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SYSTEMATIC REVIEW ARTICLE

The Relation between the Plasma Concentrations of Long-Acting Atypical Antipsychotics and Clinical Effectiveness in Patients Affected by Schizophrenia or Schizoaffective Disorder: A Comprehensive Overview

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Abstract: Atypical antipsychotic depot medications are currently recommended for patients with schizophrenia (SCZ) to prevent relapse and ameliorate the long-term prognosis of these patients. This review critically summarizes the available data about the association between the plasma concentrations of long-acting Second-Generation Antipsychotics (SGAs) and the clinical effectiveness of these compounds in patients affected by SCZ or schizoaffective disorder. Our question is if the measurement of these concentrations can be helpful for clinicians in predicting treatment response and clinical stabilization of patients. Bibliographic research on the main databases was performed, and 13 studies were finally included in this review. Contrasting results were found between plasma concentrations of long-acting injectable (LAI) risperidone and clinical amelioration according to rating scale scores. Data are too scanty to draw conclusions for olanzapine and paliperidone. In contrast, despite small sample sizes, data are quite concordant in showing a relation between long-acting SGA plasma concentrations and D2 receptor occupancy. Despite the preliminary encouraging results, particularly for D2 receptor occupancy, future research with larger samples will have to confirm the clinical usefulness of measuring LAI SGA plasma concentrations to predict the clinical response of patients affected by severe mental conditions such as SCZ.

Keywords: Second Generation Antipsychotics (SGAs), long-acting injectable (LAI), schizophrenia (SCZ), plasma concentrations, plasma levels, effectiveness, D2 occupancy.

1. INTRODUCTION

Schizophrenia (SCZ) and related disorders are chronic and persistent illnesses, and one of the main causes of global disability [1]. The long-term course of individuals with SCZ may differ depending on their symptoms, social functioning and quality of life, and it is influenced by several factors, including genetic, environmental and treatment variables [2, 3]. Particularly, antipsychotic medication still represents the cornerstone of the treatment of individuals affected by SCZ. Typical or first-generation antipsychotics (FGAs) act as antagonists of postsynaptic dopamine 2 receptors (D2Rs). While such antipsychotics have a robust efficacy against the positive symptoms of SCZ, they are considered poorly effective in treating negative symptoms [4]. Second-generation antipsychotics (SGAs) were introduced to address these unmet clinical needs, resulting to be equally effective or better than FGAs, particularly for negative, depressive and cognitive symptoms [5, 6], and relapse prevention [7, 8]. For these reasons, clinical practice guidelines recommend SGAs as first-line compounds to treat patients with SCZ, also for the reduced risk of extrapyramidal side effects generally associated with FGAs. Nevertheless, a lack of compliance to pharmacotherapy is frequent among patients with SCZ, both soon after the first episode and over longer periods [9]. As a consequence of poor adherence, relapses in SCZ can lead to serious consequences, including worsened prognosis, treatment resistance and increased health care costs [10]. Hence, long-acting injectable (LAI) antipsychotics were developed to deal with this issue, and they showed in observational "real-world" trials to be more effective than oral antipsychotics in reducing relapses and hospitalizations [11, 12]. In addition, LAI formulation provides more accurate drug delivery, reduces peak-to-trough drug concentrations and offers a higher dosing precision [13]. As happened with oral SGAs, which quickly replaced FGAs as first-line medications in treating both SCZ and severe mood disorders, there was a progressive diffusion of LAI SGAs into clinical practice [14]. However, there is a lack of robust and consistent experimental evidence that LAI SGAs are more effective in relapse prevention than FGA depots [15]; currently available LAI formulations of SGAs, including risperidone, olanzapine, paliperidone, and aripiprazole, are recommended by guidelines as the first-line choice for the maintenance treatment of non-adherent SCZ patients [16], in the light of the lower rate of side effects [17]. Furthermore, treatment with LAI SGAs may offer significant advantages both over oral antipsychotics and FGA depots in terms of treatment adherence with consequent lower risk of relapses and hospitalizations [18]. However, about one-third of patients may develop a treatment-resistant SCZ (TRS), defined as a lack of adequate response to two or more antipsychotic treatment trials [19]. TRS is associated with poor prognosis, and it constitutes a major challenge

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in the management of SCZ [20]. Currently, the gold-standard treatment of patients affected by TRS is represented by clozapine, an SGA which is very effective in the control of positive and negative symptoms, but which has critical issues, in particular, potentially severe side effects (*e.g.*, myocarditis), the need for periodic blood tests to check neutrophil count and the fact that it is not available in LAI formulation [21]. Since adequate treatment refers to taking antipsychotic at a therapeutic dose for a sufficient duration [22], TRS may occur as a result of poor adherence or other individual-related factors such as fast metabolism, in turn leading to sub-therapeutic or undetectable antipsychotic plasma concentrations [23]. Indeed, poor absorption of antipsychotics from the gastrointestinal tract and rapid metabolism of the drug due to genetic factors or induced by smoking represent the main factors that hamper the achievement of therapeutic plasma concentrations among patients in treatment with LAI antipsychotics [24]. Apart from clozapine, which demonstrated a relationship between plasma concentrations, clinical effectiveness and onset of side effects [21, 25], antipsychotic plasma concentrations testing is rarely performed in clinical practice as a result of a lack of availability of kits, patient reluctance and cost [20]. Moreover, even though most studies found a possible relationship between antipsychotic plasma concentrations and response to FGA depots, LAI SGAs have been less investigated regarding this topic [26]. In this framework, the purpose of the present review is to summarize the existing findings regarding the possible utility of plasma concentration monitoring to predict the clinical effectiveness of LAI SGAs.

2. METHODS

A bibliographic search was conducted according to the PRISMA guidelines [27] in the main databases (PubMed, PsycInfo, Medscape), selecting published papers from 2003 to 19th January 2021 and using the search string "blood OR plasma OR serum levels" combined with "LAI OR long-acting OR depot" and with "aripiprazole OR risperidone OR olanzapine OR paliperidone".

An initial search was obtained only by headings. This preliminary search was followed by a manual selection of papers, in order to select those focused and pertinent to the topic of the present article. Articles in a language different from English were excluded. Furthermore, exclusion criteria consisted of studies dealing with animal samples or paediatric populations, reviews, or a diagnosis different from SCZ or schizoaffective disorder (Fig. **1**).

An evaluation of the quality of included studies was performed, according to Qualitative Assessment Tool for Quantitative Studies (Effective Public Health Practice Project) [28], as you can see in Table **1**.

3. RESULTS

Thirteen studies were finally included, and information is summarized in Table **1**.

