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Switching from risperidone to paliperidone palmitate in schizophrenia: changes in social functioning and cognitive performance

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Abstract:	BACKGROUND: Previous studies suggest that paliperidone might show a better profile for social functioning and cognitive abilities than risperidone. We aimed to study whether switching from risperidone to paliperidone palmitate (PP) is associated with improved cognitive abilities at 3 or 6 months after the switch. METHODS: Thirty-eight patients with a DSM-IV diagnosis of schizophrenia were studied. All patients were treated with oral risperidone or RLAI and had an indication to be switched to PP by their psychiatrists. Statistical analyses were conducted in a final sample of 27 patients who completed the follow-up visits. Three assessments were completed: 1) baseline (preswitch), 2) 3 months postswitch, and 3) 6 months postswitch. Social functioning at each visit was assessed with the Personal and Social Performance Scale. Cognitive assessment was conducted at each visit with the MATRICS Consensus Cognitive Battery. Statistical analyses were performed with R. Linear mixed models were used to explore longitudinal changes in social functioning and cognitive outcomes. RESULTS: PSP scores significantly improved over time after the switch from risperidone to PP. A sensitivity analysis found a significant negative interaction between time and PP maintenance doses (greater improvement in those patients receiving lower doses when compared to higher doses). Regarding longitudinal changes in cognitive functioning, patients improved in 6 out of 10 cognitive tasks involving processing speed, working memory, visual memory, reasoning and problem solving, and attention and vigilance. CONCLUSIONS: Our study suggests that switching from risperidone to PP in patients with schizophrenia is associated with an improvement in social functioning and cognitive performance.
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RESPONSE TO REVIEWER COMMENTS

Reviewer #1: The authors did a commendable job in responding to all the reviewers' comments and revised the manuscript adequately.

I have one additional comment: please report both doses of PP before and after dose reduction and the time when the dose reduction was performed in the patients.

We have added one sentence in the Results reporting the mean (SD) doses (in risperidone equivalents) before and after the reduction.

Reviewer #2: The manuscript has been much improved.

Thanks for your review.

Reviewer #3: Author answer and explain all the concerns, they are rationale, and the revised manuscript is well organized, no more comments for authors.

Thanks for your review.

HIGHLIGHTS

We studied the switch from risperidone to paliperidone palmitate in patients with schizophrenia.

Switching to paliperidone palmitate improved social functioning and cognitive abilities.

Patients receiving lower paliperidone doses showed greater improvements in social functioning.

Reducing antipsychotic doses was associated with improvements in social cognition.

Switching from risperidone to paliperidone palmitate in schizophrenia: changes in social functioning and cognitive performance

ABSTRACT

BACKGROUND: Previous studies suggest that paliperidone might show a better profile for social functioning and cognitive abilities than risperidone. We aimed to study whether switching from risperidone to paliperidone palmitate (PP) is associated with improved cognitive abilities at 3 or 6 months after the switch.

METHODS: Thirty-eight patients with a DSM-IV diagnosis of schizophrenia were studied. All patients were treated with oral risperidone or RLAI and had an indication to be switched to PP by their psychiatrists. Statistical analyses were conducted in a final sample of 27 patients who completed the follow-up visits. Three assessments were completed: 1) baseline (preswitch), 2) 3 months postswitch, and 3) 6 months postswitch. Social functioning at each visit was assessed with the Personal and Social Performance Scale. Cognitive assessment was conducted at each visit with the MATRICS Consensus Cognitive Battery. Statistical analyses were performed with R. Linear mixed models were used to explore longitudinal changes in social functioning and cognitive outcomes.

RESULTS: PSP scores significantly improved over time after the switch from risperidone to PP. A sensitivity analysis found a significant negative interaction between time and PP maintenance doses (greater improvement in those patients receiving lower doses when compared to higher doses).

Regarding longitudinal changes in cognitive functioning, patients improved in 6 out of 10 cognitive tasks involving processing speed, working memory, visual memory, reasoning and problem solving, and attention and vigilance.

CONCLUSIONS: Our study suggests that switching from risperidone to PP in patients with schizophrenia is associated with an improvement in social functioning and cognitive performance.

INTRODUCTION

In recent years, second-generation LAI antipsychotics have been demonstrated to be effective drugs for the treatment of schizophrenia, with better outcomes in terms of rehospitalization risk (Taipale et al., 2018; Tiihonen et al., 2017), lower side effects, extrapyramidal effects (Taylor, 2009), and reduced mortality (Taipale et al., 2017) when compared to first-generation LAIs. Risperidone LAI (RLAI), the first second-generation antipsychotic with an LAI formulation, has shown improvements in functionality and quality of life over first-generation LAI antipsychotics (Lloyd et al., 2010). Previous studies also suggest that switching from oral risperidone to RLAI may improve verbal memory more than continuing with oral risperidone (Hori et al., 2018). In recent years, paliperidone palmitate (PP) as an LAI formulation has been approved. Although paliperidone, or 9-hydroxy-risperidone, is an active metabolite of risperidone, it presents pharmacokinetic and pharmacodynamic differences with respect to risperidone that make paliperidone a different drug with a better tolerability profile (Álamo and López Muñoz, 2013) and allow the administration of the treatment once per month unlike RLAI, which is administered every two weeks.

Studies exploring switching from RLAI or other LAI antipsychotics to PP suggest an improvement in personal satisfaction, quality of life and functioning (Schreiner et al., 2015). A 6-month pilot, open-label, randomized controlled study (Koshikawa et al., 2016) that included 30 patients with schizophrenia who had been treated with RLAI found greater social functioning improvements in those patients who were randomized to PP when compared to RLAI continuation.

