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Does the frequency of administration of long acting injectable antipsychotics impact psychiatric outcomes and adverse effects: A systematic review and meta-analysis

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ABSTRACT

Dosing regimens for depot antipsychotics range from two-to twelve-weekly administration. There are limited meta-analytic data regarding the effect of different injection frequencies of the same depot antipsychotic at the equivalent dose on psychiatric outcomes and adverse effects. This study investigated differences in psychiatric outcomes and adverse effects between different frequencies of depot antipsychotics through a systematic review and meta-analysis. We performed a systematic search of MEDLINE, EMBASE, Cochrane database, PsycINFO and two Chinese databases for RCTs that compared the frequency of depot antipsychotic administration. The primary outcome was psychiatric symptomatology, with secondary outcomes of quality of life, admission rates, adverse drug reactions, cost-effectiveness and compliance. Twelve studies were included in the meta-analysis. Most studies compared two- and four-weekly injections (n = 10). Different injection frequencies did not lead to differences in clinical outcomes or adverse events. However, two-weekly injections led to significantly greater improvements on the CGI-S scale than four-weekly administration. A sensitivity analysis by removing low quality studies showed lower incidence of somnolence and injection site pain for 2-weekly compared with 4-weekly injections. There were limited data on admission rates and no RCT data on cost-effectiveness or compliance. While there is limited evidence on secondary measures to support 2-weekly over 4-weekly injections, patient choice and convenience should remain the priority when considering certain antipsychotics. Cost-effectiveness and adherence should also be considered, although further studies are required to further evaluate these parameters.

1. Introduction

Antipsychotic medications are the cornerstone of treatment in schizophrenia and other psychoses, and a large body of data confirms the value of ongoing and continuous antipsychotic pharmacotherapy in controlling symptoms and preventing relapse. However, non-adherence with antipsychotic treatment is a significant issue, with estimates as high as 90% (Barkhof et al., 2012), leading to relapse and functional decline (Novick et al., 2010). Depot antipsychotics are commonly used to improve adherence and clinical outcomes such as relapse and readmission (Barkhof et al., 2012). Dosing regimens vary but include two-, four-, six-, eight- and twelve-weekly. The advantages of long-acting injectable (LAI) over oral preparations of the same medication are well known in terms of relapse prevention and adherence (Leucht et al., 2011; Tiihonen et al., 2011).

By contrast, there are limited data on the effect of differences in injection frequency of the same agent for an equivalent depot dose on outcomes. One meta-analysis reported that there were no differences in psychotic symptoms or quality of life between two- and four-weekly doses. However, four-weekly injections were more likely to lead to injection site pain (Kisely et al., 2015).

There were several limitations to this review. Firstly, it only considered differences between two- and four-weekly injection frequencies. Since that review, more preparations have entered the market that give more choice in dosing intervals including six-, eight- and twelve-weekly preparations (Risinger et al., 2017; Savitz et al., 2016). The effect of these on subsequent compliance and outcome needs clarification as many patients are currently being changed from shorter to longer dosing intervals of the same medication on the basis that this benefits both patients and the health service. In addition, the previous review only covered MEDLINE, EMBASE and PsycINFO and did not search Chinese databases.

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We therefore updated the previous review to investigate whether there is a statistically significant difference in outcomes between the 2-weekly, 4-weekly, 6-weekly, 8-weekly or 12-weekly depot of the same medication. In addition, we extended the search to the Chinese databases as above, in addition to MEDLINE, EMBASE and PsycINFO.

2. Method

We registered the study with PROSPERO (registration number: CRD42018084506), a UK based international database of prospectively registered systematic reviews in healthcare and social care fields (Booth et al., 2012). The review was conducted in line with recommendations from the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement.

2.1. Search strategy

We conducted a systematic search of MEDLINE, EMBASE, PsycINFO, Cochrane Register of Clinical Trials, and two Chinese databases, China Knowledge Resource Integrated Database, and VIP Journal Integration Platform.

Table 1 lists the search terms.

Two authors independently assessed titles and abstracts of all papers identified in the electronic searches. Two authors then independently assessed the articles at full text. Snowball searches of the reference lists of included and other relevant articles were conducted. Any difference of opinion between authors was resolved by a third author. All studies excluded at the full text level were listed in a table of excluded studies (Supplementary Table S1).

2.2. Inclusion and exclusion criteria

All relevant RCT data comparing the frequency of depot administration (e.g., two-vs four-weekly, or four-weekly vs. three-monthly) were included. Included studies had to compare equivalent doses of the same antipsychotic compound, or its active metabolite.

We measured study quality using the Cochrane Collaboration's risk of bias assessment tool (Higgins and Green, 2008). We considered random sequence generation, allocation concealment, blinding of participants and outcome assessment, incomplete outcome data, selective outcome reporting and other sources of bias. These were then stratified into high, low and unclear risk of bias. Studies with high risk of bias in blinding of participants or outcome assessment were considered to be of low quality.

Table 1
Search terms.

1.Frequency

'2 weekly' OR '2-weekly' OR '2 weeks' OR '2-weeks' OR 'two weekly' OR 'two-weekly' OR 'two weeks' OR 'two-weeks' OR '3 weekly' OR '3-weekly' OR '3 weeks' OR '3-weeks' OR 'three weekly' OR 'three-weekly' OR 'three weeks' OR 'three-weeks' OR 'once monthly' OR 'once-monthly' OR '4 weekly' OR '4-weekly' OR '4 weeks' OR '4-weeks' OR 'four weekly' OR 'four-weekly' OR 'four weeks' OR 'four-weeks' OR '6 weekly' OR '6-weekly' OR '6 weeks' OR '6-weeks' OR 'six weekly' OR 'six-weekly' OR 'six weeks' OR 'six-weeks' OR '8 weekly' OR '8-weekly' OR '8 weeks' OR '8-weeks' OR 'eight weekly' OR 'eight-weekly' OR 'eight weeks' OR 'eight-weeks' OR '12 weekly' OR '12-weekly' OR '12 weeks' OR '12-weeks' OR 'twelve weekly' OR 'twelve-weekly' OR 'twelve weeks' OR 'twelve-weeks' OR 'three monthly' OR 'three-monthly' OR '3 monthly' OR '3-monthly' OR '3 months' OR 'three months' OR '3-months' OR 'three-months' OR quarterly OR 'four times a year' OR '4 times a year' OR 'four-times-a-year' OR '4-times-a-year'

2.Depot

antipsychotic OR antipsychotics OR neuroleptic OR Neuroleptics OR Depot OR "long acting injectable" OR "long acting injectables" OR LAI OR LAIs

3. Medication

haloperidol OR fluphenazine OR flupenthixol OR flupentixol OR zuclopenthixol OR risperidone OR olanzapine OR paliperidone OR aripiprazole

2.3. Data extraction and statistical analysis

The primary outcome was psychiatric symptomatology as measured by standardised instruments, such as the Brief Psychiatric Rating Scale (BPRS), the Positive and Negative Syndrome Scale (PANSS), and the Clinical Global Impression – Severity (CGI-S) scale. We also considered the following secondary outcomes: adverse drug reactions (ADRs), quality of life, patient preference, admission rates, bed-days, cost-effectiveness and compliance as measured by the number of missed injections.

