J Psychiatry, 167*(2), 181-189. https://doi.org/10.1176/appi.ajp.2009.07081221

Kang, D., Lu, J., Liu, W., Shao, P., & Wu, R. (2022). Association between olanzapine concentration and metabolic dysfunction in drug-naive and chronic patients: similarities and differences. *Schizophrenia (Heidelb), 8*(1), 9. https://doi.org/10.1038/s41537-022-00211-5

Kaplan, G., Casoy, J., & Zummo, J. (2013). Impact of long-acting injectable antipsychotics on medication adherence and clinical, functional, and economic outcomes of schizophrenia. *Patient Prefer Adherence, 7*, 1171-1180. https://doi.org/10.2147/ppa.S53795

Kapur, S., Zipursky, R., Jones, C., Remington, G., & Houle, S. (2000). Relationship between dopamine D(2) occupancy, clinical response, and side effects: a double-blind PET study of first-episode schizophrenia. *Am J Psychiatry, 157*(4), 514-520. https://doi.org/10.1176/appi.ajp.157.4.514

Kapur, S., Zipursky, R. B., & Remington, G. (1999). Clinical and theoretical implications of 5-HT2 and D2 receptor occupancy of clozapine, risperidone, and olanzapine in schizophrenia. *Am J Psychiatry, 156*(2), 286-293. https://doi.org/10.1176/ajp.156.2.286

Kapur, S., Zipursky, R. B., Remington, G., Jones, C., DaSilva, J., Wilson, A. A., & Houle, S. (1998). 5-HT2 and D2 receptor occupancy of olanzapine in schizophrenia: a PET investigation. *Am J Psychiatry, 155*(7), 921-928. https://doi.org/10.1176/ajp.155.7.921

Kelly, D. L., Richardson, C. M., Yu, Y., & Conley, R. R. (2006). Plasma concentrations of high-dose olanzapine in a double-blind crossover study. *Human Psychopharmacology-Clinical and Experimental, 21*(6), 393-398. https://doi.org/10.1002/hup.781

Kinon, B. J., Volavka, J., Stauffer, V., Edwards, S. E., Liu-Seifert, H., Chen, L., Adams, D. H., Lindenmayer, J. P., McEvoy, J. P., Buckley, P. F., Lieberman, J. A., Meltzer, H. Y., Wilson, D. R., & Citrome, L. (2008). Standard and higher dose of olanzapine in patients with schizophrenia or schizoaffective disorder: a randomized, double-blind, fixed-dose study. *J Clin Psychopharmacol, 28*(4), 392-400. https://doi.org/10.1097/JCP.0b013e31817e63a5

Kloosterboer, S. M., Vierhout, D., Stojanova, J., Egberts, K. M., Gerlach, M., Dieleman, G. C., Hillegers, M. H. J., Passe, K. M., Gelder, T. V., Dierckx, B., & Koch, B. C. P. (2020). Psychotropic drug concentrations and clinical outcomes in children and adolescents: a systematic review. *Expert Opin Drug Saf, 19*(7), 873-890. https://doi.org/10.1080/14740338.2020.1770224

Korell, J., Green, B., Rae, A., Remmerie, B., & Vermeulen, A. (2018). Determination of plasma concentration reference ranges for oral aripiprazole, olanzapine, and quetiapine. *European journal of clinical pharmacology, 74*(5), 593-599. https://doi.org/10.1007/s00228-018-2419-3

Lafeuille, M. H., Laliberté-Auger, F., Lefebvre, P., Frois, C., Fastenau, J., & Duh, M. S. (2013). Impact of atypical long-acting injectable versus oral antipsychotics on rehospitalization rates and emergency room visits among relapsed schizophrenia patients: a retrospective database analysis. *BMC psychiatry, 13*, 221. https://doi.org/10.1186/1471-244x-13-221

Laika, B., Leucht, S., Heres, S., Schneider, H., & Steimer, W. (2010). Pharmacogenetics and olanzapine treatment: CYP1A2*1F and serotonergic polymorphisms influence therapeutic outcome. *Pharmacogenomics J, 10*(1), 20-29. https://doi.org/10.1038/tpj.2009.32

Lane, H. Y., Guo, S. C., Hwang, T. J., Chen, Y. S., Cheng, J. J., Lee, Y. C., Hong, C. J., Hwu, H. G., & Chang, W. H. (2002). Effects of olanzapine plasma concentrations on depressive symptoms in schizophrenia: A pilot study. *Journal of clinical psychopharmacology, 22*(5), 530-532. https://doi.org/10.1097/00004714-200210000-00019

Lieberman, J. A., Stroup, T. S., McEvoy, J. P., Swartz, M. S., Rosenheck, R. A., Perkins, D. O., Keefe, R. S., Davis, S. M., Davis, C. E., Lebowitz, B. D., Severe, J., & Hsiao, J. K. (2005). Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *N Engl J Med, 353*(12), 1209-1223. https://doi.org/10.1056/NEJMoa051688

Lilly (2016): *ZYPADHERA: Pulver und Lösungsmittel zur Herstellung einer Depot-Injektionssuspension*, DEZYA00286c(00281). https://www.lilly-pharma.de/assets/pdf/psychiatrie-neurologie/gebrauchsinformation-bedienungsanleitungen/zypadhera_praesentation_fuer_aerzte.pdf

Lilly, E. (2021): *ZYPREXA*, Document Id: d3dfec6e-4659-4642ea-4929f-4657d4659beb4625a4658a4657. https://uspl.lilly.com/zyprexa/zyprexa.html#pi. Retrieved 2023/01/29.

