Evidence for mood-stabilizing effects by the selective P2X7 receptor antagonist JNJ-54175446 in a sleep deprivation model in patients with major depressive disorder

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Introduction

Total sleep deprivation (TSD) results in acute but transient antidepressant effects in patients with major depressive disorder (MDD). JNJ-54175446 is a selective purine P2X7 receptor antagonist that inhibits central microglial activation and/or proliferation in vitro. In addition, JNJ-54175446 modulates amphetamine-induced (visuo)motor performance and mood in healthy volunteers.

Aim

TSD was applied to induce acute mood improvement in symptomatic MDD patients with the aim investigating JNJ-54175446's mood stabilizing effects in a proof-of-concept study.

Methods

A double-blind, placebo-controlled, randomized study in male and female patients with MDD (N=69). Patients had a baseline total Inventory of Depressive Symptomatology Clinician Rated (IDS-C) >30 and were antidepressant treatment-naïve or received a selective serotonin reuptake inhibitor for at least 6 weeks at a therapeutic dose. Patients were randomized to receive either placebo or JNJ-54175446 (150mg/d) throughout a 10-day treatment period, or placebo on days 1–3 followed by JNJ-54175446 from days 4-10 (delayed start group). Subjects underwent TSD starting Day 3 until the evening of Day 4. Effects of TSD and JNJ were evaluated using the Quick Inventory of Depressive Symptomatology (QIDS), Profile of Mood States (POMS), Snaith-Hamilton Pleasure Scale (SHAPS) and polysomnography (PSG).

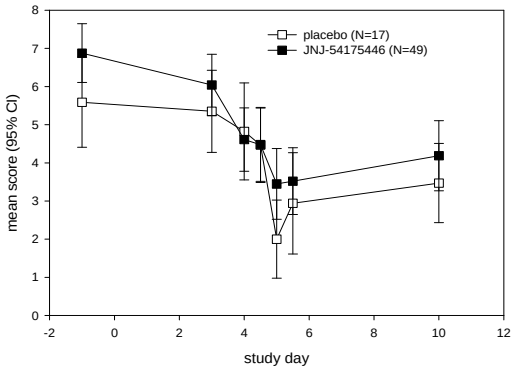
Results

TSD alleviated depressive symptoms significantly and lasted until the last study day (Day 10). Due to the protracted effect of TSD the effect of JNJ-54175446 could not be evaluated in the delayed start group. JNJ-54175446 through Days 1-10 blunted the effect of TSD in terms of self reported core depressive symptoms compared with placebo and increased total sleep time on PSG. All treatments were well-tolerated and all adverse events were mild to moderate.

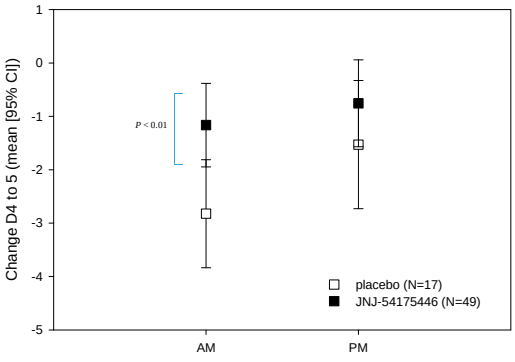
Conclusions

JNJ-54175446 attenuated TSD-induced mood improvement in MDD patients, suggesting that brain microglia may be a novel target for the development of mood stabilizing drugs.

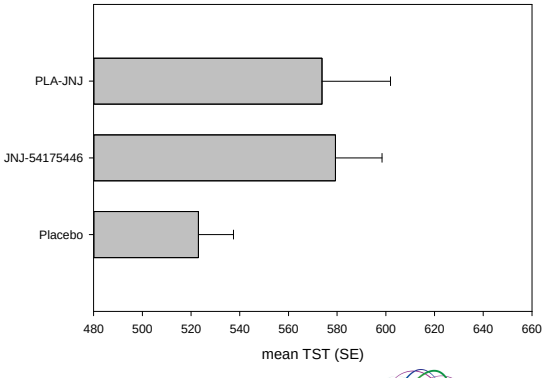
QIDS_core symptoms
(all JNJ combined)



Total QIDS core_Day 4/5 change



Total Sleep Time (Day 4/5)



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