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Original Paper

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Abstract

The persistence of psychotic, affective, cognitive, and psychosocial symptoms despite medications is commonly observed in schizophrenic patients. The present study was a 24-week double-blind, randomized, placebo-controlled trial aimed to explore the efficacy of topiramate add-on pharmacotherapy on clinical symptomatology and cognitive functioning in a sample of treatment-resistant schizophrenic patients receiving clozapine. After clinical and cognitive assessments were randomly allocated to receive either up to 200 mg/day of topiramate or a placebo. A final sample of 43 patients completed the study. The results obtained indicate that topiramate appeared to be scarcely effective for reducing clinical symptomatology in schizophrenic patients who have had an incomplete clinical response to clozapine. Regarding cognitive functioning, in our sample a trend to experience cognitive impairment in the examined domains was observed, as the patients included in the topiramate groups expressed cognitive complaints partially confirmed by a mild worsening of performances on certain cognitive tasks. Schizophrenia is a heterogeneous disorder with regard to pathophysiology; therefore, data reflecting the mean response of a sample of patients may fail to reveal therapeutic effects. More research is needed to better identify subgroups of patients with peculiar features which may account for responsivity to experimental medications and augmentation strategies.

Keywords

Clozapine, residual symptoms, schizophrenia, topiramate

Introduction

Psychopharmacological treatments have drastically modified the longitudinal course and outcome of schizophrenia. Nevertheless, it was estimated that only 10–20% of patients with schizophrenia show a good outcome, recovering to pre-illness levels of functioning, while another 15–20% show a poor outcome and are considered treatment resistant; the middle group presents residual symptoms in several domains of schizophrenia, such as cognitive, psychotic and affective symptoms, and impaired socio-occupational functioning despite medications (Tamminga and Holcomb, 2005). Beyond the dopaminergic model of schizophrenia, which has led to effective treatments for the psychotic symptoms, the dysfunction of glutamatergic transmission may be involved in the pathophysiology of schizophrenia, representing a potential target for pharmacological treatment (Goff and Coyle, 2001; Tamminga, 1999; Tuominen et al., 2005). Glutamate is the primary excitatory neurotransmitter in the brain, and glutamatergic fibres give rise to the major afferent, intrinsic and efferent pathways through the cortex (Ulas and Cotman, 1993). The assessments of free glutamate levels in the brains of patients with schizophrenia have produced conflicting results. As suggested by Hosák and Libiger (2002), an increased glutamate concentration in the cerebral tissue of patients with schizophrenia would be consistent with a defect in the pre-synaptic release of glutamate, while diminished levels would mean a degeneration of glutamatergic nerve terminals. The action of glutamate is mediated at ionotropic and metabotropic receptors. Ionotropic receptors include the *N*-methyl-D-aspartate (NMDA), α-amino-3-hydroxy-5-methyl-isoxazole-4-propionic acid (AMPA), and kainate receptors. The most persuasive evidence linking glutamatergic receptor function with schizophrenia is offered by the psychotomimetic effects induced by the dissociative anaesthetics phencyclidine (PCP) and ketamine (Corssen and Domino, 1966; Halberstadt, 1995; Haroutunian et al., 2003; Jentsch and Roth, 1999). As PCP and ketamine exert their behavioural effect by noncompetitively antagonizing the NMDA

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receptor-mediated neurotransmission (Javitt and Zukin, 1991), endogenous NMDA hypofunction may play a critical role in the pathogenesis of schizophrenia. As suggested by Olney and Farber (1995), NMDA hypofunction, combined with dopaminergic system dysfunction, would be the key mechanisms in the pathophysiology of schizophrenia. The main consequences of NMDA receptor hypofunction are diminished GABAergic tone and increase of glutamate release onto other receptors, such as AMPA/kainate, which would result in excitotoxic neuronal damage (Deutsch et al., 2001). The PCP model and the hypothesized NMDA receptor hypofunction have led to explore new therapeutic approaches which include the stimulation of NMDA receptors (Farber et al., 1999), the antagonism of AMPA/kainate receptors (Deutsch et al., 2003; Farber et al., 2002), and the inhibition of presynaptic glutamate release by lamotrigine (Anand et al., 2000; Dursun and Deakin, 2001; Tiihonen et al., 2003; Zoccali et al., 2007). Topiramate, a sulfamate substituted derivative of the monosaccharide D-fructose, is an antiepileptic drug used as adjunctive therapy for adult and children with partial-onset seizures and primary generalized tonic–clonic seizures. Its pharmacological properties include the potentiation of the inhibitory GABAergic transmission, probably through a non-benzodiazepine mechanism, and AMPA/kainate receptor antagonism (Arnone, 2005; Shank et al., 2000). In animal models of schizophrenia, topiramate was effective in attenuating the severity of popping behaviour elicited by MK-801, a high-affinity analogue of PCP. Popping behaviour, which consists of irregular episodes of intense jumping behaviour in mice, is considered an equivalent of psychotic behaviour and it has been used as a paradigm to explore new candidate medications for schizophrenia (Deutsch et al., 2002). Case reports, open-label case series, and randomized, double-blind, placebo-controlled trials of topiramate augmentation in schizophrenia showed conflicting results (see Table 1). Moreover, topiramate-induced psychosis was observed in a bipolar patient (Kober and Gabbard, 2005), and in two members of the same family treated for familial essential tremor and for migraine prophylaxis, respectively (Paixão José et al., 2008).

