

Clinical outcome and side effect of Topiramate as adjunctive treatment in outpatients with bipolar disorder at King Chulalongkorn Memorial Hospital, Thai Red Cross Society

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- Aims** : *To study clinical outcomes and side effects of topiramate as adjunctive treatment in outpatients with bipolar disorder at King Chulalongkorn Memorial Hospital, Thai Red Cross Society.*
- Method** : *The study was conducted in patients with bipolar disorder at King Chulalongkorn Memorial Hospital from August 2000 to August 2002. There are 33 bipolar cases who used topiramate as adjunctive therapy. The average dose of topiramate was 25- 500 mg per day. The Clinical Global Impression (CGI) was used to determine the efficacy of treatment in five months. The adverse effects were present in detail.*
- Result** : *There were thirty-three cases of bipolar disorder. The mean age was 38.5 year. The average duration of symptoms were 11.5 years. The patients received topiramate 152 mg per day. The study demonstrated the improvement of the patients which statistically improved the CGI scores.($P < 0.01$) Most of the commonly reported adverse effects were mild to moderate such as headache, depression, nausea/vomiting, numbness and cognitive dullness. The patients had average 3.1 kg weight loss. The co-medications were lithium, anticonvulsant, low-dose neuroleptic and antidepressants.*

Conclusion : *Outpatients with bipolar disorder who used topiramate as adjunctive therapy demonstrated improvement. The common adverse effects were headache which patients can tolerate. The interested side effect is the body weight loss.*

Keywords : *Topiramate, Adjunctive, Bipolar disorder, Outpatient, Clinical outcome, Side effects.*

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เดชา ลลิตอนันต์พงศ์, ดวงใจ กสานติกุล. ผลการรักษา และผลข้างเคียงจากการใช้ โทพิราเมต
ในการรักษาเสริมผู้ป่วยนอก โรคอารมณ์แปรปรวน โรงพยาบาลจุฬาลงกรณ์ สภากาชาดไทย.
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- วัตถุประสงค์** : เพื่อศึกษาผลการรักษา และ ผลข้างเคียงจากการเสริมการใช้ โทพิราเมต
ในผู้ป่วยนอก โรคอารมณ์แปรปรวน โรงพยาบาลจุฬาลงกรณ์ สภากาชาดไทย
- วิธีการศึกษา** : เป็นการศึกษาการรักษาผู้ป่วยนอก โรคอารมณ์แปรปรวน ในโรงพยาบาล
จุฬาลงกรณ์ ที่มารับการรักษาในช่วงสิงหาคม 2543 - สิงหาคม 2545 จำนวน
33 ราย ที่ได้รับโทพิราเมต เป็นยาเสริม โดยมีขนาดของโทพิราเมต 25 - 500
มิลลิกรัมต่อวัน การเปลี่ยนแปลงในผลการรักษา ใช้ Clinical Global Impression
(CGI) ในเวลา 5 เดือน และนำเสนอผลข้างเคียงที่เกิดขึ้นในเชิงพรรณนา
- ผลการศึกษา** : ผู้ป่วยโรคอารมณ์แปรปรวน จำนวน 33 ราย อายุเฉลี่ย 38.5 ปี เพศหญิง 25 คน
ชาย 8 คน โดยมีระยะเวลาป่วยมานาน เฉลี่ย 11.5 ปี ได้รับโทพิราเมตเฉลี่ย
152 มก. ต่อวัน ติดต่อกันนานเฉลี่ย 5.3 เดือน พบว่าผู้ป่วยมีลักษณะอาการ
ทางคลินิกดีขึ้น โดย CGI เปลี่ยนแปลงในทางดีขึ้นอย่างมีนัยสำคัญทางสถิติ
ผลข้างเคียงที่พบคือ ปวดศีรษะระดับปานกลาง ซึมเศร้า คลื่นไส้อาเจียน ชา
ตามปลายมือ-เท้า และการรับรู้ช้าลง น้ำหนักลดเฉลี่ย 3.1 กิโลกรัม ยาที่ใช้ร่วม
ด้วยคือ ลิเทียม ยาต้านชัก ยาต้านโรคจิตขนาดต่ำ หรือร่วมกับยาด้านเศร้าในราย
ที่มีอาการเศร้า
- สรุป** : ผู้ป่วยนอกโรคอารมณ์แปรปรวน ที่ได้รับการรักษาเสริมด้วยโทพิราเมต จะมี
ลักษณะอาการทางคลินิกที่ดีขึ้น โดยผลข้างเคียงที่พบบ่อยคือปวดศีรษะ ซึ่ง
ผู้ป่วยมักจะทนผลข้างเคียงของยาได้ ผลข้างเคียงที่น่าสนใจ คือ ทำให้น้ำหนัก
ตัวลดลง
- คำสำคัญ** : โทพิราเมต, การรักษาเสริม, โรคอารมณ์แปรปรวน, ผู้ป่วยนอก, ผลการรักษา,
ผลข้างเคียง

Bipolar disorder, also known as manic-depressive illness, is a serious medical illness that causes shifts in a person's mood, energy, and ability to function. Different from the normal ups-and-downs that everyone goes through, the symptoms of bipolar disorder are severe.

