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A pilot, open-label investigation of the efficacy of glucosamine for the treatment of major depression

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ABSTRACT

Introduction: Glucosamine hydrochloride normalizes GABA antagonist- and social defeat-induced behavioral alterations and upregulation of immune response genes in *Drosophila* and mice, respectively, increases hippocampal neurogenesis in mice, and demonstrates efficacy in murine behavioral models of depression. This suggests that it may have antidepressant potential in humans.

Methods: In an open label, 4-week pilot study, patients (n = 20) diagnosed with mild to moderate, nonpsychotic (unipolar) major depressive episode (DSM-IV) were treated with glucosamine in monotherapy at 1 g/day for 1 week and 2 g/day for 3 more weeks. Patients were assessed at baseline, and at 2- and 4-week follow up using the 21-item Hamilton Rating Scale for Depression (HAM-D), the Clinical Global Impression-Improvement (CGI-I) scale, and other measures. An intent-to-treat analysis with last-observation-carried-forward was conducted on the whole sample.

Results: Three patients dropped out before the first follow up; the rest completed the study. HAM-D scores dropped by a third in the sample as a whole; however, only 4 patients (20 %) were considered HAM-D responders (improvement by $\geq$ 50 %) and only 2 patients (10 %) were CGI-I responders (endpoint score of 1 or 2). There were only 2 (10 %) HAM-D remitters (endpoint score < 8). There were no serious adverse events and the treatment was well tolerated.

Conclusions: Encouraging preclinical results notwithstanding, glucosamine monotherapy does not appear to be effective against major depression. A more authoritative conclusion would require a randomized controlled trial.

1. Introduction

There is growing interest in antidepressant drugs with novel mechanisms of action. Research in the last 2 decades has suggested that induction of neuroplasticity may be the final common pathway through which antidepressants act (Andrade and Rao, 2010). Glucosamine hydrochloride, an over-the-counter nutritional supplement that is used to treat osteoarthritis (Simental-Mendía et al., 2018), stimulates neuroplasticity and demonstrates efficacy in several murine behavioral models of depression. This work, currently unpublished, and undertaken by author AS, Arvind Kumar, and Sumana Chakravarty has emerged from the Council of Scientific and Industrial Research (CSIR)-Institute of Genomics and Integrative Biology (New Delhi, India), the CSIR-Centre for Cellular & Molecular Biology (Hyderabad, India), and the CSIR-Indian Institute of Chemical Technology (Hyderabad, India). The work is summarized below.

The work began as a network project of CSIR, with screening of a library of around 2000 compounds, including existing clinical drugs and dietary supplements. In a *Drosophila* model, chronic administration of glucosamine normalized GABA antagonist-induced behavioral alteration and immune response genes upregulation in the central nervous system. As activated brain immune response is known to characterize neuropsychiatric conditions such as depression, glucosamine was tested further in chronic social defeat stress, sucrose preference test, and forced swim test murine models of depression. Glucosamine demonstrated antidepressant efficacy in all 3 models. In mice, glucosamine also normalized defeat-induced immune response genes upregulation in the hippocampus, and enhanced hippocampal neurogenesis in vivo.

Because of the extensive evidence of potential antidepressant benefit in preclinical research, the present study was conducted as a proof-of-concept, pilot, early Phase 2 investigation of the antidepressant

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potential of glucosamine.

2. Methods

This study was conducted at IQRAA International Hospital and Research Centre, Kozhikode, Kerala, India, between April 2016 and January 2017. The study was approved by the Institutional Ethics Committee at IQRAA International Hospital and Research Centre.

2.1. Design

The study was designed as a 4-week, pilot, open-label, proof-of-concept study.

2.2. Sample

The sample comprised male and (non-pregnant, non-lactating) female outpatients, aged 18–60 years, diagnosed with a (unipolar) major depressive episode (DSM-IV), who provided written informed consent for participating in the study. Patients were required to have illness that was at least mild to moderate in severity (baseline 21-item Hamilton Rating Scale for Depression [HAM-D] score of 18–24), but not very severe.

