Adjunctive Taurine in First-Episode Psychosis:
A Phase 2, Double-Blind, Randomized, Placebo-Controlled Study

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ABSTRACT

Objective: Taurine is an inhibitory neuromodulatory amino acid in the central nervous system that activates the GABA- and glycine-insensitive chloride channel and inhibits the *N*-methyl-D-aspartate receptor. It also functions as a neuroprotective agent and has a role in neural development and neurogenesis. The aim of this study was to determine the efficacy of adjunctive taurine in improving symptomatology and cognition among patients with a *DSM-IV* first-episode psychotic disorder.

Methods: 121 patients with first-episode psychosis, aged 18–25 years, attending early intervention services consented to participate in this randomized, double-blind, placebo-controlled trial conducted from January 2007 to May 2009. Patients taking low-dose antipsychotic medication were randomly assigned to receive once-daily taurine 4 g or placebo for 12 weeks. The coprimary outcomes were change in symptomatology (measured by the Brief Psychiatric Rating Scale [BPRS] total score) and change in cognition (measured by the Measurement and Treatment Research to Improve Cognition in Schizophrenia [MATRICS] Consensus Cognitive Battery composite score) at 12 weeks. Secondary outcomes included tolerability and safety and additional clinical and functioning measures.

Results: 86 participants (n = 47 taurine; n = 39 placebo) were included in the final analysis. Taurine significantly improved symptomatology measured by the BPRS total score (95% CI, 1.8–8.5; $P = .004$) and psychotic subscale (95% CI, 0.1–1.5; $P = .026$) compared to placebo. Additionally, improvements were observed in the Calgary Depression Scale for Schizophrenia (95% CI, 0.1–3.0; $P = .047$) and Global Assessment of Functioning (95% CI, 0.3–8.8; $P = .04$) scores. There was no group difference in composite cognitive score (95% CI, −1.7 to 1.0; $P = .582$). A significant group difference was found on one safety and tolerability item (psychic item 2, asthenia/lassitude/increased fatigability) of the Udvalg for Kliniske Undersogelser, with the taurine group showing a more favorable outcome ($P = .006$).

Conclusions: Adjunctive taurine did not improve cognition, but it appears to improve psychopathology in patients with first-episode psychosis. The use of taurine warrants further investigation in larger randomized studies, particularly early in the course of psychosis.

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A considerable proportion of young people with first-episode psychosis do not respond favorably to antipsychotics.[1] Ongoing symptoms and cognitive impairments are common and significantly interfere with functional recovery.[2,3] Taurine is an inhibitory neuromodulatory amino acid in the central nervous system and activates the γ-aminobutyric acid (GABA)– and glycine-insensitive chloride channel and inhibits the *N*-methyl-D-aspartate receptor. Taurine is not a structural component of any quaternary proteins or peptide bonds and resembles a peptide neurotransmitter (like epinephrine or dopamine) more than classical dietary proteins. Taurine has multiple functions in the brain such as modulation of calcium flux, neuronal excitability, osmoregulation, and membrane stabilization.[4]

Taurine has been trialled in several conditions including depression, heart failure, cardiomyopathy, retinal degeneration, and growth retardation.[5] A study by Ikeda[6] suggested that taurine had a possible role in ameliorating "psychotic states," defined as delirium, hallucinations, amentia, or convulsions. Twenty-two patients undergoing treatment for alcohol withdrawal were given 1 g of taurine 3 times daily for 7 days. Retrospective comparisons to controls showed significantly fewer taurine-treated patients experienced psychotic states (14% vs 45%, $P < .05$). In patients with a history of psychosis, the number of psychotic cases after admission was 1/16 (6.3%) for the taurine group and 11/17 (64.7%) for the controls ($P < .001$).[6] Further, a preliminary spectroscopy study[7] found that higher levels of taurine in the medial prefrontal cortex of people with schizophrenia were associated with better performance on the Stroop test and Trail Making Test A, indicating faster speed of information processing. It has also been reported that taurine concentrations are decreased in the cerebrospinal fluid (CSF) of drug-naive patients with schizophrenia and Parkinson's disease.[8,9] Whether taurine benefits patients with first-episode psychosis remains unknown.

The aim of this study was to evaluate the efficacy of taurine as an adjunctive compound for improving 2 coprimary outcomes—symptomatology and cognition—among patients with first-episode psychosis. It was hypothesized that compared with placebo, 12 weeks of taurine supplementation would

Clinical Points

- Despite treatment with antipsychotic medication, individuals with first-episode psychosis often experience persistent psychiatric symptoms and cognitive impairments.
- This study found that taurine may be an effective and tolerable adjunctive agent for improving psychopathological symptoms, but not cognitive functioning, in people with first-episode psychosis.

lead to a larger reduction in psychiatric symptoms and higher cognitive functioning.

METHODS

Design and Study Period

This was a phase 2, multicenter, parallel, double-blind, randomized, placebo-controlled study (RCT). Ethics approval was obtained from the NorthWestern Health Care Network Research and Ethics Committee, Melbourne Health, and the Southern Health Research and Ethics Committee, Southern Health. Participant recruitment occurred from January 2007 to March 2009, and the last follow-up assessment was completed in May 2009. The trial is registered with ClinicalTrials.gov, trial number NCT00420823.

Sample

People with first-episode psychosis aged 18–25 years who were receiving treatment for the first time at the Early Psychosis Prevention and Intervention Centre (EPPIC), a subprogram of Orygen Youth Health, or the Recovery and Prevention of Psychosis Service (RAPPS), a subprogram of Southern Health, in Melbourne, Australia, were eligible for study inclusion. EPPIC and RAPPS are specialized public mental health services for people aged 15–25 years who have experienced a first episode of psychosis. First-episode psychosis was defined as daily psychotic symptoms lasting longer than 1 week that were not explained by drug intoxication or organic causes. One of the following *DSM-IV* diagnoses was required for inclusion: schizophreniform disorder, schizophrenia, schizoaffective disorder, delusional disorder, mood disorder (major depressive disorder or mania) with psychotic features, or psychosis not otherwise specified. Participants must have received a minimum of 3 months of treatment prior to study entry and not be in the acute phase of illness. After giving informed written consent, participants were assessed for eligibility with the Structured Clinical Interview for *DSM-IV* Axis I disorders, Patient Edition (SCID-I/P)[10] to confirm the primary psychotic disorder. In 43% of cases, the SCID was not completed and diagnosis was obtained by clinical interview, review of records, and consultation with clinicians. Exclusion criteria included IQ < 80, substance dependence, history of clinically significant physical illness, brain surgery, infarction or neurologic impairment (eg, brain tumor, epilepsy), and, for women, being pregnant or lactating. All participants were screened for exclusion via results on laboratory testing, vital signs, and physical and neurologic examinations that were undertaken at service entry.