In department of Psychiatry, King Chulalongkorn Memorial Hospital, Thai Red Cross Society had 28,000 outpatients visit per year. There were about 2,000 bipolar disorder patient visits. The top four diagnoses were, namely: schizophrenia, anxiety disorder, depressive disorder and bipolar disorder.⁽¹⁾

Antiepileptic drugs have been found to be effective in the treatment of mania and prophylaxis of affective episodes in bipolar disorder.⁽²⁾ Carbamazepine and valproate have been widely used in these patients. Now several studies support a role for the newer antiepileptic drugs, such as lamotrigine⁽³⁾ gabapentin⁽⁴⁾ and topiramate.⁽⁵⁾

Topiramate is an anticonvulsant which has shown to be effective in manic cessation. The mechanism of action of the substance is not yet fully understood, preclinical evidence suggests that it interferes with sodium conductance, augments the effect of γ -aminobutyric acid, blocks glutamate receptors, and has weak carbonic anhydrase inhibiting properties.⁽⁶⁾

Topiramate has a favorable pharmacokinetic profile, and it is generally well tolerated in patients with epilepsy.⁽⁷⁾ The side effects (such as cognitive impairment) can usually be controlled by slow increase of the dose. Its interesting side effect is associated with substantial weight loss.

Method

The clinical observation study was conducted in patients with bipolar disorder at the Department of Psychiatry, King Chulalongkorn Memorial Hospital from August 2000 to August 2002. All bipolar patients were those who used topiramate as adjunctive mood stabilizer; other concomitant medications were also allowed.

The Clinical Global Impression (CGI; Guy, 1976) was used to determine the efficacy of treatment by the same psychiatrist two times at the beginning and five months afterward. The adverse effects were monitored in detail. There were thirty-three patients recruited into this study.

Inclusion criteria

1. Diagnosed as bipolar disorder (any types, maintenance phase or new case)
DSM-IV Diagnostic criteria ;
2. the patients used topiramate as adjunctive mood stabilizer;
3. they were older than 14 years of age.

Exclusion criteria

1. the candidate for the trial had another Axis I Diagnosis of DSM-IV;
2. the candidate for the trial had severe suicidal idea;
3. The candidate for the trial had history of severe underlying medical diseases.

Each bipolar patient was prescribed with topiramate 250 - 500 mg per day. Every patient was advised about the nature history of disease, treatment plan and the medication's side effects. Rather than topiramate, some patients may use the other

medication such as low dose neuroleptic in mild psychotic symptoms, antidepressant in depressive symptoms and benzodiazepine in neurotic symptoms. Every follow up sessions, the patients had been evaluated CGI scores by the same psychiatrist. The study concluded after 5-month follow up.

SPSS software for Windows was used in statistical analysis of the data. The results were analyzed both for as a whole group and separately according to their gender. Paired t-tests (two-tailed) were used to identify CGI differences between the beginning and the end session.

Results

Demographic data

Demographic data are shown in Table 1. Thirty-three cases of bipolar disorder were recruited

into the study. The subjects' mean age is 38.5 year (14 - 67 year). There were 25 females and 8 males and the duration of their diagnoses were 1.5 – 30 years (average 11.5 years). The average duration of treatment was 5.27 months. There was insignificant difference between male and female groups in terms of age, duration of onset and duration of treatment.

Clinical data (See Table 2)

The patients received average dose of topiramate 152 mg per day (250 -500 mg per day) and the improvement of CGI scores found in twenty cases. There was a significant difference between CGI before (4.3 ± 1.9) and after the treatment (2.1 ± 1.2) ($p < 0.01$). Four participants dropped out (acute exacerbation of symptoms and financial problem, three female and one male).

Table 1. Demographic and clinical details of male and female bipolar participants.

Sex	Female group (N= 25)	Male group (N=8)	Total (N=33)
	Mean (s.d.)	Mean (s.d.)	Mean (s.d.)
Age (years)	38.2 (12.3)	39.3 (18.3)	38.5 (13.7)
Duration of onset (years)	11.38 (5.08)	11.31 (6.23)	11.47 (6.35)
Duration of treatment (months)	5.20 (5.61)	5.28 (4.97)	5.27 (5.13)

Table 2. Clinical data of male and female participants.

