Topiramate Add-On in Treatment-Resistant Schizophrenia: A Randomized, Double-Blind, Placebo-Controlled, Crossover Trial

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Objective: We tested the hypothesis that topiramate is more effective than placebo in reducing symptoms in patients with treatment-resistant schizophrenia when combined with ongoing antipsychotic medication.

Method: Twenty-six hospitalized treatment-resistant patients with chronic DSM-IV–diagnosed schizophrenia participated in a randomized, double-blind, placebo-controlled trial in which 300 mg/day of topiramate was gradually added to their ongoing treatment (clozapine, olanzapine, risperidone, or quetiapine) over two 12-week crossover treatment periods. Data were collected from April 2003 to November 2003.

Results: In intention-to-treat analysis, topiramate was more effective than placebo in reducing Positive and Negative Syndrome Scale general psychopathologic symptoms (effect size = 0.7, p = .021), whereas no significant improvement was observed in positive or negative symptoms.

Conclusion: Glutamate antagonist topiramate may be an effective adjuvant treatment in reducing general psychopathologic symptoms in patients with schizophrenia resistant to treatment with second-generation antipsychotics.

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Less than half of schizophrenia patients obtain full response to antipsychotic drugs. Therefore, augmentation treatments are widely used for patients with partial response, although there is very little evidence from controlled trials on the efficacy of these treatments.[1] It has been recently observed in 2 randomized trials[2,3] that glutamate antagonist lamotrigine is effective in reducing positive and general psychopathologic symptoms in patients with treatment-resistant schizophrenia when combined with clozapine or other antipsychotics. The risk of exfoliative dermatitis, a relatively rare but severe adverse effect, is a factor that may limit the use of lamotrigine, especially in outpatient care. Four case reports[4–7] have been published concerning augmentation of atypical antipsychotics with another better tolerated glutamate antagonist, topiramate. Three of these reports showed positive results.[5–7] Therefore, we tested the hypothesis that topiramate is more effective than placebo in reducing symptoms

in treatment-resistant schizophrenia patients when combined with ongoing antipsychotic medication.

MATERIAL AND METHOD

The study protocol was approved by the ethical committee of Kuopio University Hospital, Kuopio, Finland, and the National Agency for Medicines, Helsinki, Finland; 36 inpatients gave their written informed consent to participate in the study. The inclusion criteria were DSM-IV[8] diagnosis of schizophrenia, aged 18 to 60 years, and a nonsatisfactory response with ongoing clozapine, olanzapine, risperidone, or quetiapine treatment (duration of antipsychotic treatment at least 4 months; in the preliminary survey, the use of typical antipsychotics was observed to be very rare in the potential study population, and, therefore, those patients were omitted from the study). The exclusion criteria included epilepsy, present anticonvulsant treatment, lithium or digitalis treatment, and severe somatic disease. Data were collected from April 2003 to November 2003.

The study was a randomized, double-blind, placebo-controlled, crossover trial. The randomization was made by a random number generator in blocks of 10 patients (Medfiles, Kuopio, Finland). The allocation sequence was produced independently and concealed until patients had entered the trial. The trial consisted of two 12-week crossover treatment periods. The clinical response was assessed with the Positive and Negative Syndrome Scale[9] (PANSS) at the beginning and the end of each treatment period.

Thirty-five patients were initially assessed eligible for the study, but 9 of them were excluded in the final checkup (3 due to refusal to participate, 1 due to hospital transfer, 3 due to somatic medical condition, and 2 due to change in the antipsychotic medication). Of the 26 patients included in the study, 5 were women. The subtypes of diagnoses were paranoid (N = 10), disorganized (N = 7), undifferentiated (N = 7), and catatonic (N = 2) schizophrenia. The patients' mean ± SD Global Assessment of Functioning (GAF) score was 32.9 ± 8.8.

During the first treatment period, 13 patients were randomly assigned to receive topiramate (group A) and 13 patients to receive placebo (group B). During the topiramate period, the gradually increased daily dose was 25 mg during week 1, 50 mg during week 2, 75 mg during week 3, 100 mg during week 4, 150 mg during week 5, 200 mg during week 6, 250 mg during week 7, and 300 mg during weeks 8 through 12 (since the usual daily dose of topiramate in neurology is 200–400 mg, and 300 mg was the aimed dose in the previous open-label augmentation study).[4] Topiramate and placebo were packed in identical looking gelatin capsules.