Although few studies have evaluated the different cognitive profiles of risperidone and paliperidone, some studies suggest that paliperidone could have a better profile than risperidone. Kim et al. (2012) conducted a 12-week randomized study comparing treatment with risperidone and paliperidone, showing an improvement in verbal

memory in the paliperidone group. One randomized clinical trial (Takekita et al., 2016) that randomized patients with schizophrenia receiving RLAI to either continue with RLAI or to switch to PP reported attention and processing speed improvements in the PP group. In another study carried out in a sample of elderly patients with schizophrenia, the change from oral risperidone to oral paliperidone was evaluated, observing an improvement in working memory (Suzuki et al., 2014). In a more recent cross-sectional study exploring the relationship between antipsychotic drugs in monotherapy and cognitive performance in adults with schizophrenia, subjects receiving paliperidone showed a better performance on cognitive tasks dealing with visual perception, attention, working memory, and processing speed than among those receiving haloperidol or risperidone (Noh et al., 2020).

There are also 'in vitro' studies that have compared the neurotoxic effect of three antipsychotics (haloperidol, risperidone and paliperidone) in an in vitro model using neuroblastoma cells (Gassó et al., 2012). This study observed a lower neurotoxicity of paliperidone compared to haloperidol (the most neurotoxic) and risperidone (it showed an intermediate neurotoxicity between haloperidol and paliperidone). This study suggested that paliperidone might have a better cognitive profile than risperidone or haloperidol.

As cognitive alterations are associated with worse social functioning in patients with schizophrenia (Fett et al., 2011; Green et al., 2004), being able to improve these alterations has become a crucial objective in the management of schizophrenia.

The main aim of our study was to analyse whether patients with schizophrenia who are switched from risperidone (oral or RLAI) to PP under pragmatic conditions improve in social functioning. We hypothesized that patients switching from risperidone to PP would improve in social functioning. Additionally, we aimed to explore whether there was cognitive improvement after the switch from risperidone to PP.

METHODS

Patients

Thirty-eight patients with a DSM-IV diagnosis of schizophrenia attending the Mental Health Care Centre of Parc Taulí Hospital (Sabadell, Spain) were consecutively recruited. All participants were receiving treatment with risperidone, but their referring psychiatrist suggested a switch to PP based on their clinical criteria. The inclusion criteria were age 18-60 years, receiving risperidone (oral or RLAI) in monotherapy and having stable antipsychotic medication without changes in dosing in the previous two months. The exclusion criteria were as follows: 1) cognitive or language alterations that prevented the administration of psychometric scales, 2) any unstable medical condition (including uncontrolled diabetes, hypertension or asthma) or a history of severe neurological pathology, 3) electroconvulsive therapy in the previous 3 months or during follow-up, 4) pregnancy or lactation, 5) alcohol, cocaine or heroin dependence or other substance abuse disorder with active consumption in the three months prior to the start of the study, and 6) intolerance or allergy to paliperidone.

All patients were informed about the study and signed a written informed consent form before participation in the study. Ethical approval was obtained by the Ethics Committee of Parc Taulí Hospital.

This study is an observational, open-label, longitudinal study, and the decision to switch from risperidone to PP was assumed by the psychiatrist in charge of the patient. Switching was conducted taking into account the recommendations of the drug data sheet for PP. For those patients who were switched from RLAI, the PP dose was multiplied by two.

Clinical assessment

Clinical diagnoses of schizophrenia were generated with the OPCRIT checklist v.4.0 after a semistructured interview by a psychiatrist. Three assessments were completed: 1) baseline (preswitch), 2) 3 months postswitch, and 3) 6 months postswitch.

Sociodemographic and clinical variables related to the course of schizophrenia were obtained by semistructured interviews at the baseline visit.

At each visit (baseline, 3 and 6 months), the following psychometric scales were administered: Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1990) for assessing positive and negative symptoms, Calgary Depression Scale for Schizophrenia (Addington et al., 1993) for assessing depressive symptoms, and the Personal and Social Performance Scale (Morosini et al., 2000) for measuring social functioning.

Cognitive assessment was conducted at each visit with the MATRICS Consensus Cognitive Battery (Nuechterlein et al., 2008), which includes 10 cognitive tests for assessing 7 cognitive domains dealing with processing speed, visual memory, verbal memory, working memory, reasoning and problem solving, attention and social cognition.

All scales and cognitive tests were administered by the same rater.

Switching and follow-up visits.

Although the initial switch from risperidone to PP was conducted according to the drug sheet, the final PP dose during follow-up was selected by the psychiatrist in charge of the patient.

Among all 38 patients who completed the baseline visit, only 27 (71.1%) had at least one follow-up visit. The reasons for not completing any follow-up visit for ten participants were as follows: 1) refused to accept LAI administration (PP) during follow-up (N=3), refusal to complete the clinical assessments (N=7), and psychotic decompensation with inpatient admission that was not related to the switch (N=1).

Among the 27 patients who completed the follow-up, the PP maintenance doses at follow-up were 50 mg (N= 5, 18.5%), 75 mg (N= 8, 29.6%), 100 mg (N= 5, 18.5%), 150 mg (N= 7, 25.9%) and 200 mg (N=2, 7.4%).

None of the 27 patients received treatment with mood stabilizers (e.g. lithium, valproate, lamotrigine or carbamazepine).

Statistical analysis

Sample size calculation was calculated with the software GLIMMPSE version 3.0 (available at https://glimmpse.samplesizeshop.org). Considering a beta error of 0.2 (statistical power of 80%), an alpha error of 0.05, and the mean and standard deviation values that were available from a previous study (Montalvo et al., 2013; Montalvo et al., 2018) that also assessed PSP changes after switching from RLAI to PP in patients with psychotic disorders (improvements in PSP from 60 to 67 were predicted, with a standard deviation of 8), the required sample size was 29. Taking into account potential drop-outs (25%), we finally considered a sample size of 38.

Longitudinal changes in PSP scores and cognitive variables were analysed with linear mixed models using R and the package lme4. Statistical analyses were conducted for 27 patients who completed at least one follow-up visit.

The main analysis, which was hypothesis-driven, used PSP scores as the main dependent variable. In this analysis, time (visit) was included as a fixed factor, along with other independent variables that were also considered fixed factors (age, sex,

baseline PANSS negative score). Subjects were included in the model as random factors. Restricted maximum likelihood (REML) was used for fitting the model and estimating the effects of the variables included in the model. We conducted a sensitivity analysis, adjusting for the PP dose when achieving the maintenance dose. This variable was used as a categorical variable (fixed factor) for the two categories: lower doses (50 and 75 mg) and higher doses (100 mg or higher). We also tested the interaction between time and PP doses. This interaction explores whether changes in PSP scores over time differ by PP dosing (higher doses compared to lower doses).

