WILEY Online Library | Stanford University Libraries | Search | Login / Register
Cite an item in Mendeley or Zotero to your library, instead.

Human Psychopharmacology
Clinical and Experimental
Volume 35, Issue 1
January 2020
Print ISSN: 0885-5773
Online ISSN: 1099-1077
Wiley Online Library
Recommended
Neuroscience Insights and Models of Addiction: Interoperability towards a unified vision of addiction
Neuroscience of Addiction: Obstacles, Challenges, and Opportunities in Addiction Neuroscience
Neuroscience of Pain, Reward, Addiction: Review, Models, Theories, Mechanisms
Alcohol Neuroscience Handbook
Psychology and Clinical Neuroscience
Cravings and Craving Management: Neuroscientific, Psychological Insights and Interventions
Cecilia M. Hillemacher, Stefan Kaes, Gerhard Bühringer, Jürgen Rehm, Hans-Jürgen Rumpf, Ulrich John
Human Psychopharmacology: Clinical and Experimental
Cognitive Function in Schizophrenia

Related Journals
Neuroscience Insights: Clinical Medicine
Addiction Neuroscience
Pain Medicine: Neuroscience Perspectives
Psychology and Neuroscience
PMR Physical Medicine and Rehabilitation
Neuroscience Insights: Neuroscience
Neuroscience Insights: Neuroscience Methods
Neuroscience Insights: Neuroscience Ethics

Differential benefits of olanzapine on executive function in schizophrenia patients: Preliminary findings

Hong Ju Jeong | Min-Ho Park | Jun-Young Lee | Jae-Ho Park | Ji-Ho Choi | Jeong-Ho Park | Ji-Hyun Park | Jae-Min Kim

First published: 14 December 2019 | https://doi.org/10.1002/hup.2714 | Citations: 0

Section: Research Paper

Funding information: National Research Foundation of Korea, Grant/Award Number: NRF-2017R1A2B4009410

Tools | Share | Cite | Rate | Email | Print | Save
Add to favorites | Add to collection | Add to my reading list | Add to my citations

Abstract

Objective

Schizophrenia patients show executive function (EF) impairments in voluntary selecting and inhibiting goal-directed behaviors. Olanzapine improves EF in patients with schizophrenia. We hypothesized that olanzapine would improve EF, as measured by antisaccade task performance.

Methods

Patients were tested at baseline (before olanzapine), 3-days post-medication, and 7-days post-medication. We used a mixed-model repeated-measures analysis of variance. Symptoms were assessed by the Positive and Negative Syndrome Scale, and the Brief Psychiatric Rating Scale. Serum levels of olanzapine, prolactin, and cortisol were measured at the antisaccade and 3-days.

Results

Both groups showed improvement on 3-days and antisaccade. However, the olanzapine group showed significantly greater improvement than the control group. Differential benefit of olanzapine on EF performance. Patients with poorer baseline antisaccade performance (high-SAE) showed significantly greater improvement on the antisaccade than low-SAE patients. Olanzapine improved EF performance in patients with schizophrenia, particularly those with poor baseline cognitive impairment and cognitive dysfunction. These findings showed significant and equivalent improvements on PANSS and BPRS scores between groups. Olanzapine-induced prolactin and cortisol levels had no effect on differences in cognitive function between groups.

Conclusions

This preliminary study provides evidence that olanzapine may be most advantageous for patients with poorer baseline EF deficits.

1 INTRODUCTION

In addition to prominent direct symptoms (e.g., hallucinations), schizophrenia patients commonly have cognitive impairments, which include deficits in attention, working memory, and executive function (EF) (Green, 2016; Kahn and Keefe, 2013; Keefe et al., 2006; Keefe et al., 2007; Orellana & Slachevsky, 2013). Many schizophrenia patients show such cognitive deficits even before the first psychotic episode (Bilder et al., 2000; Cannon et al., 2002; Fusar-Poli et al., 2012; Green & Harvey, 2014). Cognitive impairments are thought to be a prominent feature of psychotic symptoms (Hoege Carrion et al., 2006; Ortiniquez et al., 2013). Executive function (EF) is a cognitive function that controls and regulates other cognitive functions, such as participating in continually activated behaviors, intentional behaviors, flexible functions, (Miyake, et al., 2000), and thus, are important to consider when treating patients (Dell, 2004; Ortiniquez et al., 2013; Orellana & Slachevsky, 2013; Stuss & Alexander, 2000).

