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Letter to the Editor

Sodium nitroprusside for schizophrenia: could methodological variables account for the different results obtained?

We read with interest the paper by Stone *et al.* (2016) about the effect of sodium nitroprusside (SNP) in patients with schizophrenia. It was a controlled trial where 20 subjects on antipsychotics received an infusion of SNP (0.5 μg/kg per min for 4 h) or placebo. The participants were assessed at baseline, immediately after the infusion, and 4 weeks later. No differences in outcomes were found between SNP and placebo (Stone *et al.* 2016).

Previously, we reported that SNP displays antipsychotic activity in animal models of schizophrenia (Bujas-Bobanovic *et al.* 2000; Maia-de-Oliveira *et al.* 2015*a*) and in schizophrenia patients taking antipsychotics (Hallak *et al.* 2013; Maia-de-Oliveira *et al.* 2014). We found that SNP improved some cognitive deficits in schizophrenia patients (Maia-de-Oliveira *et al.* 2015*b*) and long-term ketamine-induced memory deficits in rats (Kandratavicius *et al.* 2015). Trevlopoulou *et al.* (2016) reported that SNP attenuated ketamine-induced short-term recognition memory deficits and social isolation in rats.

Stone *et al.* (2016) were not able to replicate our main findings. The authors argued that beneficial effects of SNP may occur in patients with a shorter history of illness, or with more acute exacerbation of symptoms. Hallak *et al.* (2013) used the Bech's version of the Brief Psychiatric Rating Scale that rates from 0 to 4 (Bech *et al.* 1986), while Stone *et al.* (2016) used the Overall & Goram (1962) version, which rates from 1 to 7, suggesting that in the Stone *et al.* (2016) study participants were less symptomatic. Indeed, Hallak *et al.* (2013) worked with subjects with less than 5 years of disease and who were so severely ill they were hospitalized; symptoms were also recorded at baseline and at multiple times between infusion and 4 weeks.

Stone *et al.* (2016) also seem to have worked with a population presenting other features that could potentially affect their final findings such as the presence of two schizo-affective disorder patients and seven subjects currently using cannabis; it was not clear if there was other illicit substance use. Furthermore, the majority of patients were current smokers ($n = 12$). Since it is well known that cigarette smoking induces a reduction in NO (Guo *et al.* 2006; Csordas & Bernhard, 2013), this characteristic may have influenced the SNP efficacy. Moreover, the majority of patients were black ($n = 15$, denoted as 'black British and black other'). Since black Americans and black South Africans have been reported to present with attenuated SNP vascular effects (Stein *et al.* 1997; Pienaar *et al.* 2014), perhaps the same happens concerning SNP's antipsychotic and cognitive effects; it may be inappropriate to compare these groups from three different countries, but it does raise the question of possible ethnic differences in responses to SNP.

In contrast to the Hallak *et al.* (2013) study, Stone *et al.* (2016) found significant reduction of blood pressure and increase in heart rate during the SNP treatment. Could these cardiac alterations have negatively influenced the performance of the SNP group?

We believe that several variables could account for the different results reported, which points out the importance of avoiding possible confounding factors in future studies on this drug.

Declaration of Interest

All of the authors of this letter were also authors on the Hallak *et al.* (2013) paper.

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