Concerning cognitive functioning, the use of topiramate was associated with impaired concentration and memory, slow reasoning, and speech difficulty (Duggal, 2004); poor performances on neuropsychological tasks measuring verbal fluency, verbal IQ, learning, working memory, and short-term memory (Kang et al., 2007; Lee et al., 2003; Thompson et al., 2000). By contrast, a randomized clinical trial has reported less marked cognitive effects of topiramate given as an add-on treatment at the dose of 200 mg/day (Aldenkamp et al., 2000). Data on the potential effect of adjunctive topiramate on cognitive functioning in patients with schizophrenia are still lacking; Deutsch et al. (2003) found that only verbal fluency and working memory were adversely affected by topiramate, while other cognitive measures, such as recall and recognition, were not disrupted by adjunctive topiramate.

Based on evidence from the literature, the present study was designed to explore the efficacy of topiramate add-on pharmacotherapy on clinical symptomatology and cognitive functioning in a sample of patients with treatment-resistant schizophrenia receiving clozapine.

Methods

Subjects

The study was carried out at the Psychiatry Unit of the University Hospital of Messina, Italy.

Sixty outpatients, 38 males and 22 females, aged 23–58 years, who met DSM-IV criteria for schizophrenia and demonstrated persistent positive and negative symptoms despite an adequate trial of clozapine, were included in this study. Patients scoring 25 or more on the Brief Psychiatric Rating Scale (Overall and Gorham, 1962) at the baseline evaluation were classified as partial responders or non-responders (Munro et al., 2004). The patients' age, gender, and antipsychotic mean dose are shown in Table 2. The topiramate and placebo groups were compared for the different variables. All patients had been on clozapine monotherapy at the highest tolerable range (150–650 mg/day), for at least 1 year; the dose had been stable for at least 1 month prior to the study and was left unchanged throughout the study. The patients did not receive any antidepressant or anticonvulsant drugs for a period of 2 months prior to the study. During the study, patients were allowed to take lorazepam up to 5 mg/day for insomnia or agitation. Patients with any other major psychiatric disorder, significant concurrent medical illnesses, organic brain disorder, history of substance and alcohol abuse, or mental retardation, and pregnant or lactating women were excluded. All the patients provided written informed consent after a full explanation of the protocol design which had been approved by the local ethics committee. The patients were recruited from January 2007 and the follow-up was completed by October 2008.

Study design

This trial was a 24-week double-blind, randomized, placebo-controlled trial of adjunctive topiramate to clozapine therapy in schizophrenia. After baseline evaluation, subjects were randomly assigned to receive adjunctive treatment with either topiramate or placebo under double-blind conditions, using a randomization automated system on a 1:1 basis. During the study, the randomization list was held securely and released only after study completion. Topiramate and placebo were dispensed in identical-appearing capsules; patients randomized to placebo took the same number of capsules as those assigned to topiramate.

The dose of topiramate was increased from 25 mg/day to 100 mg/day at week 4, in increments of 25 mg/week. The dose was maintained at 100 mg/day for 8 weeks until week 12. The dose was afterwards increased by a further 25 mg/week until a dosage of 200 mg/day was reached at week 16. This dosage was maintained until the end of the trial at week 24. The rationale for this unique biphasic topiramate titration scheme was chosen to test the hypothesis that the efficacy of adjunctive topiramate might be dose-dependent; the maximum dose of 200 mg per day was established according to Deutsch et al. (2003).