Clinical studies have shown that cognitive deficits in schizophrenia increase when patients are treated with typical antipsychotics (Keefe et al., 2006; Keefe et al., 2007). Atypical antipsychotics are thought to improve cognitive function, particularly EF, more than typical antipsychotics (Keefe et al., 2006; Ortiniquez et al., 2013). Executive function (EF) is a cognitive function that controls and regulates other cognitive functions, such as participating in continually activated behaviors, intentional behaviors, flexible functions, (Miyake, et al., 2000), and thus, are important to consider when treating patients (Dell, 2004; Ortiniquez et al., 2013; Orellana & Slachevsky, 2013; Stuss & Alexander, 2000).

The beneficial cognitive effects of atypical medications make them an appealing choice for treatment of schizophrenia (Keefe et al., 2006; Keefe et al., 2007). Olanzapine is a relatively inexpensive drug, widely used, considered to be Type II (Labelled off-patent drugs) and has a relatively low risk of side effects (Leucht et al., 2009; Leucht et al., 2013; Woodchurch, Puckett, Bishop, & Cates 2009). The beneficial effects of olanzapine on cognitive function have been well established (Keefe et al., 2006; Keefe et al., 2007). Olanzapine has shown advantages in EF compared with typical and atypical drugs (McGurk, Lee, Jayathilake, & Meltzer, 2004), and similar studies show similar benefits (Fujiwara et al., 2010 and Ozal et al., 2005). Olanzapine improves EF in patients with schizophrenia, including working memory, cognitive flexibility and reasoning ability (Lee et al., 2005; Tollefson, Lesem, & Walk, 2000).

A better understanding of the cognitive improvement associated with olanzapine is important because cognitive impairments are a major factor in the functional disability of schizophrenia patients (Richards & Nowlis, 2000; Green, 2000; Jahn & Nuelle, 2015). The mechanism seems are a trial and selective technique for assessing consumptions and preferences of the patient's cognitive function (Richards & Nowlis, 2000; Green, 2000). The antisaccade task is used to measure impairment in executive function (EF) in schizophrenia patients commonly have a higher rate of antisaccade errors than controls (Jazy, Wenzel, & Gaebel, 2004; Gaebel, Zerbin, & Wagner, 2011). Patients with schizophrenia show antisaccade task impairment in several processes, including suppression of reflexive saccades, such as voluntary inhibition of goal-directed behaviors, and working memory (Gaebel, Zerbin, & Wagner, 2011; Gaebel, Zerbin, & Wagner, 2011; Gaebel, Zerbin, & Wagner, 2011;

Unadjusted average pro- and antisaccade latencies and their SDs for Low-Deficit and High-Deficit subgroups at Day 0 and Day L testing sessions are reported in Table 3. There were no significant Session, Subgroup, or Subgroup by Session effects or interactions for prosaccade or antisaccade latency in the Low-Deficit and High-Deficit subgroups (all $p's > .20$).

3.3.4 Antisaccade error rate subgroup comparisons

Unadjusted average antisaccade error rates and their SDs for Low-Deficit and High-Deficit subgroups at Day 0 and Day L testing sessions are reported in Table 3. Main effects of Subgroup ($F_{1,12} = 10.97$, $p < .01$), Session ($F_{2,24} = 26.02$, $p < .0001$), and their interaction ($F_{2,24} = 7.83$, $p < .01$) on antisaccade error rate were statistically significant (Figure 3c). Planned comparisons indicated that both subgroups showed significant improvements in antisaccade errors across sessions (Day 0 to Day L; $t(24) = -2.92$, $p < .01$, Cohen's $d = 0.61$ and $t(24) = -7.11$, $p < .0001$, Cohen's $d = 1.48$ for Low-Deficit and High-Deficit subgroups respectively). There was also a significant difference between subgroups across sessions, with the Low-Deficit subgroup showing a significantly smaller reduction in antisaccade error rate (mean improvement of 6.8) from Day 0 to Day L than the High-Deficit subgroup (mean improvement of 17.0) ($t(24) = 2.96$, $p < .01$, Cohen's d for difference = 0.62) (Figure 3d). This finding is consistent with the significant correlation between baseline antisaccade error rate and antisaccade error rate change across sessions.