Randomization, Treatment, and Masking

Participants were randomly assigned to receive adjuvant taurine 4 g or placebo for 12 weeks plus antipsychotic medication as prescribed by their treating doctor (no patient was prescribed a typical antipsychotic). Participants also received standard clinical care throughout the study, which included weekly to fortnightly medical review with medication administered in line with a low-dose protocol, outpatient case management, family work, and group programs. The 4-g dose of taurine was chosen based on previous studies that had shown efficacy and tolerability. For example, dosages in studies of epilepsy ranged from 375 to 8,000 mg/d.[11–14] In 2 cardiovascular studies,[15,16] the dosage of taurine used was 6 g/d. Doses ranging between 4 g and 8 g were common.[17–19] We chose the lower dose of 4 g to maximize tolerability. Patients were randomized by a dynamic randomization method called minimization that allocates patients to treatment group by taking into account the allocation of similar patients already randomized and allocating the next treatment group "live" to best balance the treatment groups across all stratification variables.[20–22] Stratification variables included gender, age at onset of psychotic illness (before or after 18th birthday), living with caregiver (yes/no), and substance misuse (yes/no). Patients were also stratified according to whether they were prescribed risperidone at baseline. Risperidone was chosen as a stratification variable, as it was the most commonly prescribed antipsychotic based on clinical treatment guidelines at the time of the study.[23] Randomization was conducted off-site independent of the study team at the National Health and Medical Research Council Clinical Trials Centre, Sydney. Randomization codes were sent to the off-site clinical trials pharmacy that dispensed either taurine or placebo to participants to ensure allocation concealment. All study personnel, including the statistician, the participants, and the researchers who administered the assessment instruments at all time points, were blinded to treatment assignment for the entire duration of the study, including the data analysis phase.

Assessment Instruments

Experienced research assistants administered all assessment instruments and were supervised by a consultant psychiatrist and senior clinical neuropsychologist on the research team. Raters had considerable experience administering the measures and undertook reliability checks throughout the study period, including consensus ratings on training videos. Sociodemographic data, including marital status, living arrangements, and educational levels, were recorded. The National Adult Reading Test[24] was used to estimate premorbid IQ.

Symptoms and Functioning

Symptomatology was measured using the Brief Psychiatric Rating Scale expanded 24-item version 4 (BPRS)[25]

(coprimary outcome), as well as the Positive and Negative Syndrome Scale (PANSS)[26] and the Scale for the Assessment of Negative Symptoms (SANS).[27] Depression was measured using the Calgary Depression Scale for Schizophrenia (CDSS)[28] and subjective improvement using the Clinical Global Impressions–Schizophrenia (CGI-SCH).[29] The Global Assessment of Functioning (GAF)[30] was used to determine overall level of functioning.

Cognition

Cognition was assessed with the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (MCCB)[31] (coprimary outcome). It consists of 10 tests that measure cognitive performance in the following 7 domains: speed of processing (Trail Making Test Part A, Brief Assessment of Cognition in Schizophrenia: symbol coding and category fluency), attention/vigilance (Continuous Performance Test: identical pairs), working memory (Letter-number Span, Wechsler Memory Scale Spatial Span), verbal learning (Hopkins Verbal Learning Test [HVLT]), visual learning (Brief Visuospatial Memory Test), reasoning and problem solving (Neuropsychological Assessment Battery [NAB]: mazes), and social cognition (Mayer-Salovey-Caruso Emotional Intelligence Test [MSCEIT]): managing emotions).

Tolerability and Safety

Adverse events were assessed using a semistructured interview for the assessment of side effects of psychotropic medication, the Udvalg for Kliniske Undersogelser (UKU).[32] Each UKU item has a scale of 0 to 3 with 0 = absent or doubtful and 3 = serious. Each UKU item was dichotomized into the categories 0 vs ≥ 1 to compare the 2 treatment groups.

Adherence

Each participant's treating clinician rated their impression of compliance with prescribed and trial medication over the 12-week trial period using the following scale: 1 = excellent, 2 = very good, 3 = good, 4 = average, 5 = fair, 6 = poor, 7 = very poor. Blood tests were also performed to determine serum taurine levels at baseline and 12 weeks.

Statistical Analyses

Power analysis. The power analysis was based on a 1-way fixed-effects analysis of covariance (ANCOVA) with treatment group as the factor and baseline values as the covariate. Assuming that the covariate would account for 20% of the variance, the power for detecting a medium effect size is 86% for a sample size of 120 and α level of .05.

Outcome analysis. The main analysis was based on the intent-to-treat (ITT) principle. The ITT sample consisted of all randomized patients with at least 1 follow-up visit. The coprimary and secondary outcome analyses were based on this population. For each outcome measure, the 2 treatment groups were compared in terms of the change between baseline and each of the follow-up visits. The coprimary endpoint was the change from baseline to week 12 in symptoms as measured by total BPRS score and the change from baseline to week 12 in cognition as measured by the MCCB composite score. ANCOVA was used to carry out this comparison with the baseline values as the covariate. Multiple imputations were used for missing values. The multiple imputation technique used assumed that the data were missing at random. It adopted a model-based approach and utilized the expectation-maximization algorithm and data augmentation algorithm.[33–35] Logistic regression was applied to each UKU item to compare the 2 treatment groups in terms of the odds of having that particular symptom (ie, odds of item score ≥ 1); baseline UKU was included as a covariate. Logistic regression analyses were carried out only if the number of participants having that symptom at the time point was greater than 5. This cutoff point provided a reasonable safeguard for the analyses to be meaningful. All statistical tests were 2-sided, with significance set at $P < .05$. Effect sizes were interpreted according to Cohen *d* criteria[36] and computed using the *F*-statistic from the analyses and the following formula[37]:

$$d = \sqrt{F\left(\frac{n_t + n_c}{n_t\, n_c}\right)\left(\frac{n_t + n_c}{n_t + n_c - 2}\right)}$$