Data were extracted from each study, comparing the equivalent preparations of antipsychotic medications. Where studies used the same scale for each outcome, we examined both the mean differences for continuous data, and also the standardised mean difference for data that used different rating scales. The next step was to comment on the relative risk (RR) for any dichotomous outcome. Intention-to treat analyses were used, where appropriate.

Equivalent doses were determined through published tables of chlorpromazine equivalents (Andreasen et al., 2010), or in the case of paliperidone 3-monthly through published guidelines (Gopal et al., 2015).

Heterogeneity was analysed using the I^2 statistic. This is a measure is independent of the number of studies in the meta-analysis; therefore it has an increased propensity to detect heterogeneity in a smaller number of total studies. Where the estimate is 50% or over, there is possible heterogeneity. Once more accordingly, scores of between 75 and 100% indicate significant heterogeneity.

The random effects model was utilised for all the analyses, as it was not possible to exclude between-study variation even in the absence of statistical heterogeneity given the range of medications under review. In outcomes where there were more than 10 studies, our statistical plan included testing for publication bias using funnel plot asymmetry where low P-values are indicative of publication bias (Higgins and Green, 2008).

Sensitivity analyses were performed based on removing studies deemed to be of low quality.

3. Results

We found 3084 titles once duplicates were removed (Fig. 1). Of these, 89 were identified as potentially relevant following title and abstract screening and assessed for eligibility at full text level. 75 papers were excluded for reasons listed in Fig. 1. This left fourteen papers from twelve studies (Fig. 1), all of which were included in the meta-analysis. The total number of enrolled patients was 4479 at baseline and 3536 at follow-up. The total number of patients at follow-up from the Chinese database was 413. Of the twelve studies included in the meta-analyses, five were identified from the Chinese database.

All the studies identified from the Chinese database were published in Chinese language, although some of these studies were also published in English language and were identified from the Western database. This implied that the subsets of Chinese studies and Western studies were not mutually exclusive. Of note, two of the included studies were identified from both the Chinese and Western databases (Li et al., 2011; Pandina et al., 2011). One of the Chinese studies was a multi-centre trial completed in Europe, Asia and North America (Pandina et al., 2011), while the rest were completed in China.

Most studies (n = 10) compared two-weekly with four-weekly injections. Of these, eight studies compared two-weekly injections of risperidone with the equivalent four-weekly doses of its metabolite, paliperidone. Of the other studies, one study compared equivalent doses of olanzapine and the other compared equivalent doses of fluphenazine (Table 2).

There were few comparisons of other dosing frequencies. One study, which yielded two papers, compared paliperidone 1-monthly versus 3-monthly injections and lasted 48 weeks (Savitz et al., 2016, 2017).

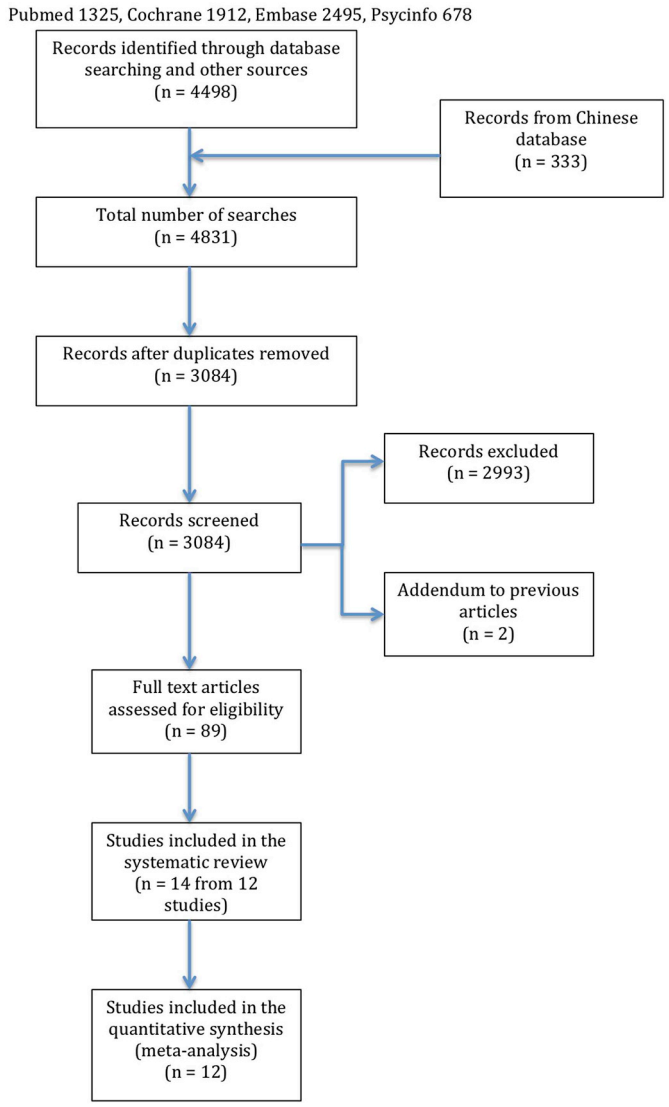

Fig. 1. PRISMA flow diagram.

Another study compared 4-weekly aripiprazole injections with 6-weekly and 8-weekly aripiprazole injections (Risinger et al., 2017). However, only data from the 4-weekly injections versus 8-weekly injections were used, as the 6-weekly injections were not of equivalent dosing when compared to the other two frequencies.

All the studies were of patients meeting DSM (II, IV or V) or ICD-10 criteria for schizophrenia and/or schizoaffective disorder (Table 2). Six studies ended at three months (Chouinard et al., 1982; Guo et al., 2017; Mi et al., 2010; Song et al., 2016; Wang et al., 2015; Yin, 2016), and one study, that was reported in two papers, ended at eight weeks (Lauriello et al., 2008; Witte et al., 2012). The other five studies (reported over six papers) lasted between six and 16 months. While the paper by Chouinard et al. (1982) lasted three months for primary efficacy measures, they continued to collect data on secondary measures of adverse drug reactions up to six months (Chouinard et al., 1982).