The following rating scales were used: the Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1962), the Scale for the Assessment of Negative Symptoms (SANS)

Table 1. Case reports, case series, open-label and randomized, double-blind, placebo-controlled trials of topiramate augmentation in schizophrenia

Study	Study design	Trial duration	Patient diagnosis	Antipsychotic(s)	Topiramate (mg/day)	Results
Dursun and Deakin (2001)	Naturalistic follow-up case-series	24 weeks	Treatment-resistant schizophrenia ($n = 9$)	Clozapine, olanzapine, flupentixol, haloperidol	225–300	No significant improvement of BPRS scores
Drapalski et al. (2001)	Case report	12 weeks	Chronic undifferentiated schizophrenia ($n = 1$)	Olanzapine	175	Significant improvement in negative symptoms
Millson et al. (2002)	Case series	9 weeks	Refractory schizophrenia ($n = 5$)	Clozapine, quetiapine, risperidone	50–250	Worsening of both positive and negative symptoms
Deutsch et al. (2003)	Open-label	17 weeks	Schizophrenia and schizoaffective disorder ($n = 12$)	Conventional and atypical	75–175	Significant improvement in positive and negative symptoms
Tiihonen et al. (2005)	Randomized, double-blind, placebo-controlled, cross-over	12 weeks	Treatment-resistant schizophrenia ($n = 22$)	Clozapine, olanzapine, quetiapine in monotherapy or combined	300	Significant improvement in general psychopathology symptoms
McDaniel et al. (2006)	Case series	1 year follow-up	Catatonia in schizophrenia or bipolar disorder ($n = 4$)	Risperidone olanzapine quetiapine	200	Complete remission of catatonic symptoms
Chengappa et al. (2007)	Randomized, placebo-controlled	16 weeks	Schizoaffective disorder, bipolar type ($n = 32$)	Conventional and atypical plus mood stabilizers (valproate and/or lithium)	100–400	No significant improvement of PANSS scores
Afshar et al. (2008)	Randomized, double-blind, placebo-controlled	8 weeks	Schizophrenia ($n = 16$)	Clozapine	300	Significant improvement of positive, negative and general psychopathology symptoms in half of patients receiving topiramate (8/16)

BPRS, Brief Psychiatric Rating Scale; PANSS, Positive and Negative Syndrome Scale.

Table 2. Demographic and clinical characteristics of the sample (clozapine plus topiramate vs clozapine plus placebo)

Parameters	Topiramate	Placebo	*p*-value[a]
Patients entered	30	30	–
Patients evaluated	19	24	–
Sex (male/female)	14/5	17/7	–
Age (years)	32.3 ± 4.6	31.5 ± 4.9	0.710
Duration of illness (years)	5.9 ± 2.2	5.1 ± 2.2	0.456
Duration of untreated psychosis (months)	8.0 ± 1.9	7.6 ± 2.1	0.656
Clozapine dose (mg/day)	333.3 ± 61.2	327.3 ± 84.7	0.941

Values are number or mean ± SD.
[a]Mann–Whitney *U*-test.

(Andreasen, 1983), the Scale for the Assessment of Positive Symptoms (SAPS) (Andreasen, 1984), and the Calgary Depression Scale for Schizophrenia (CDSS) (Addington et al., 1993). While inter-rater reliability for these assessments was not established by formal training, it is important to note that the assessments were conducted by psychiatrists with at least 5 years of clinical experience who were well versed with the use of the rating scales.

Neurocognitive functioning was assessed with the Wisconsin Card Sorting Test (WCST) (Heaton et al., 1993), the Verbal Fluency Task (Controlled Oral Word Association Test, Spreen and Benton, 1977), and the Stroop Colour-word Test (Trenerry et al., 1989). WCST is a commonly used measure of concept formation and flexibility of abstract thought in schizophrenia, though it is useful to assess executive functioning. Measures of performance included the number of completed categories and the number of perseverative errors. The tests were selected for the inclusion of functions frequently attributed to the frontal lobes and widely used in the study of cognition in schizophrenia.

Patients attended 10 visits: initial screening (week −1), randomization (week 0), and eight further visits at weeks 2, 4, 8, 12, 14, 16, 20, and 24. Data for clinical and neurocognitive assessments were collected at weeks 0, 12, and 24. Data for adverse events and extrapyramidal symptoms (elicited by non-specific questioning) were collected at each visit.