All PANSS ratings for each patient were done by the same rater. The interrater reliability index between raters (intraclass correlation) was 0.7 for the PANSS. Plasma clozapine and olanzapine levels were measured prior to and after each treatment period. The data were analyzed on an intention-to-treat (ITT) basis, and the results of observed cases (per protocol) were also analyzed. The primary outcome was PANSS total score, and scores in PANSS general psychopathologic, positive, and negative symptom scales were secondary outcomes.

Differences between baseline characteristics were tested with Student t test (2-tailed). The treatment effects adjusted for baseline scores were analyzed with analysis of repeated measures using mixed models (treatment, treatment period, and baseline scores as factors) for the differences of responses between topiramate and placebo. Since PANSS subscores correlate strongly with each other (are not independent), no correction for multiple testing was applied. Dropout data were considered as no change (estimated change: 0 points) in the parametric tests and regarded as nonresponders (estimated change: 0 points) when comparing response rates (with Fisher exact test). The effect size was calculated as described by Cohen,[10] in which a value of 0.3 is interpreted as a small effect, a value of 0.5 as a medium effect, and a value of 0.8 as a large effect.

RESULTS

Baseline mean ± SD demographic and clinical variables were similar for groups A and B concerning age (42.0 ± 11.4 vs. 45.5 ± 14.4 years; p = .50), GAF score (34.5 ± 9.2 vs. 31.3 ± 8.59; p = .36), and illness duration (17.8 ± 13.1 vs. 18.4 ± 13.5 years; p = .92). PANSS scores were slightly higher in group B (positive scores: 16.4 ± 5.8 vs. 22.4 ± 4.9, p = .01; negative scores: 21.9 ± 6.0 vs. 24.9 ± 6.8, p = .24; general psychopathologic scores: 35.9 ± 6.0 vs. 38.3 ± 8.4, p = .41; total PANSS scores: 74.2 ± 13.8 vs. 85.6 ± 17.1, p = .07). Therefore, the baseline scores were adjusted in the statistical analyses of the treatment effects.

Fourteen patients were receiving clozapine (mean ± SD dose = 598 ± 179 mg/day), 5 patients olanzapine (mean ± SD dose = 26 ± 5 mg/day), and 3 patients quetiapine (mean ± SD dose = 633 ± 208 mg/day). Four patients were receiving a combination of medications: 3 patients clozapine and olanzapine and 1 patient olanzapine and quetiapine.

Three patients discontinued topiramate (2 due to worsening of mental condition, 1 due to low leukocyte levels [3.9 10^9/L]), and 4 patients discontinued placebo (2 due to worsening of mental condition, 2 due to their will to stop the participation) during the first period. Thus, after the crossover, 9 patients started the second period with topiramate and 10 with placebo. During this period, 1 patient discontinued topiramate (due to worsening of mental condition), and, therefore, 18 patients completed the study

Table 1. PANSS Scores of Treatment-Resistant Schizophrenia Patients During Topiramate and Placebo Add-On Treatment, Mean (SD)[a]

	Topiramate (N = 22)		Change During Topiramate	Placebo (N = 23)		Change During Placebo	Effect Size[b]		
PANSS Score	Prior	After	Treatment	Prior	After	Treatment	(95% CI)	p	Statistic
Total	79.47 (4.22)	76.89 (6.67)	–2.58 (6.98)	78.90 (5.12)	78.69 (6.64)	–0.21 (5.93)	0.4 (–0.2 to 1.0)	.205	F = 1.66, df = 1,38.3
Positive symptoms	18.45 (1.37)	18.03 (2.37)	–0.42 (2.44)	19.34 (1.58)	19.00 (2.49)	–0.34 (2.21)	0.1 (–0.5 to 0.7)	.776	F = 0.082, df = 1,39.6
Negative symptoms	22.73 (1.20)	22.64 (2.59)	–0.09 (2.60)	23.33 (2.46)	22.64 (2.41)	–0.69 (1.63)	–0.2 (–0.8 to 0.3)	.433	F = 0.630, df = 1,31.8
General psychopathologic symptoms	38.32 (2.58)	36.29 (3.80)	–2.03 (4.04)	36.19 (3.07)	36.96 (4.39)	0.77 (3.81)	0.7 (0.1 to 1.3)	.021	F = 5.80, df = 1,40.4

[a]Thirteen patients started receiving topiramate during the first treatment period and 9 patients during the second treatment period, whereas 13 patients started receiving placebo during the first treatment period and 10 patients during the second treatment period.
[b]The effect size is adjusted for baseline values (analysis of repeated measures using mixed models).
Abbreviation: PANSS = Positive and Negative Syndrome Scale.

per protocol. The most frequently reported side effects were hypersalivation (23% [5 of 22] during topiramate, 48% [11 of 23] during placebo), asthenia (36% [8 of 22] during topiramate, 35% [8 of 23] during placebo), memory disturbances (27% [6 of 22] during topiramate, 35% [8 of 23] during placebo), sedation (32% [7 of 22] during topiramate, 30% [7 of 23] during placebo), and weight gain (23% [5 of 22] during topiramate, 30% [7 of 23] during placebo). The differences in side effects were not statistically significant. The weight change (mean ± SD) was –0.6 ± 3.5 kg during topiramate treatment and 0.3 ± 3.0 kg during placebo treatment (p = not significant for difference).