We further conducted analyses to explore longitudinal changes in cognition. In these exploratory analyses, one model was performed for each cognitive task (which was defined as the dependent variable). Fixed factors included time (visit), age, gender, education status and baseline PANSS negative score. Random factors included subjects. REML was used for fitting the model. These 10 linear mixed models (one for each cognitive task) were not adjusted for multiple comparisons, as they were exploratory analyses in nature (Bender and Lange, 2001). We also conducted sensitivity analyses adjusting for PP doses and for testing the interaction between time and the PP doses. As reductions in antipsychotic doses might be also associated with cognitive improvements (Tani et al., 2020; Takeuchi et al., 2013; Zhou et al., 2018) we conducted additional sensitivity analyses exploring whether the reduction of PP doses during follow-up was associated with longitudinal changes in cognitive abilities. A dichotomous variable (PP dose reduction) was set as a factor, and we tested the time x dose reduction effect for each cognitive model.

We also conducted sensitivity analyses adjusting for benzodiazepine treatment for all cognitive tasks. In these analyses, benzodiazepine treatment was set as a continuous variable of diazepam doses. The following equivalences were considered: 5 mg diacepam, 0,5 mg clonacepam, 1 mg lorazepam, 1 mg lormetazepam.

RESULTS

Sociodemographic and clinical data of participants who completed at least one follow-up visit are described in Table 1. All 27 patients completed the 3-month visit, and 23 patients (85.1%) also completed the 6-month visit. As shown in Table 1, approximately 60% of patients were switched from RLAI to PP. Of all 27 patients, 19 (70.4%) had a dose reduction during the follow-up period. In those patients with a reduction of antipsychotic doses, the mean (SD) risperidone equivalent dose before the reduction were 5.0 (0.6) mg/day and after the reduction 3.5 (0.7) mg/day. Longitudinal changes in clinical variables, including social functioning and cognitive outcomes, are described in Table 2.

A significant improvement in PSP scores over time after the switch from risperidone to PP was observed (Table 3). The sensitivity analysis, including PP doses, found a significant negative interaction between time and the PP maintenance doses. This finding suggests that patients receiving higher PP doses (100 mg or higher) reported less improvement in PSP over time than those receiving lower doses. To describe this interaction, we depicted longitudinal changes in PSP scores by the maintenance PP dose in Figure 1.

Regarding longitudinal changes in cognitive functioning, patients improved in 6 out of 10 cognitive tasks (Table 4), mainly in cognitive tasks dealing with processing speed, working memory, visual memory, reasoning and problem solving, and attention and vigilance. Sensitivity analyses did not show differences in cognitive changes over time by the PP doses. However, regarding dose reduction in PP over follow-up, a significant time x group interaction was found for the social cognitive domain, that was assessed with the Managing Emotions branch of the Mayer-Salovey-Caruso Emotional Intelligence Test (MSCEIT-ME) (Effect= 6.8; SE= 2.1; df= 45.68; t= 3.236; p= 0.002). This interaction is depicted in Figure S1 from supplementary material. As it can be

seen in the figure, there is an improvement in MSCEIT-ME scores over time in those patients with a PP dose reduction after the switch, whereas those patients without PP dose reduction worsened in social cognition.

We repeated the analyses exploring longitudinal changes in cognitive functioning also adjusted for benzodiazepine treatment, and the main results did not change.

DISCUSSION

Our study suggests that the switch from risperidone to PP in patients with schizophrenia is associated with improvements in social functioning and cognitive abilities. A greater improvement in social functioning was observed in those patients receiving lower doses of PP (50 mg or 75 mg) compared to those receiving doses of 100 mg or higher. A greater improvement in social cognition (but not in neurocognitive domains) was observed in those patients with a reduction in antipsychotic dose over the follow-up period.

The improvement in social functioning after switching from risperidone is consistent with previous studies that have reported improvements in social functioning after switching from risperidone or other antipsychotics to PP (Koshikawa et al., 2016; Schreiner et al., 2015). Other studies of switching from oral risperidone to oral paliperidone have also reported improvements in social functioning (Kim et al., 2013; Gattaz et al., 2014). Our study adds new information about the greater improvement in social functioning among those patients receiving lower PP doses. However, as our study is a nonrandomized, open-label, uncontrolled study, it is difficult to determine whether the lower improvement in social functioning by patients receiving higher PP doses is secondary to the effects of the dosing of PP or whether it could be an indicator of a more severe psychotic phenotype that requires higher doses of PP. In line with this possibility, baseline PSP scores of patients who received higher PP doses were also

lower than those of patients who were administered lower PP doses. Another possibility is that PP at higher doses might worsen negative symptoms, which in turn could limit the effectiveness of the drug in improving social functioning. Previous studies focused on first-episode psychosis have reported better functional recovery with a dose reduction strategy when compared to maintenance treatment (Wunderink et al., 2013). Evidence of a reduction in antipsychotic dosing in stable patients with chronic schizophrenia is scarce, with a recent pilot clinical trial (Huhn et al., 2021) suggesting that it might be a feasible option, although these results need to be confirmed in larger trials. Future randomized clinical trials using lower and higher PP doses are required to confirm our findings and to explore the potential benefit of lower PP doses on social functioning.

The improvement in cognitive abilities over time is also in accordance with previous studies reporting cognitive improvements with paliperidone treatment (Kim et al., 2012; Noh et al., 2020; Suzuki et al., 2014; Takekita et al., 2016). Basic laboratory studies also reinforce a potential neuroprotective effect of paliperidone due to a reduction in caspase-3 activity and protection against apoptosis (Gassó et al., 2012) and an increase in BDNF activity (Wu et al., 2018). In contrast with the social functioning outcome, PP doses did not influence longitudinal changes in cognitive abilities, suggesting that the improvement in cognitive functioning is independent of the dose of PP. All cognitive analyses were adjusted for negative symptoms, which suggests that the improvement of cognitive abilities is independent of the severity of negative symptoms.