There was adequate random allocation sequence generation in eight studies, whilst it was unclear in the other four studies. Adequate allocation concealment was unclear in three studies, low in six studies, and high in three. Only five studies were double-blinded and all of these described the blinding process adequately. Seven studies were only single-blinded, which included all the studies from the Chinese database. It was noted that more aspects of the studies from the Chinese databases were rated as unclear or high, particularly within the blinding of participants, outcomes and reporting bias (Table S1).

Six studies had less than 10% loss at follow-up (Chouinard et al., 1982; Guo et al., 2017; Lauriello et al., 2008; Song et al., 2016; Wang et al., 2015; Witte et al., 2012; Yin, 2016). Four studies had a follow-up rate of between 75% and 85% (Li et al., 2011; Mi et al., 2010; Pandina et al., 2011; Savitz et al., 2016, 2017). One paper had a follow-up of 73% (Risinger et al., 2017), whilst the final study had a follow-up of only 45% (Fleischhacker et al., 2012). Six of the papers reported both per-protocol and intention-to-treat (ITT) analyses but most studies have a greater focus on per-protocol analyses rather than ITT analyses. ITT analyses were largely limited to the assessment of secondary outcome measures, such as ADRs. In the case of the study with the lowest follow-up (Fleischhacker et al., 2012), the results of ITT analyses for primary outcomes were not disclosed, but were reported to be similar to the per-protocol analyses. Hence, this study was rated as high risk for selective reporting (Table S1). In terms of other sources of bias, half of the twelve studies were pharmaceutically funded.

Clinical outcomes were restricted to psychiatric symptom scores, quality of life and ADRs (Table 2). We used the equipercentile linkage method to combine psychiatric outcomes reported as a mix of BPRS and PANSS (Leucht et al., 2013).

Five studies reported data on plasma levels of the studied drug (Table 2). By contrast, there were no RCT data on cost effectiveness or on compliance, and patient preferences were not reported.

3.1. Psychiatric symptoms and quality of life

Studies reported on a wide range of change and endpoint scores (Table 2). The most commonly used were the PANSS and CGI-S Only two studies reported outcomes using BPRS. Both of these studies were pre-2008 studies (Chouinard et al., 1982; Lauriello et al., 2008). Quality of life ratings were based upon the Quality of Life Scale (QLS), Personal and Social Performance (PSP) scale and Short Form Health Survey (SF-36).

The results of individual studies showed minimal difference in outcomes between two-weekly and four-weekly or between monthly and three-monthly regimes in all comparisons at all time points (Table 2) with the exception of one study, where there was a statistically greater improvement in PANSS scores with two-weekly injections compared with four-weekly injections (Li et al., 2011).

On meta-analyses, there were no statistically significant differences in psychiatric symptomatology at up to 8 weeks follow-up between 2-weekly versus 4-weekly injections in terms of PANSS scores, irrespective of the antipsychotic agent compared (Fig. 2). By contrast, meta-analysis showed that 2-weekly injections were associated with significantly better CGI-S scores than 4-weekly injections (Fig. 2).

Data on eight-weekly injections were limited to one study reporting ADRs (Risinger et al., 2017), while there was only one study, yielding two papers, comparing monthly versus three-monthly injections of paliperidone, which showed the former to be non-inferior in terms of PANSS scores (Savitz et al., 2016, 2017).

The one study that reported on hospitalisation rates found no significant differences between one-monthly and three-monthly paliperidone (RR = 1.29 [95% CI = 0.68, 2.42]) (Savitz et al., 2016, 2017). Four studies reported on relapses of psychosis while on LAIs, with three of these studies comparing 2-weekly versus 4-weekly injections (Fleischhacker et al., 2012; Lauriello et al., 2008; Pandina et al., 2011). Meta-analyses showed no difference in relapse rates between 2-weekly injections versus 4-weekly injections (Fig. 3). There were similar results for the one study that reported on relapse rates comparing monthly versus 3-monthly injections (RR = 1.14 [95%CI = 0.75, 1.72] (Savitz et al., 2017; Savitz et al., 2016).

3.2. Adverse drug reactions

The main ADRs reported were extra-pyramidal side effects (EPSE) and glycaemic changes as measured by standardised instruments and rating scales such as Extrapyramidal Symptom Rating Scale (ESRS),

Table 2
Table of included studies.

Author, Year	Comparison	N	Outcomes	Summary of results
Fluphenazine				
Chouinard et al., 1982	Fluphenazine decanoate (4 weekly) vs fluphenazine enanthate (2 weekly)	Randomised = 50 Completed = 48 (24 each in 2 weekly and 4 weekly)	Endpoint: 28 weeks. Outcomes recorded at 10, 12, 26 & 28 weeks. Psychiatric symptoms – BPRS (endpoint) ADRs • Use of anti-Parkinsonian medication • Treatment emergent symptoms & ESRS: akathisia, akinesia, dyskinesia, dystonia, dyskinetic movement, hypokinetic factors • CGI-S: tardive dyskinesia	Patient inclusion: DSM-II with schizophrenia. BPRS: At 10, 12 & 26 weeks = no difference between both groups. At 28 weeks = higher BPRS score in 4-weekly group. Anti-Parkinsonian medication: no clinically relevant differences between both groups. ESRS: At 10 and 12 weeks, the 2-weekly group had significantly higher rates of hypokinetic factor and total Parkinsonian symptoms. However, there were no differences at 26 and 28 weeks. Dyskinetic movements: no difference, but there was a significant increase in mean total score for dyskinetic movements from 26 to 28 weeks in the 4-weekly group. CGI-S: no difference between both groups.
Olanzapine				
Lauriello et al., 2008 Witte et al., 2012	Olanzapine 210 mg 2 weekly, 300 mg 2 weekly, 405 mg 4 weekly & placebo 2 weekly	Randomised = 404 Completed = 402 • 210mg/2 wks = 106 • 300mg/2 wks = 98 • 405mg/4 wks = 100 • Placebo = 98	Endpoint = 8 weeks Psychiatric symptoms (ITT, LOCF) • PANSS (change) • PANSS derived BPRS • CGI-S • QLS (endpoint) • SF-36 (endpoint) ADRs (ITT, LOCF) • TEAEs – change in BSL, akathisia, EPSE, dyskinesia	Patient inclusion: DSM-IV with schizophrenia. Responses of 210 mg 2 weekly and 405 mg 4 weekly compared to placebo were similar for PANSS, BPRS, CGI-S, QLS and SF-36 for total and sub-scores except for: • 2 weekly regime was significantly better than placebo for QLS interpersonal relations while 4 weekly regime was not. • 4 weekly regime was significantly better than placebo for SF-36 mental component scores while 2 weekly regime was not. Improvement in PANSS correlated with QOL & SF-36. No difference between LAI regimes of 210 mg 2 weekly and 405 mg 4 weekly in psychiatric symptoms or TEAEs. Olanzapine plasma levels did not reach steady state in 8 weeks. No data was presented about any differences in plasma levels between the treatment groups.
Paliperidone				
Mi et al., 2010	Paliperidone (initial dose 150 mg on day 1 and 100 mg on day 8 and 4 weekly) vs Risperidone LAI (initial 25 mg on day 8 and then once-2 weekly	Randomised = 133 • PP 4 wkly = 71 • Ris 2 wkly = 62 Completed = 106 • No information on group numbers	End point: 12 weeks. Psychiatric symptoms • PANSS • CIG-S • PSP	Patient inclusion: DSM-IV with schizophrenia. PANSS, CGI-S, PSP: No statistically significant difference between both groups.
Li et al., 2011	Paliperidone palmitate 4 weekly vs risperidone LAI 2 weekly	Randomised = 452 Completed = 350 • PP 4 wkly = 165 • Ris 2 wkly = 185	Endpoint = 13 weeks. Outcomes measured at 1, 5, 9 & 13 weeks Psychiatric symptoms (ITT, LOCF) • PANSS (change) • CGI-S • PSP ADRs (ITT, LOCF) • Use of anti-Parkinsonian meds • TEAEs – akathisia,tremor, EPSE, insomnia, cardiac events, weight gain, prolactin levels, injection site pain	Patient inclusion: DSM-IV with schizophrenia. PANSS: 2 weekly regime had significantly greater improvement using mean difference but not least square means. CGI-S, PSP: No differences in both groups. TEAEs: Similar in both groups. Plasma levels not measured, but study used same doses as Pandina et al., 2011.