Lin, Y. C., Ellingrod, V. L., Bishop, J. R., & Miller, D. D. (2006). The relationship between P-glycoprotein (PGP) polymorphisms and response to olanzapine treatment in schizophrenia. *Therapeutic Drug Monitoring, 28*(5), 668-672. https://doi.org/10.1097/01.ftd.0000246761.82377.a6

Lindenmayer, J. P. (2010). Long-acting injectable antipsychotics: focus on olanzapine pamoate. *Neuropsychiatr Dis Treat, 6*, 261-267. https://doi.org/10.2147/ndt.s3072

Lu, M. L., Wu, Y. X., Chen, C. H., Kuo, P. T., Chen, Y. H., Lin, C. H., & Wu, T. H. (2016). Application of Plasma Levels of Olanzapine and N-Desmethyl-Olanzapine to Monitor Clinical Efficacy in Patients with Schizophrenia. *PLoS ONE, 11*(2), Article e0148539. https://doi.org/10.1371/journal.pone.0148539

Lucas, R. A., Gilfillan, D. J., & Bergstrom, R. F. (1998). A pharmacokinetic interaction between carbamazepine and olanzapine: observations on possible mechanism. *European journal of clinical pharmacology, 54*(8), 639-643. https://doi.org/10.1007/s002280050527

Luedecke, D., Schottle, D., Karow, A., Lambert, M., & Naber, D. (2015). Post-Injection Delirium/Sedation Syndrome in Patients Treated with Olanzapine Pamoate: Mechanism, Incidence, and Management. *CNS drugs, 29*(1), 41-46. https://doi.org/10.1007/s40263-014-0216-9

Lutz, R., Köhnlein, O., Schmauß, M., & Messer, T. (2004). Zum Umgang mit dem modernen atypischen Neuroleptikum Olanzapin im klinischen Alltag unter besonderer Berücksichtigung des Therapeutischen Drug-Monitorings (TDM) an einer psychiatrischen Versorgungsklinik = Management of the Atypical Antipsychotic Olanzapine in a Clinical Environment with Particular Regard to Therapeutic Drug Monitoring (TDM) in a German State Hospital. *Psychiatrische Praxis, 31*(Suppl1), S181-S183. https://doi.org/10.1055/s-2004-828466

Mamo, D., Kapur, S., Keshavan, M., Laruelle, M., Taylor, C. C., Kothare, P. A., Barsoum, P., & McDonnell, D. (2008). D2 receptor occupancy of olanzapine pamoate depot using positron emission tomography: an open-label study in patients with schizophrenia. *Neuropsychopharmacology, 33*(2), 298-304. https://doi.org/10.1038/sj.npp.1301409

Mauri, M. C., Maffini, M., Di Pace, C., Reggiori, A., Paletta, S., Moliterno, D., Rovera, C., & Altamura, C. A. (2015). "Long-acting" olanzapine in maintenance therapy of schizophrenia: A study with plasma levels. *International journal of psychiatry in clinical practice, 19*(2), 99-105. https://doi.org/10.3109/13651501.2014.1000928

Mauri, M. C., Paletta, S., Maffini, M., Colasanti, A., Dragogna, F., Di Pace, C., & Altamura, A. C. (2014). CLINICAL PHARMACOLOGY OF ATYPICAL ANTIPSYCHOTICS: AN UPDATE. *Excli Journal, 13*, 1163-1191.

Mauri, M. C., Steinhilber, C. P. C., Marino, R., Invernizzi, E., Fiorentini, A., Cerveri, G., Baldi, M. L., & Barale, F. (2005). Clinical outcome and olanzapine plasma levels in acute schizophrenia. *European psychiatry, 20*(1), 55-60. https://doi.org/10.1016/j.eurpsy.2004.09.009

McCormick, P. N., Wilson, V. S., Wilson, A. A., & Remington, G. J. (2013). Acutely administered antipsychotic drugs are highly selective for dopamine D2 over D3 receptors. *Pharmacological Research, 70*(1), 66-71. https://doi.org/10.1016/j.phrs.2013.01.002

McDonnell, D. P., Landry, J., & Detke, H. C. (2014). Long-term safety and efficacy of olanzapine long-acting injection in patients with schizophrenia or schizoaffective disorder: a 6-year, multinational, single-arm, open-label study. *International clinical psychopharmacology, 29*(6), 322-331. https://doi.org/10.1097/yic.0000000000000038

McEvoy, J. P. (2006). Risks versus benefits of different types of long-acting injectable antipsychotics. *J Clin Psychiatry, 67 Suppl 5*, 15-18.

Meftah, A. M., Deckler, E., Citrome, L., & Kantrowitz, J. T. (2020). New discoveries for an old drug: a review of recent olanzapine research. *Postgrad Med, 132*(1), 80-90. https://doi.org/10.1080/00325481.2019.1701823

Meyers, K. J., Upadhyaya, H. P., Landry, J. L., Chhabra-Khanna, R., Falk, D. M., Seetharama Rao, B., & Jones, M. E. (2017). Postinjection delirium/sedation syndrome in patients with schizophrenia receiving olanzapine long-acting

injection: results from a large observational study. *BJPsych Open, 3*(4), 186-192. https://doi.org/10.1192/bjpo.bp.116.004382

Mitchell, M., Kothare, P., Bergstrom, R., Zhao, F. Y., Jen, K. Y., Walker, D., Johnson, J., & McDonnell, D. (2013). Single- and Multiple-Dose Pharmacokinetic, Safety, and Tolerability Profiles of Olanzapine Long-Acting Injection: An Open-Label, Multicenter, Nonrandomized Study in Patients With Schizophrenia. *Clinical therapeutics, 35*(12), 1890-1908. https://doi.org/10.1016/j.clinthera.2013.09.023

Muratore, A. F., & Attia, E. (2021). Current Therapeutic Approaches to Anorexia Nervosa: State of the Art. *Clin Ther, 43*(1), 85-94. https://doi.org/10.1016/j.clinthera.2020.11.006

Navari, R. M., Qin, R., Ruddy, K. J., Liu, H., Powell, S. F., Bajaj, M., Dietrich, L., Biggs, D., Lafky, J. M., & Loprinzi, C. L. (2016). Olanzapine for the Prevention of Chemotherapy-Induced Nausea and Vomiting. *N Engl J Med, 375*(2), 134-142. https://doi.org/10.1056/NEJMoa1515725

Noel, C. (2019). A review of a recently published guidelines' "strong recommendation" for therapeutic drug monitoring of olanzapine, haloperidol, perphenazine, and fluphenazine. *Ment Health Clin, 9*(4), 287-293. https://doi.org/10.9740/mhc.2019.07.287