Previous research suggests that dose reduction in antipsychotic treatment in patients with schizophrenia is associated with cognitive improvements (Singh et al., 2022; Takeuchi et al., 2013; Tani et al., 2020; Zhou et al., 2018), particularly in neurocognitive domains dealing with processing speed (Singh et al., 2022; Takeuchi et al., 2013; Tani et al., 2020), verbal and working memory (Takeuchi et al., 2013; Zhou et al., 2018) and

attention (Singh et al., 2022). We failed to find an association between antipsychotic dose reduction and performance in neurocognitive domains. We found, however, an improvement in social cognitive tasks. Although most previous studies have focused on neurocognitive domains, other studies that also explored changes in MATRICS domains after a reduction in antipsychotic doses did not report improvements in the MSCEIT-ME task (Zhou et al., 2018). The greater improvement in social cognition in those patients with a reduction in PP doses during follow-up is a finding that needs to be replicated by other studies, as studies assessing social cognition are lacking.

The improvement in social functioning after the switch might be partially explained by an improvement in cognitive abilities, as it is known that cognitive impairments are predictors of social functioning in schizophrenia (Cowman et al., 2021). Interestingly, social cognition is one of the cognitive domains most strongly associated with concurrent and long-term social functioning (Cowman et al., 2021). Our findings highlight the need to study whether the antipsychotic reduction in stable patients with schizophrenia might improve social cognition abilities which in turn improve social functioning. This hypothesis would be in accordance with previous studies that have reported superior long-term recovery rates with antipsychotic dose reduction strategies when compared with maintaining the antipsychotic dose (Wunderink et al., 2013).

The better cognitive profile of paliperidone compared to risperidone could be partially explained by pharmacodynamic differences between the two drugs. In contrast to risperidone, paliperidone has a low affinity for muscarinic receptors, with scarcely any central or peripheral anticholinergic effects, which might be beneficial for cognitive effects (Álamo and López Muñoz, 2013). Paliperidone shows a faster speed of dissociation from the D2 receptor (1 min) than risperidone (27 min). It has been suggested that faster dissociation times from dopamine D2 receptors better accommodate physiological dopamine transmission, with fewer extrapyramidal effects

associated with nigrostriatal modulation and potentially benefiting cognitive outcomes (Álamo and López Muñoz, 2013).

A clinical implication of our study is that among patients with schizophrenia receiving risperidone, a switch to PP might be followed by an improvement in social functioning and cognitive performance. Therefore, in patients with schizophrenia receiving risperidone with some degree of cognitive impairment, switching to PP could be a feasible therapeutic strategy to alleviate this type of adverse effect.

Some limitations of our study need to be mentioned. First, the open-label, nonrandomized and uncontrolled design of our study includes the possibility of selection biases regarding the population that was offered to be switched from risperidone to PP, as well as in the analyses of PP doses, as they were decided by routine clinical practice. Second, the relatively small sample size, with 28.9% of patients not completing the follow-up, limits the statistical power to detect small longitudinal changes in the studied outcomes or to assess sex differences in the longitudinal changes, particularly because the number of women in our study was low. Although the drop-out rate of our study might be considered substantial (39.5% missed at least one follow-up assessment), it is important to mention that similar drop-out rates have been reported in clinical trials including patients with schizophrenia and follow-up periods of 6 months (40% drop-outs in Kim et al., 2021; 30% drop-outs in Takekita et al., 2016). Third, we did not assess risperidone or paliperidone concentrations in plasma, which could be useful to control for potential differences in social functioning during PP dosing.

There are, however, some strengths that merit discussion. First, we explored the switch from risperidone to PP, including patients with schizophrenia who were receiving antipsychotic monotherapy with stable medication for two months. Second, we included extensive phenotyping with the administration of psychometric scales and a full

cognitive battery. Third, we included a follow-up of 6 months, which allowed us to detect longitudinal changes in social functioning and cognitive performance.

In conclusion, our study suggests that switching from risperidone to PP among patients with schizophrenia is associated with an improvement in social functioning and cognitive performance in tasks dealing with processing speed, visual and working memory, reasoning and problem solving, and attention. A greater improvement in social functioning was observed in those patients who received lower doses of PP during follow-up.

REFERENCES

Addington, D., Addington, J., Maticka-Tyndale, E., 1993. Assessing depression in schizophrenia: the Calgary Depression Scale. Br. J. Psychiatry. Suppl. 39–44.

Álamo, C., López Muñoz, F., 2013. The Pharmacological Role and Clinical Applications of Antipsychotics' Active Metabolites: Paliperidone versus Risperidone. Clin. Exp. Pharmacol. 3, 1-12. https://doi.org/10.4172/2161-1459.1000117

Bender, R., Lange, S., 2001. Adjusting for multiple testing--when and how? J. Clin. Epidemiol. 54, 343–349.

Cowman, M., Holleran, L., Lonergan, E., O'Connor, K., Birchwood, M., Donohoe, G., 2021. Cognitive Predictors of Social and Occupational Functioning in Early Psychosis: A Systematic Review and Meta-analysis of Cross-Sectional and Longitudinal Data. Schizophr. Bull. 47, 1243-1253. doi: 10.1093/schbul/sbab033.

