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Efficacy of Auditory Processing–Focused Cognitive Remediation Therapy

To the Editor: In the June 2016 issue of the *Journal*, Kantrowitz et al[1] reported that "the change from prestabilization was statistically significant for MCCB composite score"[1(p799)] for patients who were randomized and completed at least 1 cognitive remediation therapy (CRT) vs video game control session, with $d = 0.42$ and $P < .001$ based on 1-sample paired t test across the 2 randomized groups (see the abstract and the Results under "Cognitive remediation period" heading). This methodology is fundamentally flawed in that (*a*) the 2 randomized groups should not be pooled, as this is in conflict with the design of the study and reduces interpretability of the study results; (*b*) the significant reported differences between the groups at randomization baseline add to the difficulty in pooling these groups; (*c*) the assessment of the true effect of CRT (vs nonspecific control) in this study would require estimation of change in MATRICS Consensus Cognitive Battery (MCCB) scores from the randomization baseline (week 8), not the prestabilization baseline (week 0) as reported by Kantrowitz et al[1]; and (*d*) the application of a 1-sample paired t test to 2 independent samples in a randomized controlled design violates the basic statistical analysis principle that the choice of statistical test should be governed by the study design.

It can be shown that the effect size $d = 0.42$ for change from prestabilization [= C – A] as reported by Kantrowitz et al[1] is the sum of 2 components (C – B) + (B – A): (1) the effect of lurasidone monotherapy on MCCB composite score compared with *prestabilization* baseline [= B – A, $d_{\text{lurasidone}} = (32.3 - 29)/11.3 = 3.3/11.3 = 0.29$, $P < .001$] (Tables 1 and 2 in the article)[1] and (2) the effect of CRT or video game control combined with lurasidone treatment on MCCB composite score compared with the *randomization* baseline [= C – B, $d_{\text{CRT or video game}} = (33.8 - 32.3)/11.3 = 1.5/11.3 = 0.13$] (Table 2).[1] Therefore, nearly 70% of the effect size for MCCB composite score ($d = 0.42$) was associated with lurasidone treatment before randomization, which is consistent with the observed effect size of 0.37 at week 6 for lurasidone versus placebo in Harvey et al.[2] The remaining 30% ($d_{\text{CRT or video game}} = 0.13$) was associated with cognitive remediation or video game sessions in combination with lurasidone treatment in the period after randomization. Attribution of the change in MCCB score to the relevant study treatment intervention is obscured by reporting the change from prestabilization baseline to study endpoint without regard to study phase or specific treatment within each phase.

In addition, Kantrowitz et al[1] noted that the CRT group had significantly better MCCB domain scores (for visual learning and reasoning and problem solving) at randomization baseline compared to the video game control group. The between-group difference at randomization trended toward significance for MCCB composite score favoring the CRT group ($P = .08$). These randomization baseline differences can only have resulted from randomization failure (not "retrospective" differences in randomized group change during the stabilization phase); this can arise due to site-based randomization with many incomplete blocks for sites with few subjects. The significant trend and the small-to-moderate effect sizes reported for MCCB domains favoring the CRT group at midpoint and/or study completion are misleading because of the bias due to the presence of significant baseline differences at randomization.

Figure 1 in Kantrowitz et al[1] shows parallel and continued improvement from randomization baseline in MCCB composite score during both CRT and video game control sessions combined with lurasidone treatment, indicating that this combined treatment strategy was able to maintain the cognitive benefits achieved in the early lurasidone stabilization phase, perhaps in part by engaging and motivating patients, which in itself may provide cognitive benefit.[3] The authors should acknowledge the significant improvement in MCCB score associated with lurasidone treatment in the stabilization phase, the randomization failure, and the lack of significant between-group differences (comparing CRT vs nonspecific video game control) at study completion in the abstract and the article.

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Dr Kantrowitz and Colleagues Reply

To the Editor: We thank Drs Siu and Agid for their interest in our recent report.[1] Treating cognitive impairments in schizophrenia is important, and we hope to encourage continued research in this area.

Drs Siu and Agid raise several important points of emphasis that we have already covered in detail in our published report. We strongly agree with their assertion that we "should acknowledge the significant improvement in MCCB scores associated with lurasidone treatment in the stabilization phase," as we did so in Table 1 in our published report. We felt that the continued across-group improvement over the full study was also worthy of highlighting. Our reference to the 0.42 effect size was limited to this purpose. One-sample tests were not used to assess the effect of auditory processing–focused cognitive remediation.

Drs Siu and Agid suggest that we should have focused on the fact that this improvement occurred during open-label lurasidone treatment. We agree that a procognitive impact of lurasidone is possible, and we noted this in the abstract and devoted a subsection in the Discussion to this possibility entitled "Impact of Lurasidone." However, we concluded that a direct relationship between lurasidone and cognitive improvement was possible but difficult to clearly interpret from the results of this study because, as we pointed out, "all participants were receiving lurasidone open label," in contrast to the placebo-controlled, randomized study[2] cited by Drs Siu and Agid.

Additionally, we also agree that the "between-group difference at randomization," mentioned by Siu and Agid, in several MCCB domains was important to highlight. Accordingly, the trend-level difference was mentioned in the abstract Results subsection and, moreover, discussed at length in the Results and in a subsection of the Discussion entitled "Between-Group Differences at Randomization."

Finally, we also agree that it was important to highlight that there were no "significant between-group differences" between auditory-focused treatment and nonspecific control "at study completion." In fact, this was also clearly stated in the abstract, Results, and Discussion. The study was limited by having all subjects receive open-label lurasidone, and future studies should consider a 2-by-2 design.

References

1. Kantrowitz JT, Sharif Z, Medalia A, et al. A multicenter, rater-blinded, randomized controlled study of auditory processing–focused cognitive remediation combined with open-label lurasidone in patients with schizophrenia and schizoaffective disorder. *J Clin Psychiatry*. 2016;77(6):799–806.
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