**Supplementary S1: PRISMA Checklist**

|  |  |  |  |
| --- | --- | --- | --- |
| **Section/topic**  | **#** | **Checklist item**  | **Reported on page #**  |
| **TITLE**  |  |
| Title  | 1 | Identify the report as a systematic review, meta-analysis, or both.  |  Page 1 |
| **ABSTRACT**  |  |
| Structured summary  | 2 | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.  | Page 2 |
| **INTRODUCTION**  |  |
| Rationale  | 3 | Describe the rationale for the review in the context of what is already known.  | Pages 3 & 4 |
| Objectives  | 4 | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).  | Page 4 |
| **METHODS**  |  |
| Protocol and registration  | 5 | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.  | N/A Page 5 |
| Eligibility criteria  | 6 | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.  | Page 5 |
| Information sources  | 7 | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.  | Page 5 |
| Search  | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.  | Page 5 |
| Study selection  | 9 | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).  | Page 6 |
| Data collection process  | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.  | Page 6 |
| Data items  | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.  | Page 6 &  |
|  | 12 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.  | Page 6  |
| Summary measures  | 13 | State the principal summary measures (e.g., risk ratio, difference in means).  | Page 6 |
| Synthesis of results  | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I2) for each meta-analysis.  | Page 6 |

Page 1 of 2

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| --- | --- | --- | --- |
| **Section/topic**  | **#** | **Checklist item**  | **Reported on page #**  |
| Risk of bias across studies  | 15 | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).  | Page 6 |
| Additional analyses  | 16 | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.  | Page 6 |
| **RESULTS**  |  |
| Study selection  | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.  | Page 7& table 1 |
| Study characteristics  | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.  | Page 7  |
| Risk of bias within studies  | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).  | Page 8 & figure 2 |
| Results of individual studies  | 20 | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.  | Pages 8 & 9, and tables 1& supplementary s2 |
| Synthesis of results  | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency.  | Pages 8 & 9  |
| Risk of bias across studies  | 22 | Present results of any assessment of risk of bias across studies (see Item 15).  | Page 8 |
| Additional analysis  | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).  | Page 9 & tables S3-6].  |
| **DISCUSSION**  |  |
| Summary of evidence  | 24 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).  | Page 10 |
| Limitations  | 25 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).  | Pages 10 &11 |
| Conclusions  | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research.  | Page11 |
| **FUNDING**  |  |
| Funding  | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.  | Page 12 |