4 DISCUSSION

4.1 Summary of eye-movement and clinical results

Treatment with OLZ resulted in significant improvements in executive function as measured by performance on an eye-movement task (antisaccade), while showing no effects on sensorimotor performance (prosaccade task). The magnitude of the improvement on antisaccade errors was significantly correlated with the magnitude of the baseline deficit on the antisaccade task. In contrast, changes in Stroop and PANSS scores did not significantly correlate with baseline deficit on antisaccade task. Further, on the antisaccade task, the High-Deficit patient subgroup improved more (greater reduction in antisaccade errors) across sessions than the Low-Deficit subgroup, indicating that treatment with OLZ resulted in significantly greater improvement in patients who were most impaired at baseline. In contrast, there was no significant difference across sessions in the Stroop task for the Low-Deficit and High-Deficit subgroups. These results suggest that antisaccade task performance may be a more sensitive measure of executive function change than the neuropsychological Stroop task. The High- and Low-Deficit patient subgroups also did not differ in magnitude of clinical improvement (as measured by the PANSS) during treatment with OLZ, indicating that the improvement in executive function was not dependent on the magnitude of improvement in severity of clinical symptoms.

4.2 Measuring executive function

Both the antisaccade task and Stroop task are considered measures of executive function (Diamond, 2013; Everling & Fischer, 1998) that require inhibition of a prepotent or reflexive response and the generation of another action, although the exact processes involved remain debatable (Cutsuridis et al., 2014). One possible explanation for the differences in sensitivity of the two tasks is that the Stroop task involves more complex visual stimuli, involvement of word processing, and longer response durations than simple eye-movement tasks, increasing variability and introducing additional sources of heterogeneity. Recent modeling of spatial attention and memory (Patel, Red, Lin, & Sereno, 2015) has demonstrated that even when both processes share a common neural substrate, a simple (single) disruption of the network resulted in the appearance of a dissociation between memory and attentional processes. Without additional physiological or behavioral evidence that can specify involvement of precise neural substrates or separable cognitive processes, it is reasonable to interpret poor performance on the antisaccade and Stroop to indicate a deficit in cognition or executive function, more specifically. Nevertheless, our findings do suggest that the antisaccade task may be a more robust or sensitive measure of executive function changes than the Stroop task.

4.3 Concerns about practice effects

Other studies assessing cognitive improvements on neuropsychological tests during treatment with atypical psychotics have reported significant practice effects of repeated neuropsychological assessments (T. E. Goldberg et al., 2007), which complicates the interpretation of whether these drugs truly improve executive function per se, or reflect practice effects. On the antisaccade task only, we demonstrate that the schizophrenia patients show greater improvement than control participants (Figure 1d), consistent with improvement beyond practice or ceiling effects.

4.4 Olanzapine versus typical antipsychotics

Previous work has demonstrated that treatment with OLZ results in greater overall improvement in executive function than haloperidol does (Leucht, Pitschel-Walz, Abraham, & Kissling, 1999). Our findings that treatment with OLZ improves executive function in both High-Deficit and Low-Deficit subgroups are in agreement. All schizophrenia patients showed a reduction in antisaccade errors regardless of the magnitude of their baseline impairment. This finding contrasts with a previous report examining the effects of the typical neuroleptic haloperidol (Babin et al., 2011), which showed that haloperidol improved antisaccade task performance only in schizophrenia patients who were more impaired before treatment but worsened performance in patients who were less impaired before treatment, resulting in a U-shaped effect of haloperidol on antisaccade error rates. Similar effects in patient subgroups were only partially reflected in performance on the Stroop task (i.e., no change for the overall patient group; marginally significant worsened performance for low-deficit patients; and non-significant improvement for high-deficit patients).

