Effects of augmentation agents in autistic disorder patients treated with risperidone: a systematic review and a meta-analysis

Efeito de estratégias de potencialização da risperidona em pacientes com transtorno do espectro autista: revisão sistemática e metanálise

Different studies highlight the importance of augmentative strategies to risperidone as an effective pharmacological approach for treating behavioral symptoms associated with autistic spectrum disorder (ASD).[1] The objective of the present study was to assess the combined clinical effects of different add-on pharmacological therapies to risperidone in the management of patients with ASD.

After searching MEDLINE and EMBASE databases, we performed a systematic review following the PRISMA statement guidelines.[2] We also looked for controlled trials by contacting experts and searching the website clinicaltrials.gov. The criteria used to select articles were: 1) English language; 2) randomized, controlled trials; 3) mean and standard deviation values provided; and 4) response and remission rates provided. We excluded controlled trials assessing therapies different from our study objective. We opted to use Hedges' g to measure the effect size as it is appropriate for small sample sizes. The pooled effect size was weighted by the inverse variance method and measured under the random effect model. Heterogeneity was assessed using I^2 index. We further used funnel plots to check for the existence of publication bias.

A total of 6 out of 51 randomized controlled trials met the eligibility criteria (n = 231, mean age = 8.25 years)[3-9] (Table 1). In each trial reporting autistic symptoms, patients were clinically assessed by the Aberrant Behavior Checklist – Community version (ABC-C).[10] Association of drugs with risperidone included: amantadine, N-acetylcysteine, topiramate, pentoxifylline, riluzole, and celecoxib.

Considering continuous reductions of autistic symptoms based on ABC-C scores, we found a significant clinical difference between the active control group and the placebo group for the irritability domain (Hedge's g = 1.23; 95% confidence interval [95%CI] 0.825-1.641; p = 0.000) and lethargy domain (Hedge's g = 0.735; 95%CI -0.163-1.307; p = 0.02). No significant difference was found for hyperactivity (Hedge's g = 0.651; 95%CI -0.098-1.402; p = 0.08) or stereotypic movements (Hedge's g = 0.892; 95%CI -0.021-1.806; p = 0.056) (Figure 1).

Table 1 - Demographic characteristics and clinical protocols

Author	Year	Placebo (n)	Active (n)	Mean age (y)	Augmentation strategy	Active dosage (mg/d)	Risperidone dosage (mg/d)
Mohammadi et al.[10]	2013	20	20	8	Amantadine	100-150	1-2
Ghanizadeh et al.[8]	2013	17	14	9.5	NAC	0.76	0.92
Rezaei et al.[4]	2010	20	20	7.5	Topiramate	150	2.5
Akhondzadeh et al.[3]	2010	20	20	8	Pentoxifylline	500	2.5
Ghaleiha et al.[7]	2013	20	20	8.5	Riluzole	1.2	1.6
Asadabadi et al.[5]	2013	20	20	8	Celecoxib	300	3

NAC = N-acetylcysteine; y = years.