Fett, A.K.J., Viechtbauer, W., Dominguez, M. de G., Penn, D.L., van Os, J., Krabbendam, L., 2011. The relationship between neurocognition and social cognition with functional outcomes in schizophrenia: A meta-analysis. Neurosci. Biobehav. Rev. 35, 573-588. https://doi.org/10.1016/j.neubiorev.2010.07.001

Gassó, P., Mas, S., Molina, O., Bernardo, M., Lafuente, A., Parellada, E., 2012. Neurotoxic/neuroprotective activity of haloperidol, risperidone and paliperidone in neuroblastoma cells. Prog. Neuro-Psychopharmacology Biol. Psychiatry 36, 71–77. https://doi.org/10.1016/j.pnpbp.2011.08.010

Gattaz, W.F., Campos, J.A., Lacerda, A.L., Henna, E., Ruschel, S.I., Bressan, R.A., de Oliveira, I.R., Rocha, F.L., Grabowski, H.M., Sacomani, E. Jr., Louzã, M.R., Quevedo, J., Elkis, H., Zorzetto Filho, D., Périco Cde, A., Lawson, F.L., Appolinário, J.C., 2014. Switching from oral risperidone to flexibly dosed oral paliperidone extended-release: Core symptoms, satisfaction, and quality of life in

patients with stable but symptomatic schizophrenia: The RISPALI study. Curr. Med. Res. Opin. 30, 695-709. doi: 10.1185/03007995.2013.869201.

Green, M.F., Kern, R.S., Heaton, R.K., 2004. Longitudinal studies of cognition and functional outcome in schizophrenia: Implications for MATRICS. Schizophr. Res. 72, 41–51. https://doi.org/10.1016/j.schres.2004.09.009

Hori, H., Katsuki, A., Atake, K., Yoshimura, R., 2018. Effects of Continuing Oral Risperidone vs. Switching from Risperidone to Risperidone Long-Acting Injection on Cognitive Function in Stable Schizophrenia Patients: A Pilot Study. Front Psychiatry. 9, 74. doi: 10.3389/fpsyt.2018.00074.

Huhn, M., Leucht, C., Rothe, P., Dold, M., Heres, S., Bornschein, S., Schneider-Axmann, T., Hasan, A., Leucht, S., 2021. Reducing antipsychotic drugs in stable patients with chronic schizophrenia or schizoaffective disorder: a randomized controlled pilot trial. Eur. Arch. Psychiatry Clin. Neurosci. 271, 293-302. https://doi.org/10.1007/s00406-020-01109-y

Kay, S.R., Fiszbein, A., Vital-Herne, M., Fuentes, L.S., 1990. The Positive and Negative Syndrome Scale--Spanish adaptation. J. Nerv. Ment. Dis. 178, 510–517. https://doi.org/10.1097/00005053-199017880-00007

Kim, E.Y., Chang, S.M., Shim, J.C., Joo, E.J., Kim, J.J., Kim, Y.S., Ahn, Y.M., 2013. Long-term effectiveness of flexibly dosed paliperidone extended-release: Comparison among patients with schizophrenia switching from risperidone and other antipsychotic agents. Curr. Med. Res. Opin. 29, 1231-1240. https://doi.org/10.1185/03007995.2013.816277

Kim, S., Kim, S., Koh, M., Choi, G., Kim, J.J., Paik, I.H., Kim, S.H., Choi, Y.S., Lee, Y., Suh, J., Takeuchi, H., Uchida, H., Kim, E., 2021. Effects of Long-Acting Injectable Paliperidone Palmitate on Clinical and Functional Outcomes in Patients With Schizophrenia Based on Illness Duration. J Clin Psychiatry. 82, 20m13446. doi:

10.4088/JCP.20m13446. PMID: 33434958.

Kim, S.W., Chung, Y.C., Lee, Y.H., Lee, J.H., Kim, S.Y., Bae, K.Y., Kim, J.M., Shin, I.S., Yoon, J.S., 2012. Paliperidone ER versus risperidone for neurocognitive function in patients with schizophrenia: A randomized, open-label, controlled trial. Int. Clin. Psychopharmacol. 27, 267-274. https://doi.org/10.1097/YIC.0b013e328356acad

Koshikawa, Y., Takekita, Y., Kato, M., Sakai, S., Onohara, A., Sunada, N., Nishida, K., Yoshimura, M., Fabbri, C., Serretti, A., 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, 35-42. https://doi.org/10.1159/000442209

Lloyd, K., Latif, M.A., Simpson, S., Shrestha, K.L., 2010. Switching stable patients with schizophrenia from depot and oral antipsychotics to long-acting injectable risperidone: Efficacy, quality of life and functional outcome. Hum. Psychopharmacol. 25, 243-252. https://doi.org/10.1002/hup.1108

Montalvo, I., Ortega, L., López, X., Solé, M., Monseny, R., Franch, J., Vilella, E., Labad, J., 2013. Changes in prolactin levels and sexual function in young psychotic patients after switching from long-acting injectable risperidone to paliperidone palmitate. Int. Clin. Psychopharmacol. 28, 46-49. doi: 10.1097/YIC.0b013e32835ba832.

Montalvo, I. 2018. Hiperprolactinemia en psicosis tempranas: impacto en el rendimiento cognitivo y la funcionalidad de los pacientes [PhD thesis]. Universitat Rovira i Virgili, Reus. Spain. http://hdl.handle.net/10803/586259

Morosini, P.L., Magliano, L., Brambilla, L., Ugolini, S., Pioli, R., 2000. Development, reliability and acceptability of a new version of the DSM-IV Social and Occupational Functioning Assessment Scale (SOFAS) to assess routine social

functioning., Acta psychiatrica Scandinavica. 101, 323-329. https://doi.org/10.1034/j.1600-0447.2000.101004323.x

Noh, S., Na, E., Park, S.J., Kim, S.H., Evins, A.E., Roh, S., 2020. Effects of various antipsychotics on driving-related cognitive performance in adults with schizophrenia. J. Psychiatr. Res. 131,152-159. https://doi.org/10.1016/j.jpsychires.2020.08.029

Nuechterlein, K.H., Green, M.F., Kern, R.S., Baade, L.E., Barch, D.M., Cohen, J.D., Essock, S., Fenton, W.S., Frese, F.J., Gold, J.M., Goldberg, T., Heaton, R.K., Keefe, R.S.E., Kraemer, H., Mesholam-Gately, R., Seidman, L.J., Stover, E., Weinberger, D.R., Young, A.S., Zalcman, S., Marder, S.R., 2008. The MATRICS Consensus Cognitive Battery, part 1: test selection, reliability, and validity. Am. J. Psychiatry 165, 203–213. https://doi.org/10.1176/appi.ajp.2007.07010042