Nordström, A. L., Farde, L., Wiesel, F. A., Forslund, K., Pauli, S., Halldin, C., & Uppfeldt, G. (1993). Central D2-dopamine receptor occupancy in relation to antipsychotic drug effects: a double-blind PET study of schizophrenic patients. *Biol Psychiatry, 33*(4), 227-235. https://doi.org/10.1016/0006-3223(93)90288-o

Novakovic, V., Adel, T., Peselow, E., & Lindenmayer, J. P. (2013). Long-acting injectable antipsychotics and the development of postinjection delirium/sedation syndrome (PDSS). *Clin Neuropharmacol, 36*(2), 59-62. https://doi.org/10.1097/WNF.0b013e3182854f70

Novick, D., Montgomery, W., Treuer, T., Moneta, M. V., & Haro, J. M. (2017). Real-world Effectiveness of Antipsychotics for the Treatment of Negative Symptoms in Patients with Schizophrenia with Predominantly Negative Symptoms. *Pharmacopsychiatry, 50*(2), 56-63. https://doi.org/10.1055/s-0042-112818

Nozawa, M., Ohnuma, T., Matsubara, Y., Sakai, Y., Hatano, T., Hanzawa, R., Shibata, N., & Arai, H. (2008). The relationship between the response of clinical symptoms and plasma olanzapine concentration, based on pharmacogenetics. *Therapeutic Drug Monitoring, 30*(1), 35-40. https://doi.org/10.1097/FTD.0b013e31816336fd

Nyberg, S., Farde, L., Halldin, C., Dahl, M. L., & Bertilsson, L. (1995). D2 dopamine receptor occupancy during low-dose treatment with haloperidol decanoate. *Am J Psychiatry, 152*(2), 173-178. https://doi.org/10.1176/ajp.152.2.173

Olesen, O. V., & Linnet, K. (1999). Olanzapine serum concentrations in psychiatric patients given standard doses: The influence of comedication. *Therapeutic Drug Monitoring, 21*(1), 87-90. https://doi.org/10.1097/00007691-199902000-00013

Park, E. J., Amatya, S., Kim, M. S., Park, J. H., Seol, E., Lee, H., Shin, Y. H., & Na, D. H. (2013). Long-acting injectable formulations of antipsychotic drugs for the treatment of schizophrenia. *Arch Pharm Res, 36*(6), 651-659. https://doi.org/10.1007/s12272-013-0105-7

Patel, M. X., Bowskill, S., Couchman, L., Lay, V., Taylor, D., Spencer, E. P., & Flanagan, R. J. (2011). Plasma Olanzapine in Relation to Prescribed Dose and Other Factors Data From a Therapeutic Drug Monitoring Service, 1999-2009. *Journal of clinical psychopharmacology, 31*(4), 411-417. https://doi.org/10.1097/JCP.0b013e318221b408

Pennazio, F., Brasso, C., Villari, V., & Rocca, P. (2022). Current Status of Therapeutic Drug Monitoring in Mental Health Treatment: A Review. *Pharmaceutics, 14*(12). https://doi.org/10.3390/pharmaceutics14122674

Perry, P. J., Lund, B. C., Sanger, T., & Besley, C. (2001). Olanzapine plasma concentrations and clinical response: Acute phase results of the North American Olanzapine Trial. *Journal of clinical psychopharmacology, 21*(1), 14-20. https://doi.org/10.1097/00004714-200102000-00004

Perry, P. J., Sanger, T., & Beasley, C. (1997). Olanzapine plasma concentrations and clinical response in acutely ill schizophrenic patients. *J Clin Psychopharmacol, 17*(6), 472-477. https://doi.org/10.1097/00004714-199712000-00006

Raposo, N. R. B., Ferreira, A. S., & Gattaz, W. F. (2011). Body Mass Index Increase, Serum Leptin, Adiponectin, Neuropeptide Y and Lipid Levels during Treatment with Olanzapine and Haloperidol. *Pharmacopsychiatry, 44*(5), 169-172. https://doi.org/10.1055/s-0031-1280793

Samara, M. T., Dold, M., Gianatsi, M., Nikolakopoulou, A., Helfer, B., Salanti, G., & Leucht, S. (2016). Efficacy, Acceptability, and Tolerability of Antipsychotics in Treatment-Resistant Schizophrenia: A Network Meta-analysis. *JAMA psychiatry, 73*(3), 199-210. https://doi.org/10.1001/jamapsychiatry.2015.2955

Schoretsanitis, G., Baumann, P., Conca, A., Dietmaier, O., Giupponi, G., Grunder, G., Hahn, M., Hart, X., Havemann-Reinecke, U., Hefner, G., Kuzin, M., Mossner, R., Piacentino, D., Steimer, W., Zernig, G., & Hiemke, C. (2021). Therapeutic Drug Monitoring of Long-Acting Injectable Antipsychotic Drugs. *Ther Drug Monit, 43*(1), 79-102. https://doi.org/10.1097/FTD.0000000000000830

Schoretsanitis, G., Dubath, C., Grosu, C., Piras, M., Laaboub, N., Ranjbar, S., Ansermot, N., Crettol, S., Vandenberghe, F., Gamma, F., von Gunten, A., Plessen, K. J., Seifritz, E., Conus, P., & Eap, C. B. (2022). Olanzapine-associated dose-dependent alterations for weight and metabolic parameters in a prospective cohort. *Basic Clin Pharmacol Toxicol, 130*(4), 531-541. https://doi.org/10.1111/bcpt.13715

Schoretsanitis, G., Kane, J. M., Correll, C. U., Marder, S. R., Citrome, L., Newcomer, J. W., Robinson, D. G., Goff, D. C., Kelly, D. L., Freudenreich, O., Piacentino, D., Paulzen, M., Conca, A., Zernig, G., Haen, E., Baumann, P., Hiemke, C., Gründer, G., & ASCP. (2020). Blood Levels to Optimize Antipsychotic Treatment in Clinical Practice: A Joint Consensus Statement of the American Society of Clinical Psychopharmacology and the Therapeutic Drug Monitoring Task Force of the Arbeitsgemeinschaft für Neuropsychopharmakologie und Pharmakopsychiatrie. *J Clin Psychiatry, 81*(3). https://doi.org/10.4088/JCP.19cs13169

Schultz, S. H., North, S. W., & Shields, C. G. (2007). Schizophrenia: a review. *Am Fam Physician, 75*(12), 1821-1829.

