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Proof-of-concept randomized controlled trial of pregnenolone in schizophrenia (Article)

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Abstract

Rationale: Preclinical and clinical data suggest that pregnenolone may be a promising therapeutic in schizophrenia. Pregnenolone is neuroprotective and enhances learning and memory, myelination, and microtubule polymerization. Treatment with pregnenolone elevates allopregnanolone (a neurosteroid that enhances $GABA_A$ receptor responses) and pregnenolone sulfate (a positive NMDA receptor modulator). Pregnenolone could thus potentially mitigate GABA dysregulation and/or NMDA receptor hypofunction in schizophrenia via metabolism to other neurosteroids. Objective: The objective of this study is to conduct a randomized controlled trial of adjunctive pregnenolone in schizophrenia. Methods: Following a placebo lead-in, 120 participants were randomized to pregnenolone or placebo for 8 weeks (Institute for Mental Health, Singapore). Primary endpoints were changes in MATRICS Consensus Cognitive Battery (MCCB) composite scores (cognitive symptoms), UCSD Performance-based Skills Assessment - Brief (UPSA-B) composite scores (functional capacity), and Scale for Assessment of Negative Symptoms (SANS) total scores (negative symptoms). A modified intent-to-treat analysis approach was utilized. Results: No significant changes compared to placebo were demonstrated in composite MCCB scores. In contrast, participants randomized to pregnenolone (n = 56) demonstrated greater improvements in functional capacity (UPSA-B composite changes) compared to placebo (n = 55), p = 0.03. Pregnenolone was also superior to placebo in the communication subscale of the UPSA-B ($p < 0.001$). Serum pregnenolone changes post-treatment were correlated with UPSA-B composite score changes in females ($r_s = 0.497$, $p < 0.042$, n = 17) but not in males. Mean total SANS scores were very low at baseline and did not improve further post-treatment. Pregnenolone was well-tolerated. Conclusions: Pregnenolone improved functional capacity in participants with schizophrenia, but did not improve cognitive symptoms over an 8-w[illegible] treatment period. Neurosteroid changes correlated with functional improvements in female participants. Neurosteroid interventions may exhibit promise as new therapeutic leads for schizophrenia.