Among these, seven consider the efficacy of antipsychotic drugs on the basis of direct outcome indicators, such as rating scale scores, while six consider indirect outcome indicators, such as D2 receptors occupancy. In general, most studies investigate the relationship between effectiveness and plasma concentrations of risperidone, while fewer studies analyse olanzapine or paliperidone. Table **2** reports the main findings of each study.

Regarding risperidone, none of the included five studies found a direct association between plasma concentrations of risperidone and/or its metabolite (9-OH-risperidone, 9-OH-RSP) and the clinical response. Bai and collaborators [29] found an association between plasma concentrations and risk of relapse, although adopting a categorical approach. The authors, in fact, noticed that patients taking 25 mg or 37.5 mg of risperidone, compared to those taking 50 mg biweekly, had not only lower plasma concentrations of risperidone and 9-OH-RSP, but also an increased tendency to relapse. The only study that explored the use of LAI risperidone in TRS [30] adopted a slightly different approach. They split the sample in patients who achieved treatment response versus non-responders and then computed for each subject the Metabolic Ratio (MR), defined as the ratio between 9-OH-RSP and risperidone plasma concentrations. The authors found that MR was the strongest predictor of treatment response both at the Brief Psychiatry Rating Scale (BPRS) and at the Positive and Negative Syndrome Scale (PANSS). Interestingly, the same authors found a strong and direct correlation between the active moiety, that is, the sum of risperidone and 9-OH-RSP plasma concentrations, and side effects at Simpson-Angus Scale (SAS). The remaining three studies, both adopting the PANSS [31, 32] or the Clinical Global Impression (CGI) [33], did not find an association between clinical improvement and plasma concentrations of risperidone and its metabolites.

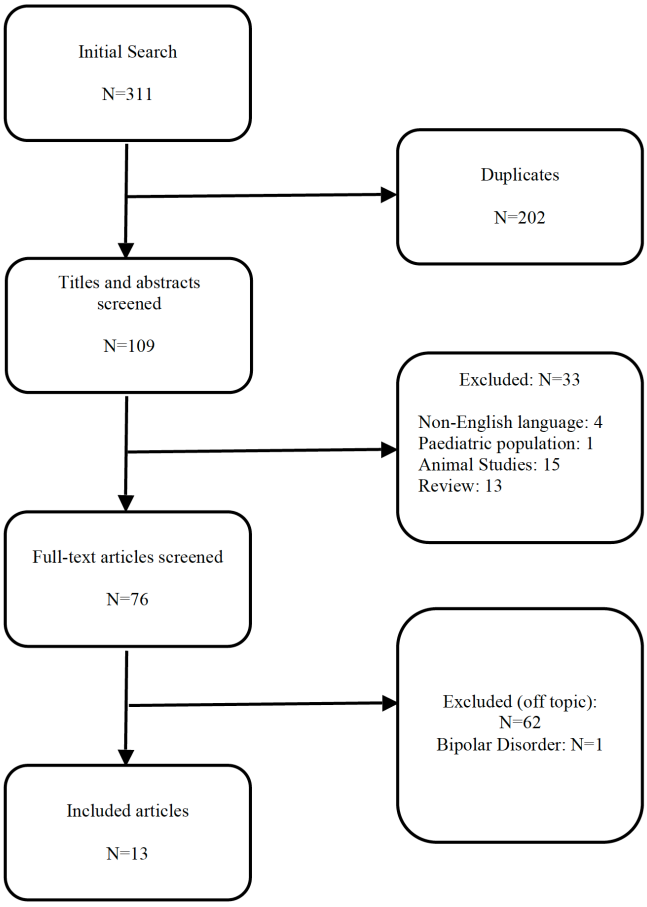

Fig. (1). Prisma Diagram for reviews.

When exploring the indirect outcomes (*i.e.*, D2 receptor occupancy) of risperidone, none of the included positron emission tomography (PET) studies found a direct linear association between the plasma concentrations and the receptor occupancy. The only one that found an association [34], instead, hypothesized the existence of a saturating hyperbole equation to explain the D2 receptor occupancy, with maximum efficacy at a plasma dosage of active moiety corresponding to 10.3 ng/mL. The other two studies found an association between the dosage of LAI risperidone dose and the D2 receptor occupancy [35, 36], but they failed in detecting a parallel clinical improvement. The correspondence between the D2 receptor occupancy, estimated from plasma concentrations of risperidone plus 9-OH-RSP, and clinical efficacy (measured by Brief Psychiatric Rating Scale-BPRS) was also questioned by two studies by Ikai and colleagues, who did not observe the expected associations [37, 38].

Table 1. Summary of the included studies.