Soderberg, M. M., & Dahl, M. L. (2013). Pharmacogenetics of olanzapine metabolism. *Pharmacogenomics, 14*(11), 1319-1336. https://doi.org/10.2217/pgs.13.120

Spanarello, S., & La Ferla, T. (2014). The pharmacokinetics of long-acting antipsychotic medications. *Curr Clin Pharmacol, 9*(3), 310-317. https://doi.org/10.2174/15748847113089990051

Steen, N. E., Aas, M., Simonsen, C., Dieset, I., Tesli, M., Nerhus, M., Gardsjord, E., Morch, R., Agartz, I., Melle, I., Ueland, T., Spigset, O., & Andreassen, O. A. (2017). Serum levels of second-generation antipsychotics are associated with cognitive function in psychotic disorders. *World journal of biological psychiatry, 18*(6), 471-482. https://doi.org/10.1080/15622975.2016.1245441

Sutherland, A., Naessens, K., Plugge, E., Ware, L., Head, K., Burton, M. J., & Wee, B. (2018). Olanzapine for the prevention and treatment of cancer-related nausea and vomiting in adults. *Cochrane Database Syst Rev, 9*(9), Cd012555. https://doi.org/10.1002/14651858.CD012555.pub2

Tveito, M., Smith, R. L., Molden, E., Haslemo, T., Refsum, H., Hartberg, C., Correll, C. U., & Hoiseth, G. (2018). Age Impacts Olanzapine Exposure Differently During Use of Oral Versus Long-Acting Injectable Formulations: An Observational Study Including 8,288 Patients. *Journal of clinical psychopharmacology, 38*(6), 570-576. https://doi.org/10.1097/jcp.0000000000000961

Ulrich, S., Wurthmann, C., Brosz, M., & Meyer, F. P. (1998). The relationship between serum concentration and therapeutic effect of haloperidol in patients with acute schizophrenia. *Clin Pharmacokinet, 34*(3), 227-263. https://doi.org/10.2165/00003088-199834030-00005

Veselinović, T., Scharpenberg, M., Heinze, M., Cordes, J., Mühlbauer, B., Juckel, G., Rüther, E., Paulzen, M., Haen, E., Hiemke, C., Timm, J., & Gründer, G. (2019). Dopamine D2 Receptor Occupancy Estimated From Plasma Concentrations of Four Different Antipsychotics and the Subjective Experience of Physical and Mental Well-Being in Schizophrenia: Results From the Randomized NeSSy Trial. *J Clin Psychopharmacol, 39*(6), 550-560. https://doi.org/10.1097/jcp.0000000000001131

WHO (2019): *International Statistical Classification of Diseases and Related Health Problems 10th Revision*. https://icd.who.int/browse10/2019/en. Retrieved 2023/02/19.

Xiao, T., Wang, Z., Li, G., Huang, S., Zhu, X., Liu, S., Li, X., Hu, J., Shang, D., & Wen, Y. (2021). What to Do About Missed Doses? A Retrospective Study of Olanzapine in the Elderly. *Drug Des Devel Ther, 15*, 3411-3423. https://doi.org/10.2147/dddt.S316110

Yang, T., Liu, Q., Lu, M., Ma, L., Zhou, Y., & Cui, Y. (2017). Efficacy of olanzapine for the prophylaxis of chemotherapy-induced nausea and vomiting: a meta-analysis. *Br J Clin Pharmacol, 83*(7), 1369-1379. https://doi.org/10.1111/bcp.13242

Zabala, A., Bustillo, M., Querejeta, I., Alonso, M., Mentxaka, O., Gonzalez-Pinto, A., Ugarte, A., Meana, J. J., Gutierrez, M., & Segarra, R. (2017). A Pilot Study of the Usefulness of a Single Olanzapine Plasma Concentration as an Indicator of Early Drug Effect in a Small Sample of First-Episode Psychosis Patients. *Journal of clinical psychopharmacology, 37*(5), 569-577. https://doi.org/10.1097/jcp.0000000000000770

Zernig, G., & Hiemke, C. (2020). *Pharmacokinetic and Pharmacodynamic Principles* (P. Riederer, Laux, G., Nagatsu, T., Le, W., Riederer, C., Ed.). Springer, Cham. https://doi.org/https://doi.org/10.1007/978-3-319-56015-1_1-1

Zhang, J. P., Gallego, J. A., Robinson, D. G., Malhotra, A. K., Kane, J. M., & Correll, C. U. (2013). Efficacy and safety of individual second-generation vs. first-generation antipsychotics in first-episode psychosis: a systematic review and meta-analysis. *Int J Neuropsychopharmacol, 16*(6), 1205-1218. https://doi.org/10.1017/s1461145712001277

OWN PUBLICATION AND CO-AUTHORSHIP

Wesner, K., Hiemke, C., Bergemann, N., Egberts, K., Fekete, S., Gerlach, M., Havemann-Reinecke, U., Lense, X., Riemer, T., Schoretsanitis, G., Uhr, M., Zernig, G., Gründer, G., Hart, X.M. Therapeutic Reference Range for Olanzapine in Schizophrenia: Systematic Review on Blood Concentrations, Clinical Effects, and Dopamine Receptor Occupancy. *The Journal of Clinical Psychiatry.*2023 Jul;84(5):22r14626. https://doi.org/10.4088/jcp.22r14626

Hart, X. M., Eichentopf, L., Lense, X., Riemer, T., Wesner, K., Hiemke, C., & Gründer, G. (2021). Therapeutic Reference Ranges for Psychotropic Drugs: A Protocol for Systematic Reviews. *Front Psychiatry, 12*, 787043. https://doi.org/10.3389/fpsyt.2021.787043

Results of the systematic review have been presented as a poster presentation at the 34th ECNP (European College of Neuropsychopharmacology) congress in Lisbon, Portugal, October 5, 2021, and at the 14th AGNP (Arbeitsgemeinschaft für Neuropsychopharmakologie und Pharmakopsychiatrie) TDM conference in Mannheim, Germany, June 23, 2022.