The measured effects during the topiramate and placebo treatment periods are shown in Table 1. Topiramate was markedly more effective than placebo in reducing general psychopathologic symptoms (effect size = 0.7, p = .021), whereas no substantial beneficial effect was observed for positive or negative symptoms (when data on patients with placebo were omitted, effect size was 0.5; p = not significant for general psychopathologic symptoms prior vs. after topiramate). The greatest reductions (between topiramate vs. placebo) were observed in depression (PANSS item G6), preoccupation (PANSS item G15), and guilt feelings (PANSS item G3). Three patients (14%) had over 20% reduction in general psychopathologic symptom scores during topiramate treatment versus 0 patients during placebo treatment (p = .11 for difference, Fisher exact test). When only the first period was included in the ITT analysis (N = 13 + 13), the mean ± SD change in general psychopathologic score was –2.84 ± 3.93 with topiramate versus 0.91 ± 3.93 with placebo (effect size = 1.0, t = 2.43, df = 24, p = .023; adjusted for baseline score). Among patients receiving clozapine (N = 14), the effect size for general psychopathologic score was 0.5, and among male patients (N = 21), the effect size was 0.4. In observed cases analysis (per protocol), the beneficial effect of topiramate in reducing general psychological symptoms was slightly more robust (effect size = 0.8, t = 2.54, df = 36, p = .016; adjusted for baseline score) than in ITT analysis.

The mean ± SD plasma clozapine levels did not increase substantially during topiramate treatment (1.91 ± 0.88 μmol/L prior, 1.44 ± 0.54 μmol/L after; plasma levels available from 12 subjects) or with placebo (1.63 ± 0.78 μmol/L prior, 1.91 ± 0.68 μmol/L after; plasma levels available from 11 subjects), nor did plasma olanzapine levels with topiramate (246 ± 85 nmol/L prior, 222 ± 118 nmol/L after; plasma levels available from 5 subjects) or with placebo (251 ± 130 nmol/L prior, 260 ± 92 nmol/L after; plasma levels available from 5 subjects).

DISCUSSION

This study suggests that topiramate may be an effective and relatively well tolerated add-on medication in reducing general psychopathologic symptoms among chronic patients with treatment-resistant schizophrenia. The possibility of a confounding carryover effect is excluded by our observation of a significant effect already in the first phase of the trial. Due to small sample size, the results must be considered preliminary. While general psychopathologic symptoms decreased during topiramate treatment, there was a slight increase in this score during placebo treatment, implying that in the crossover design, the symptoms started to worsen after the switch from active medication to placebo.

Since topiramate decreases the presynaptic release of glutamate and acts as an antagonist for postsynaptic kainate receptors, the results imply that excessive glutamate neurotransmission via kainate receptors may contribute to general psychopathologic symptoms of schizophrenia. The results imply that the therapeutic effect of topiramate may differ from lamotrigine, which has been

reported to have beneficial effect on both positive and general psychopathologic symptoms.[2,3] This effect may be explained by the slightly different pharmacologic profiles of lamotrigine and topiramate: lamotrigine's mechanism of action is associated with predominant attenuation of glutamate excitatory neurotransmission, whereas topiramate is an agent having a mixed profile with both γ-aminobutyric acid (GABA)–ergic and antiglutamatergic actions.[11]

What is the clinical relevance of these findings? Our results suggest that about 10% to 20% of chronically ill schizophrenia patients may receive clinically relevant benefit from adjuvant topiramate treatment in general psychopathologic symptoms such as depression and guilt feelings. Although pharmacologic studies generally focus on the change in positive or negative symptoms, it has been observed that depressive symptoms (which are included in the PANSS general psychopathologic symptom score) contribute more to the quality of life of schizophrenia patients than positive or negative symptoms.[12,13] Therefore, topiramate add-on treatment may improve the quality of life in a subgroup of chronically seriously ill patients suffering from general psychopathologic symptoms such as depression.

Drug names: clozapine (Clozaril, FazaClo, and others), lamotrigine (Lamictal), lithium (Eskalith, Lithobid, and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), topiramate (Topamax).

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