Psychiatry Research 279 (2019) 109–110

Contents lists available at ScienceDirect

Psychiatry Research

journal homepage: www.elsevier.com/locate/psychres

Comment on "Therapeutic effect of sertindole on neurocognitive deficit independently of positive and negative symptoms response: A case report"

To the Editors:

We read with great interest the article by Fountoulakis (2017) about the potential therapeutic effect of sertindole on cognitive deficits in schizophrenia.

Cognitive deficits, mainly in the domains of executive functions, episodic memory, and speed of processing or attention, have been consistently reported in schizophrenia patients, mostly independent of phases of illness, often preceding the onset of other symptoms, and they are currently viewed as a core, enduring feature of the illness. *The benefit for cognitive dysfunctions from available antipsychotics is limited*; currently, there are no approved *treatments for* cognitive symptoms in schizophrenia. Thus, restoring cognition functioning in people with schizophrenia represents an urgent unmet need, and finding treatment options aimed at addressing cognitive impairments is a priority for research.

Sertindole is an atypical antipsychotic approved in the EU for once-daily use in patients with schizophrenia who are intolerant to at least one other antipsychotic agent.

Despite sertindole's demonstrated efficacy in treating positive and negative symptoms, cardiac safety remains a major concern when considering it for the treatment of schizophrenia (Spina and Zoccali, 2008; Muscatello et al., 2010, 2014; Zoccali et al., 2015).

The effectiveness of sertindole on cognition needs further clarification. Sertindole was more effective than haloperidol in improving cognitive functions (Gallhofer et al., 2007), *because the effect of haloperidol on cognition is, at best, neutral and, at worst, deleterious, the choice of comparator drug in this study is problematic.* Sertindole was further compared with olanzapine without demonstrating efficacy on cognition in a study which has included only nine patients (four completers, *two* in the sertindole group and *two* in the olanzapine group) (Nielsen et al., 2014). Nevertheless, a simple pairwise and multiple-treatment (MT) *meta-analyses surprisingly* states that sertindole had a positive effect on executive function compared to clozapine, olanzapine, ziprasidone, and first-generation antipsychotics (FGAs), although such findings were almost exclusively driven by the results of the haloperidol study (Nielsen et al., 2015).

In his case report, Fountoulakis (2017) showed that a female patient with refractory schizophrenia, to be considered moderately ill, and almost cognitively preserved according to baseline PANSS scores (total score = 75, disorganized/concrete or cognitive factor subscore = 5), significantly improved in neurocognitive functioning after one month of sertindole treatment, as assessed by neuropsychological measures. *Table 1 shows that the average change of all 8 tests was 21% with up to 37.5% improvement in 3 out of 8 neurocognitive indices, including the cube and the clock test. The Author's conclusion is that* the improvement was independent from clinical symptoms, which remained unchanged. *Nevertheless, no statistical significance values were reported for neurocognitive measures, and a change of −12.50% and −12.82% was described in Negative and General Psychopatology PANSS subscales, respectively.*

Although interesting, *such a* finding raises several concerns of methodological nature. When investigating executive and cognitive functions, the length of the test-retest intervals should be chosen with the aim of reducing possible sources of bias that may affect a person's performance on executive and cognitive tasks, such as procedural learning, development of test-taking strategies (*e.g.,* deep encoding, and/or practice effects (Bartels et al., 2010)). Practice effects are defined as increase in a subject's test score from one administration to the next; common causes of practice-induced score gains are recall effects, procedural learning, reduced anxiety in or growing familiarity with the testing environment. Retest scores are assumed to be highest at short intervals and decrease with time. Regarding the different cognitive domains, executive functions showed highest score increases over time as a result of a higher repetition rate or the use of less alternate forms (Bartels et al., 2010). *Furthermore, a robust set of findings shows that larger practice effects are generally observed between the initial and second assessments, independently of diagnostic groups: in schizophrenia patients treated with second-generation antipsychotics, practice effects are not different from healthy controls (Goldberg et al., 2010).*

When considering the patient's cognitive improvement at one-month retest, the possibility that the observed improvement was due the efficacy of sertindole is highly questionable, because the length of the test–retest interval is too short, and the role of practice effects has not been taken into account. *Moreover, although the Author stated that the observed cognitive improvement was independent of the response in clinical symptoms, negative and general psychopathology symptoms were reduced after one-month treatment (see Table 1). Thus, it is not possible to exclude an indirect effect of negative symptoms reduction on cognitive improvement. In clinical practice, the above aspects can constitute confounding factors and can lead to incorrect conclusions about patient's changes in cognitive functioning over time.*