*From:*  Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**

**Supplementary S2: Additional information on studies**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Study**  | **Study location**  | **Participants details**  | **Duration** | **Functioning was primary study outcome/Analyses**  | **Industry sponsor/ Trial number** |
| Alphs et al., (2015)  | Multi-center: US Centers | Mean age= 38.1(±10·5) years; Diagnosis=Schizophrenia;Outpatients | 65 weeks | NoITT | YesNCT01157351  |
| Ascher-Svanum et al., (2014) | Multi-center: International  | Mean age= 40.9(±10.9) years;Diagnosis: Schizophrenia;Outpatients | 104 weeks | NoITT | YesNCT00320489 |
| Bai, et al., (2006) Berwaerts et al., (2015) | Single center: TaiwanMulti-center: International | Mean age: 44.7(± 9.2) years;Diagnosis: Schizophrenia:out-patients Mean age: 37.8(±11.0) yearsDiagnosis: Schizophrenia;Inpatient or out-patients | 12 weeks60 weeks | YesITTNoITT |  Yes NCS932314B480002YesNCT01529515 |
| Buckley et al., (2015) | Multi-center: US centers | Mean age= 38·2(±12·1) years; Diagnosis: Schizoaffective or Schizophrenia; inpatients or outpatients |  130 weeks | NoITT | No NCT00330863  |
| Fleischhacker et al.,(2014) 2RCTs | Multi-center: International | 1Mean age=41·2(±10·4) years 2Mean age =40.6(10.8) yearsDiagnosis: Schizophrenia outpatients |  138 weeks 252 weeks  | NoITT | Yes 1NCT00706654  2NCT00705783  |
|  |  |  |  |  |  |
| Fu et al., (2015) | Multi-center: international | Mean age =38·6 (nr) years; Diagnosis: Schizoaffective; inpatients or outpatients | 65 weeks | NoITT | YesNCT01193153  |
| **Study** | **Study locations** | **Participants details** | **Duration** | **Functioning was primary study outcome/Analyses** | **Industry sponsor/ Trial number** |
| Hough et al., (2010)  | Multi-center: International | Mean age= 38·8(±11·4) years;Diagnosis: schizophrenia; out-patients | 24 weeks | NoITT | Yes  NCT00111189  |
| Isitt et al., (2016)  | Multi-center: US centers | Mean age=41·2 (±9·27) years; Diagnosis: Schizophrenia; in-patients  |  8 weeks | NoITT | YesNCT02109562 |
| Kane et al, (2003) Kane et al., (2014) | Multi-center: US centersMulti-center: International  | Mean age=37.7 (±9.8) years;Diagnosis: Schizophrenia;outpatients or inpatientsMean age=42·1(±11·0) years; Diagnosis= Schizophrenia;in-patients or out-patients | 12 weeks12 weeks |  No ITT NoITT | Yes Ris-USA-121 Yes  NCT01663532  |
| Koshikawa et al., (2016) | Single center: Osaka, Japan | Mean age=46·4(±10·3) years;Diagnosis: schizophrenia or schizoaffective; out-patients | 26 weeks |  YesITT |  NoUMIN000014470 |
| Keks et al., (2007) | Multi-center: International | Mean age= 32·6(±10·4) years; Diagnosis= Schizophrenia or schizoaffective disorders; in- patients or out-patients | 52 weeks | NoITT | YesNCT00236457 |
| Meltzer et al., (2014) | Multi-center: US centers | Mean age=41·0(±11·4) years; Diagnosis: schizophrenia or schizoaffective disorder;in-patients or out-patients | 26 weeks | NoITT | Yes NCT00539071  |
|  |  |  |  |  |  |
| **Study** | **Study Location** | **Participants details** | **Duration** | **Functioning was primary study outcome/Analyses**  | **Industry** s**ponsor/ Trial number** |
| Nabar et al., (2015) NCT00604279 (2013)NCT00992407 (2014)Padina et al., (2010)Padina et al., (2011)  | Multi-center: InternationalMulti-centre: ChinaSingle Centre: KoreaMulti-center: InternationalMulti-center: International | Mean age= 42·6 (±10·9) years;Diagnosis: Schizophrenia;  in-patients or out-patientsMean age: 31.7 (±10.88) years;Diagnosis: Schizophrenia outpatientMean age: 34.5 (±10.00) yearsDiagnosis: Schizophrenia or schizoaffective disordersoutpatient Mean age: 39.3 (±10.55) yearsDiagnosis: SchizophreniaoutpatientMean age: 38.9 (±11.98) years;Diagnosis: Schizophrenia Outpatient or outpatients | 28 weeks14 weeks 52 weeks   13weeks13 weeks | YesITT  NoPer-protocolYesPer-protocolNoITTNoITT |  Yes NCT01795547  Yes NCT00604279YesNCT00992407 YesNCT00590577YesNCT00589914 |

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Study** | **Study Location** | **Participants details** | **Duration** |  **Functioning was primary study** **Outcome/Analyses**  |  **Industry** s**ponsor/ Trial umber**  |
| Rosenheck et al, (2011)  | Multi-center: US centers | Mean age=50·9(± 9·3) years; Diagnosis: schizophrenia or schizoaffective disorder; inpatient or outpatient | 104 weeks | NoITT |  Yes NCT00132314  |
| Rouillon et al., (2013) | Multi-center: International | Mean age= 41·6 (±12·8) years; Diagnosis: Schizophrenia or Schizoaffective in-patients or inpatient | 104 weeks  | NoITT |  YesNCT00216476  |
| Schreiner et al., (2015) | Multi-center: International | Mean age= 32·6 (±10·7) years; Diagnosis: Schizophrenia; in-patients | 104 weeks  | NoITT | Yes NCT01081769  |
| Simpson et al, (2006) Witte et al., (2012) | Multi-center: InternationalMulti-center: International | Mean age= 40·9(±11·0) years Diagnosis: Schizophrenia or Schizoaffective out-patientsMean age= 40·8 (±11·2) years; Diagnosis: Schizophrenia;Inpatients or outpatients  | 52 weeks8 weeks |  No ITT No ITT | YesNCT00297388Yes NCT00088478  |
| Wykes, et al., (2013) | Multi-center: International | Mean age: 36·8(±10·8) years;Diagnosis: Schizophrenia; in-patients or out-patients | 104 weeks | No ITT | Yes NCT00256997  |