Patients were excluded if they had had antidepressant exposure in any dose in the past week, or exposure to an antidepressant in adequate doses for at least 1 week during the past 4 weeks. Patients were also excluded if any psychotropic medication had been initiated in the past week; however, if they were receiving a benzodiazepine that had been initiated prior to the past week, the medication was continued unchanged during the study. Finally, patients were excluded if they had suicidal ideation or behavior, agitation, psychotic symptoms, unstable medical comorbidity, significant psychiatric comorbidity, or alcohol or substance abuse.

2.3. Treatment

Patients received open-label glucosamine (K Natuer Pharmaceuticals, Punjab, India) in monotherapy in the dose of 1 g/day for the first week and 2 g/day for the rest of the study. Treatment was administered in two divided doses.

Permitted medications included hypnotics such as zolpidem in the maximum dose of 10 mg at night, and anxiolytics such as clonazepam in a maximum dose of 0.5 mg/day. Provision was made to take patients out of the study if they required any other psychotropic drug for the primary symptoms of the depressive illness. Provision was also made to take patients out of the study if they were considered to be clinically worsening at the 2-week follow up visit or at an unscheduled visit.

Patients who were considered to have clinically improved with glucosamine and who were willing to continue with the treatment were offered a further 4 weeks of treatment in the same dose.

2.4. Assessments

Assessments were obtained at baseline, and at 2- and 4-week follow up. Assessment instruments included the 21-item Hamilton Rating Scale for Depression (HAM-D), the Montgomery-Asberg Depression Rating Scale (MADRS), and the Clinical Global Impression-Severity (CGI-S) and -Improvement (CGI-I) scales. The Systematic Assessment for Treatment Emergent Effects side effect symptom checklist was also administered at all study visits. The CGI-I was obtained only at follow up visits. Only global impressions were recorded at the 8-week follow up.

The primary outcome was the response rate, defined as an at least 50 % attenuation of HAM-D scores. Secondary outcomes included HAM-D remission, defined as an endpoint HAM-D score < 8; CGI-I response, defined as an endpoint CGI-I score of 1 or 2; and improvement in HAM-D and MADRS ratings.

2.5. Statistical analysis

The sample size was pragmatically set at 20 because this was a pilot study to determine whether or not the results were sufficiently good to justify a randomized controlled trial. An intent-to-treat analysis was conducted on the full sample with last-observation-carried-forward wherever data were missing. The data were analyzed using one-way repeated measures multivariate analysis of variance with Pillai's trace as the statistical criterion; assessment week was the within subjects factor.

3. Results

3.1. Sample description

The age of the sample ranged from 20 to 59 years; the mean (standard deviation) (M[SD]) age was 38.0 (10.7) years. The sample was 65 % female. Most patients (n = 16; 80 %) were married. The sample had a M(SD) education of 10.5 (3.1) years.

3.2. Patient disposition

Three patients dropped out of the study even before the first (2-week) follow up assessment; the reasons for drop out could not be ascertained. The remaining 17 patients completed the 4-week study. Three patients were considered sufficiently improved to continue into the 4-week extension phase. At the end of this extension phase, only 1 patient maintained improvement; the other 2 were judged to have relapsed into depression.

3.3. Additional medication use

Between baseline and the 2 week follow up, patients used a mean of only 2 tablets of clonazepam (0.25 mg); between the 2- and 4-week follow up, use dropped to a mean of only 0.65 tablets of the drug.

