

Systematic Review

## Tonabersat for Migraine Prophylaxis: A Systematic Review

Yue Cao, MM, and Ou Jin Zheng, MD

From: First Affiliated Hospital,  
Guangxi Medical Center,  
Nanning, Guangxi, China

Address Correspondence:  
Ou Jin Zheng, MD  
First Affiliated Hospital  
Guangxi Medical University  
Department of Neurology  
6 Shuangyong Road  
Nanning, Guangxi China  
E-mail: gxzhzy@hotmail.com

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**Background:** Randomized clinical trials assessing the efficacy and tolerability of tonabersat compared with placebo as prophylaxis for migraine were systematically reviewed in this study. By analyzing all available data, we aimed to establish an overall estimate of any association in order to more accurately inform clinicians and care-givers about how to prevent migraines.

**Objective:** To evaluate the efficacy and tolerability of tonabersat when it is used for migraine prevention.

**Study Design:** Systematic review of tonabersat for migraine prophylaxis.

**Methods:** Computerized database search of The Cochrane Pain, Palliative & Supportive Care Trials Register, The Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library), Pubmed, and EMBASE for randomized, double-blind, placebo-controlled trials on tonabersat for migraine until January, 2013. We also searched the ongoing trials. We did not impose any language restrictions.

The quality assessment and clinical relevance criteria utilized were the Cochrane Pain, Palliative & Supportive Care review group criteria as utilized for randomized trials.

**Outcome Measures:** The primary outcome measure was the change in mean number of migraine headache days. The secondary outcome measures were change in attacks, responder rates, the reduction of the consumption of rescue medication, and adverse events.

**Results:** For this systematic review, 133 studies were identified. Of these, 131 studies were excluded, and a total of 2 studies (after removal of duplicate publications) met inclusion criteria for methodological quality assessment with the randomized trial study. The evidence for tonabersat for migration prophylaxis failed to demonstrate a reduction when compared to placebo because of a lack of evidence. But the good tolerability supports further exploration of tonabersat in the prevention of migraine attacks.

**Limitations:** The limitation of this systematic review was a lack of available evidence.

**Conclusion:** There is fair evidence for migraine prophylaxis, but a lack of available evidence for tonabersat for migraine prophylaxis. Although tonabersat failed to demonstrate a significantly greater reduction of migraine headache days than placebo, it was well tolerated. Future work should further investigate the utility of tonabersat in the preventive management of migraine.

**Key words:** Systematic review, tonabersat, migraine, prophylaxis

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**M**igraine is a recurrent, primary headache disorder associated with significant morbidity as well as high direct and indirect costs (1). It has been estimated that the global

prevalence among adults of current headache disorder is 47%. Half to three quarters of the adults aged 18–65 years in the world have had headaches in the last year, and among those individuals, more than 10% have

reported having a migraine (2). Calcium antagonists,  $\beta$ -blockers, antiepileptics, antidepressants, vitamins, minerals, and herbal agents are common prophylactic drugs and may be effective for some people (3- 5). But the existing treatments' efficacy is not satisfied (6- 9); thus, there is a substantial need for the development of a preventive effect in migraine to improve efficacy and reduce side effects.

Tonabersat (SB-220453), a novel benzoylamino benzopyran compound, inhibits cortical spreading depression (10). Tonabersat acts uniquely at a stereospecific binding site that could be associated with the neuronal glial gap junction (11). The efficacy and safety of tonabersat taken in the dose of 15, 20, 25, 40, or 80 mg were examined in 3 multicenter, randomized double-blind, placebo-controlled, parallel-group trials when used at the onset of migraine with or without aura (1,12).

To our knowledge, there is no comprehensive review consolidating the results of previous studies on this subject. For this reason, our aim was to evaluate the efficacy and tolerability of tonabersat when used as migraine prevention.

## **1.0 METHODS**

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### **1.1 Criteria for Considering Studies for This Review**

#### **1.1.1 Types of Studies**

To be included in the review studies needed to meet all of the following criteria:

1. randomized controlled trial in which an adequate method of concealment of randomization is used (e.g. sequential allocation of sealed packages of medication, sealed opaque envelopes, telephone randomization);
2. double, single, or unblinded trial;
3. placebo controlled;
4. parallel group or cross-over study.

#### **1.1.2 Types of Patients**

Patients who have migraine, with or without aura, by the definition of the second edition of the International Classification of Headache Disorders.

#### **1.1.3 Types of Interventions**

The treatment groups receive tonabersat.

The control groups receive placebo or another drug.

#### **1.1.4 Types of Outcome Measures**

The primary outcome measure was the change in mean number of migraine headache days.

The secondary outcome measures were change in attacks, responder rates, the reduction of the consumption of rescue medication, and adverse events.

### **1.2 Search Strategy and Citations Library**

#### **1.2.1 Electronic Searches**

We searched the following databases:

1. The Cochrane Pain, Palliative & Supportive Care Trials Register;
2. The Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library)
3. Pubmed
4. EMBASE
5. Clinical Trials.gov
6. WHO International Clinical Trials Registry Platform (ICTRP).

We did not impose any language restrictions.

#### **1.2.2 Searching Other Resources**

We checked the reference lists of retrieved reports to check for additional reports of relevant studies.

### **1.3 Data Collection and Analysis**

#### **1.3.1 Selection of Studies**

The process for selecting studies for inclusion in the review involved merging search results using reference management software and removing duplicates of the same report. We examined titles and abstracts to remove obviously irrelevant reports. We retrieved the full texts of these reports and examined studies for compliance with eligibility criteria. Disagreements were resolved by discussion.