-	Quality	Type of Study	Sample and Treatment	Plasma Assays	Results
Direct outcomes (rating scales scores)					
Bai *et al*., 2007	2	48-week randomized, prospective, single-blind study (Taiwan, March 2004 to May 2005)	50 inpatients with schizophrenia: -25 (48% female, mean age 48.1 SD 14.1) treated with oral RSP (mean dose: 4.7 ± 1.7 mg/day); -25 (52% female, mean age 44.7 SD 9.2) treated with RSP LAI biweekly at dosages of 25, 37.5 or 50 mg	Plasma measures of RSP and 9-OH-RSP done at baseline and 4, 8, 12, 24, 36, 48 weeks	● There was no significant difference in PANSS scores between the two groups, but the group receiving RSP LAI showed reduced UKU Side Effect Rating Scale (p=0.048), Simpson-Angus Scale (p=0.028), and serum concentration of RSP metabolites (p=0.028). ● Among the group treated with RSP LAI, patients who received 25 or 37.5 mg biweekly showed increased PANSS scores (p=0.058) at a borderline significant level, decreased serum 9-OH-RSP (p=0.023) concentrations, decreased total RSP metabolites concentrations (p=0.028) and an increased tendency to relapse compared to patients taking 50 mg RSP LAI dose.
Lai *et al*., 2009	3	12-week open label study (China)	25 patients with schizophrenia or schizoaffective disorder (47.6% female, mean age 43.0 SD 10.5), treated with RSP LAI (mean dose 31.25 mg every 2 weeks)	RSP plus 9-OH-RSP (mean concentration 29.1 ng/mL at 12th week)	● Participants whose last dose was 25 mg had lower plasma levels of active moiety than those with 37.5. mg (20.1 SD 13.8 *vs*. 39.6 SD 26.7 ng/mL, p=0.06). ● No correlation between plasma concentration of active moiety at week 12 and scores of PANSS (total scores or sub-score-positive, negative and general) and ESRS were found. ● Levels of active moiety of RSP resulted to be higher in Chinese patients than in Caucasian patients.
Volonteri *et al*., 2010	2	Open-label, non-randomized study	30 outpatients with treatment resistant schizophrenia (53% female, mean age 50.6 SD 13.1), treated with RSP LAI at variable dosages for 6 months	RSP plus 9-OH-RSP measured at steady-state (after the 4th injection of RSP LAI, before the subsequent injection, T2: 2 months)	● There was a significant positive relationship between plasma levels of active moiety and SAS scores (p<0.001). ● No differences in plasma levels of the active moiety between BPRS responders and non-responders (25.66 SD 32.93 *vs*. 20.81 SD 8.10 ng/mL) were found. Although, BPRS responders had a significantly higher mean metabolic ratio (MR, calculated as 9-OH-RSP/RSP plasma levels) than non-responders (3.41 SD 1.87 *vs*. 1.60 SD 0.98 ng/mL; p=0.016). ● The mean MR was significantly higher in PANSS responders than in non-responders at T2 (3.24 SD 1.79 *vs*. 1.46 SD 0.99 ng/mL; p=0.02), but no significant differences on RSP and 9-OH-RSP levels between BPRS and PANSS responders and non-responders at T2 were found. ● A higher MR was strongly predictive of a treatment response (odds ratio = 9.88; p<0.001). ● There was no correlation between plasma RSP, 9-OH- RSP, or active moiety levels and age, gender, or other clinical variables (illness duration, schizophrenia subtypes).
Choong *et al*., 2013	3	Naturalistic cross-sectional study (Switzerland, February 2007 to December 2009)	42 patients with schizophrenia or schizoaffective disorder (29% female, mean age 35, age range 18-63) treated with at least 4 consecutive unchanged doses of RSP LAI	Median concentration of RSP (5 ng/mL at day 0, 5 ng/mL at day 7), 9-OH-RSP (12 ng/mL at day 0, 15.5 ng/mL at day 7) and active moiety (21 ng/mL at day 0, 21 ng/mL at day 7), no SD reported	● No significant correlations were found between CGI scores and biweekly dose of RSP LAI (p>0.9), dose-adjusted* RSP (p>0.1), 9-OH-RSP (p>0.7), and active moiety (p>0.3) plasma levels at baseline, at day 7, and using a mixed model performed to take into account the 2 time points (data not reported). ● There were no associations between SAS scores and RSP LAI dosage, RSP, 9-OH-RSP and active moiety plasma levels.
Meltzer *et al*., 2014	1	Six-month randomized, double-blind, multi-center, controlled trial (March 2008 to December 2011)	160 patients with treatment resistant schizophrenia or schizoaffective disorder: - 78 (28.2% female, mean age 41.0 SD 11.4) treated with RSP LAI 100 mg biweekly; - 82 (26.8% female, mean age 39.2 SD 10.6) treated with RSP LAI 50 mg biweekly.	RSP (mean concentration 17.7 ng/mL SD 24.5 at week 6, 17.6 ng/mL SD 23.7 at week 24); 9-OH-RSP (mean concentration 22.4 ng/mL SD 15.6 at week 6, 26.5 ng/mL SD 16.7 at week 24); RSP plus 9-OH-RSP levels (mean concentration of active moiety 40.1 ng/mL SD 31.3 at week 6, 44.1 ng/mL SD 32.3 at week 24)	● Mean concentration of active moiety did not differ between the 100 mg- and the 50 mg- group (55.86 SD 38.82 *vs*. 30.31 SD 23.89 ng/mL at week 6; 62.36 SD 38.01 *vs*. 29.63 SD 15.81 ng/mL at week 24) ● The ratio of 9-OH-RSP to RSP was similar in both 100 mg- and 50 mg- treatment groups (3.11 SD 2.46 *vs*. 2.79 SD 2.34 ng/mL at week 6; 3.32 SD 2.36 *vs*. 4.67 SD 7.08 ng/mL at week 24). ● Regression analysis, adjusted for the baseline PANSS ratings, indicated that none of the selected plasmatic measures may predict changes in PANSS scores in either group at 6 or 24 weeks.

(Table 1) Contd....