A sigmoid function is common in drug response profiles (McKim, 2002). We have previously shown that if one assumes that the sigmoidal drug response profiles are different for participants who have different baseline responses, then a simple model can explain the differential inverted-U shaped effect of haloperidol on antisaccade error rates in schizophrenia patients (Babin et al., 2011). In that model, we assumed that increasing haloperidol dose would *increase* or overall negatively impact antisaccade error rates (or executive function) and that more cognitively intact patients may be more resilient to the cognitive effects of the drug. In the model here, we assume that increasing olanzapine dose will *reduce* antisaccade error rates and that the normalizing effect of olanzapine on error rate starts at a lower dose. Similar to haloperidol, we assume that the magnitude of the drug effect increases with dose in those subjects whose baseline cognitive deficit (i.e., antisaccade error rate) is worse (see Figure 4a). Figure 4b illustrates an example relationship between baseline error rate and change in response from baseline for administered dose illustrated in Figure 4a—the larger the baseline error rate, the greater the difference between baseline and Day L performance. In other words, Figure 4b illustrates that the magnitude of the improvement is significantly greater in the high deficit subgroup than the low deficit subgroup. Notably, in contrast to the haloperidol model, neither subgroup shows worsened performance. Our data shown in Figure 2 are consistent with this model.

Figure 4 Open in figure viewer | PowerPoint

Hypothetical sigmoidal dose–response curves for numerous participants that differ in their initial baseline performance on the antisaccade task. (a) Each curve represents the hypothetical change in per cent error for a participant on the antisaccade task as a function of a drug dose, such as olanzapine. The vertical dotted line represents the actual dose that may be administered to all participants. It is clearly seen that the change in per cent error from no dose (0) to administered dose depends on the participant's initial baseline performance. The change in per cent error increases as we move from the bottom curves to the top curves. To obtain all of the sigmoidal curves, we systematically varied two parameters: (1) The baseline response curve and (2) the dose at which the performance changes, with the assumption here being that the more cognitively intact patients (represented by curves near the bottom) may be more resilient to the cognitive effects of the drug. (b) Example relationship between baseline (Day 0) response and change in response from the baseline obtained from the hypothetical dose–response curves and the administered dose illustrated in Figure 4a

The difference in binding mechanisms between haloperidol and olanzapine may also play a role in the contrasting results of haloperidol and olanzapine on antisaccade performance. Although both medications block dopamine transmission at the D2 receptor, olanzapine's strong affinity for and activation of serotonin receptors may contribute to its beneficial effect on cognitive performance even in the lower deficit subgroup (Meltzer & Massey, 2011). Serotonergic mechanisms may be involved in improved antisaccade performance in patients regardless of severity of cognitive impairment. That is, serotonergic mechanisms may compensate for the deleterious effects of dopaminergic blocking in the low deficit subgroup whereas in the high deficit subgroup, serotonergic mechanisms may add further benefit to the beneficial effects of dopaminergic blocking in these more cognitively impaired patients. Therefore, these findings suggest that olanzapine, unlike haloperidol, may be beneficial even for schizophrenia patients who are less impaired.

4.5 Regression toward the mean

We find that the change in antisaccade error rate with OLZ treatment is dependent on baseline error rate, that is, during treatment with OLZ the High-Deficit subgroup had a larger reduction than the Low-Deficit subgroup. An alternative explanation is that there is no effect of medication and that improvement over time is merely regression to the mean. Taking these findings by themselves, such an interpretation is possible. However, we think this interpretation unlikely for several reasons. First, we observed a significantly greater reduction in error rate in the schizophrenia group as a whole compared to the controls across sessions. Although one might argue this is a "regression-toward-the-mean" group effect, this group effect across session did not occur in a prior study using the exact same tests, apparatus, and conditions (e.g., in the same inpatient ward) examining treatment with haloperidol in schizophrenia patients (Babin et al., 2011). Further, in the Babin et al. study, the low deficit schizophrenia subgroup actually became more impaired during treatment with haloperidol than at baseline, whereas the high deficit group showed a reduction in errors. Treatment with OLZ, in contrast, resulted in significant greater improvement in antisaccade performance in both patient subgroups. Hence, there are differential treatment effects across sessions and sessions by subgroups in these studies. Demonstrating that baseline antisaccade error rates (i.e., the measure defining low and high deficit patients) result in different antisaccade error rate changes, depending on medication treatments, in these subgroups, suggests that changes with treatment cannot simply be explained by regression to the mean. That is, low-deficit patients show improvement with olanzapine treatment but greater impairment with haloperidol. Finally, the baseline performance model that we have proposed is simple and can explain both haloperidol and olanzapine findings without assuming there is regression to the mean in one but not the other study. The only thing we alter in the model is that one drug is beneficial and the other is not beneficial with respect to executive function. Additional work with more patients, perhaps in a cross-over design, directly comparing medications such as haloperidol and OLZ in the same populations of low and high deficit patients would help to tease apart how medications are influencing the findings and test whether baseline cognitive performance can predict medication efficacy in improving executive function.