In addition to a physical examination, systolic and diastolic blood pressure, heart rate and body weight were all measured at each assessment. A routine set of laboratory investigations (blood profile, prothrombin time (PT), activated partial thromboplastin time (aPTT), fibrinogen, basal glucose, cholesterol, triglycerids, uric acid, azotemy, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, total and direct bilirubine, gamma-glutamyl transferase (GGT), iron, erythrocyte sedimentation rate (ESR)) was performed on all patients on admission and at the end of the study.

Statistical analysis

Data obtained from completers underwent check and quality control and, subsequently, descriptive and inferential statistical analysis. No last observation carried forward was performed. Comparison between the groups at baseline and at end of week 24 was performed using the Mann–Whitney *U*-test for two independent samples.

The within-group differences in efficacy ratings between baseline and final test were analysed by the Wilcoxon rank sum test. Taking into account that multiple correlations increase the risk of Type 1 errors, a Bonferroni correction was applied and a significance value of $p < 0.002$ was chosen.

The statistical analysis was performed with Statistical Package for the Social Sciences (SPSS) 11.5 software (SPSS Inc, Chicago, IL, USA).

Results

Forty-three patients completed the study and were included in the analyses of efficacy (Table 2). There were 17 premature dropouts, 11 in the topiramate group and six in the placebo group. Of the topiramate group, four dropouts were due to concurrent illness and seven due to non-compliance with the visits. Of the placebo group, two dropouts were due to non-compliance and four patients changed their mind about participating in the study.

At the baseline visit (day 0), there were no significant differences between clozapine and control groups on SANS, SAPS, BPRS, CDSS, Stroop test, verbal fluency, and WCST scores (Table 3).

The measured effects during the topiramate and placebo treatment in active group are shown in Tables 3 and 4. No significant improvement was observed in negative, positive, affective and overall clinical symptomatology over the time of treatment (from baseline to week 24). In clozapine group, only the Bizarre behaviour score of the SAPS scale showed a significant reduction in topiramate group, but not in the placebo group. With regard to cognitive functioning, as measured by Stroop test, verbal fluency and WCST, topiramate augmentation of clozapine had no significant effects (see Tables 5 and 6).

At T0, the topiramate-treated patients mean body weight (SD) was 79.67 kg (8.2) versus 78.67 kg (9.4) at the end of the trial (week 24); the difference was not statistically significant ($Z = -1.186$; $p = 0.236$). There were no serious adverse events in the study. Furthermore, no clinically significant changes in vital signs and laboratory values were observed. However, certain adverse events, ranging from 'mild' to 'moderate', were noted more frequently in the topiramate group: asthenia, sedation, and paresthaesia. In the placebo group, constipation and hypersalivation were the most reported side effects. Cognitive complaints in the topiramate group included: word-finding difficulties, memory disturbances, and slow reasoning; the decrement in cognitive functioning was partially confirmed by our statistical data, as the performances to certain cognitive tasks were slightly worsened, although not statistically significant (Tables 5 and 6).

Table 3. Clinical changes in clozapine patients receiving topiramate versus placebo at baseline and week 24

	Topiramate		Placebo		Mann–Whitney *U*-test			
	Baseline	Week 24	Baseline	Week 24	Difference at baseline		Difference at week 24	
SANS								
Affective flattening	9.9 (10.4)	4.6 (3.9)	11.2 (9.6)	10.5 (8.6)	43.000	0.656	33.000	0.230
Alogia	8.3 (7.8)	3.4 (4.0)	9.0 (7.8)	8.8 (7.1)	47.000	0.882	26.500	0.080
Avolition/apathy	5.6 (4.2)	5.3 (3.3)	6.1 (3.8)	6.2 (3.8)	47.000	0.882	43.500	0.656
Anhedonia/Asociality	12.2 (7.7)	5.4 (6.7)	12.4 (6.8)	11.1 (6.3)	48.500	0.941	25.500	0.067
Attention	3.8 (4.1)	1.9 (2.8)	3.6 (3.6)	4.4 (3.3)	49.500	1.000	20.000	0.025
Total score	39.8 (32.5)	20.7 (15.7)	42.3 (29.9)	41.0 (27.3)	47.000	0.882	28.000	0.112
SAPS								
Hallucinations	7.1 (10.4)	4.2 (5.2)	8.0 (9.6)	7.2 (7.8)	43.000	0.656	31.500	0.175
Delusions	8.7 (6.2)	4.1 (6.3)	9.8 (5.7)	9.5 (5.2)	44.500	0.710	20.000	0.025
Bizarre behaviour	0.7 (1.4)	0.1 (0.3)	1.3 (1.6)	1.9 (1.2)	38.500	0.412	6.500	$p < 0.002$
Thought disorders	5.7 (6.6)	2.2 (3.4)	6.3 (6.6)	5.9 (6.2)	45.000	0.766	27.000	0.095
Total score	21.2 (19.2)	10.7 (14.5)	24.6 (18.4)	23.8 (16.3)	43.500	0.656	23.000	0.046
BPRS total score	35.6 (9.7)	32.1 (7.5)	36.1 (9.4)	36.6 (9.9)	43.000	0.656	38.500	0.412
CDSS total score	7.6 (4.5)	5.8 (4.6)	8.0 (4.2)	6.9 (3.0)	49.500	1.000	36.000	0.331