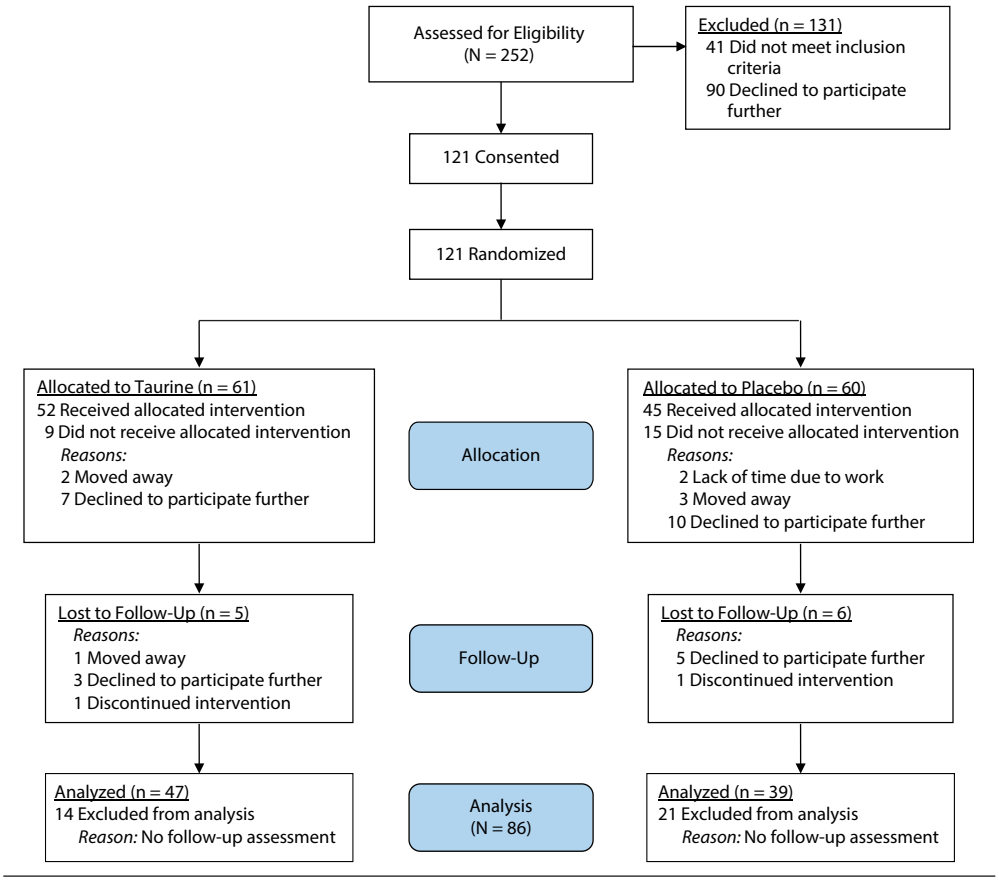
d = effect size, F = *F*-statistics, and n_t, n_c = sample size of taurine and placebo groups, respectively. The analysis was performed using S-PLUS 6 for Windows (Insightful Corp, Seattle, Washington) and SPSS for Windows version 16.0 (SPSS Inc, Chicago, Illinois).

RESULTS

Sample Characteristics

Participants (N = 121) were randomly assigned to receive either taurine 4 g or placebo. Ninety-seven participants started the study; 11 of these had no follow-up data and were excluded from the analysis. Therefore, 86 participants were included in the final analysis of which 47 were allocated to the taurine group and 39 to the placebo group (Figure 1). On average, participants had been receiving treatment for 9–10 months prior to entering the trial. Of the 86 participants included in the final analysis, 70.9% had baseline data on antipsychotic dosage (37 participants in the taurine group and 24 in the placebo group). Of these participants, 62.2% in the taurine group and 70.8% in the placebo group were prescribed antipsychotic medication at baseline. An equal number were taking risperidone in both groups (n = 13) at baseline, and other participants in both groups were taking aripiprazole, amisulpride, olanzapine, or quetiapine. One participant in the placebo group was taking clozapine. Among those who were prescribed antipsychotics at baseline, the mean (SD) doses in chlorpromazine equivalents[38] were 263.6 (127.1) mg and 364.4 (213.5) mg for the taurine and placebo groups, respectively, suggesting that the placebo group had a higher mean baseline dose. However, 2 of the participants in the placebo group had unusually high doses (750 and 900), which inflated the corresponding mean. The

Figure 1. Participant Flow



median dose of the 2 groups was very similar: 300 for taurine and 320 for placebo. The baseline demographic and clinical characteristics are presented in Table 1.

Attrition

The 2 groups did not significantly differ in attrition at either time point. At 6 weeks, 14 (29.8%) participants from the taurine group and 11 (28.2%) from the placebo group did not complete the assessment ($P = .87$). At 12 weeks, 12 (25.5%) participants from the taurine group and 6 (15.4%) from the placebo group were not assessed ($P = .25$).

Adherence

Clinicians' impressions of compliance with trial medication did not differ between the 2 groups, with a mean ± SD rating of 2.3 ± 1.7 in the taurine group and 2.4 ± 1.7 in the placebo group ($P = .74$), indicating "very good" compliance in both groups. Clinicians' impressions of compliance with other medication also did not significantly differ between groups (taurine: 1.7 ± 1.1, placebo: 2.3 ± 1.6, $P = .11$), indicating "excellent" to "very good" compliance.

The change in serum taurine levels between the 2 groups was significantly different ($P = .004$), with the taurine group showing a large mean ± SD increase (89.9 ± 153.4) and the placebo group showing a negligible mean change (−10.5 ± 38.9) over 12 weeks.

Table 1. Demographic and Clinical Characteristics of the 2 Treatment Groups at Baseline

Characteristic	Taurine (n = 47)	Placebo (n = 39)
Demographic		
Female, n (%)	15 (31.9)	11 (28.2)
Age (y), mean ± SD	21.4 ± 2.3	21.3 ± 2.3
Years completed education, mean ± SD	12.1 ± 2.2	12.6 ± 2.3
Non-white, n (%)	14 (29.8)	14 (35.9)
Living with caregiver, n (%)	27 (57.4)	26 (66.7)
Right-handed, n (%)	42 (89.4)	36 (92.3)
Drink tea or coffee, n (%)	39 (83.0)	32 (82.1)
Premorbid IQ, mean ± SD	100.3 ± 10.1	99.7 ± 12.0
Clinical		
Family history of psychiatric illness, n (%)	34 (72.3)	26 (66.7)
Family of history of schizophrenia, n (%)	7 (14.9)	11 (28.2)
Have had thoughts of self-harm, n (%)	21 (44.7)	16 (41.0)
Have had thoughts of suicide, n (%)	35 (74.5)	32 (82.1)
Have made suicide attempts, n (%)	19 (40.4)	14 (35.9)
Number of suicide attempts, mean ± SD	0.8 ± 1.3	0.6 ± 0.8
Duration of treatment (d), mean ± SD	296.5 ± 221.2[a]	274.8 ± 261.5[b]
Dose of antipsychotic (CPZ equivalence), mean ± SD	263.6 ± 127.1[c]	364.4 ± 213.5[d]
Diagnosis, n (%)		
Schizophrenia	17 (36.2)	21 (53.8)
Schizophreniform disorder	7 (14.9)	6 (15.4)
Schizoaffective disorder	3 (6.4)	4 (10.3)
Mood disorder with psychotic features	1 (2.1)	0 (0.0)
Delusional disorder	2 (4.3)	1 (2.6)
Psychosis not otherwise specified	13 (27.7)	5 (12.8)

[a]n = 34. [b]n = 33. [c]n = 37. [d]n = 24.
Abbreviations: CPZ = chlorpromazine (equivalence calculated using Gardner et al[36]), SD = standard deviation.