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Table 2 (*continued*)

Author, Year	Comparison	N	Outcomes	Summary of results
Pandina et al., 2011	Paliperidone palmitate (initial loading of 150 mg eq on day 1 and 100 mg eq on day 8 and flexible dosing 4 weekly) vs risperidone LAI 2 weekly (with initial 25 mg on days 8 and 22 and flexible dosing from day 36)	Randomised = 1220 Completed = 927 ● PP 4 wkly = 456 ● Ris 2 wkly = 471	End point: 13 weeks. Outcomes measured at 1, 4, 15, 22, 36, 64 & 92 days Psychiatric symptoms ● PANSS ● CGI-S ● PSP (LOCF) ADRs (ITT, LOCF) ● TEAEs – akathisia, dyskinesia, hyperkinesia, EPSE, cardiac events, weight gain, prolactin levels, injection site pain	Patient inclusion: DSM-IV with schizophrenia. PANSS: Mean change similar between both groups, PP non-inferior. CGI-S, PSP: Similar improvements in both groups. TEAEs: Higher rates of insomnia, injection site pain & anxiety in PP 4 weekly group. Higher rates of constipation in RIS-LAI group. EPSE & use of anti-EPS meds: No clinically relevant differences between both groups. Median plasma levels of paliperidone in both groups reached steady state in around 15 days and remained at approximately 20 ng/mL throughout the study.
Fleischhacker et al., 2012	Paliperidone palmitate (50 mg eq. on days 1 and 8 and flexible dosing 4 weekly) vs risperidone LAI (2 weekly injections of 25 mg on days 8 and 22 and flexible dosing from day 36 with allowed oral supplementation)	Randomised = 749 Completed = 339 Primary efficacy, total = 570 Primary efficacy, PP = 288 Primary efficacy, RIS-LAI = 282 Secondary efficacy, total = 674 Secondary efficacy, PP = 343 Secondary efficacy, RIS-LAI = 331	Endpoint: 372 days Psychiatric symptoms (LOCF) ● PANSS ● PSP ● CGI-S ADRs (ITT) ● Use of anti-Parkinsonian meds ● TEAEs – akathisia, dyskinesia, hyperkinesia, EPSE, cardiac events, injection site pain	Patient inclusion: DSM-IV with schizophrenia. PANSS: Greater change in RIS-LAI than PP based on LSM difference. Mean change in PANSS similar in RIS-LAI group. PSP: No difference between both groups. CGI-S: Reduction of symptoms greater in 2 weekly group. TEAEs: Proportion of serious TEAEs was slightly higher in 4 weekly group. EPSE: No difference between both groups. Median plasma levels of paliperidone were higher for RIS-LAI group (20 ng/mL) compared with PP group (7.5 ng/mL) at day 64 and remained so throughout the study.
Wang et al., 2015	Paliperidone palmitate (initial loading of 150 mg on day 1 and 100 mg on day 8 and flexible dosing 4 weekly) vs Risperidone LAI (25 mg on day 8 and flexible dosing 2 weekly)	Randomised = 63 Completed = 60 ● PP 4 wkly = 30 ● Ris 2 wkly = 30	End point: 92 days. Psychiatric symptoms ● PANSS ● CIG-S ● PSP. ADRs (AIMS, Barnes, SAS) ● TEAEs – Insomnia, tremor, akathisia, tachycardia	Patient inclusion: DSM-IV with schizophrenia. PANSS, CGI-S: On days 8, 36, 64, 92, no statistically significant difference between both groups. PSP: On day 92, no statistically significant difference between both groups. TEAEs: No statistical difference between groups using AIMS, SAS or Barnes.
Savitz et al., 2016 Savitz et al., 2017	Paliperidone palmitate 3 monthly vs paliperidone palmitate 1 monthly	Randomised = 1016 Completed = 842 ● PP1M = 420 ● PP3M = 422	End point: 48 weeks. Primary efficacy = percentage of patients who remained relapse free at 48 weeks (per protocol). Secondary efficacy: psychiatric symptoms (ITT) ● PANSS ● CGI-S ● PSP ADRs (ITT) ● TEAEs – akathisia, dyskinesia, hyperkinesia, EPSE, cardiac events, weight gain, prolactin levels, injection site pain	Patient inclusion: DSM-IV with schizophrenia. Primary efficacy: similar percentage of patients in both groups experienced relapse. PANSS: Similar improvements in both groups, no statistically significant difference. CGI-S, PSP: No difference between both groups. TEAEs: Similar in both groups. EPSE: Similar in both groups. Plasma concentration were similar for equivalent dosing of PP!M and PP3M from day 120 of the study and remained so throughout. ● 50 mg PP1M and 175 mg PP3M = 15 ng/mL ● 75 mg PP1M and 263 mg PP3M = 20 ng/mL ● 100 mg PP1M and 350 mg PP3M = 25 ng/mL ● 150 mg PP1M and 525 mg PP3M = 40 ng/mL