BPRS, Brief Psychiatric Rating Scale; CDSS, Calgary Depression Scale for Schizophrenia; SANS, Scale for the Assessment of Negative Symptoms; SAPS, Scale for the Assessment of Positive Symptoms.

Table 4. Cognitive functions at baseline and at week 24 in clozapine patients receiving topiramate versus placebo

	Topiramate		Placebo		Mann–Whitney *U*-test			
	Baseline	Week 24	Baseline	Week 24	Difference at baseline		Difference at week 24	
Stroop test	50.0 (24.0)	39.8 (17.8)	61.7 (17.2)	63.4 (12.5)	36.000	0.331	12.000	0.003
Phonemic fluency	24.2 (17.0)	20.3 (10.2)	21.9 (13.0)	20.6 (11.0)	48.500	0.941	47.000	0.882
Semantic fluency	35.0 (9.5)	32.3 (8.4)	33.7 (7.5)	33.4 (8.9)	44.500	0.710	41.000	0.552
WCST								
Perseverative errors	30.1 (24.4)	35.9 (25.6)	36.0 (23.0)	36.4 (21.8)	40.500	0.503	49.000	1.000
Categories	2.1 (2.6)	2.1 (2.3)	2.0 (2.1)	1.8 (1.7)	48.500	0.941	48.000	0.941

WCST, Wisconsin Card Sorting Test.

Table 5. Clinical changes in clozapine patients receiving topiramate at baseline, at week 12, and at week 24

	Baseline	Week 12	Week 24	Difference baseline vs week 12[a]		Difference baseline vs week 24[a]	
SANS							
Affective flattening	9.9 (10.4)	10.0 (9.6)	4.6 (3.9)	−0.316	0.752	−1.550	0.121
Alogia	8.3 (7.8)	6.0 (6.8)	3.4 (4.0)	−0.954	0.340	−1.476	0.140
Avolition/apathy	5.6 (4.2)	4.8 (2.5)	5.3 (3.3)	−0.730	0.465	−0.431	0.666
Anhedonia/Asociality	12.2 (7.7)	11.4 (5.2)	5.4 (6.7)	−0.105	0.916	−2.375	0.018
Attention	3.8 (4.1)	3.1 (3.8)	1.9 (2.8)	−1.069	0.285	−2.060	0.039
Total score	39.8 (32.5)	35.3 (25.2)	20.7 (15.7)	−0.178	0.859	−1.965	0.049
SAPS							
Hallucinations	7.1 (10.4)	4.9 (7.1)	4.2 (5.2)	−2.058	0.040	−1.160	0.246
Delusions	8.7 (6.2)	7.2 (7.4)	4.1 (6.3)	−0.509	0.611	−1.749	0.073
Bizarre behaviour	0.7 (1.4)	0.9 (1.8)	0.1 (0.3)	−0.378	0.705	−1.342	0.180
Thought disorders	5.7 (6.6)	4.4 (7.2)	2.2 (3.4)	−0.106	0.916	−1.581	0.114
Total score	21.2 (19.2)	17.4 (18.1)	10.7 (14.5)	−0.568	0.570	−1.544	0.123
BPRS total score	35.6 (9.7)	36.0 (11.5)	32.1 (7.5)	−0.341	0.733	−2.113	0.035
CDSS total score	7.6 (4.5)	6.2 (4.7)	5.8 (4.6)	−1.947	0.052	−1.586	0.113

BPRS, Brief Psychiatric Rating Scale; CDSS, Calgary Depression Scale for Schizophrenia; SANS, Scale for the Assessment of Negative Symptoms; SAPS, Scale for the Assessment of Positive Symptoms.
[a]Wilcoxon test.