Table 2. Psychopathology Scores at Baseline and Change in Scores at Weeks 6 and 12

		Based on Participants With Available Data						Based on Multiple Imputation					
		Baseline		Week 6 Minus Baseline		Week 12 Minus Baseline		Week 6 ANCOVA			Week 12 ANCOVA		
Measure	Group	Mean	SD	Mean	SD	Mean	SD	*P* Value[a]	D	95% CI for D	*P* Value[a]	D	95% CI for D
BPRS Total	Taurine	46.5	14.3	−5.2	9.9	−8.5	10.7	.217	2.9	(−1.6 to 7.4)	**.004**	5.2	(1.8 to 8.5)
	Placebo	48.6	14.4	−3.2	9.9	−4.0	10.3						
BPRS Psychotic	Taurine	8.8	4.9	−1.6	3.6	−2.3	4.6	.170	0.5	(−0.2 to 1.3)	**.026**	0.8	(0.1 to 1.5)
	Placebo	10.2	4.8	−1.8	4.6	−1.5	4.2						
CDSS Total	Taurine	5.4	5.0	−1.4	4.0	−2.3	4.2	.119	1.3	(−0.3 to 3.0)	**.047**	1.5	(0.1 to 3.0)
	Placebo	4.6	4.1	−0.1	3.3	0.0	3.4						
CGI													
Severity of Illness	Taurine	2.8	1.3	−0.3	0.6	−0.4	0.9	.591	−0.1	(−0.5 to 0.3)	.986	0.0	(−0.4 to 0.4)
	Placebo	3.2	1.2	−0.5	0.9	−0.5	1.1						
Global Improvement[b]	Taurine	NA	NA	3.3	0.9	3.0	1.1	.438	0.2	(−0.3 to 0.8)	.180	0.4	(−0.2 to 0.9)
	Placebo	NA	NA	3.4	1.2	3.3	1.4						
Efficacy Index[b]	Taurine	NA	NA	8.6	4.1	7.5	4.5	.140	1.8	(−0.5 to 4.1)	.073	2.2	(−0.1 to 4.6)
	Placebo	NA	NA	10.0	4.6	9.0	4.6						
GAF[c]	Taurine	58.8	15.2	NA	NA	6.5	12.3	NA	NA	NA	**.040**	4.6	(0.3 to 8.8)
	Placebo	56.8	13.2	NA	NA	1.8	10.6						
PANSS													
Total	Taurine	61.3	17.1	−5.8	12.6	−8.3	12.4	.230	3.4	(−2.1 to 8.9)	.052	4.7	(0.1 to 9.4)
	Placebo	65.4	17.0	−4.2	11.7	−3.8	11.6						
Positive	Taurine	14.3	5.9	−2.1	3.9	−2.8	5.4	.751	0.4	(−2.1 to 2.9)	.209	1.3	(−0.7 to 3.3)
	Placebo	15.6	6.6	−2.2	5.6	−2.0	6.0						
Negative	Taurine	14.1	4.4	−0.6	5.1	−0.5	4.4	.243	1.9	(−1.2 to 5.0)	.446	0.9	(−1.4 to 3.3)
	Placebo	14.8	5.2	−0.1	5.9	0.5	5.4						
General	Taurine	32.9	9.8	−3.1	7.3	−5.1	7.4	.279	1.8	(−1.4 to 5.0)	**.042**	2.7	(0.2 to 5.2)
	Placebo	34.9	9.6	−1.9	6.7	−2.3	6.8						
SANS													
Total	Taurine	17.7	11.0	−1.0	8.9	−1.8	10.4	.781	0.6	(−3.6 to 4.8)	.153	3.1	(−1.1 to 7.3)
	Placebo	19.7	12.7	−1.6	8.9	1.8	8.9						
Affective Flattening/Blunting	Taurine	4.7	4.7	0.4	4.5	−0.5	4.6	.842	0.3	(−2.2 to 2.7)	.295	1.1	(−0.9 to 3.1)
	Placebo	5.9	6.1	−0.9	4.9	0.2	4.8						
Alogia	Taurine	1.9	2.1	0.4	1.9	0.3	2.5	.474	−0.3	(−1.2 to 0.6)	.571	−0.3	(−1.5 to 0.8)
	Placebo	3.0	3.2	−0.5	1.8	−0.6	2.5						
Avolition Apathy	Taurine	3.4	2.9	−0.2	3.2	−0.2	3.3	.079	1.0	(−0.1 to 2.1)	.232	0.8	(−0.5 to 2.2)
	Placebo	3.8	3.3	0.5	2.4	0.7	2.6						
Anhedonia Asociality	Taurine	5.3	4.1	−1.1	2.9	−0.8	3.3	.721	−0.2	(−1.4 to 0.9)	.062	1.5	(0.0 to 3.0)
	Placebo	5.2	3.7	−0.9	3.2	1.2	3.3						
Attention	Taurine	2.4	2.0	−0.5	1.9	−0.6	2.3	.404	0.3	(−0.5 to 1.2)	.787	0.1	(−0.7 to 0.9)
	Placebo	1.8	1.6	0.1	1.5	0.1	1.7						

[a]The *P* values are for testing for group difference using ANCOVA with baseline score as a covariate except CGI Global Improvement and CGI Efficacy Index for which baseline CGI Severity of illness score was used as the covariate. Bold values represent significant at $P < .05$.
[b]For CGI Global Improvement and CGI Efficacy Index, since there were no baseline scores, the descriptive statistics were based on the actual scores at week 6 and week 12, ie, not change scores. Similarly, the ANCOVA analysis was based on the actual scores, not change scores.
[c]Not assessed at 6 weeks, therefore not applicable (NA).
Abbreviations: ANCOVA = analysis of covariance, BPRS = Brief Psychiatric Rating Scale, CDSS = Calgary Depression Scale for Schizophrenia, CI = confidence interval, CGI = Clinical Global Impressions scale, D = estimated mean group difference, GAF = Global Assessment of Functioning, PANSS = Positive and Negative Syndrome Scale, SANS = Scale for the Assessment of Negative Symptoms, SD = standard deviation.