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Table 2 (*continued*)

Author, Year	Comparison	N	Outcomes	Summary of results
Song et al., 2016	Paliperidone palmitate (initial dose of 150 mg on day 1 and 100 mg on day 8 and flexible dosing 4 weekly) vs Risperidone LAI (25 mg on day 1 and day 16, and then flexible dosing 2 weekly)	Randomised = 80 Completed = 79 ● PP 4 wkly = 39 ● Ris 2 wkly = 40	End point: 12 weeks. Psychiatric symptoms ● PANSS ADRs ● TEAEs – Insomnia, somnolence, dystonia, akathisia, dizziness, injection site pain, weight gain, constipation, nausea/vomiting.	Patient inclusion: ICD-10 with schizophrenia. PANSS: At the end of weeks 2, 4, 8, 12, no statistically significant difference between groups. ADRs: Weight gain higher occurrence in Risperidone LAI group. No other statistically significant difference between groups for other ADRs.
Yin (2016)	Paliperidone palmitate (initial loading of 150 mg on day 1 and 100 mg on day 8 and flexible dosing 4 weekly) vs Risperidone LAI (dose of 25 mg on day 8 and then once-2 weekly)	Randomised = 80, all completed ● PP 4 wkly = 40 ● Ris 2 wkly = 40	End point: 12 weeks. Psychiatric symptoms ● PANSS ● PSP ● MSQ ADRs ● TEAEs – PP: injection site pain, swelling, elevated prolactin levels, weight gain, dry mouth, insomnia, constipation; Ris: nausea & vomiting, insomnia, weight gain, constipation, dry mouth	Patient inclusion: Clinically diagnosed Schizophrenia patients, did not mention the diagnostic reference. PANSS, PSP, MSQ: At weeks 4, 8, 12, no statistically significant difference between groups. TEAEs: No statistically significant difference between both groups
Guo et al., 2017	Paliperidone palmitate (initial dose of 150 mg in w0 and w1 and flexible dosing 4 weekly) vs Risperidone LAI (initial dose of 25 mg in w0 and then flexible dosing 2 weekly)	Randomised = 96 Completed = 87 ● PP 4 wkly = 39 ● Ris 2 wkly = 48	End point: 12 weeks. Psychiatric symptoms ● PANSS ● PSP ADRs: Barnes, AIMS ● TEAEs – weight gain, constipation, somnolence, dystonia, tremor, akathisia, EPSE	Patient inclusion: DSM-IV with schizophrenia. PANSS, PSP: At 1, 5, 9, 13 weeks, no statistically significant difference between both groups. ADRs: At 1, 5, 9, 13 weeks, no statistically significant difference between both groups. EPSE: no statistically significant difference between both groups.
Aripiprazole				
Risinger et al., 2017	Aripiprazole lauroxil (AL) 441 mg 4 weekly vs 882 mg 6 weekly vs 1064 mg 8 weekly	Randomised = 139 Completed = 103 ● AL 4wkly = 28 ● AL 6wkly = 21 ● AL 8wkly = 27 ● AL S8wkly = 27 (not being developed further, data not analysed further in paper)	End point: 44 weeks. ADRs ● TEAEs – Dyskinesia, EPSE, weight gain, nasopharyngitis, vomiting, injection site pain	Patient inclusion: DSM-V with schizophrenia or schizoaffective disorder TEAEs: no difference between all groups EPSE: no difference between all groups Mean plasma levels of aripiprazole across all groups were similar at approximately 125 ng/mL for the 4 weekly group, 131 ng/mL for the 6 weekly group and 140 ng/mL for the 8 weekly group. Mean half-life across all groups were similar at around 55 days.

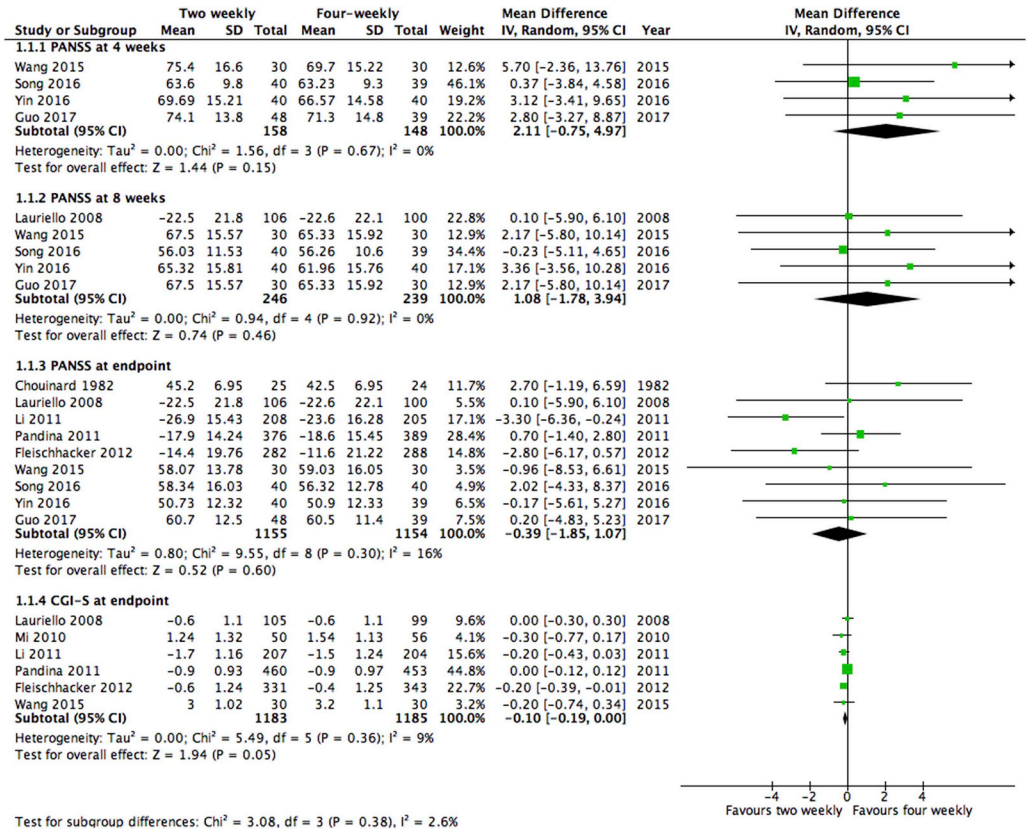

Fig. 2. Psychiatric symptoms for 2-weekly vs 4-weekly injections.