7. TABULAR APPENDIX

Figure 16. Search string for literature search

Medline via 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

Table 2. Study type specific quality assessment - Randomized controlled studies

Bias by Randomization	1.1	-
	1.2	-
	1.3	Rating corresponds to the whole randomized sample; if only data to efficacy sample, the item cannot be rated [NI]; (criteria: age [either documented no significant difference or tolerated deviation from mean in dependence of group size: < 20 25%; 20-49 20%; 50+ 15%], sex [either documented no significant difference or tolerated deviation from mean without dependence of group size 15%]; baseline-symptom severity [[hierarchically [only the top rank respectively; top rank rating based upon structured interviews; second rank global instruments; last rank rating based upon self-assessment with questionnaire], [either documented no significant difference or tolerated deviation from mean without dependence of group size 15%]], rate Y if age/gender or baseline-symptom severity is different. Accepted will be i) tables with information on p-values, which show no significant differences in critical parameters. ii) written text that claims no differences in critical parameters specifically iii) generalized statement that claims no differences among all parameters
Bias by Intervention	2.1./2.1.*	(Focus on de-blinding by characteristic adverse events (AE)) Rate PN/N if frequency of AEs are comparable [statistically no difference or in frequent AEs [Occupancy > 10%] a difference of > 50%; NI if no information on AE provided)
	2.2./2.2.*	Rate Y/PY if 2.1. is Y/PY. If 2.1 N/PN/NI: Focus on instrumental interventions such as ECG or laboratory assessments (Laboratory only if statistically significant differences)
	2.3.	(Consider drop-outs, if they are/could be related to a knowledge about the intervention such as AEs.)
	2.4.	Rate PY if drop-out because of AEs or lack of treatment effect
	2.5.	-
	2.6.	(If missing values occurred due to analytical problems or drug concentrations below the detection limit, this analysis can be regarded as modified ITT)
	2.7.	> 5% drop-out rate
	2.3.*	(Focus on AE dropouts, check if AE dropouts were comparable between groups)
	2.4.*	Y/PY only if authors claim that there were problems with the implementation of the intervention
	2.5.*	Y/PY only if authors claim that there were problems with patients' adherence
	2.6.*	-
Bias by Missing Data	3.1.	If 2.6. Y/PY or 2.7. N/PN, then Y/PY
	3.2.	-
	3.3.	(Example: drop-out due to missing therapeutic effect or AEs)

	3.4.	
Bias by Outcome assessment	4.1.	i) Clinical effect assessment: for N/PN established instrument and trained/experienced rater (If expert team conducts study, who published previous studies who fulfilled criteria and information is missing in current article, PN is possible.) ii) Imaging studies: for N/PN expert statement on imaging methodology states no critical methodological flaws In studies with i) and ii): both methods will be rated separately und the lowest rating counts. iii) Concentration studies without clinical effects: rate analytical methodology according to item 5 of general items
	4.2.	If structured assessment: N/PN
	4.3.	Rate N/PN, if blinding is predefined by design, even if 2.2 Y/PY
	4.4.	Rate N/PN for outcome related to objective measurement (e.g. PET scan or drug concentration measurement)
	4.5.	-
Bias by result reporting	5.1.	Rate NI if no information on statistical analysis were provided (external protocols (e.g. ClinicalTrials) are considered if they were linked to the article; otherwise use method section as reference)
	5.2	-
	5.3.	-

AE: adverse events; ECG: electrocardiogram; ITT: intention-to-treat; N: no; NI: no information; PET: Positron Emission Tomography; PN: partially no; PY: partially yes; Y: yes;
Specific adaption of the Item according to Cochrane Tool RoB 2.0 in regard to the research question (Cochrane, 2008)

Table 3. Level of Evidence grading

Level of Evidence (LoE)		
Evidence for a concentration/ effect relationship is:	Grade	Explanation
Strong	A	At least two independent RCT's with a low risk of bias show a concentration/effect relationship. AND No negative RCT's with a low risk of bias exist. If there are contradicting results from RCT's, the majority of RCT's AND/OR a meta-analysis with low risk of bias shows a relationship.
Limited	B	One RCT with a moderate risk of bias shows a concentration/effect relationship. AND No negative studies exist. OR Meta-analysis with a moderate risk of bias that shows a relationship.
Low	C	One or more prospective open studies (with a minimum of 10 evaluable patients per group) using a control group, but no randomization, or using no control group, show a concentration/effect relationship. OR One or more well-conducted case control or cohort studies (with a minimum of 10 evaluable patients) with a moderate probability that the concentration/effect relationship is causal. OR RCT's AND/OR meta-analysis with a high risk of bias show concentration/effect relationship.
No evidence	D	Insufficient data do not allow evaluation if a concentration/effect relationship exists. OR Evidence is given that a concentration/effect relationship does not exist.

RCT: Randomized Controlled Trial;

Note. Modified after "Table I. New WFSBP grading system (level of evidence)" by (Hasan et al., 2019)