Symptomatology

Descriptive statistics based on multiple imputation for baseline psychopathology scores, change in baseline scores, and ANCOVA results are presented in Table 2. There was no significant difference in symptom change between the 2 groups at week 6 (all $P > .05$). However, at week 12, there was a significant group difference in the coprimary outcome of BPRS total score ($P = .004$), with the taurine group showing a larger improvement than the placebo group. The effect size for this group difference was 0.67, indicating a medium effect. There was a significant improvement in psychotic symptoms as measured by the BPRS Psychotic subscale (suspiciousness, hallucinations, unusual thought content, conceptual disorganization) ($P = .026$, effect size = 0.49), and marginally nonsignificant group difference as measured by the PANSS ($P = .052$, effect size = 0.43) at week 12. Additionally, the CDSS total ($P = .047$), GAF ($P = .040$), and PANSS General ($P = .042$) scores were significantly improved in the taurine group compared to the placebo group at week 12. The effect sizes were again moderate, 0.44, 0.46, and 0.46, respectively. There was no significant difference between the groups in negative symptoms at 6 or 12 weeks ($P > .05$).

Cognition

Table 3 shows baseline scores, change in baseline scores, and ANCOVA results based on multiple imputation for the cognition variables. There was no difference in the coprimary MCCB cognitive composite score between the taurine and placebo group at either 6 ($P = .389$) or 12 weeks ($P = .582$). Regarding individual cognitive domains,

Table 3. Cognition *t* Scores at Baseline and Change in Scores at Weeks 6 and 12

		Based on Participants With Available Data						Based on Multiple Imputation					
		Baseline		Week 6 Minus Baseline		Week 12 Minus Baseline		Week 6 ANCOVA			Week 12 ANCOVA		
Measure[a]	Group	Mean	SD	Mean	SD	Mean	SD	*P* Value[b]	D	95% CI for D	*P* Value[b]	D	95% CI for D
Composite	Taurine	35.1	12.1	3.3	6.2	5.0	5.6	.389	−0.7	(−2.1 to 0.8)	.582	−0.4	(−1.7 to 1.0)
	Placebo	36.1	10.7	4.0	3.7	5.5	6.3						
Speed of processing	Taurine	38.9	12.4	3.5	6.2	6.2	6.9	.117	−1.4	(−3.0 to 0.3)	.694	0.4	(−1.5 to 2.2)
	Placebo	38.7	13.3	6.1	7.1	5.6	8.0						
Attention/vigilance	Taurine	33.8	9.6	3.5	7.5	5.8	7.9	.439	0.8	(−1.2 to 2.7)	.261	1.1	(−0.8 to 3.0)
	Placebo	37.8	11.1	2.4	6.6	3.2	7.7						
Working memory	Taurine	40.9	12.0	1.4	8.4	2.6	8.3	.954	0.1	(−2.0 to 2.2)	.811	0.2	(−1.6 to 2.0)
	Placebo	39.9	12.2	1.5	6.9	2.8	8.9						
Verbal learning	Taurine	40.0	8.6	−1.5	9.5	1.2	8.4	.639	0.5	(−1.7 to 2.8)	.987	0.0	(−2.3 to 2.3)
	Placebo	41.3	9.9	−2.5	8.4	1.3	10.5						
Visual learning	Taurine	39.6	12.5	3.6	8.3	2.5	9.1	.458	−0.8	(−2.8 to 1.3)	.104	−1.7	(−3.7 to 0.3)
	Placebo	38.8	12.1	6.0	10.7	5.5	10.9						
Reasoning	Taurine	43.5	10.6	0.9	10.8	2.7	8.3	**.031**	−2.1	(−3.9 to −0.2)	.346	−0.8	(−2.4 to 0.8)
	Placebo	47.5	9.5	3.5	6.1	1.5	6.8						
Social cognition	Taurine	40.6	12.7	1.1	7.2	0.5	5.9	.875	0.2	(−1.8 to 2.1)	.362	−0.9	(−2.8 to 1.0)
	Placebo	39.5	9.6	2.5	10.1	3.3	9.9						

[a]Cognition scores were based on the MATRICS Consensus Cognitive Battery (MCCB).
[b]The *P* values are for testing for group difference using ANCOVA with baseline score as a covariate.
Abbreviations: ANCOVA = analysis of covariance, CI = confidence interval, D = estimated mean group difference, MATRICS = Measurement and Treatment Research to Improve Cognition in Schizophrenia, SD = standard deviation.

a significant improvement in the reasoning and problem solving domain was observed at week 6 ($P = .031$) in the placebo group; however this difference was not significant at week 12 ($P = .346$).

Safety and Tolerability

There were low rates of side-effect symptoms at week 6 and week 12 in both groups (see Supplementary eTable 1). A significant group difference was observed on only 1 item, psychic item 2 (asthenia/lassitude/increased fatigability) at week 12, with a more favorable outcome shown by the taurine group (4.7% vs 14.0%; $P = .006$).

DISCUSSION

To our knowledge, this study is the first to examine the efficacy of taurine supplementation in a population with first-episode psychosis. The coprimary outcomes were total symptomatology (BPRS) and cognition (MCCB). Relative to placebo, taurine resulted in significant improvements in total symptomatology but not cognition over 12 weeks, indicating that the overall result of this RCT was technically negative. Nevertheless, in addition to total psychopathology, statistically significant improvements were observed in several secondary outcomes including general symptomatology, positive symptoms, depression, and general functioning in participants receiving taurine relative to those receiving placebo. These findings could certainly be viewed as clinically important (though arguably nonspecific), as all effect sizes were well within the medium range and this group was nonacute but moderately unwell (mean BPRS at baseline was 47.5) who on average had been receiving low-dose antipsychotic treatment for 9–10 months prior to entering the study. It is possible that positive symptoms in particular were already responding somewhat to antipsychotic medication over the trial period, with further response with the addition of taurine. Hence, taurine could be interpreted as having a complementary effect, which suggests that taurine could be used as a second-line adjunctive step and not necessarily concurrent with first-medication used.

Previous evidence suggests that taurine may play a protective role in regard to the expression of psychosis. A study investigating taurine supplementation in people with alcohol dependence reported a lower rate of psychotic states during alcohol withdrawal in those who were taurine supplemented.[6] Metabonomic profiling in a chronic phencyclidine rat model of schizophrenia revealed changes in the levels of taurine in addition to glutamate, glutamine, glycine, and pyruvate; these changes were also identified in the prefrontal cortex of people with schizophrenia.[39] Furthermore, taurine concentrations are found to be decreased in the CSF of drug-naive patients with schizophrenia.[8,9] However, as noted in the current study, the effects of taurine were relatively general, with significant effects being observed in depression and general symptoms, in addition to positive symptoms. These findings are consistent with a previous study showing that CSF levels of taurine correlated negatively with depression and behavioral disturbances among patients with Alzheimer's disease.[40] Elevated plasma taurine levels have been observed in depressed individuals when compared with healthy controls,[41–43] and serum taurine may be modulated by antidepressants.[44] Moreover, taurine supplementation has been shown to have an antidepressant-like effect in rats.[45,46] Thus, further investigation into the effects of taurine on psychiatric symptoms in general appears warranted.