Barnes Akathisia Rating Scale (BARS) and Abnormal Involuntary Movements Scale (AIMS) (Table 2). Meta-analyses were possible only for comparisons of two- and four-weekly injections. Table S2 shows that there were no differences between dosing frequencies for EPSE, metabolic parameters, injection site pain, dry mouth and anxiety. In studies where weight gain or prolactin levels were reported, there were no statistically significant findings between the two- and four-weekly injections (Table S2). The comparison of monthly and two-monthly aripiprazole injections also reported no difference in ADRs including injection site pain, weight gain, metabolic markers and EPSE (Risinger et al., 2017). Similarly, in the one study comparing monthly to 3-monthly paliperidone, there were similar rates of the following side effects: EPSE, suicidality, agitation, aggression, somnolence and sedation, tachycardia, orthostatic hypotension, QT prolongation, and weight gain (Savitz et al., 2016, 2017).

3.3. Plasma levels

Five studies presented data on plasma levels (Table 2). Of these, one study on olanzapine did not reach steady state plasma levels during the duration of the study. The effect of this on the study outcomes was unclear, as they did not present data on the differences between treatment groups. However, the authors commented that the subjects could possibly have benefited greatly if steady state had been reached during the study duration (Lauriello et al., 2008; Witte et al., 2012). Three studies compared the plasma level of the active metabolite, paliperidone, in the two-weekly risperidone arm versus the four-weekly paliperidone arm. Of these, one study showed the two-weekly risperidone arm having consistently greater median plasma levels than the four-weekly paliperidone arm (20 vs 7.5 ng/ml) (Fleischhacker et al., 2012). This study argued that 7.5 ng/ml of paliperidone corresponds to 60% D2-receptor occupancy, which is within the range necessary for efficacy, albeit at the lower end (Fleischhacker et al., 2012). Another subsequent study used a higher dosing regimen for paliperidone, resulting in median plasma levels of 20 ng/ml in both arms (Pandina et al., 2011), while another study used this same higher paliperidone dosing regimen, without measuring plasma levels, with the assumption that plasma levels will be similar (Li et al., 2011). In the only study comparing monthly versus three-monthly injections, plasma levels of paliperidone were measured as similar in both frequency arms, ranging

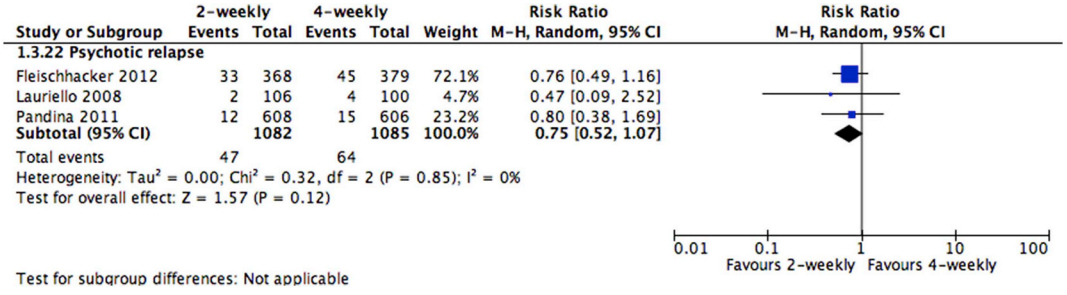

Fig. 3. Psychiatric outcomes for 2-weekly vs 4-weekly injections.

from 15 ng/ml to 25 ng/ml of paliperidone, although this was dose dependent (Savitz et al., 2016, 2017). One study on aripiprazole depot reported comparable mean plasma levels between the four-weekly and eight-weekly injections at 125–140 ng/ml of aripiprazole (Risinger et al., 2017). The authors reported this as within the approved aripiprazole dose regimens.

3.4. Sensitivity analyses

We undertook sensitivity analyses of the effect of removing all the low quality studies, which also happened to be the Chinese database studies. This resulted in a statistically significant difference favouring 2-weekly injections over 4-weekly injections in terms of both injection site pain (RR = 0.16; 95% CI = 0.07–0.38) and somnolence (RR = 0.61; 95% CI = 0.39–0.95). This applied to both comparisons of different doses of olanzapine, as well as risperidone to its active metabolite paliperidone. By contrast, a further sensitivity analysis of removing a study with reported suboptimal bioavailability (Fleischhacker et al., 2012), made no difference to the study results.

3.5. Heterogeneity and publication bias

None of the results for psychiatric outcomes showed heterogeneity and only six of the 24 ADRs had I^2 values that were greater than 50% (Table S2). Publication bias could not be tested, as there were insufficient studies for each of the outcomes.

4. Discussion

We were able to identify twelve RCTs with 4479 participants providing data on the effect of dosing frequency for equivalent doses on clinical outcomes. Of these, most compared 2- versus 4-weekly injections, with one study comparing psychiatric outcomes for monthly versus 3-monthly injections. Different injection frequencies did not seem to lead to statistically significant difference in clinical outcomes based on PANSS or BPRS scores. However, there was evidence to suggest that 2-weekly injections are better than 4-weekly injections for clinical outcomes based on CGI-S scores (Fig. 2). This is consistent with findings in one of the included studies, where two-weekly risperidone injections also produced greater improvements in PANSS scores compared with four-weekly paliperidone injections (Li et al., 2011), although this difference was not observed in the meta-analyses (Fig. 2). By taking into consideration the overall results of the PANSS, BPRS and CGI-S scores, there does not seem to be strong evidence to support one dosing frequency over another.

While some data on psychiatric relapse and hospitalisations were reported, it is unclear if this translated to economic savings, as there were no RCT data on cost effectiveness based on different frequencies of antipsychotic injections, with most literature based on industry funded economic modelling (Arikan et al., 2017; Dalton et al., 2011; Mehnert et al., 2012; Zeidler et al., 2013).

In terms of adverse events, we found no significant differences between different dosing frequencies. However, when sensitivity analyses were performed by removing lower quality studies, two-weekly injections were less likely to cause injection site pain and somnolence than four-weekly injections. This finding was independent of the antipsychotic studied, being found in studies comparing risperidone and its active metabolite, paliperidone, as well as a study comparing different frequencies of olanzapine LAI. There was no difference between monthly injections versus: two-monthly (aripiprazole); or three-monthly (paliperidone) injections for both of these parameters. However, the sample size for the study comparing monthly versus two-monthly aripiprazole injections were small (n = 35 in each arm) (Risinger et al., 2017). The reasons for this are unclear, as injection site pain does not seem to be dependent on injection volume, dose, or site of administration (Atkins et al., 2014; Kern Sliwa et al., 2018). This may potentially be due to different injection techniques, although there is also the suggestion that the incidence of injection site pain reduces with an increasing number of injections received (Atkins et al., 2014). One explanation might be that patients who were not susceptible to injection site pain tended to stay on the injections longer and so became desensitised to the injections over time (Atkins et al., 2014). Meanwhile, there is limited previous data on the effect of different dosing frequencies on somnolence.