-	Quality	Type of Study	Sample and Treatment	Plasma Assays	Results
Mauri *et al*., 2015	2	9-month prospective study (Italy)	25 patients with schizophrenia (48% female, mean age 35.38 SD 10.04) treated with olanzapine LAI once every 28 days (different dosages, but same dose for each patient until the end of the study)	Olanzapine plasma levels measured every month, before next injection (mean concentration 20.59 SD 14.66 ng/ml)	● Olanzapine plasma levels revealed a fast fall after the first injection; there was a statistically significant relationship between a lesser variation of olanzapine plasma levels and improvement in BPRS score (p=0.01).
Mauri *et al*., 2017	2	12-month prospective observational study (Italy)	21 outpatients with schizophrenia or schizoaffective disorder (28.6% female, mean age 40.66 SD 12.17) treated with PP at variable dosages.	PP plasma levels (range from 7 to 67.2 ng/mL, mean concentration 17.5 SD 7.3 ng/mL at T1-1 month, 29.6 SD 16.1 ng/mL at T5-5 months), measured at every monthly administration of PP.	● The mean of plasma level at T1 (1 month) was 17.5 SD 7.3 *vs*. 29.6 SD 16.1 ng/mL at T5 (5 months) ($p < 0.001$), followed by steady state levels and only a mild increase until T12 (12 months). ● The intra-individual variations of the paliperidone plasma levels (PL), evaluated as coefficient of variation (CV), and the intra-individual variations of the BPRS score, were positively related (BPRS CV=6.4959+0.1328*CV PL). ● There was a statistically significant relationship between a lesser variation of paliperidone plasma levels and the intra-individual BPRS CV during the study ($p = 0.005$).
Indirect outcomes (e.g. D2 receptor occupancy)					
Gefvert *et al*., 2005	3	Open-label non-randomized trial (Sweden).	13 patients with schizophrenia (8% female, age range 24-54) treated with RSP LAI every two weeks at variable dosages. 9 were studied with [^{11}C]-raclopride PET (8 after the 5th injection, 1 after the 3rd injection)	RSP plus 9-OH-RSP level (range 4.4-8.8 ng/mL for 25 mg RSP receivers, 15.0-31.1 ng/mL for 50 mg-RSP receivers, 22.5-26.3 ng/mL for 75 mg- RSP receivers)	● Higher doses were generally associated with higher D2 occupancy. D2 receptor occupancy ranged from 25% to 48% in subjects receiving 25 mg, 59–83% in ones receiving 50 mg, and 62–72 % in those ones receiving 75 mg. ● From baseline to end-point, mean PANSS total scores showed a 4% reduction in the 25-mg group (from 57.0 to 54.8), a 21% reduction in the 50-mg group (from 62.8 to 49.8), and a 11% reduction in the 75-mg group (from 61.0 to 54.5).
Remington *et al*., 2006	2	Short-term prospective study (Canada)	9 patients with stable schizophrenia or schizoaffective disorder (22% female, mean age 34 SD 9) and treated with RSP LAI at variable dosages, scanned twice with [^{11}C]-raclopride PET to measure D2 occupancy, once preinjection and once postinjection.	RSP plus 9-OH-RSP levels measured both pre-injection (5 days before the next injection) and post-injection (3 days after injection)	● Mean post- and pre-injection D2 occupancy levels for the 25-, 50-, and 75 mg doses were 71.0% and 54.0%, 74.4% and 65.4%, and 81.5% and 75.0%, respectively. ● A comparison across all doses between post-injection and pre-injection indicated a significant reduction in both D2 occupancy ($p=0.006$) and plasma concentrations of RSP plus 9-OH-RSP ($p=0.01$). ● The estimated plasma concentration associated with 50% D2 occupancy (ED50) was 11.06 ng/ml.
Mamo *et al*., 2008	2	6-month multicenter, open-label study (Canada and USA)	14 patients with schizophrenia (36% female, mean age) initially treated with oral olanzapine and then with olanzapine LAI 300 mg every 4 weeks, with a total of 6 injections, and studied with [11C]-raclopride PET at baseline plus no more than three of the following time points: 4, 8, 12, 16, 20 or 24 weeks before administration of next injection.	Olanzapine plasma levels at baseline and at week 4 of each cycle (mean plasma concentration 37.4 SD 31.2 ng/mL at baseline, 20.3 SD 11.2 ng/mL at steady state, after 8 weeks)	● Mean striatal D2 receptor occupancy, as measured by [11C]-raclopride PET, was 69.1% SD 15.2% at baseline with oral olanzapine (5–20 mg/day) and 50% on olanzapine LAI at steady state. Following an initial decline, occupancy returned to 84% of baseline oral olanzapine occupancy after six injections. ● Over the study period, D2 receptor occupancy and plasma olanzapine concentrations were significantly correlated ($p<0.001$). ● Olanzapine LAI resulted in mean D2 receptor occupancy of approximately 60% or higher at the end of the 6-month study period.
Uchida *et al*., 2008	3	Cross-sectional (Canada, from May to October 2003)	7 patients with schizophrenia or schizoaffective disorder (14% female, age range from 18 to 59) treated with at least 3 injections of RSP LAI 50 mg and studied with PET using [^{11}C]raclopride to measure D2 binding potential	RSP plus 9-OH-RSP (mean concentration 16.6 SD 12.3 ng/mL)	● Mean dopamine D2 receptor occupancy was 56% SD 24%. ● D2 occupancy was above the occupancy threshold associated with clinical response (60%) in 3 subjects. • The mean +/- SD total plasma level of risperidone plus 9-hydroxyrisperidone was 16.6 +/- 12.3 ng/mL (range: 5.7-40.8). ● The relationship between plasma levels of RSP plus 9-OH-RSP and D2 receptor occupancy could be fit to the saturating hyperbole equation: occupancy=a×(plasma level/[plasma level+ED50]), where a is the maximum receptor occupancy and ED50 is the estimated plasma RSP plus 9-OH-RSP concentration (ng/mL) associated with 50% maximal receptor occupancy. ● The maximal occupancy (a) ± SE calculated with this regression equation for D2 receptor occupancy resulted with plasma levels of 111 SD 33 ng/mL, with the estimated ED50 of 13.0 ng/mL (95% confidence interval: 0.0 to 36.0). When the maximal occupancy was constrained to 100%, the estimated ED50 was 10.3 ng/mL (95% confidence interval: 4.4 to 16.2).

(Table 1) Contd....

-	Quality	Type of Study	Sample and Treatment	Plasma Assays	Results
Ikai *et al*., 2012	3	Cross-sectional (Japan, 2011)	36 patients with schizophrenia (58.3% female, mean age 49.3 SD 14.0), treated with RSP LAI as monotherapy for at least three months (mean dose 38.2 SD 11.6 mg; mean interval of injections 16.5 SD 14 days)	One plasma sample taken immediately before the injection of RSP LAI for plasma concentrations of RSP plus 9-OH-RSP (mean concentration 22.5 SD 15.0 ng/ml)	● Mean dopamine D2 receptor occupancy (estimated from plasma concentrations of RSP plus 9-OH-RSP) was 62.1% SD 15.4%. ● 52.8% of patients (n=19) did not shown an occupancy ≥65%, while 13.9% (n=5) showed a D2 occupancy as high as over 80%. ● No correlations observed between estimated D2 receptor occupancy and BPRS, SAS, AIMS and BAS total scores.
Ikai *et al*., 2016	3	Naturalistic 3-year follow up study (Japan, 2015)	52 outpatients with schizophrenia (50.9% female, mean age 48.3 SD 14.0) treated for 3 years with RSP LAI (mean dose 40.9 SD 11.4 mg), of whom only 36 completed the study and only 10 provided plasma samples. Data were compared with the same patients collected 3 years earlier.	One plasma sample taken from 10 patients (19%) immediately before the injection of RSP LAI for plasma concentrations of RSP plus 9-OH-RSP	● Mean concentration of RSP plus 9-OH-RSP significantly increased from 22.9 SD 25.6 to 31.8 SD 17.5 ng/ml (p=0.02), while estimated dopamine D2 receptor occupancy (estimated from plasma concentrations of RSP plus 9-OH-RSP) increased from 63.0 SD 10.9 to 69.0 SD 11.0, but it was not statistically significant (p=0.12).

Legend:

AIMS: Abnormal Involuntary Movement Scale; BAS: Barnes Akathisia Scale; BD: bipolar disorder; BPRS: Brief Psychiatric Rating Scale; CGI: Clinical Global Impression Scale; CV: coefficient of variations; ESRS: Extrapiramidal Symptoms Rating Scale; LAI: long-acting injectable; MRS: Young Mania Rating Scale; PANSS: Positive and Negative Symptoms Scale; PET: positron emission tomography; PL: paliperidone plasma levels; RSP: risperidone; PP: paliperidone palmitate; SAS: Simpson-Angus Scale; SD: standard deviation; 9-OH-RSP: 9-hydroxyrisperidone.

*=Normalized by the dose.

Global rating was performed according to these criteria (Qualitative Assessment Tool for Quantitative Studies):

1) Selection Bias (sample size power and number of subjects who agreed to participate into the study).