Findings in relation to taurine and neural migration may be informative in relation to the neurodevelopmental

hypothesis of schizophrenia. Taurine is present in high levels in fetal brain tissue and decreases in the adult, suggesting it has a role in early brain development.[47] It has been reported that taurine deficiency results in delayed cell differentiation and migration in the cerebellum, pyramidal cells, and visual cortex in cats and monkeys.[48,49] Taurine has also been shown to improve maturation of auditory-evoked responses in preterm infants.[50] Hernández-Benitez et al[47] have also shown that taurine promotes neural development in adult brain regions. Within the subventricular zone of the cultured adult mouse brain, taurine activates stem cells and neural precursor cells to differentiate into neurons rather than astrocytes. The subventricular zone is one of the few regions in the brain in which neurogenesis continues throughout adulthood. The actions of taurine on adult subventricular stem cells and progenitor cells are not mimicked by glycine, GABA, or alanine.[49]

Cognitive enhancement remains a significant challenge in the field of drug development and novel therapies.[51] Most deficits develop premorbidly and are considered to be a neurodevelopmental trait feature of psychotic illness, with the biological mechanisms remaining largely elusive. One previous study[7] found significant correlations between taurine levels in the medial prefrontal cortex of people with chronic schizophrenia and performance on tasks of information processing speed. Interestingly, higher levels of taurine were associated with a shorter duration of illness.[7] It is possible that supplements such as taurine may need to be trialled in the prodromal stage, or even earlier in life, if they are to influence cognitive function.

Taurine had superior tolerability when compared to placebo in the asthenia/lassitude/increased fatigability domain (psychic item 2) of the UKU. Consistent with this finding is that taurine has been reported to be a strong activator of GABA receptors in the thalamus. The thalamus is involved in "behavioral state control," helping to regulate transitions between sleep and wakefulness.[52] There were no reports of serious adverse events, and there were no differences between the 2 groups in terms of side-effect profile, indicating that taurine appears to be safe in this population. It must be noted that logistic regression analyses could not be performed for most of the UKU items due to the low number of participants endorsing side effects. The optimal dosage of taurine remains an important question for future research. Given that the 4-g dose was well tolerated, it is possible that greater efficacy might be achieved at higher doses.

Strengths of this study include that it was a double-blind design with a large sample for a phase 2 study. However, a number of limitations need to be acknowledged. First, prescription of atypical antipsychotics was nonstandardized, and there were missing data on dosages for approximately 30% of the participants. Second, consumption of energy drinks that contain taurine was not recorded, so the effects of dietary taurine intake (above the trial medication) are unknown. Third, that a large percentage of participants were not diagnosed using the SCID is also a limitation of the study. Fourth, compliance measured via clinical impression may have been unreliable. Finally, although the original sample size was not retained, there was still reasonable power (72%) to detect the targeted medium effect size.

In conclusion, although overall findings of the trial were negative, taurine had a statistically significant and clinically important effect on symptomatology and functioning in patients with first-episode psychosis and was found to be safe and well tolerated. The findings of the current study and those reviewed herein suggest that the properties of taurine and its potential therapeutic benefits in early psychosis warrant further investigation.

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Supplementary material: See accompanying pages.

REFERENCES

1. Gallego JA, Robinson DG, Sevy SM, et al. Time to treatment response in first-episode schizophrenia: should acute treatment trials last several months? *J Clin Psychiatry*. 2011;72(12):1691–1696. *10.4088/JCP.10m06349*
2. Ventura J, Subotnik KL, Gitlin MJ, et al. Negative symptoms and functioning during the first year after a recent onset of schizophrenia and 8 years later. *Schizophr Res*. 2015;161(2–3):407–413.
3. Mesholam-Gately RI, Giuliano AJ, Goff KP, et al. Neurocognition in first-episode schizophrenia: a meta-analytic review. *Neuropsychology*. 2009;23(3):315–336.
4. Huxtable RJ. Physiological actions of taurine. *Physiol Rev*. 1992;72(1):101–163.
5. Lourenço R, Camilo ME. Taurine: a conditionally essential amino acid in humans? an overview in health and disease. *Nutr Hosp*. 2002;17(6):262–270.
6. Ikeda H. Effects of taurine on alcohol withdrawal. *Lancet*. 1977;2(8036):509.
7. Shirayama Y, Obata T, Matsuzawa D, et al. Specific metabolites in the medial prefrontal cortex are associated with the neurocognitive deficits in schizophrenia: a preliminary study. *Neuroimage*. 2010;49(3):2783–2790.
8. Do KQ, Lauer CJ, Schreiber W, et al. gamma-Glutamylglutamine and taurine concentrations are decreased in the cerebrospinal fluid of drug-naive patients with schizophrenic disorders. *J Neurochem*. 1995;65(6):2652–2662.
9. Engelborghs S, Marescau B, De Deyn PP. Amino acids and biogenic amines in cerebrospinal fluid of patients with Parkinson's disease. *Neurochem Res*. 2003;28(8):1145–1150.
10. First M, Spitzer R, Gibbon M, et al. *Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version, Patient Edition (SCID-I/P)*. New York, NY: Biometrics Research Department, New York State Psychiatric Institute; 2001.
11. Takahashi R, Nakane Y. Clinical trial of taurine in epilepsy. In: Barbeau A, Huxtable RJ, eds. *Taurine and Neurological Disease*. New York, NY: Raven Press; 1978:375–385.
12. Mantovani J, DeVivo DC. Effects of taurine on seizures and growth hormone release in epileptic patients. *Arch Neurol*. 1979;36(11):672–674.
13. Fukuyama Y, Ochiai Y. Therapeutic trial by taurine for intractable childhood epilepsies. *Brain Dev*. 1982;4(1):63–69.
14. Bergamini L, Mutani R, Delsedime M, et al. First clinical experience on the antiepileptic action of taurine. *Eur Neurol*. 1974;11(5):261–269.
15. Azuma J, Takihara K, Awata N, et al. Taurine and failing heart: experimental and clinical aspects. *Prog Clin Biol Res* 1985;179:195-213.
16. Fujita T, Katsuyuki A, Noda H, et al. Effects of increased adrenomedullary activity and taurine in young patients with borderline hypertension. Circulation. 1987;75:525-32.
17. Hardison WGM, Grundy SM. Effect of bile acid conjugation pattern on bile acid metabolism in normal humans. *Gastroenterology*. 1983;84(3):617–620.
18. Mizushima S, Nara Y, Sawamura M, et al. Effects