Given the limited evidence for differences in clinical outcomes or ADRs between two-weekly and four-weekly depot administration, patient preference and convenience should still govern the choice of antipsychotic depot treatment. This needs to be balanced with consideration of the therapeutic alliance, patient engagement and augmentation with non-pharmacological interventions to enhance recovery. Given the results of our sensitivity analysis, patients should be warmed of the increased risk of injection site pain and somnolence with the four-weekly LAIs as opposed to two-weekly LAIs. Further considerations of cost effectiveness and benefits of increasing or reducing patient contact should also be taken into account when choosing the appropriate antipsychotic depot treatment. Unfortunately, no “ideal interval” was found for dosing frequencies with LAIs and further studies will need to be completed, including those of RCTs involving cost effectiveness based on different frequencies of antipsychotic injections.

There are even less data concerning the differences between monthly versus 8-weekly or three-monthly preparations. In the case of the former, this was limited to one study of ADRs that did not consider psychiatric outcomes; in the latter, there were just two papers from the same study.

Unlike the previous meta-analysis, we were able to include comparisons of several different dosing frequencies, as these are newly available on the market. We also used studies identified from the Chinese databases, which meant that we were able to include a further seven studies. This doubled the number of patients in the meta-analysis from 1714 subjects to 3536 subjects.

Several limitations were observed in this study. While this meta-analysis had a limited number of included studies (n = 12), the size of most of the studies was relatively large. The number of subjects who participated in the studies was 4479, with 3536 included in the meta-analyses. Hence, it is unlikely that a lack of difference in clinical outcomes between the groups were solely due to a type II error. However, there were 2629 subjects within the two-weekly versus four-weekly comparison, with the remaining 907 subjects within the monthly versus two-monthly or three-monthly comparison. It was noted that there was only one study that compared a monthly versus two-monthly dosing regimen (Risinger et al., 2017) and one of monthly versus three-monthly administration (Savitz et al., 2016, 2017). Both of these studies were pharmaceutically funded.

Most of the studies (n = 8) compared 2-weekly risperidone LAI versus 4-weekly paliperidone LAI. While there are slight differences in pharmacokinetics of risperidone and paliperidone, paliperidone is the active metabolite of risperidone, which results in both drugs having the same active ingredient. Where provided, the plasma levels broadly showed that different dose frequencies broadly achieved similar plasma levels or D2 blockade. In all but one study where plasma levels were measured, these reached steady state before the study's end (Table 2). One study had suboptimal bioavailability of the drug studied in one arm, but removal of the study in a sensitivity analysis had no effect on the outcomes.

Although most of our results showed no evidence of heterogeneity, we were unable to explore this further with sensitivity analyses, due to the low study numbers. Therefore, random-effects modelling were used throughout to account for heterogeneity in our analyses (Higgins and Green, 2008).

In addition to this, the studies in the meta-analysis ranged from those published in 1982–2017 (Table 2). It is acknowledged that the pool of subjects may have changed over this period of 35 years, with a

higher rate of placebo response found in more recent studies (Leucht et al., 2018). Similarly, it is also acknowledged that the pool of subjects from trials done in China may differ from those done in Europe and North America. Further sensitivity analysis completed by removing the 1982 study (Chouinard et al., 1982), and so performing meta-analysis only on studies published in the last 10 years, did not yield any further statistically significant results.

In conclusion, the low study numbers suggest that further studies are indicated, particularly within the monthly versus two-monthly and three-monthly comparisons, to allow more robust meta-analyses to be conducted in the future. While there is some evidence to support 2-weekly injections over 4-weekly injections based on CGI-S scores, these results should be interpreted with caution. In addition, long-term studies will assist in further delineating the effects of the frequency of administration of depot antipsychotics on longer-term outcomes. Subsequent RCTs should also include cost-effectiveness as an outcome. Claims that new depot preparations are more advantageous over others require careful appraisal.

Conflicts of interest

Steve Kisely has received honoraria for the design and delivery of a workshop on motivational interviewing from Janssen.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychires.2018.12.004.

References

Andreasen, N.C., Pressler, M., Nopoulos, P., Miller, D., Ho, B.-C., 2010. Antipsychotic dose equivalents and dose-years: a standardized method for comparing exposure to different drugs. Biol. Psychiatry 67 (3), 255–262.

Arikan, Y., Koral, S., Baris, H., Malhan, S., Oksuz, E., 2017. Cost-effectiveness analysis of the paliperidone palmitate 3-month formulation versus 1-month formulation from a healthcare payer perspective. Value Health 20 (9), A713.

Atkins, S., Detke, H.C., McDonnell, D.P., Case, M.G., Wang, S., 2014. A pooled analysis of injection site-related adverse events in patients with schizophrenia treated with olanzapine long-acting injection. BMC Psychiatry 14 7-7.

Barkhof, E., Meijer, C.J., de Sonneville, L.M., Linszen, D.H., de Haan, L., 2012. Interventions to improve adherence to antipsychotic medication in patients with schizophrenia–a review of the past decade. Eur. Psychiatry: J. Asso. Eur. Psychiatr. 27 (1), 9–18.

Booth, A., Clarke, M., Dooley, G., Ghersi, D., Moher, D., Petticrew, M., Stewart, L., 2012. The nuts and bolts of PROSPERO: an international prospective register of systematic reviews. Syst. Rev. 1 (1), 2.

Chouinard, G., Annable, L., Ross-Chouinard, A., 1982. Fluphenazine enanthate and fluphenazine decanoate in the treatment of schizophrenic outpatients: Extrapyramidal symptoms and therapeutic effect. Am. J. Psychiatry 139 (3), 312–318.

Dalton, A., Lambert, T., Schrover, R., Hertel, J., Smith, D.K., 2011. The cost associated with administering risperidone long-acting injections in the Australian community. BMC Health Serv. Res. 11 (1), 236.

Fleischhacker, W.W., Gopal, S., Lane, R., Gassmann-Mayer, C., Lim, P., Hough, D., Remmerie, B., Eerdekens, M., 2012. A randomized trial of paliperidone palmitate and risperidone long-acting injectable in schizophrenia. Int. J. Neuropsychopharmacol. 15 (1), 107–118.