2) Study Design (randomized versus non-randomized trials).

3) Confounders (Yes/No).

4) Blinding (Yes/No).

5) Data collection methods (self reported data, observations by investigators or medical records).

6) Presence of description of numbers and reasons for withdrawals and drop-outs.

Legend:

1=Strong (no weak ratings according to above criteria).

2= Moderate (one weak rating according to above criteria).

3= Weak (two or more weak ratings according to above criteria).

Table 2. Main findings for each study.

-	Type of Outcome	Presence of Relation between Plasma Concentrations and Outcome	Presence of Relation between Plasma Levels and Side Effects
Bai *et al*., 2007	Clinical	No	Yes
Lai *et al*., 2009	Clinical	No	No
Volonteri *et al*., 2010	Clinical	No	Yes
Choong *et al*., 2013	Clinical	No	No
Meltzer *et al*., 2014	Clinical	No	Not studied
Mauri *et al*., 2015	Clinical	Yes	Not studied
Mauri *et al*., 2017	Clinical	Yes	Not studied
Gefvert *et al*., 2005	D2 receptor occupancy	Yes	Not studied
Remington *et al*., 2006	D2 receptor occupancy	Yes	Not studied
Mamo *et al*., 2008	D2 receptor occupancy	Yes	Not studied
Uchida *et al*., 2008	D2 receptor occupancy	Yes	Not studied
Ikai *et al*., 2012	D2 receptor occupancy	No	No
Ikai *et al*., 2016	D2 receptor occupancy	No	Not studied

The studies that evaluated the plasma concentration of olanzapine are fewer but more encouraging. Mauri and colleagues [39] reported that the variation of the olanzapine concentration was the strongest predictor of clinical benefit. Specifically, the authors found that the lesser the variation of olanzapine plasma concentrations, the greater the probability of at least 20% improvement at the BPRS. Furthermore, the D2 receptors occupancy was found to correlate directly with the plasma concentrations of olanzapine [40].

To our knowledge, only one study evaluated the association between the plasma concentrations of paliperidone and the clinical outcome in schizophrenia and related disorders [41]. With an approach similar to the previous study, the authors highlighted how a

lesser variability in the paliperidone plasma concentrations was associated with a smaller intra-individual variation at BPRS, regardless of the administered dose of LAI paliperidone. This means that greater clinical stability was associated with a steadier plasma concentration.

Until now, surprisingly, no study investigated the relationship between plasma concentration of LAI aripiprazole and clinical effectiveness in subjects affected by SCZ, although aripiprazole is labelled for the treatment of these patients [42].

4. DISCUSSION

The present manuscript had the objective to study the relationship between plasma concentrations of LAI atypical antipsychotics and clinical effectiveness as measured by direct (clinical) and indirect (experimental) parameters. This topic can have clinical utility to predict treatment response and prognosis of patients affected by severe mental disorders (*e.g.*, SCZ) and treated with LAI SGAs [43].

With regard to LAI risperidone, the available data poorly supports a linear association between antipsychotic plasma concentrations and clinical changes, as shown by rating scale scores. Of note, two long-term studies (one randomized trial and one open-label study) for a total of 80 patients [29, 30] report encouraging results about a sort of relationship between clinical symptoms and plasma antipsychotic concentrations, but either using a categorical approach [29] or calculating different pharmacokinetic parameters such as MR [30]. In addition, no significant relation was found by 2 open-label trials and one double-blind study for a total of 227 subjects [31-32]. With regard to the other compounds, two long-term small-sample studies from the same research group attested as a lesser variation of plasma concentrations respectively of paliperidone [41] and olanzapine [39] was associated with amelioration of BPRS scores, once again not supporting a direct linear association between plasma concentrations of LAI SGAs and clinical symptoms.

Concerning indirect outcomes, we found several articles about D2 receptor occupancy and plasma concentrations of SGA. It was demonstrated that patients affected by schizophrenia and treated with antipsychotics have a good clinical response when the D2 occupancy rate is between 65 and 80%, while over 80% patients show extrapyramidal side effects and hyperprolactinemia [44, 45]. D2 receptor occupancy in relation to LAI SGA plasma concentrations was mainly investigated by PET in small-sample studies of patients treated with risperidone [34-36], with the exception of the study by Mamo and collaborators [40] who tested olanzapine and also performed the longest follow-up. All the studies found a positive association between receptor occupancy and LAI SGA plasma concentrations [40] or dose [35, 36]. Of note, Uchida and co-authors proposed a non-linear association between D2 receptor occupancy and LAI risperidone plasma concentrations [34]. Only two studies with risperidone from the same research group [37, 38] failed to find significant associations between D2 receptor occupancy, antipsychotic plasma concentrations and clinical effectiveness, but receptor occupancy was calculated with an indirect method. Anyhow, the etiology of SCZ spectrum disorders is complex and includes the modulation of many different receptors and pathways as well as the dopamine ones.

Taken as a whole, contrasting and few data were published about the association between LAI SGA plasma concentrations and clinical changes as measured by rating scales in patients affected by SCZ. With regard to D2 receptor occupancy, data are more concordant and promising, but studies with larger samples are necessary to draw definitive conclusions. Furthermore, as proposed by Uchida and co-authors [34], it is likely that the relation between LAI SGAs plasma concentrations and receptor occupancy may be explained by a saturating hyperbole equation.

Further considerations should be reported. First, testing LAI SGAs plasma concentrations or their active metabolites allows to overcome the inter-individual variability in cytochrome (CYP) functioning and consequently in the concentrations of active metabolites for the same dose of antipsychotic [46, 47]. This aspect is particularly important for fast or poor metabolizers in whom the study of the interplay between oral doses of antipsychotics, their plasma concentrations and clinical effectiveness may be more complex with respect to LAI compounds.

Second, the lack of a convincing association between LAI SGA plasma concentrations and direct/indirect parameters of clinical effectiveness can not only be explained by a non-linear relationship [34], but also by the fact that D2 receptor dysfunction represents only one of the mechanisms underlying SCZ [5]. In this sense, other biological factors might be more directly related to LAI SGA plasma concentrations and be concomitantly reliable biomarkers of clinical amelioration (*e.g.*, Brain-Derived Neurotrophic Factor-BDNF or sex steroids plasma concentrations) [48, 49]. Third, numerous factors can influence antipsychotic plasma concentrations (*e.g.*, fast metabolizers or substance misuse) [46, 50] or hamper patients' clinical amelioration, including metabolic syndrome [51] and tardive dyskinesia, which usually consists of repetitive and involuntary movements mostly in the oral, lingual and buccal areas [52]. While it has been reported a relationship between plasma concentration of antipsychotic and onset of extrapyramidal symptoms for oral treatment with haloperidol [53], fluphenazine [54] and amisulpride [55], this relation seems to be unclear at the moment for SGAs (both oral and LAI) [29, 30, 31, 33].