Table 4. Detailed information on all included trials for oral olanzapine

Author, year	Country	Design	Subjects	Mean Dose (range) [mg/d]	Mean OLZ Conc. (range) [ng/ml]	Comment	TDM score	Study score
(Perry et al., 2001; Perry et al., 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 et al., 1996)	N = 84, SCZ, 85% males, mean age 36.8 ± 10.2y (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 ± 8.4y (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 nonsmokers, OLZ BLs were lower than 20 ng/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 ± 11y (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)	Germany	CSS, TDM study on OLZ, clinical improvement and side effects	N = 216, multiple psychiatric Dx (73% SCZ), 61.6% males, age: 39.6 ± 15.3y	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 in-patients 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 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 ± 9.0y	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, BAS)	7/10	high
(Lin et al., 2006)	USA	re-analysis from (Ellingrod et al., 2002) 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 ± 8.8y (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 ± 9.60y	15.7 ± 5.3 (5 - 20)	NA	improvement of individual BPRS scores (sus-piciousness, 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), nonsmoker: 3.8 (1.8) (ng/ml)/(mg/d)	6/10	6/10
(Citrome et al., 2009)	USA	data derived from (Kinon et al., 2008), 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 ± 11y (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 ± 14.7y (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 (ICD-10; (WHO, 2019))	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 ± 12y (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)	Japan	RCT, newly admitted emergency cases including involuntary admissions, co-medication allowed, flexible doses	N = 22 (N = 5 with BL), SCZ, SD, schizo-phreniform disorder, 40% males, 18 - 64y	23.0 ± 10.2	47.9 ± 21.6[A]	nonresponding 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 ± 1.5y	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 effects	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 ± 12.1y (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 ± 1.8y	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 “nonresponders” (psychotic and eating disorders), no association between OLZ BLs and occurrence of ADRs	5/10	3/8
(Steen et al., 2017)	Norway	prospective CSS on cognitive function (TOP study); flexible doses, control groups: QUE, ARI, RIS	N = 222, multiple Dx; 55.2% males, median age 28y	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 sub-sample), negative ass. between processing speed and OLZ BLs (BD sub-sample)	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 ± 12.9y (18 - 65)	17.0 ± 3.5	41.9 ± 32.3	focus on estimation of D_2RO, no corr. of OLZ BLs (and consequently D_2RO) and subjective well-being	8/10	high
(Arnaiz et al., 2021)	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	median C/D ratio (SD): 2.0 (2.9) (ng/ml)/(mg/d), 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)	Norway	data derived from BeSt InTro study, semi RCT, efficacy and side effects compared to ARI and AMI (Johnsen et al., 2020), AP co-medication allowed, flexible doses	N = 52, 37% males, SCZ spectrum disorders, mean age: 32.2 ± 13.3y	12.3 ± 3.8 (2.5 - 20)	Norway: 30.1 ± 17.0; Austria: 17.7 ± 7.2	no sex diff. in C/D, 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)

ADR: Adverse Drug Reaction; AMI: Amisulpride; AP: antipsychotics; ARI: Aripiprazole; BAS: Barnes Akathisia Rating Scale; BD: Bipolar Disorder; BL: blood level; BMI: Body-Mass-Index; BPRS: Brief Psychiatric Rating Scale; C/D: Concentration-to-dose; CGI: Clinical Global Impressions scale; CLO: Clozapine; CS: Cohort Study; CSS: Cross-Sectional Study; CYP: Cytochrome P450; Dx: diagnoses; D_2RO: D_2-receptor occupancy; EPS: Extrapyramidal Symptoms**;** FEP: First Episode Psychosis**;** HAL: Haloperidol; MADRS: Montgomery-Åsberg Depression Rating Scale; MAS: Bech-Rafaelsen Mania Scale; NA: not available; OLZ: olanzapine; PANSS**:** Positive and Negative Syndrome Scale; PGP: P-Glycoprotein; QUE: Quetiapine; RCT: Randomized Controlled Trial; RIS: Risperidone; ROC: Receiver Operating Characteristic; SANS: Scale for the Assessment of Negative Symptoms; SAS: Simpson-Angus Scale; SCZ: Schizophrenia; SD: Schizoaffective Disorder; TDM: Therapeutic Drug Monitoring; TOP: Thematically Organized Psychosis; UGT: UDP Glucuronosyltransferase; UKU: Udvalg for Kliniske Undersøgelser Side Effects Rating Scale; WAIS: Wechsler Adult Intelligence Scale; YMRS: Young Mania Rating Scale

Table 5. Detailed information on all included trials for olanzapine 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)	26 diff.	RCT on efficacy and tolerability of OLZ LAI	N = 1062, SCZ, 65.2% males, mean age: 38.9y (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	median concentrations given, stability rate: 95% high- dose group, 69% very low-dose group, EPS were minimal, very small decrease in all groups	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 judge-ment, concomitant psychotropic medica-tion was allowed	N = 931, SCZ, SD, 66.7% males, mean age: 39.3 ± 11.7y (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)	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 ± 9.09y	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: 35.4y (20- 55)	oral dose: 19.5 ± 11.3 injection: 334.7 ± 60.9	NA	20.6 ± 14.7 (4.0 - 78.9)	210 - 300 - 405 mg every 4 weeks; no sign. positive corr. between OLZ dose and BL at any times; steady state reached at fourth injection, simultaneous to the maximum reduction of the BPRS and PANSS scores, no PDSS	8/10	9/10

AE: Adverse Event; BL: blood level; BPRS: Brief Psychiatric Rating Scale; C/D: Concentration-to-dose; CGI-S: Clinical Global Impressions scale; Severity of illness; CS: Cohort Study; EPS: Extrapyramidal Symptoms**;** LAI: Long- Acting Injectable; NA: not available; OLZ: olanzapine; PANSS**:** Positive and Negative Syndrome Scale; PDSS: Post-injection Delirium/Sedation Syndrome; RCT: Randomized Controlled Trial; SCZ: schizophrenia; SD: Schizoaffective Disorder/Standard Deviation; TDM: Therapeutic Drug Monitoring

Table 6. Neuroimaging studies reporting D_2-receptor occupancy and olanzapine blood concentrations

Author, year	Country	PET tracer	Design	Subjects	Mean dose (range) [mg/d]	Mean OLZ Conc. (range) [ng/ml]	Mean RO (%) (range)	EC_{50} [ng/ml]	EC_{65} (est. from EC_{50}) [ng/ml]	EC_{80} (est. from EC_{50}) [ng/ml]	Comment	TDM score	Study score
(Kapur et al., 1998)	Canada	[11C] raclopride	RCT, PET scan at steady state 12h post dose, fixed, multiple doses until scan	N = 12, SCZ, 73.3% males, mean age: 27y (19 - 44)	17* (5 - 40)	46* (9.2 - 181.4)	73* (43 - 88)	ED 50 (4,5 mg): 10.3	19***	41***	expected rel. between dose/BL and D_2RO was that of a saturating rectangular hyperbola, 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 12-13h 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: 26.8y (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, 12-14h post dose	N = 17, BD, 64.7% males, mean age: 33.4 ± 9.8y (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 schizo-phreniform disorder, 58.3% males, age: 28 ± 7y	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 weeks 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 weeks	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. correlation (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 correlation 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 ≥ 50y), control group: RIS, PET scan at baseline and ≥ 2 weeks after final target dose and 14-16h 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} ('un-constrained 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)