Gopal, S., Vermeulen, A., Nandy, P., Ravenstijn, P., Nuamah, I., Buron Vidal, J.A., Berwaerts, J., Savitz, A., Hough, D., Samtani, M.N., 2015. Practical guidance for dosing and switching from paliperidone palmitate 1 monthly to 3 monthly formulation in schizophrenia. Curr. Med. Res. Opin. 31 (11), 2043–2054.

Guo, L., Zhang, R.-g., Qiao, Y.-t., Chen, Y.-c., Wang, H.-n., 2017. Efficacy and safety of paliperidone palmitate or long-acting injectable risperidone in patients with schizophrenia. Prog. Mod. Biomed. 17 (04), 688–691.

Higgins, J.P., Green, S., 2008. Cochrane Handbook for Systematic Reviews of Interventions. Wiley Online Library.

Kern Sliwa, J., Savitz, A., Nuamah, I., Mathews, M., Gopal, S., Elefant, E., Najarian, D., Alphs, L., 2018. An assessment of injection site reaction and injection site pain of 1-month and 3-month long-acting injectable formulations of paliperidone palmitate. Psychiatr. Care 54, 530–538.

Kisely, S., Sawyer, E., Robinson, G., Siskind, D., 2015. A systematic review and meta-analysis of the effect of depot antipsychotic frequency on compliance and outcome. Schizophr. Res. 166 (1–3), 178–186.

Lauriello, J., Lambert, T., Andersen, S., Lin, D., Taylor, C.C., McDonnell, D., 2008. An 8-week, double-blind, randomized, placebo-controlled study of olanzapine long-acting injection in acutely ill patients with schizophrenia. J. Clin. Psychiatr. 69 (5), 790–799.

Leucht, C., Chaimani, A., Leucht, S., 2018. Systematic review, meta-analysis and meta-regression of predictors of placebo response in acute schizophrenia. Schizophr. Bull. 44 (Suppl. 1) S94-S94.

Leucht, C., Heres, S., Kane, J.M., Kissling, W., Davis, J.M., Leucht, S., 2011. Oral versus depot antipsychotic drugs for schizophrenia—a critical systematic review and meta-analysis of randomised long-term trials. Schizophr. Res. 127 (1), 83–92.

Leucht, S., Rothe, P., Davis, J.M., Engel, R.R., 2013. Equipercentile linking of the BPRS and the PANSS. Eur. Neuropsychopharmacol. 23 (8), 956–959.

Li, H., Rui, Q., Ning, X., Xu, H., Gu, N., 2011. A comparative study of paliperidone palmitate and risperidone long-acting injectable therapy in schizophrenia. Prog. Neuro-Psychopharmacol. Biol. Psychiatr. 35 (4), 1002–1008.

Mehnert, A., Nicholl, D., Pudas, H., Martin, M., McGuire, A., 2012. Cost effectiveness of paliperidone palmitate versus risperidone long-acting injectable and olanzapine pamoate for the treatment of patients with schizophrenia in Sweden. J. Med. Econ. 15 (5), 844–861.

Mi, W.-f., Du, B., Liu, Y.-q., Liu, F.-h., Xiao, W.-d., Lu, T.-l., Li, L.-z., Huang, L., Yue, W.-h., Zhang, H.-y., 2010. Association of multidrug resistance 1 gene polymorphism with the clinical efficacy of paliperidone and risperidone in schizophrenic patients. Chin. J. Psychiatry 43 (3), 167–171.

Novick, D., Haro, J.M., Suarez, D., Perez, V., Dittmann, R.W., Haddad, P.M., 2010. Predictors and clinical consequences of non-adherence with antipsychotic medication in the outpatient treatment of schizophrenia. Psychiatr. Res. 176 (2–3), 109–113.

Pandina, G., Lane, R., Gopal, S., Gassmann-Mayer, C., Hough, D., Remmerie, B., Simpson, G., 2011. A double-blind study of paliperidone palmitate and risperidone long-acting injectable in adults with schizophrenia. Prog. Neuro-Psychopharmacol. Biol. Psychiatr. 35 (1), 218–226.

Risinger, R., Hard, M., Weiden, P.J., Fratantonio, J., 2017. A phase-1 study comparing pharmacokinetic and safety profiles of three different dose intervals of aripiprazole lauroxil. Psychopharmacol. Bull. 47 (3), 26–34.

Savitz, A.J., Xu, H., Gopal, S., Nuamah, I., Ravenstijn, P., Hough, D., Mathews, M., Feng, Y., Yu, L., Takahashi, M., Liu, D., Wang, G., Yoon, J.-S., Chen, J.-J., 2017. Efficacy and safety of paliperidone palmitate three-monthly formulation in East Asian patients with schizophrenia: subgroup analysis of a global, randomized, double-blind, Phase III, noninferiority study. Neuropsychiatric Dis. Treat. 13.

Savitz, A.J., Xu, H., Gopal, S., Nuamah, I., Ravenstijn, P., Janik, A., Schotte, A., Hough, D., Fleischhacker, W.W., 2016. Efficacy and safety of paliperidone palmitate 3-month formulation for patients with schizophrenia: a randomized, multicenter, double-blind, noninferiority study. Int. J. Neuropsychopharmacol. 19 (7), 1–14.

Song, G., Yang, J., Lu, G., 2016. Comparison of efficacy of paliperidone palmitate and risperidone for depot suspension in the treatment of schizophrenia. Herald Med. 35 (10), 1072–1075.

Tiihonen, J., Haukka, J., Taylor, M., Haddad, P.M., Patel, M.X., Korhonen, P., 2011. A nationwide cohort study of oral and depot antipsychotics after first hospitalization for schizophrenia. Am. J. Psychiatry 168 (6), 603–609.

Wang, J., Zhou, X.-l., Liu, W., Zhang, X.-f., Li, W., Chen, D., Yan, J.-x., Du, B., 2015. Clinical effect of paliperidone palmitate and risperdal consta in the treatment of patients with schizophrenia. Chin. J. Clin. Pharmacol. 31 (12), 1124–1126.

Witte, M.M., Case, M.G., Schuh, K.J., Ascher-Svanum, H., 2012. Effects of olanzapine long-acting injection on levels of functioning among acutely ill patients with schizophrenia. Curr. Med. Res. Opin. 28 (3), 315–323.

Yin, E., 2016. Clinical efficacy of two long-acting antipsychotics in the treatment of patients with schizophrenia. J. Clin. Res. 33 (10), 2066–2068.

Zeidler, J., Mahlich, J., Greiner, W., Heres, S., 2013. Cost effectiveness of paliperidone palmitate for the treatment of schizophrenia in Germany. Appl. Health Econ. Health Policy 11 (5), 509–521.