Schreiner, A., Bergmans, P., Cherubin, P., Keim, S., Llorca, P.M., Cosar, B., Petralia, A., Corrivetti, G., Hargarter, L., 2015. Paliperidone palmitate in non-acute patients with schizophrenia previously unsuccessfully treated with risperidone long-acting therapy or frequently used conventional depot antipsychotics. J. Psychopharmacol. 29, 910-922. https://doi.org/10.1177/0269881115586284

Suzuki, H., Gen, K., Inoue, Y., Hibino, H., Mikami, A., Matsumoto, H., Mikami, K., 2014. The influence of switching from risperidone to paliperidone on the extrapyramidal symptoms and cognitive function in elderly patients with schizophrenia: A preliminary open-label trial. Int. J. Psychiatry Clin. Pract. 18, 58-62. https://doi.org/10.3109/13651501.2013.845218

Singh, A., Kumar, V., Pathak, H., Jacob, A.A., Venkatasubramanian, G., Varambally, S., Rao, N.P., 2022. Effect of antipsychotic dose reduction on cognitive function in schizophrenia. Psychiatry Res. 308, 114383. doi: 10.1016/j.psychres.2021.114383.

Taipale, H., Mehtälä, J., Tanskanen, A., Tiihonen, J., 2018. Comparative Effectiveness of Antipsychotic Drugs for Rehospitalization in Schizophrenia-A Nationwide Study With 20-

Year Follow-up. Schizophr. Bull. 44, 1381-1387. https://doi.org/10.1093/schbul/sbx176

Taipale, H., Mittendorfer-Rutz, E., Alexanderson, K., Majak, M., Mehtälä, J., Hoti, F., Jedenius, E., Enkusson, D., Leval, A., Sermon, J., Tanskanen, A., Tiihonen, J., 2017. Antipsychotics and mortality in a nationwide cohort of 29,823 patients with schizophrenia. Schizophr. Res. 197, 274-280. https://doi.org/10.1016/j.schres.2017.12.010

Takekita, Y., Koshikawa, Y., Fabbri, C., Sakai, S., Sunada, N., Onohara, A., Nishida, K., Yoshimura, M., Kato, M., Serretti, A., Kinoshita, T., 2016. Cognitive function and risperidone long-acting injection vs. paliperidone palmitate in schizophrenia: A 6-month, open-label, randomized, pilot trial. BMC Psychiatry. 16, 172. https://doi.org/10.1186/s12888-016-0883-9

Tani, H., Takasu, S., Uchida, H., Suzuki, T., Mimura, M., Takeuchi, H., 2020. Factors associated with successful antipsychotic dose reduction in schizophrenia: a systematic review of prospective clinical trials and meta-analysis of randomized controlled trials. Neuropsychopharmacology. 45, 887-901. doi: 10.1038/s41386-019-0573-7.

Takeuchi, H., Suzuki, T., Remington, G., Bies, R.R., Abe, T., Graff-Guerrero, A., Watanabe, K., Mimura, M., Uchida, H., 2013. Effects of risperidone and olanzapine dose reduction on cognitive function in stable patients with schizophrenia: an open-label, randomized, controlled, pilot study. Schizophr Bull. 39, 993-998. doi: 10.1093/schbul/sbt090.

Taylor, D., 2009. Psychopharmacology and adverse effects of antipsychotic long-acting injections: A review. Br. J. Psychiatry. 52, S13-S19. https://doi.org/10.1192/bjp.195.52.s13

Tiihonen, J., Mittendorfer-Rutz, E., Majak, M., Mehtälä, J., Hoti, F., Jedenius, E., Enkusson, D., Leval, A., Sermon, J., Tanskanen, A., Taipale, H., 2017. Real-world

effectiveness of antipsychotic treatments in a nationwide cohort of 29 823 patients with schizophrenia. JAMA Psychiatry. 74, 686-693. https://doi.org/10.1001/jamapsychiatry.2017.1322

Wu, R.Q., Lin, C.G., Zhang, W., Lin, X.D., Chen, X.S., Chen, C., Zhang, L.J., Huang, Z.Y., Chen, G.D., Xu, D.L., Lin, Z.G., Zhang, M.D., 2018. Effects of Risperidone and Paliperidone on Brain-Derived Neurotrophic Factor and N400 in First-Episode Schizophrenia. Chin. Med. J. (Engl). 131, 2297-2301. https://doi.org/10.4103/0366-6999.241802

Wunderink, L., Nieboer, R.M., Wiersma, D., Sytema, S., Nienhuis, F.J., 2013. Recovery in Remitted First-Episode Psychosis at 7 Years of Follow-up of an Early Dose Reduction/Discontinuation or Maintenance Treatment Strategy. JAMA Psychiatry 70, 913-920. https://doi.org/10.1001/jamapsychiatry.2013.19

Zhou, Y., Li, G., Li, D., Cui, H., Ning, Y., 2018. Dose reduction of risperidone and olanzapine can improve cognitive function and negative symptoms in stable schizophrenic patients: A single-blinded, 52-week, randomized controlled study. J Psychopharmacol. 32, 524-532. doi: 10.1177/0269881118756062.

Table 1. Baseline sociodemographic and clinical variables of 27 patients with schizophrenia who completed the follow-up visits.

	N (%) or mean (SD)
Female sex	5 (18.5%)
Age (years)	35.0 (12.4)
Education status (years of study)	9.7 (2.5)
Ethnicity	
European Caucasian	18 (66.7%)
Latinoamerican	4 (14.8%)
Arab (Maghreb)	1 (3.7%)
Sub-Saharan African	3 (11.1%)
Gipsy	1 (3.7%)
Civil status	
Single	21 (77.8%)
Married or stable couple	5 (18.5%)
Divorced	1 (3.7%)
Smoking	18 (66.7%)
Cannabis use (not abuse/dependence)	5 (18.5%)
Age at onset of schizophrenia	26.1 (7.4)
Number of previous psychotic episodes	2.3 (1.6)
Number of previous inpatient admissions	1.7 (1.5)
Baseline treatment	
Oral risperidone	11 (40.7%)
Oral risperidone dose (mg/day)	4.7 (0.8)
RLAI	16 (59.3%)
RLAI dose (mg/2 weeks)	44.9 (6.0)
Antidepressant treatment	7 (25.9%)
Benzodiazepine treatment	10 (37.0%)
Diazepam equivalent doses (mg/day)†	14.5 (1.7)
Dose reduction at follow-up	19 (70.4%)

Abbreviations: RLAI= risperidone long-acting injectable.