AP: Antipsychotic; BD: Bipolar Disorder; BL: blood level; CLO: Clozapine; CS: Cohort Study; CSS: Cross-Sectional Study; D_2RO: D_2-receptor occupancy; EC: Effective Concentration; ED: Effective Dose; EPS: Extrapyramidal Symptoms; FLB 457: Benzamide; IBZM: Iodobenzamide; LAI: Long- Acting Injectable; LLS: Late-Life Schizophrenia; OLZ: olanzapine; PANSS: Positive and Negative Syndrome Scale; PET: Positron Emission Tomography; p.i.: Post-injection; QUE: Quetiapine; RCT: Randomized Controlled Trial; RIS: Risperidone; RO: receptor occupancy; SCZ: Schizophrenia; SD: Standard Deviation/ Schizoaffective Disorder; SPECT: Single-Photon Emission Computerized Tomography; TDM: Therapeutic Drug Monitoring ; w: week(s)

Table 7. Rating result of general quality criteria for the therapeutic drug monitoring component for all studies (TDM score) (Hart et al., 2021)

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

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

LAI: Long-Acting Injectable; OLZ: olanzapine; TDM: Therapeutic Drug Monitoring

Table 8. Study type specific quality assessment - cohort studies (Hart et al., 2021)

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

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

Table 9. Study type specific quality assessment - cross-sectional studies (Hart et al., 2021)

No	Study	Selection (Max 4 p):				Comparability (Max 2 p):	Outcome (Max 2 p)		Total score
		Q1	Q2	Q3	Q4	Q5	Q6	Q7	(x/8)
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	oo	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

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

Table 10. Studies reporting a concentration/effect or concentration/side effect relationship

Reference	Indication	No. of subjects treated with OLZ	Dose design	PD comed. (except BZ)	TDM-Score*	Efficacy	Side effects	Comments
concentration/effect studies considered for LoE grading								
Mauri et al., 2005	SCZ	54	flexible	N	7/10	**positive**	NF	CS, correlation between OLZ BL and BPRS and PANSS improvement was curvilinear; BPRS, PANSS, HRS-D, EPSE (NF)
Lin et al., 2006	SCZ	41	fixed	N	9/10	**positive**	NA	CS, Corr. of BL and positive symptom reduction was found (BPRS); SANS (NF)
Laika et al., 2010	mDx	73	flexible	Y	8/10	**positive**	NF	CS, CYP1A2 genotyping, positive concentration/effect relationship found only for SCZ patients (PDS, CGI-S), DOTES (NF)
Zabala et al., 2017	mDx	23	flexible	Y	7/10	**negative**	NF	CS, negative curvilinear relationship between OLZ BL in FEP patients in improvement of psychotic symptoms (PANSS), no BL correlated improvement for depressive symptoms (MADRS), UKU (NF)
additional findings								
Lu et al., 2016	SCZ	151	flexible	N	7/10	**positive**	NA	CSS, positive correlation for OLZ C/D ratio and PANSS in total sample, no such correlation for subgroup of smokers
Carrillo et al., 2003	mDx	17	fixed	N	7/10	**positive**	NF	CS, percentage decrease in BPRS consistently correlated with the steady state OLZ C/D ratio, different dosages for non-/ smokers, UKU (NF)
Arnaiz et al., 2020	FEP	47	flexible	Y	6/10	**positive**	NA	CSS, positive concentration/effect relationship found for C/D ratio and PANSS, but not for OLZ BL
Nozawa et al., 2008	SCZ	51	flexible	NA	6/10	partly	NA	improvement of individual BPRS scores (suspiciousness, hallucinations, blunted affect) was significantly correlated with OLZ BL
Raposo et al., 2011	SCZ	18	flexible	N	5/10	partly	NA	positive correlation of OLZ BL with negative symptoms (PANSS)
Bech et al., 2006	AM	20	flexible	Y	4/10	partly	NA	positive correlation for MAS in a subgroup of 8 female found, YMRS (NF)

Perry et al., 2001	SCZ	84	flexible	N	8/10	NF	NF	no linear or curvilinear relationship between BPRS score change and OLZ BL (12h post dose), (Perry et al., 1997): possibility of curvilinear relationship was suggested, CGI (NA), SAS, BARS, AIMS (NF)
Kelly et al., 2006	TRSCZ	13	fixed	N	7/10	NF	partly	crossover study with CLO, anticholinergic effects seen at greater frequency with higher OLZ BL; BPRS (NF), CGI (NF), SAS, BARS
Mauri et al., 2015	SCZ, SD	25 (N = 11 for 36 weeks)	fixed	N	8/10	NF	NA	focus on relation between OLZ BL and clinical outcome on chronic SCZ patients switched to OLZ LAI, less variation of OLZ BL was most predictable factor associated with clinical benefit, BPRS (NF), PANSS (NF), no PDSS
Lane et al., 2002	SCZ	13	flexible	N	8/10	NF	NA	focus on depressive symptoms in SCZ patients (MADRS)
Fellows et al., 2003	SCZ	53	flexible	Y	7/10	NA	NF	no significant correlations between side effects (SAS, AIMS, BAS) and OLZ BL at 6 weeks, C/D ratios used, PANSS (NA)
Italiano et al., 2015	SCZ	25	flexible	N	8/10	NF	NA	CS with focus on different OLZ formulations (branded/generic); PANSS
Veselinović et al., 2019	SCZ	14	flexible	N	9/10	NA	NA	no correlation of OLZ BL (and consequently D_2RO) and subjective well-being; PANSS, CGI, SAS, AIMS, BARS
Citrome et al., 2009	SCZ, SD	380	fixed	Y	7/10	NF	NA	RCT comparing different OLZ doses on patients with suboptimal response to current treatment; PANSS
Fekete et al., 2017	mDx	115	flexible	Y	5/10	NF	NF	children and adolescent, validation of therapeutic reference range, CGI, UKU