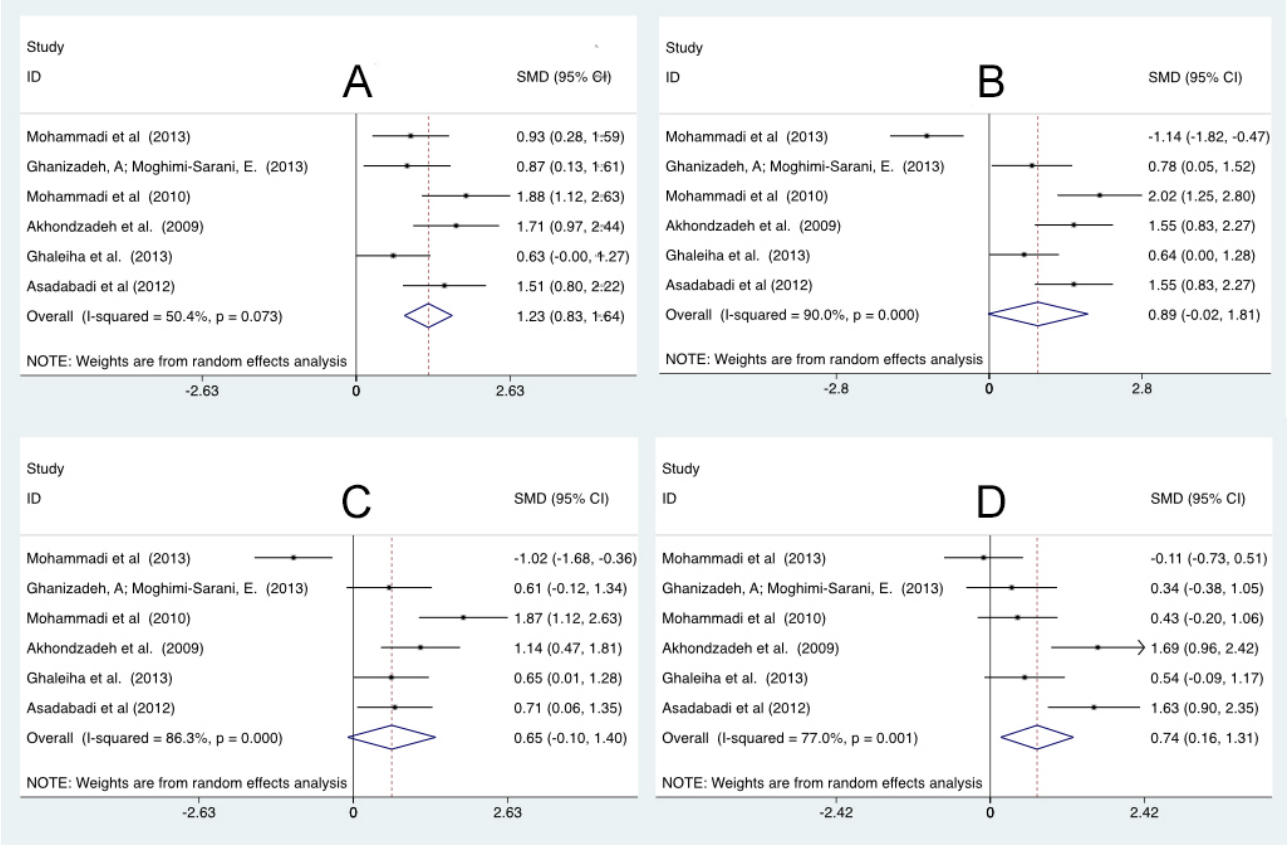

Figure 1 - Forest plot of effect sizes (Hedges' g) for active versus placebo group treatment: A) irritability; B) hyperactivity; C) stereotypic behavior; D) lethargy. 95%CI = 95% confidence interval; SMD = standardized mean difference.

Statistical analysis underscored the heterogeneity among studies (I^2: 50.4%). Meta-regression analysis for possible confounding factors – such as baseline severity scores, age, sample size, and augmentation strategy – revealed no significant correlation with effect size. All studies were within the limits of Begg & Mazumdar's rank correlation test. Moreover, no study individually influenced the pooled effect size as assessed by the "metainf" command in Stata. In other words, our results suggested no difference between augmentation strategies in the subgroup analysis.

We found augmentation strategies to risperidone to be effective for amelioration of both irritability and lethargy in autistic patients. However, some limitations of the study – such as small number of trials and high heterogeneity – are factors that compromise its external validity. Nevertheless, we believe that the results presented underscore the benefits of combined therapy in comparison to risperidone alone and may work as a hypothesis-driven scenario for further clinical trials. The effectiveness of augmentation treatments to risperidone and the appropriate robustness of the strategy for treating autism are still unclear.

Augmentation strategies are promising tools for ameliorating both irritability and lethargy in patients with ASD. Further trials with larger samples will help to clarify the precise effects of augmentation strategies for this population.

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