**Supplementary S3: Risk of Bias of all studies**

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**Supplementary S4: Meta-regression of predictors**

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| --- | --- | --- | --- | --- | --- |
|  **Study Group** **(Placebo or Oral)** | **Predictors** | **Comparison** | Coefficient (95% CI) | P value | **Egger’s test** **p-value\*** |
| All studies |  |  |  |  | 0.790  |
| Oral studies only | Year of publication (continuous) |  | 0.043 (-0.041, 0.126) | 0.274 | 0.873 |
| Oral studies only | Year of publication (binary) | ≥ 2014 versus ≤2014 | 0.078 (-0.325,0.480) | 0.668 |  |
| Oral studies only | Trial duration (continuous) |  | 0.001 (-0.005, 0.007) | 0.702 |  |
| Oral studies only | Study setting | Inpatient versus Outpatient | -0.106 (-0.688, 0.476) | 0.680# |  |
|  |  | Both versus Outpatient | 0.060 (-0.390, 0.510) | 0.761 |  |
| Oral studies only | Functioning as primary outcome | Yes versus No | -0.202 (-0.827, 0.423) | 0.477 |  |
| Oral studies only | Industry sponsorship | Yes versus No | -0.301 (-0.864, 0.263) | 0.254 |  |
| Oral studies only | Study design | Blinded versus Open-label | -0.219 (-0.598,0.161) | 0.220 |  |
| Oral studies only | Length of trial | Long versus Short | 0.193 (-0.641, 1.027) | 0.608 |  |
| Oral studies only | Baseline CGI-S for LAI-A group |  | 0.031 (-0.130, 0.192) | 0.664 |  |
| Placebo studies only | Year of publication (continuous) |  | 0.002 (-0.026, 0.030) | 0.893 |  0.168  |
| Placebo studies only | Year of publication (binary) | ≥2014 versus ≤2014 | -0.049 (-0.235, 0.137) | 0.554 |  |
| Placebo studies only | Trial duration (continuous) |  | -0.0001 (-0.005, 0.003) | 0.711 |  |
| Placebo studies only | Study setting | Inpatient versus Outpatient | -0.164 (-0.516, 0.188) | 0.298## |  |
| Placebo studies only |  | Both versus Outpatient | -0.053 (-0.254, 0.148) | 0.545 |  |
| Placebo studies only | Functioning as primary outcome | All  |  |  |  |
| Placebo studies only | Industry sponsorship | All |  |  |  |
| Placebo studies only | Study design | All double-blind |  |  |  |
| Placebo studies only | Length of trial | Long versus Short | 0.009 (-0.175, 0.193) | 0.908 |  |
| Placebo studies only | Baseline CGI-S for LAI-A group |  | -0.003 (-0.101,0.095) | 0.850 |  |

\*Null hypothesis is no in small-study effects; #global p- value==0.8017; ##global P value=0.5376; CGI-S=Clinical global impression-severity; 95% CI= 95% Confidence Interval

**Supplementary S5: Funnel plot for all studies and Egger test**

Egger test for all studies

------------------------------------------------------------------------------

 Std\_Eff | Coef. Std. Err. t P>|t| [95% Conf. Interval]

-------------+----------------------------------------------------------------

 slope | .220656 .1624294 1.36 0.192 -.12204 .5633521

 bias | .3945513 1.461057 0.27 0.790 -2.68801 3.477112

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**Supplementary S6: Funnel plot for placebo-controlled studies and Egger test.**



Egger test for placebo-controlled trials

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 Std\_Eff | Coef. Std. Err. t P>|t| [95% Conf. Interval]

-------------+----------------------------------------------------------------

 slope | .785327 .2575515 3.05 0.019 .1763146 1.394339

 bias | -3.390889 2.20685 -1.54 0.168 -8.609261 1.827483

**Supplementary S7: Funnel plot for oral-controlled studies and Egger test.**



Egger test for oral-controlled trials

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 Std\_Eff | Coef. Std. Err. t P>|t| [95% Conf. Interval]

-------------+----------------------------------------------------------------

 slope | .1938582 .1913737 1.01 0.341 -.2474505 .6351668

 bias | -.2954459 1.791686 -0.16 0.873 -4.427082 3.83619

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**References**

**All reports on included studies based on clinical trial numbers**

**NCT01157351**

 Alphs L, Mao L, Lynn Starr H, Benson C. A pragmatic analysis comparing once-monthly paliperidone palmitate versus daily oral antipsychotic treatment in patients with schizophrenia. Schizophr Res. 2016 Feb;170(2-3):259-64. doi: 10.1016/j.schres.2015.12.012. Epub 2015 Dec 29.