AIMS: Abnormal Involuntary Movement Scale; AM: Acute Mania; BAS: Barnes Akathisia Rating Scale; BARS: Brief Adherence Rating Scale; BL: Blood level; BPRS: Brief Psychiatric Rating Scale; BZ: Benzodiazepines; C/D: Concentration-to-dose; CGI-S: Clinical Global Impressions scale; Severity of illness; CLO: Clozapine; CS: Cohort Study; CSS: Cross-Sectional Study; CYP: Cytochrome P450; DOTES: Dosage Record Treatment Emergent Symptom Scale; D_2RO: D_2- receptor occupancy; EPSE: Rating Scale for Extrapyramidal Side Effects; FEP: First Episode Psychosis; HRS-D: Hamilton Rating Scale for Depression; LoE: Level of Evidence; MADRS: Montgomery- Åsberg Depression Rating Scale**;** MAS: Bech- Rafaelsen Mania Scale; mDx: multiple diagnoses; NA: Not Available; NF: Not Found; N: No; OLZ: Olanzapine; PANSS: Positive and Negative Syndrome Scale; PD: Pharmacodynamically(active); PDS: Paranoid-Depressivity Scale; PDSS: Post-injection Delirium/ Sedation Syndrome; RCT: Randomized Controlled Trial; SANS: Scale for the Assessment of Negative Symptoms; SAS: Simpson- Angus Scale; SCZ: Schizophrenia; SD: Schizoaffective Disorder; TDM: Therapeutic Drug Monitoring; TRSCZ: Therapy-resistant SCZ; UKU: Udvalg for Kliniske Undersøgelser Side Effects Rating Scale ; Y: Yes; YMRS: Young Mania Rating Scale

Table 11. Studies investigating a breakpoint or therapeutic reference range for clinical improvement

Reference	Study type	Breakpoint (ng/ml)	Suggested therapeutic RR (ng/ml)	Time post dose (h)	Comment
(Perry et al., 1997)	CES	9.3		24	ROC-analysis, breakpoint for improvement of BPRS and PANSS scores, data derived from (Beasley et al., 1996), response ≙ ≥ 20% decrease of BPRS
(Lu et al., 2016)	CES	22.8		12	cut-off level determined via ROC analysis
(Perry et al., 2001)	CES	23.2		12	ROC-analysis, threshold as a significant predictor of therapeutic response, data derived from (Beasley et al., 1996), response ≙ ≥ 20% decrease of BPRS
(Fellows et al., 2003)	CES	23 - 25		12	ROC-analysis, very modest predictor of therapeutic response in acutely ill patients with SCZ, response ≙ ≥ 20% decrease of PANSS
(Lane et al., 2002)	CES	36		12	threshold for improvement of depressive symptoms, response ≙ ≥ 50% decrease of MADRS
(Xiao et al., 2021)	COS		8 - 45	10-23	TDM study with focus on missing doses of OLZ and their influence on OLZ BL in elderly patients, mean age: 73.4y (65 - 96y), N = 140 (57% male), only Chinese pat., no information about diagnoses, mean OLZ BL: 26.5 ng/ml, mean dose: 7.9 mg/d
(Olesen & Linnet, 1999)	COS		8 - 47**	12	TDM study, N = 56 (39% male), no information about diagnoses, median OLZ BL: 20 ng/ml, median dose: 15 mg/d
(Junutula et al., 2021)	COS		20 - 40	NA	ADR observed at a OLZ BL > 80 ng/ml, TDM study, SCZ pat., N = 61, 18 - 60y, 48% male, mean conc.16.3 ng/ml, median dose: 10 mg/d
(Mauri et al., 2005)	CES		20 - 50	12	clinical effect on positive, negative and affective symptoms estimated within RR
(Zabala et al., 2017)	CES		23 - 78	12	response of psychotic symptoms was associated within RR, response ≙ ≥ 30% decrease of PANSS

** converted from nmol/l

ADR: Adverse Drug Reaction; BL: Blood Level; BPRS: Brief Psychiatric Rating Scale; CES: Concentration/effect study; COS: Concentration Study; MADRS: Montgomery-Åsberg Depression Rating Scale; NA: Not Available; OLZ: Olanzapine; PANSS: Positive and Negative Syndrome Scale; ROC: Receiver Operating Characteristic; RR: Reference Range; SCZ: Schizophrenia; TDM: Therapeutic Drug Monitoring

8. CURRICULUM VITAE

PERSONAL DATA

Name:	Katja Wesner
Date of birth:	30.06.1984
Place of birth:	Elsterwerda, Germany
Family status:	Single
Father:	Jochen Wesner
Mother:	Martina Wesner

SCHOOL HISTORY

1996 - 2003	Elsterschloss-Gymnasium, Elsterwerda
27.06.2003	Abitur

UNIVERSITY HISTORY

10/2005 - 10/2011	Studies in Human Medicine at Ruprecht Karls University of Heidelberg
30.08.2007	First section of the medical examination
20.10.2011	Second section of the medical examination
31.10.2011	Approbation

PROFESSIONAL HISTORY

16.03.2018	Specialist in General Medicine

9. ACKNOWLEDGMENT

I would like to express my gratitude to my primary supervisor, Prof. Dr. Gerhard Gründer, for assigning this topic to me and his guidance throughout the entire process.

I wish to extend my special thanks to Dr. Xenia M. Hart for supervision, guidance, prompt feedback at all times, and her support to finalize this project.

The assistance provided by Johann Renner was greatly appreciated.

Thanks should also go to the following people for support and collaboration on this work: Prof. Dr. Christoph Hiemke, Xenija Lense, Luzie Eichentopf, Dr. Thomas Riemer, and Dr. Georgios Schoretsanitis.