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Nitric Oxide Synthase Mediation of Darbepoetin's Cognitive Benefits: A Paradoxical Effect?

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Recently, Kajitani *et al* (2010) reported observations to support that enhanced nitric oxide signaling might be the mechanistic basis for erythropoietin's cognitive benefits in schizophrenia. However, numerous studies have suggested that enhanced nitric oxide signaling might adversely impact schizophrenia. For example, increased nitric oxide signaling has been demonstrated to underlie the information-processing deficits in the phencyclidine model of schizophrenia (Palsson *et al*, 2010); intriguingly, the nitric oxide synthase inhibitor (N (G)-nitro-L-arginine methyl ester (L-NAME)) used by the authors in this study (Kajitani *et al*, 2010) has been reported to ameliorate the phencyclidine-induced cognitive deficits (Klamer *et al*, 2001). Moreover, treatment with minocycline, a nitric oxide synthase inhibitor, improved cognitive deficits in schizophrenia patients in a double-blind, randomized, placebo-controlled study (Levkovitz *et al*, 2010). Also, neuronal nitric oxide synthase haplotype association with schizophrenia has been speculated as an instance of increased predisposition towards this devastating disorder, yet also improving cognitive domains (Reif *et al*, 2006). Contextually, it is important to note that the beneficial effects of erythropoietin on cognitive deficits in schizophrenia have been demonstrated in patients that were stabilized with antipsychotic treatment; these patients did not have severe positive symptoms (Ehrenreich *et al*, 2007). If the enhanced nitric oxide signaling is indeed the predominant mechanistic basis for erythropoietin's benefits (Kajitani *et al*, 2010), then, this is an issue of concern because of the potential of this mechanism to worsen schizophrenia symptoms—perhaps with long-term use.

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