CONCLUSION

Finally, it is necessary to highlight that the selected studies for the purposes of the present review are extremely heterogeneous in terms of follow-up (short versus long-term), type of included patients (schizoaffective, SCZ and treatment-resistant subjects) and study design. Of note, only one article investigated the relationship between plasma concentrations of LAI aripiprazole and BD [56], so that this field of study, particularly for subjects affected by severe mood disorders and for some type of LAI SGAs (*e.g.*, olanzapine or aripiprazole), does not appear to be comprehensively explored by the currently available literature. In conclusion, future studies with larger samples will have to confirm the clinical usefulness of measuring LAI SGA plasma concentrations as a complementary exam to monitor the clinical status of patients affected by severe mental conditions [57].

CONSENT FOR PUBLICATION

Not applicable.

PRISMA guidelines and methodology were followed

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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REFERENCES

[1] GBD 2017 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990-2017: A systematic analysis for the Global Burden of Disease Study 2017. Lancet 2018; 392(10159): 1789-858.

http://dx.doi.org/10.1016/S0140-6736(18)32279-7 PMID: 30496104

[2] Buoli M, Serati M, Caldiroli A, Cremaschi L, Altamura AC. Neurodevelopmental *versus* Neurodegenerative Model of Schizophrenia and Bipolar Disorder: Comparison with Physiological Brain Development and Aging. Psychiatr Danub 2017; 29(1): 24-7. http://dx.doi.org/10.24869/psyd.2017.24 PMID: 28291970

[3] Vita A, Barlati S. Recovery from schizophrenia: Is it possible? Curr Opin Psychiatry 2018; 31(3): 246-55. http://dx.doi.org/10.1097/YCO.0000000000000407 PMID: 29474266

[4] Bressan RA, Costa DC, Jones HM, Ell PJ, Pilowsky LS. Typical antipsychotic drugs -- D(2) receptor occupancy and depressive symptoms in schizophrenia. Schizophr Res 2002; 56(1-2): 31-6. http://dx.doi.org/10.1016/S0920-9964(01)00185-2 PMID: 12084417

[5] Capuzzi E, Caldiroli A, Ciscato V, Russo S, Buoli M. Experimental Serotonergic Agents for the Treatment of Schizophrenia. J Exp Pharmacol 2021; 13: 49-67. http://dx.doi.org/10.2147/JEP.S259317 PMID: 33574716

[6] Chen AT, Nasrallah HA. Neuroprotective effects of the second generation antipsychotics. Schizophr Res 2019; 208: 1-7. http://dx.doi.org/10.1016/j.schres.2019.04.009 PMID: 30982644

[7] Buoli M, Kahn RS, Serati M, Altamura AC, Cahn W. Haloperidol *versus* second-generation antipsychotics in the long-term treatment of schizophrenia. Hum Psychopharmacol 2016; 31(4): 325-31. http://dx.doi.org/10.1002/hup.2542 PMID: 27297936

[8] Leucht S, Corves C, Arbter D, Engel RR, Li C, Davis JM. Second-generation *versus* first-generation antipsychotic drugs for schizophrenia: A meta-analysis. Lancet 2009; 373(9657): 31-41. http://dx.doi.org/10.1016/S0140-6736(08)61764-X PMID: 19058842

[9] Kane JM, Kishimoto T, Correll CU. Non-adherence to medication in patients with psychotic disorders: Epidemiology, contributing factors and management strategies. World Psychiatry 2013; 12(3): 216-26. http://dx.doi.org/10.1002/wps.20060 PMID: 24096780

[10] Novick D, Haro JM, Suarez D, Perez V, Dittmann RW, Haddad PM. Predictors and clinical consequences of non-adherence with antipsychotic medication in the outpatient treatment of schizophrenia. Psychiatry Res 2010; 176(2-3): 109-13. http://dx.doi.org/10.1016/j.psychres.2009.05.004 PMID: 20185182

[11] Fang SC, Liao DL, Huang CY, Hsu CC, Cheng SL, Shao YJ. The effectiveness of long-acting injectable antipsychotics *versus* oral antipsychotics in the maintenance treatment of outpatients with chronic schizophrenia. Hum Psychopharmacol 2020; 35(3): e2729. http://dx.doi.org/10.1002/hup.2729 PMID: 32182388

[12] Kishimoto T, Hagi K, Nitta M, *et al.* Effectiveness of Long-Acting Injectable *vs* Oral Antipsychotics in Patients With Schizophrenia: A Meta-analysis of Prospective and Retrospective Cohort Studies. Schizophr Bull 2018; 44(3): 603-19. http://dx.doi.org/10.1093/schbul/sbx090 PMID: 29868849

[13] Correll CU, Lauriello J. Using long-acting injectable antipsychotics to enhance the potential for recovery in schizophrenia. J Clin Psychiatry 2020; 81(4): MS19053AH5C. http://dx.doi.org/10.4088/JCP.MS19053AH5C

[14] Biagi E, Capuzzi E, Colmegna F, *et al.* Long-Acting Injectable Antipsychotics in Schizophrenia: Literature Review and Practical Perspective, with a Focus on Aripiprazole Once-Monthly. Adv Ther 2017; 34(5): 1036-48. http://dx.doi.org/10.1007/s12325-017-0507-x PMID: 28382557

[15] Saucedo Uribe E, Carranza Navarro F, Guerrero Medrano AF, *et al.* Preliminary efficacy and tolerability profiles of first *versus* second-generation Long-Acting Injectable Antipsychotics in schizophrenia: A systematic review and meta-analysis. J Psychiatr Res 2020; 129: 222-33. http://dx.doi.org/10.1016/j.jpsychires.2020.06.013 PMID: 32805530

[16] Olagunju AT, Clark SR, Baune BT. Long-acting atypical antipsychotics in schizophrenia: A systematic review and meta-analyses of effects on functional outcome. Aust N Z J Psychiatry 2019; 53(6): 509-27. http://dx.doi.org/10.1177/0004867419837358 PMID: 30957510

[17] Pilon D, Joshi K, Tandon N, *et al.* Treatment patterns in Medicaid patients with schizophrenia initiated on a first- or second-generation long-acting injectable *versus* oral antipsychotic. Patient Prefer Adherence 2017; 11: 619-29. http://dx.doi.org/10.2147/PPA.S127623 PMID: 28356723