4.6 Future directions and limitations

Although OLZ treatment results in beneficial effects on executive function, some caution is warranted, given the metabolic side effects of OLZ. In addition, it would be interesting to examine whether the short-term effects of OLZ we observed on cognition are lasting and stable. Although our sample sizes are small, as clinical practice moves toward individualized treatment plans, it is critical that biobehavioral measures are sensitive and reliable *at an individual level*. Further, small sample sizes have long been used when measuring eye-movements in schizophrenia patients (for recent work see: Meyhofer et al., 2017; Seymour et al., 2017; Thakkar et al., 2018). We use eye-movement measures in the present study to examine the effect of a drug treatment and demonstrate robust preliminary findings that significant differences can be observed using the antisaccade task. In addition to having a small sample, our sample, on average, had relatively late age of onset (29.8 years) and short duration of illness (7.2 years). Additional work with larger samples, that vary systematically in relevant clinical dimensions (e.g., positive vs. negative symptomology, age of onset, and duration of illness) will be needed to see to how these changes in antisaccade performance relate to other variables (e.g., clinical measures, drug response, pharmacological profile) and to what extent the findings are generalizable.

Though previous work has divided schizophrenia patients into at least three cognitive subgroups (Hall et al., 2012; Lewandowski, Sperry, Cohen, & Ongur, 2014; Ohi et al., 2017), based on performance on the antisaccade task, we selected a median split of schizophrenia patients into High-Deficit and Low-Deficit subgroups due to the small sample size. It is possible that some other method of generating meaningful subgroups in a larger sample may be informative.

5 CONCLUSIONS

We show that olanzapine, unlike haloperidol, improves the executive function component of cognition in all schizophrenia patients, as measured by the antisaccade task. Patients with greater cognitive deficits before treatment showed greater cognitive improvements than those with lesser deficits. Given that cognition is one of the strongest predictors of long-term prognosis in schizophrenia patients, these findings suggest that olanzapine may have certain advantages especially in patients with more severe cognitive deficits. Additional studies with larger samples would clarify the robustness of the preliminary findings reported here.

ACKNOWLEDGMENTS

The authors would like to thank Stuart Red for training and guidance on project related procedures, and Eliana Klier for valuable comments on the manuscript. The authors would also like to thank Nina G. Williams and Al Sillah for their assistance in aspects of data collection. This work was supported by the National Alliance for Research on Schizophrenia and Depression Investigator Award (ABS).

AUTHOR CONTRIBUTIONS

N.M. worked on data collection, data analysis, and manuscript preparation and review. M.W. was involved in manuscript preparation and review. S.B. contributed to the study design, data collection, and initial analysis. S.P. was involved in data analysis and manuscript review. A.W. contributed to subject recruitment, clinical testing, evaluation and diagnosis. A.C. worked on data analysis and manuscript preparation and review. A.S. contributed to study formulation, design, data collection and analysis, and manuscript preparation. All authors contributed by drafting parts of the work, have approved the final version, and agreed to be accountable for all aspects of the work.

CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationship that could be construed as a potential conflict of interest.

REFERENCES

Citing Literature

Download PDF

ABOUT WILEY ONLINE LIBRARY
Privacy Policy
Terms of Use
About Cookies
Manage Cookies
Accessibility
Wiley Research DE&I Statement and Publishing Policies

HELP & SUPPORT
Contact Us
Training and Support
DMCA & Reporting Piracy
Sitemap

OPPORTUNITIES
Subscription Agents
Advertisers & Corporate Partners

CONNECT WITH WILEY
The Wiley Network
Wiley Press Room

WILEY

Copyright © 1999-2026 John Wiley & Sons, Inc or related companies. All rights reserved, including rights for text and data mining and training of artificial intelligence technologies or similar technologies.