3.4. Efficacy outcomes

Only 4 patients (20 %) were HAM-D responders and only 2 patients (10 %) were HAM-D remitters. Two patients (10 %) were responders on

Table 1
Efficacy outcomes at baseline and at 2- and 4-week follow up visits.*

	Baseline	2 weeks	4 weeks	Significance
HAM-D	23.9 (5.1)	18.8 (6.1)	16.1 (6.5)	$F = 14.42$; df = 2,18; $P < 0.001$
MADRS	27.0 (6.4)	21.6 (8.4)	18.5 (10.3)	$F = 15.80$; df = 2,18; $P < 0.001$
CGI-S	4.3 (0.5)	3.9 (0.7)	4.0 (0.8)	$F = 2.87$; df = 2,18; $P = 0.09$
CGI-I	Not applicable	3.2 (0.4)	3.3 (0.8)	$F = 0.14$; df = 1,15; $P = 0.72$

Abbreviations: HAM-D, Hamilton Rating Scale for Depression; MADRS, Montgomery-Asberg Depression Rating Scale; CGI-S, Clinical Global Impression-Severity; CGI-I, Clinical Global Impression-Improvement.

* Data presented are mean (standard deviation).

CGI-I.

The M(SD) HAM-D, MADRS, CGI-S, and CGI-I scores are presented in Table 1. There was statistically significant improvement in HAM-D and MADRS scores; the magnitude of improvement in the group as a whole, however, was small, at 33 % and 31 %, respectively. Global improvement, assessed using CGI-S and CGI-I, was not statistically significant for either measure.

3.5. Adverse effect outcomes

Patients were assessed for headache, dizziness/faintness, blurred vision and other eye symptoms, ear symptoms, dry mouth, other oral conditions, throat symptoms, chest pain, breathing complaints, cough, palpitations, abdominal pain, nausea, vomiting, bowel movement disturbances, and other treatment-emergent symptoms. There were no symptoms the prevalence of which increased with treatment, relative to the prevalence in the sample at baseline. In no patient did a symptom emerge that had not already been present at baseline. No patient developed an intercurrent illness.

4. Discussion

To our knowledge, our study is the first evaluation of glucosamine in depression. In our study, there was an only 20 % response to glucosamine during 4 weeks of open-label treatment. This is a disappointingly low response rate for a drug that is being evaluated for antidepressant potential. As a comparison, in a 30-year meta-analytic review of 142 antidepressant randomized controlled trials (RCTs) for major depression, Undurraga and Baldessarini (2012) found the average placebo response rate to be 37 % and the average drug response rate to be 54 % across a mean trial duration of 7.2 weeks. In a meta-analysis of 11 RCTs of vortioxetine that were 6–8 weeks in duration, Thase et al. (2016) found an identical 37 % placebo response rate relative to a 46–51 % vortioxetine response rate. There are no recent data on placebo vs drug response in Indian RCTs, and this is partly because, to our knowledge, no placebo-controlled antidepressant trials from India have been published for at least the past 2–3 decades (Avasthi et al., 2010; Sarkar and Grover, 2014).

We were unable to find meta-analysis or pooled analysis data for drug vs placebo 4-week antidepressant outcomes. It is possible that 4 weeks is too short a period to evaluate a potential antidepressant drug, as we did in our study. However, given that there was negligible change in CGI scores across the 4 weeks (Table 1), implying a global impression of clinical status quo, and given that only 3 (15 %) patients showed sufficient improvement to be considered for the 4-week extension phase, we conservatively consider that glucosamine does not warrant further clinical evaluation as an antidepressant.

5. Limitations

There are limitations to this conclusion. One, as already stated, is that 4 weeks is too short a period for evaluation. Perhaps an 8-week trial would have been a better possibility. Another is that patients knew that they were receiving an unproven drug, and this may have diminished the placebo response. However, this holds true in all studies of new drugs that are being evaluated for antidepressant potential. The only way of knowing for certain would be to conduct an adequately powered, placebo-controlled RCT, and this might be challenging to fund considering that glucosamine is out of patent and available over the counter.

Author roles

Dr Sharma was responsible for the idea and for the technical review on glucosamine that is presented in the introduction. Dr Suresh Kumar drafted the application for ethical approval and conducted the study. Dr Andrade designed the study, performed the statistical analysis, and drafted the manuscript. All authors reviewed and finalized the manuscript.

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Declaration of Competing Interest

The authors have no other conflicts to declare that are relevant to the submitted work.

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