[18] Salgueiro M, Segarra R. Long-acting injectable second-generation antipsychotics in first-episode psychosis: A narrative review. Int Clin Psychopharmacol 2019; 34(2): 51-6. http://dx.doi.org/10.1097/YIC.0000000000000249 PMID: 30540617

[19] Howes OD, McCutcheon R, Agid O, *et al.* Treatment-Resistant Schizophrenia: Treatment Response and Resistance in Psychosis (TRRIP) Working Group Consensus Guidelines on Diagnosis and Terminology. Am J Psychiatry 2017; 174(3): 216-29. http://dx.doi.org/10.1176/appi.ajp.2016.16050503 PMID: 27919182

[20] Bozzatello P, Bellino S, Rocca P. Predictive Factors of Treatment Resistance in First Episode of Psychosis: A Systematic Review. Front Psychiatry 2019; 10: 67. http://dx.doi.org/10.3389/fpsyt.2019.00067 PMID: 30863323

[21] Siskind D, Siskind V, Kisely S. Clozapine Response Rates among People with Treatment-Resistant Schizophrenia: Data from a Systematic Review and Meta-Analysis. Can J Psychiatry 2017; 62(11): 772-7. http://dx.doi.org/10.1177/0706743717718167 PMID: 28655284

[22] National Collaborating Centre for Mental Health (UK). Psychosis and Schizophrenia in Adults: Treatment and Management. UK: National Institute for Health and Care Excellence 2014.

[23] McCutcheon R, Beck K, Bloomfield MA, Marques TR, Rogdaki M, Howes OD. Treatment resistant or resistant to treatment? Antipsychotic plasma levels in patients with poorly controlled psychotic symptoms. J Psychopharmacol 2015; 29(8): 892-7. http://dx.doi.org/10.1177/0269881115576688 PMID: 25788157

[24] Patel MX, Bowskill S, Couchman L, *et al.* Plasma olanzapine in relation to prescribed dose and other factors: Data from a therapeutic drug monitoring service, 1999-2009. J Clin Psychopharmacol 2011; 31(4): 411-7. http://dx.doi.org/10.1097/JCP.0b013e318221b408 PMID: 21694620

[25] Yada Y, Kitagawa K, Sakamoto S, *et al.* The relationship between plasma clozapine concentration and clinical outcome: A cross-sectional study. Acta Psychiatr Scand 2021; 143(3): 227-37. http://dx.doi.org/10.1111/acps.13264 PMID: 33274435

[26] Horvitz-Lennon M, Mattke S, Predmore Z, Howes OD. The role of antipsychotic plasma levels in the treatment of schizophrenia. Am J Psychiatry 2017; 174(5): 421-6. http://dx.doi.org/10.1176/appi.ajp.2016.16040402 PMID: 28457153

[27] Liberati A, Altman DG, Tetzlaff J, *et al.* The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: Explanation and elaboration. PLoS Med 2009; 6(7): e1000100. http://dx.doi.org/10.1371/journal.pmed.1000100 PMID: 19621070

[28] Armijo-Olivo S, Stiles CR, Hagen NA, Biondo PD, Cummings GG. Assessment of study quality for systematic reviews: A comparison of the Cochrane Collaboration Risk of Bias Tool and the Effective Public Health Practice Project Quality Assessment Tool: Methodological research. J Eval Clin Pract 2012; 18(1): 12-8. http://dx.doi.org/10.1111/j.1365-2753.2010.01516.x PMID: 20698919

[29] Bai YM, Ting Chen T, Chen JY, *et al.* Equivalent switching dose from oral risperidone to risperidone long-acting injection: A 48-week randomized, prospective, single-blind pharmacokinetic study. J Clin Psychiatry 2007; 68(8): 1218-25. http://dx.doi.org/10.4088/JCP.v68n0808 PMID: 17854246

[30] Volonteri LS, Cerveri G, De Gaspari IF, *et al.* Long-acting injectable risperidone and metabolic ratio: A possible index of clinical outcome in treatment-resistant schizophrenic patients. Psychopharmacology (Berl) 2010; 210(4): 489-97. http://dx.doi.org/10.1007/s00213-010-1852-5 PMID: 20422405

[31] Lai YC, Huang MC, Chen CH, Tsai CJ, Pan CH, Chiu CC. Pharmacokinetics and efficacy of a direct switch from conventional depot to risperidone long-acting injection in Chinese patients with

schizophrenic and schizoaffective disorders. Psychiatry Clin Neurosci 2009; 63(4): 440-8. http://dx.doi.org/10.1111/j.1440-1819.2009.01977.x PMID: 19457210

[32] Meltzer HY, Lindenmayer JP, Kwentus J, Share DB, Johnson R, Jayathilake K. A six month randomized controlled trial of long acting injectable risperidone 50 and 100mg in treatment resistant schizophrenia. Schizophr Res 2014; 154(1-3): 14-22. http://dx.doi.org/10.1016/j.schres.2014.02.015 PMID: 24630262

[33] Choong E, Polari A, Kamdem RH, *et al.* Pharmacogenetic study on risperidone long-acting injection: Influence of cytochrome P450 2D6 and pregnane X receptor on risperidone exposure and drug-induced side-effects. J Clin Psychopharmacol 2013; 33(3): 289-98. http://dx.doi.org/10.1097/JCP.0b013e31828f62cd PMID: 23609392

[34] Uchida H, Mamo DC, Kapur S, *et al.* Monthly administration of long-acting injectable risperidone and striatal dopamine D2 receptor occupancy for the management of schizophrenia. J Clin Psychiatry 2008; 69(8): 1281-6. http://dx.doi.org/10.4088/JCP.v69n0811 PMID: 18642974

[35] Gefvert O, Eriksson B, Persson P, *et al.* Pharmacokinetics and D2 receptor occupancy of long-acting injectable risperidone (Risperdal Consta) in patients with schizophrenia. Int J Neuropsychopharmacol 2005; 8(1): 27-36. http://dx.doi.org/10.1017/S1461145704004924 PMID: 15710053

[36] Remington G, Mamo D, Labelle A, *et al.* A PET study evaluating dopamine D2 receptor occupancy for long-acting injectable risperidone. Am J Psychiatry 2006; 163(3): 396-401. http://dx.doi.org/10.1176/appi.ajp.163.3.396 PMID: 16513859

[37] Ikai S, Remington G, Suzuki T, *et al.* A cross-sectional study of plasma risperidone levels with risperidone long-acting injectable: Implications for dopamine D2 receptor occupancy during maintenance treatment in schizophrenia. J Clin Psychiatry 2012; 73(8): 1147-52. http://dx.doi.org/10.4088/JCP.12m07638 PMID: 22967779