Table 6. Cognitive functions at baseline, at week 12, and at week 24 in clozapine patients receiving topiramate

	Baseline	Week 12	Week 24	Difference baseline vs week 12[a]		Difference baseline vs week 24[a]	
Stroop test	50.0 (24.0)	40.7 (20.3)	39.8 (17.8)	−1.602	0.109	−1.009	0.313
Phonemic fluency	24.2 (17.0)	23.1 (13.8)	20.3 (10.2)	−0.416	0.677	−1.009	0.313
Semantic fluency	35.0 (9.5)	35.1 (7.7)	32.3 (8.4)	0.000	1.000	−0.852	0.394
WCST							
Perseverative errors	30.1 (24.4)	30.3 (25.4)	35.9 (25.6)	0.000	1.000	−1.263	0.206
Categories	2.1 (2.6)	1.8 (2.5)	2.1 (2.3)	−1.089	0.276	0.000	1.000

WCST, Wisconsin Card Sorting Test.
[a]Wilcoxon test.

Discussion

Based on our findings, adjunctive topiramate treatment appeared to be scarcely effective for reducing clinical symptomathology in patients with schizophrenia who have had an incomplete clinical response to clozapine. Examining SANS and SAPS subscales, a significant reduction of Bizarre behaviour score emerged at the end of the trial in patients receiving clozapine plus topiramate. SAPS Bizarre behaviour subscale includes: clothing and appearance, social and sexual behaviour, aggressive behaviour, and stereotyped behaviour. Factor analyses and other analysis conducted at item-level evidenced that Bizarre behaviour subscale seems to identify a symptomatic cluster that is relatively independent from other symptom dimensions measured by SAPS subscales (Andreasen et al., 1995; John et al., 2003; Peralta and Cuesta, 1999). Neverthless, topiramate has been demonstrated to improve aggression, disruptive and self-injurious behaviours in intellectual disabled subjects (Janowsky et al., 2003), impulsivity in OCD (Ramos Rios et al., 2007), disruptive behaviours in bipolar patients (Barzman and Delbello, 2006), and catatonia (McDaniel et al., 2006). The improvement in Bizarre behaviour found in our study is congruent with the results of a previous research by Gobbi et al. (2006) who reported the efficacy of topiramate in decreasing aggressive behaviours independently from its effect on psychotic symptoms that remained unchanged throughout the observational period. The supposed neurobiological mechanism by which topiramate exerts its behavioural effect still remains speculative; it may be hypothesized a positive modulatory effect on the activity of gamma-aminobutyric acid and a negative modulatory effect on glutamate.