Sex	Female group (N= 22)	Male group (N=7)	Total (N=29)
	Mean (s.d.)	Mean (s.d.)	Mean (s.d.)
Average dose of topiramate (mg. Per day)	139.0 (126.26)	193.75 (86.34)	152.27 (118.97)
CGI scores Improvement	2 (1.5)*	3.13 (1.81)*	2.27 (1.63)*

* $p < 0.01$

Side effect Data (See Table 3)

The side effects included moderate headache six cases, dysphoria mood two cases, nausea and vomiting two cases, peripheral anesthesia one case, cognitive dullness one case. The average weight loss was 3.1 kg (-10 to +6 kg). There was a significant difference between weight loss in male group (-5.0 ± 3.7 kg) and female group (-2.5 ± 3.69 kg). ($P=0.03$)

Combine Medication Data (See Table 4)

Within the total group, 30 (90.90 %) were receiving more than one medical agent. Participants were divided into two groups, all of the males and 27 females had combined treatment. The concomitant medications were lithium, carbamazepine, fluoxetine, perphenazine and others.

Table 3. Side effect data of female and male participants.

Sex	Female group (N= 22)	Male group (N=7)	Total (N=29)
No side effect (except weight loss)	15 (68.18 %)	6 (85.71 %)	21 (72.41 %)
Side effects	7 (31.82 %)	1 (14.29 %)	8 (27.59 %)
Headache	6	1	7
Dysphoria mood	2	0	2
Nausia and vomiting	2	0	2
Periperal anesthsia	1	0	1
Cognitive dullness	1	0	1
Weight loss	21	6	27
Weight loss (kg)	-2.5 (3.53)	-5.0 (3.69)	-3.1 (3.67)

Table 4. Frequency of concomitants medication use in the study population.

Sex	Female group (N= 25)		Male group (N=8)	
	N	%	N	%
Lithium	5	20	3	37.5
Carbamazepine	4	16	3	37.5
Fluoxetine	3	12	1	12.5
Perphenazine	2	8	0	0
Tinaneptine,	2	8	0	0
Verapamil	2	8	0	0
Clonazepam	1	4	1	12.5
Valproate	1	4	1	12.5
Diazepam	1	4	0	0
Olanzapine	1	4	0	0
Risperidone	1	4	0	0
Other antidepressants	3	12	0	0

Discussion

Topiramate was effective in the treatment bipolar disorder by improving CGI score consistent with a previous study that antiepileptic drugs could be used in the treatment of several non-epileptic neurological conditions and psychiatric disorders.⁽⁸⁾

The common but tolerable adverse effects were weight loss and headache. A good result occurred in good compliant cases. There was no severe adverse effect detected during the 5-month follow up. One study of long-term used of topiramate in epilepsy demonstrated that its adverse effects were the main reason to discontinue the drug.⁽⁹⁾

In bipolar disorder, lithium maintenance showed striking long-term reductions of depression as well as manic morbidity in both bipolar disorder subtypes, with greater overall benefits in type II patients who had earlier treatment.⁽¹⁰⁾

Lithium maintenance also was associated with marked reduction of life-threatening suicidal acts.⁽¹¹⁾

However, the impact of lithium prophylaxis on the course of bipolar disorder is severely limited by the high dropout rate. Patients no longer had a higher frequency of psychotic features in the index episode than those who were still on lithium.⁽¹²⁾

Binge eating disorder is associated with obesity. Topiramate is an antiepileptic agent associated with weight loss. Topiramate was efficacious and relatively well tolerated in the short-term treatment of binge eating disorder associated with obesity.⁽¹³⁾

Stressful events produced headache in bipolar patients may urge the patients to take sweets of high calories in order to relieve their symptoms and subsequently increase their weight. Small

open-label and controlled trials suggest that the antiepileptic drug, topiramate, is effective for migraine prevention. Topiramate showed significant efficacy in migraine prevention within the first month of treatment, an effect maintained for the duration of the double-blind phase.⁽¹⁴⁾

Sex differentiation between males and females may be the predictive factor of the treatment outcomes. Bipolar disorder generally predominates in the female population than male. This study shows the better outcome of treatment in male patients. Males show lesser side effects of medication than female and better improve CGI scores. Weight loss seems to be the only side effect that was clearly shown in the male patients.

The weight loss associated with topiramate in both human obesity and animal models of obesity is due to the loss of fat rather than the lean body mass.⁽¹⁵⁾ In the animal model, topiramate inhibits fat deposition either by reducing food intake or stimulating energy expenditure.⁽¹⁶⁾ The mechanisms by which topiramate affect the food intake and energy expenditure still remain unknown.

Topiramate may be an alternative choice in long-term treatment of bipolar disorder who cannot tolerate weight gain side effect especially female patients. Controlled studies should be done to support this point.

Limitation of this study

The study is limited by the absence of control group of patients especially those who had monotherapy of topiramate. Another limitation was in the measurement, only CGI rating may not be an adequate tool to evaluate the outcome.

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