Since cognitive deficits are a core feature of schizophrenia, neuropsychological assessment now occupies a key place in a substantial number of clinical trials of antipsychotics. In clinical studies that monitor cognitive changes across time, or that assess the effectiveness of an intervention, practice effects can easily lead to false conclusions and inaccurate estimates of change, if not correctly integrated into interpretation of cognitive results. In intervention studies, treatment effects might be overestimated, particularly if the study sample is underpowered (case reports, case series, small samples), and in the absence of an adequate control group. On the other hand, since practice effects usually lead to better scores at retesting, in longitudinal studies they may result in underestimation of cognitive decline, and diseases characterized by slow deterioration of cognitive abilities can go undetected.

https://doi.org/10.1016/j.psychres.2018.02.044
Received 9 October 2017; Received in revised form 5 December 2017; Accepted 19 February 2018
Available online 30 March 2018
0165-1781/

On the basis of such sparse and incomplete evidence, the effective role of sertindole in treating cognitive dysfunctions remains to be further explored and firmly established, and head-to-head comparisons with other second-generation antipsychotics (SGAs) in independent, double-blind, randomized, and well-powered clinical trials are needed.

References

Bartels, C., Wegrzyn, M., Wiedl, A., Ackermann, V., Ehrenreich, H., 2010. Practice effects in healthy adults: a longitudinal study on frequent repetitive cognitive testing. BMC Neurosci. 11, 1–18.

Fountoulakis, K.N., 2017. Therapeutic effect of sertindole on neurocognitive deficit independently of positive and negative symptoms response: a case report. Psychiatry Res. S0165–1781 (17), 30280–30289.

Gallhofer, B., Jaanson, P., Mittoux, A., Tanghøj, P., Lis, S., Krieger, S., 2007. Course of recovery of cognitive impairment in patients with schizophrenia: a randomised double-blind study comparing sertindole and haloperidol. Pharmacopsychiatry 40, 275–286.

Goldberg, T.E., Keefe, R.S., Goldman, R.S., Robinson, D.G., Harvey, P.D., 2010. Circumstances under which practice does not make perfect: a review of the practice effect literature in schizophrenia and its relevance to clinical treatment studies. Neuropsychopharmacology 35, 1053–1062.

Muscatello, M.R., Bruno, A., Pandolfo, G., Micò, U., Settineri, S., Zoccali, R., 2010. Emerging treatments in the management of schizophrenia - focus on sertindole. Drug Des. Dev. Ther. 4, 187–201.

Muscatello, M.R., Bruno, A., Micali Bellinghieri, P., Pandolfo, G., Zoccali, R.A., 2014. Sertindole in schizophrenia: efficacy and safety issues. Exp Opin. Pharmacother. 15, 1943–1953.

Nielsen, R.E., Odur, F., Ostergaard, T., Munk-Jørgensen, P., Nielsen, J., 2014. Comparison of the effects of Sertindole and Olanzapine on cognition (SEROLA): a double-blind randomized 12-week study of patients diagnosed with schizophrenia. Ther. Adv. Psychopharmacol. 4, 4–14.

Nielsen, R.E., Levander, S., Kjaersdam Telléus, G., Jensen, S.O., Østergaard Christensen, T., Leucht, S., 2015. Second-generation antipsychotic effect on cognition in patients with schizophrenia-a meta-analysis of randomized clinical trials. Acta Psychiatr. Scand. 131, 185–196.

Spina, E., Zoccali, R., 2008. Sertindole: pharmacological and clinical profile and role in the treatment of schizophrenia. Expert Opin. Drug. Metab. Toxicol. 4, 629–638.

Zoccali, R.A., Bruno, A., Muscatello, M.R., 2015. Efficacy and safety of sertindole in schizophrenia: a clinical review. J. Clin. Psychopharmacol. 35, 286–295.

Maria Rosaria A. Muscatello*

Psychiatry Unit, Department of Biomedical and Dental Sciences and Morphofunctional Imaging, University of Messina Azienda Ospedaliera Universitaria "G. Martino", Via Consolare Valeria n. 1, 98125 Messina, Italy

E-mail address: mmuscatello@unime.it

Antonio Bruno

Psychiatry Unit, Department of Biomedical and Dental Sciences and Morphofunctional Imaging, University of Messina, Messina, Italy

Rocco A. Zoccali

Psychiatry Unit, Department of Biomedical and Dental Sciences and Morphofunctional Imaging, University of Messina, Messina, Italy

* Corresponding author.