The low rate of dropouts in the sample during the 24-week treatment period suggests that topiramate augmentation was reasonable and well tolerated at 200 mg/day dosage. Unexpectedly, in our sample, adjunctive topiramate was not associated with weight loss. Weight loss and body mass index reduction have been reported in several studies involving topiramate (Dursun and Devarajan, 2000; Lin et al., 2005). Interpretation of the overall tolerability of treatment is limited by the non-systematic evaluation of any side effects. The failure to observe a good clinical response of topiramate augmentation in partial-responder schizophrenic patients is in contrast with previous reports that found adjunctive topiramate effective when added to ongoing antipsychotic medications (Afshar et al., 2008; Deutsch et al., 2003; Drapalski et al., 2001; McDaniel et al., 2006). Differences in methodology must be taken into account, as earlier studies reporting beneficial effects of topiramate augmentation were mainly open-label trials, case reports, and case series. Open studies may be confounded by patients and clinicians expectations and bias toward favourable outcomes. Expectation biases may result in assigning favourable scores on clinical rating scales for newer treatments that randomized, double-blind studies usually avoid. It must also be considered that the course of schizophrenia, such as other psychiatric disorders, is episodic in nature and results in open-label studies may be confounded by spontaneous improvements being improperly attributed to the effect of the augmentation treatment. Also double-blind, placebo-controlled studies are affected by spontaneous improvements, but the random assignment to an active drug or placebo should result in the inclusion of nearly equal numbers of spontaneously recovering patients in each treatment group. Partial results on the efficacy of topiramate add-on in patients with treatment-resistant schizophrenia were reported by Tiihonen et al. (2005) who observed only a reduction of general psychopathological symptoms (mainly depression, preoccupation, and guilt feelings), whereas no significant improvement in positive and negative symptoms was found. The authors suggested that the therapeutic effect of topiramate may differ from that of lamotrigine, which has shown benefits for both positive and general psychopathological symptoms in schizophrenia (Tiihonen et al., 2009; Zoccali et al., 2007). One proposed mechanism is that lamotrigine, by preventing excessive glutamate release, may have a potential to maintain optimal glutamate levels in patients with schizophrenia (Gray and Risch, 2009). As suggested by Dursun and Deakin (2001), it may be hypothesized that glutamate hyperfunction in schizophrenia may have primarily a presynaptic basis; whereas lamotrigine is a glutamate release inhibitor, topiramate is a glutamate kainate/AMPA antagonist and the role of these receptors as potential targets for therapeutical approaches in schizophrenia needs further investigation. A recent study on animal models (Jardemark et al., 2009) showed that topiramate had differential effects on prefrontal glutamatergic transmission when combined with clozapine or raclopride; the combination of topiramate and raclopride significantly potentiates NMDA receptor-mediated glutamatergic transmission in the medial prefrontal cortex. In contrast, adjunctive topiramate impaired the facilitation of prefrontal glutamatergic transmission generated by a high but clinically relevant concentration of clozapine. These findings may help explain the lack of improvement or

the deterioration (Millson et al., 2002) of both positive and negative symptoms when topiramate was used as adjunctive treatment to schizophrenic patients receiving clozapine. Beyond these possibilities, it must also be considered that, in the present study, the dose levels of topiramate (200 mg/day) were lower than those used in previous double-blind, placebo-controlled trials in patients with schizophrenia that obtained positive findings (Afshar et al., 2008; Tiihonen et al., 2005). In our study, the dose of 200 mg/day was established with the aim to rule out or minimize the risk of cognitive impairment, a well-known dose-dependent side effect during topiramate treatment, as described in a number of studies (Arif et al., 2009; Gilliam et al., 2003; Lee et al., 2003; Thompson et al., 2000). Despite using a lower dose, in our sample a trend to experience cognitive impairment in the examined domains (phonemic fluency and perseverative errors at WCST) was observed, as the patients included in the topiramate group expressed cognitive complaints partially confirmed by a mild worsening of performances on certain cognitive tasks. It must be recognized, however, that cognitive functioning was almost preserved in our study population and this may reflect the relatively young age of the participants (Kurtz, 2005). The results from an open study by Deutsch et al. (2003) on 12 patients with schizophrenia or schizoaffective disorder selected for the persistence of severe negative symptoms demonstrated that topiramate treatment (up to 175 mg/day) improved negative symptoms and general psychopathology as measured by PANSS affecting adversely only certain aspects of cognition, such as verbal fluency and working memory, whereas recall and recognition were not disrupted by topiramate. However, in the cited study, the possibility that the improvement in negative symptoms was mainly due to an effect on depressive symptomatology could not be ruled out because the study sample was also formed by schizoaffective patients and no specific measures of depressive symptoms were used.

Taking into account the limitations, such as the low dose of topiramate, and the selection of patients, this study is clinically relevant for several reasons. Negative and residual symptoms are difficult to treat and there is a main need for the development on new therapeutic strategies for schizophrenia with innovative mechanisms of action which may improve the deficit state of patients with schizophrenia and, consequently, quality of life and socialization. Currently available drugs for mono- or adjunctive therapy of schizophrenia act on dopamine D2 receptor; theoretically, topiramate has the ability to antagonize progressive neurodegeneration secondary to excitotoxicity and to balance neurotransmission along hypothesized circuits in the cerebral cortex and hippocampus. Our findings showed that the addition of topiramate to clozapine does not appear to improve residual negative and positive symptoms in patients with schizophrenia who have failed to respond sufficiently to antipsychotics. On the other hand, it must be specified that schizophrenia is a heterogeneous disorder with regard to pathophysiology; therefore, data reflecting the mean response of a sample of patients may fail to reveal therapeutic effects. More research is needed to better identify subgroups of patients with peculiar features which may account for responsivity to experimental medications and which drug combinations and augmentation strategies are more beneficial in patients with refractory schizophrenia.

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