Alphs L, Bossie C, Mao L, Lee E, Starr HL. Treatment effect with paliperidone palmitate compared with oral antipsychotics in patients with recent-onset versus more chronic schizophrenia and a history of criminal justice system involvement. Early Interv Psychiatry. 2018 Feb;12(1):55-65. doi: 10.1111/eip.12271. Epub 2015 Sep 25.

Alphs L, Benson C, Cheshire-Kinney K, Lindenmayer JP, Mao L, Rodriguez SC, Starr HL. Real-world outcomes of paliperidone palmitate compared to daily oral antipsychotic therapy in schizophrenia: a randomized, open-label, review board-blinded 15-month study. J Clin Psychiatry. 2015 May;76(5):554-61. doi: 10.4088/JCP.14m09584.

Alphs L, Mao L, Rodriguez SC, Hulihan J, Starr HL. Design and rationale of the Paliperidone Palmitate Research in Demonstrating Effectiveness (PRIDE) study: a novel comparative trial of once-monthly paliperidone palmitate versus daily oral antipsychotic treatment for delaying time to treatment failure in persons with schizophrenia. J Clin Psychiatry. 2014 Dec;75(12):1388-93. doi: 10.4088/JCP.13m08965**.**

**NCT00320489**

Ascher-Svanum, H., Novick, D., Haro, J. M., Bertsch, J., McDonnell, D., & Detke, H. (2014). Long-term functional improvements in the 2-year treatment of schizophrenia outpatients with olanzapine long-acting injection. Neuropsychiatr Dis Treat, 10, 1125-1131. doi: 10.2147/ndt.s61409

Atkins S, Detke HC, McDonnell DP, Case MG, Wang S. A pooled analysis of injection site-related adverse events in patients with schizophrenia treated with olanzapine long-acting injection. BMC Psychiatry. 2014 Jan 14;14:7. doi: 10.1186/1471-244X-14-7.

Peuskens J, Porsdal V, Pecenak J, Handest P, D'yachkova Y, Brousil R, Deberdt W. Schizophrenia symptoms and functioning in patients receiving long-term treatment with olanzapine long-acting injection formulation: a pooled analysis. BMC Psychiatry. 2012 Aug 31;12:130. doi: 10.1186/1471-244X-12-130.

McDonnell DP, Detke HC, Bergstrom RF, Kothare P, Johnson J, Stickelmeyer M, Sanchez-Felix MV, Sorsaburu S, Mitchell MI. Post-injection delirium/sedation syndrome in patients with schizophrenia treated with olanzapine long-acting injection, II: investigations of mechanism. BMC Psychiatry. 2010 Jun 10;10:45. doi: 10.1186/1471-244X-10-45.

Detke HC, McDonnell DP, Brunner E, Zhao F, Sorsaburu S, Stefaniak VJ, Corya SA. Post-injection delirium/sedation syndrome in patients with schizophrenia treated with olanzapine long-acting injection, I: analysis of cases. BMC Psychiatry. 2010 Jun 10;10:43. doi: 10.1186/1471-244X-10-43.

**NCS932314B480002**

Bai 2006 {published data only} Bai YM, Chen TT, Wu B, Hung CH, Lin WK, Hu TM, et al. A comparative efficacy and safety study of long-acting risperidone injection and risperidone oral tablets among hospitalized patients: 12-week randomized, single-blind study. Pharmacopsychiatry 2006;39(4):135–

**NCT01529515**

Berwaerts J, Liu Y, Gopal S, Nuamah I, Xu H, Savitz A, Coppola D, Schotte A, Remmerie B, Maruta N, Hough DW. Efficacy and Safety of the 3-Month Formulation of Paliperidone Palmitate vs Placebo for Relapse Prevention of Schizophrenia: A Randomized Clinical Trial. JAMA Psychiatry. 2015 Aug;72(8):830-9. doi: 10.1001/jamapsychiatry.2015.0241.