of oral taurine supplementation on lipids and sympathetic nerve tone. *Adv Exp Med Biol*. 1996;403:615–622.
19. Azuma J, Sawamura A, Awata N, et al. Double-blind randomized crossover trial of taurine in congestive heart failure. *Curr Ther Res*. 1983;34:543–557.
20. Verberk WJ, Kroon AA, Kessels AG, et al. Comparison of randomization techniques for clinical trials with data from the HOMERUS-trial. *Blood Press*. 2005;14(5):306–314.
21. Treasure T, MacRae KD. Minimisation: the platinum standard for trials? randomisation doesn't guarantee similarity of groups; minimisation does. *BMJ*. 1998;317(7155):362–363.
22. Pocock SJ, Simon R. Sequential treatment assignment with balancing for prognostic factors in the controlled clinical trial. *Biometrics*. 1975;31(1):103–115.
23. Early Psychosis Guidelines Writing Group. *Australian Clinical Guidelines for Early Psychosis*. 2nd ed. Melbourne, Australia: Orygen Youth Health; 2010.
24. Nelson HE, Willison J. *National Adult Reading Test (NART): Test Manual*. 2nd ed. Windsor, UK: NFER Nelson; 1991.
25. Ventura J, Lukoff D, Nuechterlein KH, et al. *Brief Psychiatric Rating Scale (BPRS) Expanded Version (4.0). Scales, Anchor Points, and Administration Manual*. West Los Angeles, CA: UCLA Department of Psychiatry and Behavioral Sciences; 1993.
26. Kay SR, Fiszbein A, Opler LA. The Positive and Negative Syndrome Scale (PANSS) for schizophrenia. *Schizophr Bull*. 1987;13(2):261–276.
27. Andreasen NC. *Scale for the Assessment of Negative Symptoms (SANS)*. Iowa City, IA: University of Iowa; 1984.
28. Addington D, Addington J, Schissel B. A depression rating scale for schizophrenics. *Schizophr Res*. 1990;3(4):247–251.
29. Haro JM, Kamath SA, Ochoa S, et al; SOHO Study Group. The Clinical Global Impression-Schizophrenia scale: a simple instrument to measure the diversity of symptoms present in schizophrenia. *Acta Psychiatr Scand suppl*. 2003;107(416):16–23.
30. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Text Revision (DSM-IV-TR)*. 4th ed. Washington, DC: American Psychiatric Association; 2000.
31. Nuechterlein KH, Green MF. *MATRICS Consensus Cognitive Battery (MCCB)*. Los Angeles, CA: MATRICS Assessment Inc.; 2006.
32. Lingjaerde O, Ahlfors UG, Bech P, et al. The UKU side effect rating scale: a new comprehensive rating scale for psychotropic drugs and a cross-sectional study of side effects in neuroleptic-treated patients. *Acta Psychiatr Scand suppl*. 1987;334:1–100.
33. Little R, Rubin D. *Statistical Analysis With Missing Data*. New York: Wiley and Sons; 1987.
34. Schafer J. *Analysis of Incomplete Multivariate Data*. London, UK: Chapman and Hall; 1997.
35. Dempster A, Laird N, Rubin D. Maximum likelihood estimation from incomplete data via the EM algorithm. *J Royal Stat Soc*. 1977;39(1):1–38.
36. Cohen J. *Statistical Power Analysis for the Behavioral Sciences*. 2nd ed. Hillsdale, NJ: Lawrence Earlbaum Associates; 1988.
37. Thalheimer W, Cook S. How to calculate effect sizes from published research articles: a simplified methodology. http://www.bwgriffin.com/gsu/courses/edur9131/content/Effect_Sizes_pdf5.pdf. 2002. Accessed August 9, 2012.
38. Gardner DM, Murphy AL, O'Donnell H, et al. International consensus study of antipsychotic dosing. *Am J Psychiatry*. 2010;167(6):686–693.
39. Wesseling H, Chan MK, Tsang TM, et al. A combined metabonomic and proteomic approach identifies frontal cortex changes in a chronic phencyclidine rat model in relation to human schizophrenia brain pathology. *Neuropsychopharmacology*. 2013;38(12):2532–2544.
40. Vermeiren Y, Le Bastard N, Van Hemelrijck A, et al. Behavioral correlates of cerebrospinal fluid amino acid and biogenic amine neurotransmitter alterations in dementia. *Alzheimers Dement*. 2013;9(5):488–498.
41. Altamura C, Maes M, Dai J, et al. Plasma concentrations of excitatory amino acids, serine, glycine, taurine and histidine in major depression. *Eur Neuropsychopharmacol*. 1995;5(suppl):71–75.
42. American Psychiatric Association. *Diagnostic and Statistical Manual for Mental Disorders*. Fourth Edition, Text Revision. Washington, DC: American Psychiatric Association; 2000.
43. Mitani H, Shirayama Y, Yamada T, et al. Correlation between plasma levels of glutamate, alanine and serine with severity of depression. *Prog Neuropsychopharmacol Biol Psychiatry*. 2006;30(6):1155–1158.
44. Maes M, Verkerk R, Vandoolaeghe E, et al. Serum levels of excitatory amino acids, serine, glycine, histidine, threonine, taurine, alanine and arginine in treatment-resistant depression: modulation by treatment with antidepressants and prediction of clinical responsivity. *Acta Psychiatr Scand*. 1998;97(4):302–308.
45. Caletti G, Olguins DB, Pedrollo EF, et al. Antidepressant effect of taurine in diabetic rats. *Amino Acids*. 2012;43(4):1525–1533.
46. Toyoda A, Iio W. Antidepressant-like effect of chronic taurine administration and its hippocampal signal transduction in rats. *Adv Exp Med Biol*. 2013;775:29–43.
47. Hernández-Benítez R, Pasantes-Morales H, Saldaña IT, et al. Taurine stimulates proliferation of mice embryonic cultured neural progenitor cells. *J Neurosci Res*. 2010;88(8):1673–1681.
48. Palackal T, Moretz R, Wisniewski H, et al. Abnormal visual cortex development in the kitten associated with maternal dietary taurine deprivation. *J Neurosci Res*. 1986;15(2):223–239.
49. Maar T, Morán J, Schousboe A, et al. Taurine deficiency in dissociated mouse cerebellar cultures affects neuronal migration. *Int J Dev Neurosci*. 1995;13(5):491–502.
50. Tyson JE, Lasky R, Flood D, et al. Randomized trial of taurine supplementation for infants less than or equal to 1,300-gram birth weight: effect on auditory brainstem-evoked responses. *Pediatrics*. 1989;83(3):406–415.
51. Kroken RA, Løberg E-M, Drønen T, et al. A critical review of pro-cognitive drug targets in psychosis: convergence on myelination and inflammation. *Front Psychiatry*. 2014;5(11):11.
52. Jia F, Yue M, Chandra D, et al. Taurine is a potent activator of extrasynaptic GABA(A) receptors in the thalamus. *J Neurosci*. 2008;28(1):106–115.