†Calculated in those patients receiving benzodiazepines.

Table 2. Longitudinal changes in continuous variables.

	Baseline	3 months	6 months
Risperidone/paliperidone dose (mg/day)[†]	4.4 (2.7)	3.8 (2.1)	3.6 (2.0)
PANSS positive score	9.6 (3.0)	8.9 (2.9)	9.3 (2.8)
PANSS negative score	21.1 (5.6)	19.2 (6.1)	17.8 (6.1)
PANSS general score	23.6 (5.1)	22.0 (4.3)	21.9 (4.0)
PANSS total score	54.2 (11.7)	50.1 (11.7)	49.2 (10.9)
CDSS	0.4 (1.1)	0.1 (0.4)	0.1 (0.3)
PSP	59.7 (11.7)	64.4 (13.4)	67.0 (14.4)
MCCB cognitive tasks (raw data)[‡]			
TMT (seconds)	46.6 (23.4)	38.9 (19.7)	37.1 (19.5)
BACS-SC	38.8 (13.5)	44.2 (13.6)	43.9 (14.3)
Fluency	18.0 (4.7)	18.6 (4.6)	18.9 (5.0)
HVLT-R	23.7 (5.5)	23.1 (5.6)	22.3 (6.8)
BVMT-R	22.3 (9.1)	24.2 (7.9)	25.1 (7.3)
WMS-III-SS	14.4 (3.8)	15.4 (3.9)	15.8 (3.9)
LNS	12.3 (3.0)	12.0 (3.0)	12.4 (3.5)
NAB Mazes	16.5 (7.9)	18.0 (7.1)	18.9 (7.0)
CPT-IP	1.82 (0.67)	2.11 (0.71)	2.1 (0.5)
MSCEIT-ME	82.0 (10.4)	83.7 (11.7)	84.1 (14.7)
MCCB cognitive tasks (Z-scores)			
TMT	0.26 (1.11)	-0.10 (0.93)	-0.19 (0.92)
BACS-SC	-0.24 (0.98)	0.15 (0.98)	0.12 (1.04)
Fluency	-0.10 (1.0)	0.03 (0.98)	0.09 (1.06)
HVLT-R	0.11 (0.94)	-0.003 (0.96)	-0.13 (1.15)
BVMT-R	-0.18 (1.12)	0.06 (0.97)	0.16 (0.89)
WMS-III-SS	-0.20 (0.99)	0.07 (1.01)	0.16 (0.89)
LNS	0.02 (0.96)	-0.06 (0.96)	0.05 (1.14)
NAB Mazes	-0.16 (1.08)	0.03 (0.97)	0.16 (0.95)
CPT-IP	-0.27 (1.02)	0.17 (1.09)	0.11 (0.81)
MSCEIT-ME	-0.10 (0.86)	0.04 (0.96)	0.08 (1.22)

[†]Risperidone and paliperidone doses were calculated using the international consensus of antipsychotic dosing by Gardner et al., 2010 (Am J Psychiatry 2010; 167: 686-693).

[‡]Higher scores for all cognitive tasks reflect better cognitive performance with the exception of TMT. As TMT is measured in seconds, higher values in this test indicate worse cognitive performance.

Abbreviation: PANSS= Positive and Negative Syndrome Scale; CDSS= Calgary Depression Scale for Schizophrenia; PSP= Personal and Social Performance Scale; TMT= Trail Making Test, Part A; BACS-SC= Brief Assessment of Cognition in Schizophrenia (BACS) Symbol-Coding; HVLT-R= Hopkins Verbal Learning Test – Revised, BVMT-R= Brief Visuospatial Memory Test – Revised; WMS-III-SS= Wechsler Memory Scale – 3rd Ed – Spatial Spain; LNS= Letter-Number-Span; NAB= Neuropsychological Assessment Battery; CPT-CEIP= Continuous Performance Test – Identical Pairs; MSCEIT-ME= Mayer-Salovey-Caruso Emotional Intelligence Test – Managing Emotions.

Table 3. Results of the linear mixed models exploring longitudinal changes in social functioning (PSP scores).

	Model 1 (main analysis)					Model 2 (sensitivity analysis)				
Fixed effects	Estimate	SE	df	t	p	Estimate	SE	df	t	p
Intercept	94.76	6.88	25.07	13.78	<0.001	94.19	6.40	25.62	14.72	<0.001
Time (visit)	3.11	0.66	48.71	4.70	<0.001	4.61	0.87	47.23	5.31	<0.001
Female	-1.34	4.56	23.44	-0.29	0.857	-1.04	4.11	22.27	-0.25	0.803
Age	-0.09	0.17	23.07	-0.53	0.604	-0.03	0.16	21.83	-0.195	0.847
Baseline PANSS negative score	-1.62	0.36	23.13	-4.46	<0.001	-1.66	0.33	21.92	-5.07	<0.001
High PP dose (100 mg or higher vs. lower doses)						-1.11	3.87	49.42	-0.29	0.776
Time × High PP dose						-3.21	1.26	47.60	-2.55	0.014