[38] Ikai S, Suzuki T, Mimura M, Uchida H. Plasma levels and estimated dopamine D_2 receptor occupancy of long-acting injectable risperidone during maintenance treatment of schizophrenia: A 3-year follow-up study. Psychopharmacology (Berl) 2016; 233(23-24): 4003-10. http://dx.doi.org/10.1007/s00213-016-4428-1 PMID: 27631410

[39] Mauri MC, Maffini M, Di Pace C, *et al.* "Long-acting" olanzapine in maintenance therapy of schizophrenia: A study with plasma levels. Int J Psychiatry Clin Pract 2015; 19(2): 99-105. http://dx.doi.org/10.3109/13651501.2014.1000928 PMID: 25547438

[40] Mamo D, Kapur S, Keshavan M, *et al.* D2 receptor occupancy of olanzapine pamoate depot using positron emission tomography: An open-label study in patients with schizophrenia. Neuropsychopharmacology 2008; 33(2): 298-304. http://dx.doi.org/10.1038/sj.npp.1301409 PMID: 17443131

[41] Mauri MC, Reggiori A, Paletta S, Di Pace C, Altamura AC. Paliperidone for the treatment of schizophrenia and schizoaffective disorders - a drug safety evaluation. Expert Opin Drug Saf 2017; 16(3): 365-79. http://dx.doi.org/10.1080/14740338.2017.1288716 PMID: 28140680

[42] Kumar A, Singh H, Mishra A, Mishra AK. Aripiprazole: An FDA approved bioactive compound to treat schizophrenia- A mini review. Curr Drug Discov Technol 2020; 17(1): 23-9. http://dx.doi.org/10.2174/1570163815666181008151718 PMID: 30306873

[43] Arnaiz JA, Rodrigues-Silva C, Mezquida G, *et al.* The usefulness of Olanzapine plasma concentrations in monitoring treatment efficacy and metabolic disturbances in first-episode psychosis. Psychopharmacology (Berl) 2020. http://dx.doi.org/10.1007/s00213-020-05715-5 PMID: 33230696

[44] Nord M, Farde L. Antipsychotic occupancy of dopamine receptors in schizophrenia. CNS Neurosci Ther 2011; 17(2): 97-103. http://dx.doi.org/10.1111/j.1755-5949.2010.00222.x PMID: 21143431

[45] Kapur S, Zipursky R, Jones C, Remington G, Houle S. Relationship between dopamine D(2) occupancy, clinical response, and side effects: A double-blind PET study of first-episode schizophrenia. Am J Psychiatry 2000; 157(4): 514-20. http://dx.doi.org/10.1176/appi.ajp.157.4.514 PMID: 10739409

[46] de Leon J, Wynn G, Sandson NB. The pharmacokinetics of paliperidone *versus* risperidone. Psychosomatics 2010; 51(1): 80-8. http://dx.doi.org/10.1016/S0033-3182(10)70664-2 PMID: 20118446

[47] Schoretsanitis G, de Leon J, Haen E, *et al.* Pharmacokinetics of risperidone in different application forms - Comparing long-acting injectable and oral formulations. Eur Neuropsychopharmacol 2018; 28(1): 130-7. http://dx.doi.org/10.1016/j.euroneuro.2017.11.009 PMID: 29153926

[48] Buoli M, Caldiroli A, Serati M, Grassi S, Altamura AC. Sex Steroids and Major Psychoses: Which Role for DHEA-S and Progesterone. Neuropsychobiology 2016; 73(3): 178-83. http://dx.doi.org/10.1159/000444922 PMID: 27100685

[49] Heitz U, Papmeyer M, Studerus E, *et al.* Plasma and serum brain-derived neurotrophic factor (BDNF) levels and their association with neurocognition in at-risk mental state, first episode psychosis and chronic schizophrenia patients. World J Biol Psychiatry 2019; 20(7): 545-54. http://dx.doi.org/10.1080/15622975.2018.1462532 PMID: 29938562

[50] Correll CU, Sliwa JK, Najarian DM, Saklad SR. Practical considerations for managing breakthrough psychosis and symptomatic worsening in patients with schizophrenia on long-acting injectable antipsychotics. CNS Spectr 2018; 1-17. http://dx.doi.org/10.1017/S1092852918001098 PMID: 30587268

[51] Chen S, Xia X, Deng C, *et al.* The correlation between metabolic syndrome and neurocognitive and social cognitive performance of patients with schizophrenia. Psychiatry Res 2020; 288: 112941. http://dx.doi.org/10.1016/j.psychres.2020.112941 PMID: 32334274

[52] Correll CU, Kane JM, Citrome LL. Epidemiology, Prevention, and Assessment of Tardive Dyskinesia and Advances in Treatment. J Clin Psychiatry 2017; 78(8): 1136-47. http://dx.doi.org/10.4088/JCP.tv17016ah4c PMID: 29022654

[53] Lane HY, Lin HN, Hu OY, Chen CC, Jann MW, Chang WH. Blood levels of reduced haloperidol *versus* clinical efficacy and extrapyramidal side effects of haloperidol. Prog Neuropsychopharmacol Biol Psychiatry 1997; 21(2): 299-311. http://dx.doi.org/10.1016/S0278-5846(97)00007-9 PMID: 9061775

[54] Levinson DF, Simpson GM, Lo ES, *et al.* Fluphenazine plasma levels, dosage, efficacy, and side effects. Am J Psychiatry 1995; 152(5): 765-71. http://dx.doi.org/10.1176/ajp.152.5.765 PMID: 7726317

[55] Sparshatt A, Taylor D, Patel MX, Kapur S. Amisulpride - dose, plasma concentration, occupancy and response: Implications for therapeutic drug monitoring. Acta Psychiatr Scand 2009; 120(6): 416-28. http://dx.doi.org/10.1111/j.1600-0447.2009.01429.x PMID: 19573049

[56] Mauri MC, Reggiori A, Minutillo A, *et al.* Paliperidone LAI and Aripiprazole LAI Plasma Level Monitoring in the Prophylaxis of Bipolar Disorder Type I with Manic Predominance. Pharmacopsychiatry 2020; 53(5): 209-19. http://dx.doi.org/10.1055/a-1113-7862 PMID: 32155657

[57] Altamura AC, Moliterno D, Paletta S, *et al.* Effect of quetiapine and norquetiapine on anxiety and depression in major psychoses using a pharmacokinetic approach: A prospective observational study. Clin Drug Investig 2012; 32(3): 213-9. http://dx.doi.org/10.2165/11597330-000000000-00000 PMID: 22299714