Supplementary material follows this article.

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Supplementary Material

Article Title: Adjunctive Taurine in First-Episode Psychosis: A Phase 2, Double-Blind, Randomized, Placebo-Controlled Study

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List of Supplementary Material for the article

1. eTable 1 — Side Effects at Weeks 6 and 12 Based on the UKU Scale and Logistic Regression Analyses

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Supplementary Table. Side effects at weeks 6 and 12 based on the UKU scale and logistic regression analyses

UKU Domain	UKU Item	Group	% of participants having the symptom (i.e., severity score ≥1)			Logistic regression p-value*	
			Baseline	Week 6	Week 12	Week 6	Week 12
Psychic	1	Taurine	14.0	4.7	2.3	.827	NA
		Placebo	9.3	4.7	1.2		
	2	Taurine	22.1	9.3	4.7	.922	**.006**
		Placebo	16.3	8.1	14.0		
	3	Taurine	10.5	3.5	2.3	NA	.088
		Placebo	8.1	2.3	8.1		
	4	Taurine	8.1	3.5	1.2	.729	NA
		Placebo	10.5	3.5	1.2		
	5	Taurine	5.8	3.5	0	.794	NA
		Placebo	5.8	3.5	1.2		
	6	Taurine	9.3	3.5	3.5	NA	NA
		Placebo	5.8	2.3	2.3		
	7	Taurine	5.8	4.7	2.3	.478	.790
		Placebo	8.1	2.3	4.7		
	8	Taurine	2.3	1.2	0	NA	NA
		Placebo	2.3	2.3	0		
	9	Taurine	4.7	1.2	1.2	NA	NA
		Placebo	5.8	2.3	2.3		
	10	Taurine	3.5	1.2	1.2	NA	NA
		Placebo	4.7	3.5	1.2		
Neurological	1	Taurine	1.2	0	1.2	NA	NA
		Placebo	1.2	1.2	1.2		
	2	Taurine	3.5	1.2	1.2	NA	NA

		Placebo	1.2	1.2	0		
	3	Taurine	3.5	1.2	0	NA	NA
		Placebo	2.3	0	0		
	4	Taurine	1.2	1.2	0	NA	NA
		Placebo	3.5	1.2	0		
	5	Taurine	3.5	2.3	1.2	NA	NA
		Placebo	3.5	2.3	1.2		
	6	Taurine	1.2	0	1.2	NA	NA
		Placebo	1.2	0	1.2		
	7	Taurine	0	0	0	NA	NA
		Placebo	0	0	0		
	8	Taurine	0	0	0	NA	NA
		Placebo	0	0	0		
Autonomic	1	Taurine	2.3	0	0	NA	NA
		Placebo	0	0	0		
	2	Taurine	4.7	2.3	1.2	NA	NA
		Placebo	1.2	2.3	2.3		
	3	Taurine	9.3	2.3	1.2	NA	NA
		Placebo	2.3	3.5	1.2		
	4	Taurine	3.5	3.5	0	NA	NA
		Placebo	4.7	2.3	2.3		
	5	Taurine	0	1.2	0	NA	NA
		Placebo	2.3	0	1.2		
	6	Taurine	1.2	3.5	1.2	NA	NA
		Placebo	1.2	0	0		
	7	Taurine	0	0	1.2	NA	NA
		Placebo	0	0	0		

	8	Taurine	2.3	1.2	0	NA	NA
		Placebo	2.3	1.2	0		
	9	Taurine	7.0	3.5	1.2	NA	NA
		Placebo	5.8	2.3	4.7		
	10	Taurine	2.3	0	0	NA	NA
		Placebo	2.3	2.3	1.2		
	11	Taurine	4.7	2.3	1.2	NA	NA
		Placebo	1.2	0	0		
Other	1a	Taurine	0	0	0	NA	NA
		Placebo	0	0	0		
	1b	Taurine	0	0	0	NA	NA
		Placebo	0	0	0		
	1c	Taurine	0	0	0	NA	NA
		Placebo	0	0	0		
	1d	Taurine	0	0	0	NA	NA
		Placebo	0	0	0		
	1e	Taurine	0	0	0	NA	NA
		Placebo	1.2	0	0		
	2	Taurine	1.2	0	0	NA	NA
		Placebo	0	0	0		
	3	Taurine	2.3	2.3	1.2	NA	NA
		Placebo	1.2	0	1.2		
	4	Taurine	0	0	0	NA	NA
		Placebo	0	0	0		
	5	Taurine	10.5	5.8	7	.353	.520
		Placebo	4.7	2.3	5.8		
	6	Taurine	2.3	1.2	1.2	NA	NA

	Placebo	0	0	1.2		
7	Taurine	1.2	0	0	NA	NA
	Placebo	0	0	0		
8	Taurine	3.5	2.3	0	NA	NA
	Placebo	2.3	0	0		
9	Taurine	0	0	0	NA	NA
	Placebo	0	0	0		
10	Taurine	0	0	0	NA	NA
	Placebo	1.2	1.2	0		
11	Taurine	1.2	1.2	0	NA	NA
	Placebo	0	0	0		
12	Taurine	5.8	2.3	0	NA	NA
	Placebo	3.5	3.5	4.7		
13	Taurine	0	0	0	NA	NA
	Placebo	0	2.3	2.3		
14	Taurine	0	0	0	NA	NA
	Placebo	0	0	1.2		
15	Taurine	0	0	0	NA	NA
	Placebo	0	0	1.2		
16	Taurine	1.2	1.2	0	NA	NA
	Placebo	0	0	0		
17a	Taurine	3.5	1.2	0	NA	NA
	Placebo	4.7	1.2	0		
17b	Taurine	0	0	1.2	NA	NA
	Placebo	0	0	0		
17c	Taurine	0	0	0	NA	NA
	Placebo	0	0	0		

	18	Taurine	0	0	0	NA	NA
		Placebo	0	0	0		
	19	Taurine	0	0	0	NA	NA
		Placebo	0	0	0		

*The p-values are for testing for group difference using logistic regression with baseline score as a covariate.

'NA' means that logistic regression was not done because the number of participants having the symptom at the time point concerned is less than 6.