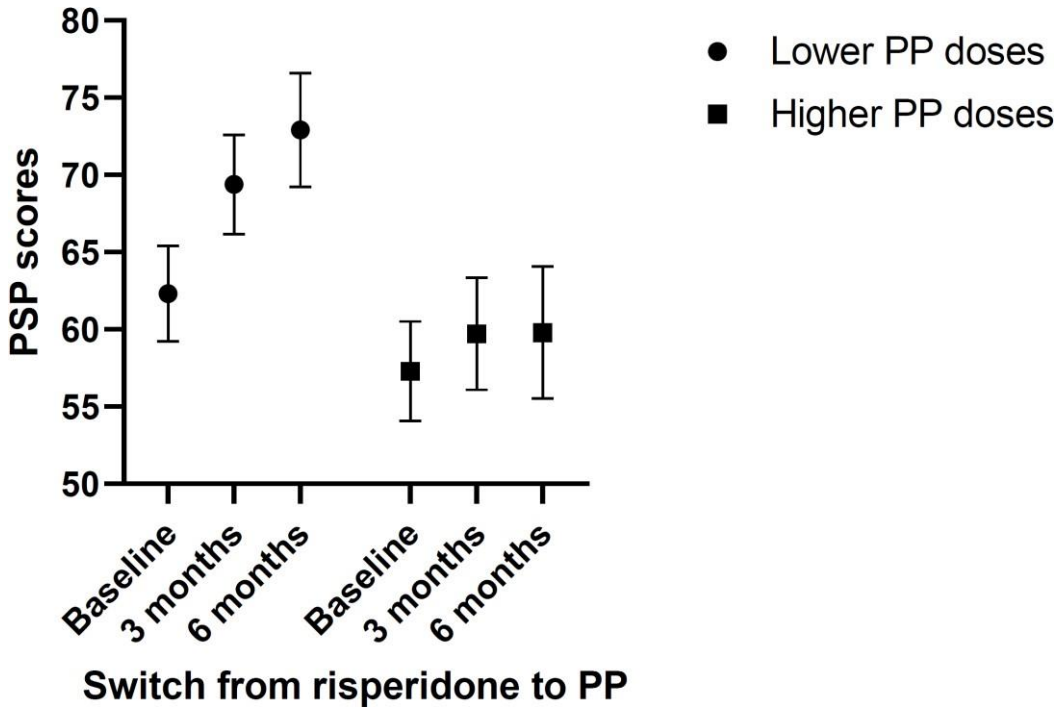
Abbreviations: SE= Standard error; df= degress of freedom; PSP= Personal and Social Performance Scale; PANSS= Positive and Negative Syndrome Scale; PP= Paliperidone palmitate.

Table 4. Results of the linear mixed models exploring longitudinal changes in cognitive functioning.

	Time (visit)		Female		Age		Education level		PANSS negative score (baseline)	
Cognitive task	t	p	t	p	t	p	t	p	t	p
TMT	-3.75	<0.001	-050	0.623	2.22	0.037	-0.37	0.715	3.66	0.001
BACS-SC	4.38	<0.001	0.38	0.710	-1.78	0.089	1.09	0.288	-2.25	0.035
Fluency	1.38	0.174	-0.70	0.493	-0.09	0.927	1.13	0.270	-1.71	0.102
HVLTR-T	-1.62	0.111	1.16	0.259	-1.04	0.309	1.24	0.229	-0.76	0.458
BVMT-R	2.58	0.013	-0.84	0.410	-2.48	0.021	1.40	0.176	0.05	0.964
WMS-III-SS	2.39	0.021	-1.19	0.244	-1.07	0.297	0.26	0.801	-2.56	0.018
LNS	0.61	0.548	-0.17	0.864	-0.86	0.400	1.25	0.226	-1.33	0.201
NAB Mazes	3.73	<0.001	-0.61	0.546	-1.32	0.200	-0.39	0.702	-1.83	0.081
CPT-IP	2.73	0.009	-0.08	0.936	0.03	0.978	0.44	0.662	-0.75	0.464
MSCEIT-ME	0.88	0.384	-0.45	0.659	-1.41	0.174	-0.76	0.456	-1.26	0.221

Abbreviations: PANSS= Positive and Negative Syndrome Scale; TMT= Trail Making Test, Part A; BACS-SC= Brief Assessment of Cognition in Schizophrenia (BACS) Symbol-Coding; HVLT-R= Hopkins Verbal Learning Test – Revised, BVMT-R= Brief Visuospatial Memory Test – Revised; WMS-III-SS= Wechsler Memory Scale – 3rd Ed – Spatial Spain; LNS= Letter-Number-Span; NAB= Neuropsychological Assessment Battery; CPT-IP= Continuous Performance Test – Identical Pairs; MSCEIT-ME= Mayer-Salovey-Caruso Emotional Intelligence Test (MSCEIT) – Managing Emotions

Figure 1. Longitudinal changes in PSP scores after switching from risperidone to paliperidone palmitate among 27 patients with follow-up data.



Abbreviations: PSP= Personal and Social Performance Scale; PP= Paliperidone palmitate

Lower PP doses: 50 mg or 75 mg of PP; higher PP doses: 100 mg or higher doses of PP

Data are represented as the mean ± standard deviation.

CONFLICT OF INTEREST

JL has received honouraria for lectures or advisory boards from Janssen, Otsuka, Lundbeck and Angelini. AGR and AA have received honouraria or paid travel from Janssen, Lundbeck-Otsuka and Angelini.

ETHICS STATEMENT

The study was carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans.

All patients were informed about the study and signed a written informed consent form before participation in the study. Ethical approval was obtained by the Ethics Committee of Parc Taulí Hospital.

CRediT author statement

Meritxell Tost: Data curation, Investigation, Methodology, Resources, Writing - original draft, Writing - review & editing; Alexandre González-Rodríguez: Investigation, Resources; Raquel Aguayo: Investigation, Resources; Aida Álvarez: Investigation, Resources; Itziar Montalvo, Investigation, Methodology, Resources; Juan David Barbero: Investigation, Resources; Rosa Gabernet: Investigation, Resources; Eduard Izquierdo: Investigation, Resources; Igor Merodio: Investigation, Resources; José Antonio Monreal: Resources, Writing - review & editing; Diego Palao, Writing - review & editing; Javier Labad: Conceptualization, Formal analysis, Investigation, Software, Supervision, Visualization, Project administration, Writing - review & editing.

Switching from risperidone to paliperidone palmitate in schizophrenia: changes in social functioning and cognitive performance

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