Biomarker guided treatment optimization in major depression – focus on mineralocorticoid receptor function

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SUBMISSION DETAILS

What is the Methodological Question Being Addressed? Major depression is a heterogeneous disorder, both from a phenomenological and biological perspective. No pharmacotherapy has been approved for a specific biologically defined subgroups of major depression. Personalized treatment approaches are urgently needed in order to increase the clinical efficacy for a defined population of patients.

Introduction Markers of mineralocorticoid (MR) function appear to predict treatment outcome of depression. These include low systolic blood pressure and high salivary aldosterone/cortisol ratio, which may imply peripheral MR dysfunction and a reactive increase in aldosterone secretion. These markers appear to be stable over the course of antidepressant treatment (Murck et al., 2019). Reversal of these markers may reverse therapy refractoriness. Aldosterone acts selectively in specific areas, including the nucleus of the solitary tract (Buttner et al., 2015). We identified a molecular target, the 11-beta-hydroxysteroid-dehydrogenase-type 2 (11-beta-HSD-2), and an inhibitor of this enzyme, i.e. glycyrrhizin, with the envisioned property. Glycyrrhizin, which is the main active component of an extract from Glycyrrhiza glabra, thereby regulates blood pressure and electrolyte, and reduces the concentration of the stress hormone aldosterone.

Methods We administered Glycyrrhiza glabra (GG) extract containing 7-8 % of glycyrrhizin in a dose of 2 x 700 mg daily adjunct to hospitalized patients with major depression, who were treated with standard antidepressants. Assessments of biomarkers and psychopathology (Hamilton depression rating scale, HRDS, and clinical global , CGI-S) were done at baseline and approx. 2 and 6 weeks later. 12 subjects were treated with GG and compared to 55 subjects, who were treated with standard of care only, in an open label fashion. The change from baseline to week 2 for relevant parameters was assessed using an analysis of variance using treatment, gender and rater as factors.

Results In the GG group, blood pressure increased slightly, whereas it dropped in the standard group, indication target engagement. After two weeks of treatment the Hamilton-Depression Rating Scale change from baseline as well as the CGI-S showed a significant superiority of adjunct GG compared to standard treatment (both $p < 0.05$). A larger clinical benefit was observed in subjects with lower systolic blood pressure, which confirms subgroup specificity. Overall clinical benefit correlated significantly with a reduction in heart rate and a shortening of total sleep time, which points to a specific profile of the GG effect.

Conclusion Our results show that specific treatment of depression may be possible. We suggest that inhibition of 11-beta-HSD-2 by Glycyrrhiza Glabra extract may normalize moderators of therapy

refractoriness and improve clinical outcome in depression in a specific subgroup of depression.

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Keywords

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Therapy refractory depression
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Guidelines I have read and understand the Poster Guidelines

Disclosures if applicable HM is the owner of Murck-Neuroscience LLC, Westfield, NJ. He holds a patent in the area of therapy refractory depression.

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