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**NCT00330863**

Buckley PF, Schooler NR, Goff DC, Hsiao J, Kopelowicz A, Lauriello J, Manschreck T, Mendelowitz AJ, Miller del D, Severe JB, Wilson DR, Ames D, Bustillo J, Mintz J, Kane JM; PROACTIVE Study. Comparison of SGA oral medications and a long-acting injectable SGA: the PROACTIVE study. Schizophr Bull. 2015 Mar;41(2):449-59. doi: 10.1093/schbul/sbu067. Epub 2014 May 27.

**NCT00705783 &** **NCT00706654**

Fleischhacker WW, Baker RA, Eramo A, et al. (2014) Effects of aripiprazole once-monthly on domains of personal and social performance: results from 2 multicenter, randomized, double-blind studies. Schizophr Res, 159(2-3), 415-420

Kane JM, Sanchez R, Perry PP, Jin N, Johnson BR, Forbes RA, McQuade RD, Carson WH, Fleischhacker WW. Aripiprazole intramuscular depot as maintenance treatment in patients with schizophrenia: a 52-week, multicenter, randomized, double-blind, placebo-controlled study. J Clin Psychiatry. 2012 May;73(5):617-24. doi: 10.4088/JCP.11m07530.

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**NCT01193153**

Fu DJ, Turkoz I, Simonson RB, Walling DP, Schooler NR, Lindenmayer JP, Canuso CM, Alphs L. Paliperidone palmitate once-monthly reduces risk of relapse of psychotic, depressive, and manic symptoms and maintains functioning in a double-blind, randomized study of schizoaffective disorder. J Clin Psychiatry. 2015 Mar;76(3):253-62. doi: 10.4088/JCP.14m09416.

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**NCT00111189**

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Kozma CM, Slaton T, Dirani R, Fastenau J, Gopal S, Hough D. Changes in schizophrenia-related hospitalization and ER use among patients receiving paliperidone palmitate: results from a clinical trial with a 52-week open-label extension (OLE). Curr Med Res Opin. 2011 Aug;27(8):1603-11. doi: 10.1185/03007995.2011.595000. Epub 2011 Jun 22.

**NCT02109562**

Isitt, J. J., Nadipelli, V. R., Kouassi, A., Fava, M., & Heidbreder, C. (2016). Health-related quality of life in acute schizophrenia patients treated with RBP-7000 once monthly risperidone: An 8-week, randomized, double-blind, placebo-controlled, multicenter phase 3 study. Schizophr Res, 174(1-3), 126-131. doi: 10.1016/j.schres.2016.03.020

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**NCT01663532**

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**UMIN000014470**

Koshikawa, Y., Takekita, Y., Kato, M., Sakai, S., Onohara, A., Sunada, N., . . . Kinoshita, T. (2016). The Comparative Effects of Risperidone Long-Acting Injection and Paliperidone Palmitate on Social Functioning in Schizophrenia: A 6-Month, Open-Label, Randomized Controlled Pilot Trial. Neuropsychobiology, 73(1), 35-42. doi: 10.1159/000442209

**NCT00236457**

Keks, N. A., Ingham, M., Khan, A., & Karcher, K. (2007). Long-acting injectable risperidone v. olanzapine tablets for schizophrenia or schizoaffective disorder. Randomised, controlled, open-label study. Br J Psychiatry, 191, 131-139. doi: 10.1192/bjp.bp.105.017020

**NCT00539071**

Meltzer, H. Y., Lindenmayer, J. P., Kwentus, J., Share, D. B., Johnson, R., & Jayathilake, K. (2014). A six month randomized controlled trial of long acting injectable risperidone 50 and 100mg in treatment resistant schizophrenia. Schizophr Res, 154(1-3), 14-22. doi: 10.1016/j.schres.2014.02.015

**NCT01795547**

Naber D, Hansen K, Forray C, Baker RA, Sapin C, Beillat M, Peters-Strickland T, Nylander AG, Hertel P, Andersen HS, Eramo A, Loze JY, Potkin SG. Qualify: a randomized head-to-head study of aripiprazole once-monthly and paliperidone palmitate in the treatment of schizophrenia. Schizophr Res. 2015 Oct;168(1-2):498-504. doi: 10.1016/j.schres.2015.07.007. Epub 2015 Jul 29.

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**NCT00604279**

nr

**NCT00992407**

Nr

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