#### **1.3.2 Inclusion and Exclusion Criteria**

We included:

1. Controlled trials in which allocation to treatment was explicitly randomized,
2. Placebo controlled,
3. Double blinded trials,
4. Patients with migraine, with or without aura by the definition of the second edition of the International Classification of Headache Disorders.

A clearly inappropriate method of randomization (for example, open alternation), open label trials, and patients with headaches of various types were excluded.

**1.3.3 Methodological Quality or Validity Assessment**

The methodological quality of the studies was evaluated according to the guidelines in the Cochrane Handbook for Systematic Reviews of Interventions (Table 1 [13]). Each study was evaluated by 2 authors for stated criteria and any disagreements were resolved by discussion.

**1.3.4 Data Extraction and Management**

We extracted the following information from included trials and resolved any disagreements by mutual discussion.

1. Methodology and trial design
  - a. Method of randomization concealment
  - b. Method of blinding
  - c. Duration of baseline period
  - d. Duration of treatment period
  - e. Duration of “wash-out” period in cross-over

- studies
  - f. Dose(s) of tonabersat tested
  - g. Description of withdrawals and drop-outs
2. Patient and demographic information
  - a. Total number of patients allocated to each treatment group
  - b. Age/gender
  - c. Duration
3. Outcomes
 

We recorded the number of patients experiencing each outcome (see types of outcome measures).

**1.3.5 Assessment of Heterogeneity**

Clinical heterogeneity was assessed by comparing study designs and the characteristics of the patients recruited into trials that met our inclusion criteria. We used the I<sup>2</sup> statistic to measure heterogeneity among the trials in each analysis. If the I<sup>2</sup> statistic was more than 50%, we identified it as substantial heterogeneity, we explored it by prespecified subgroup analysis.

**1.3.6 Data Synthesis**

We analyzed data in a meta-analysis using Review Manager 5.2.

Table 1. *Assessing risk of bias.*

Domain	Support for Judgement	Review Authors' Judgment
<b>Selection</b>		
Random sequence generation	Describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.	High/low/unclear
Allocation concealment	Describe the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen in advance of, or during, enrollment.	High/low/unclear
<b>Performance bias</b>		
Blinding of participants and personnel	Describe all measures used, if any, to blind study patients and personnel from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective.	High/low/unclear
<b>Detection bias</b>		
Blinding of outcome assessment	Describe all measures used, if any, to blind outcome assessors from knowledge of which intervention a patient received. Provide any information relating to whether the intended blinding was effective.	High/low/unclear
<b>Attrition Bias</b>		
Incomplete outcome data	Describe the completeness of outcome data for each main outcome, including attrition and exclusions reported, the numbers in each intervention group (compared with total randomized participants), reasons for in analyses performed by the review authors.	High/low/unclear
<b>Reporting Bias</b>		
Selective reporting	State how the possibility of selective outcome reporting was examined by the review authors, and what was found.	High/low/unclear
Other bias		
Other sources of bias	State any important concerns about bias not addressed in the other domains in the tool.	High/low/unclear

Adapted and modified from Cochrane Handbook (13).

### 1.4 Outcome of the Studies

In the randomized trials, the study was judged to be positive if the tonabersat for migraine prophylaxis was clinically relevant and effective, either with a placebo control or active control. The difference in effect for the primary outcome measure is statistically significant at the conventional 5% level. No difference between the study treatments or no improvement from baseline is identified in a negative study.

## 2.0 RESULTS

### 2.1 Description of the Studies

See the Table 2 and Table 3 for more details.

### 2.2 Results of the Search

For this systematic review, 133 studies were identified. Of these, 131 studies were excluded, and a total of 2 studies (after removal of duplicate publications) met inclusion criteria for methodological quality assessment with one randomized trial study. Full details of the individual studies are provided in Fig. 1.

Two randomized controlled trials were included. The first was a parallel design and the second was a crossover design. The remaining 2 studies (14,15) described by 9 papers, 6 papers separately, fulfilled the inclusion criteria and we included these in the review (described in the Table 2). Two studies (12,16) were excluded (described in Table 3). Due to significant meth-

odological heterogeneity, clinical heterogeneity, and differences in outcome measures, it was not possible to perform a meta-analysis of the results. Therefore, we presented a summary of the included studies with change in mean number of migraine headache days, change in attacks, responder rates, the reduction of the consumption of rescue medication, and adverse events.

### 2.3 Risk of Bias in Included Studies

For graphical representations of our evaluation please refer to risk of bias in Fig. 2.

The study by Goadsby et al (14) reported that it was a randomized, double-blind, placebo-controlled, proof-of-concept study. However, neither the method of allocation concealment nor the method of generating the random sequence was described. The study was performed in a double-blind fashion; it may have used identical study medication. There were 33 patients who gave no reason for leaving study, one patient was unwilling to continue, one patient was withdrawn (lack of compliance), one patient was withdrawn by the investigator, and one patient (from tonabersat) was excluded from the ITT population because he did not provide usable efficacy data. These were described in detail, so we judged the study to have a low risk.

The randomization schedule of the study by Hauge et al (15) was generated by the Penn Pharmaceutical Services (Tredegar, UK) according to a computer-generated random code. Neither block nor stratification was

Table 2. *Characteristics of studies considered for inclusion.*

Study	Study Design	Patients (n)	Age	Migraine Attacks	Dosing Regimen	Treatment Duration
Hauge et al (2009)	Randomized, double-blind, placebo-controlled crossover trial	39	18 – 65	at least one aura attack per month during the past 3 months	Tonabersat: 40 mg Placebo: 40mg	two 12-week treatment periods (Treatment Periods I and II), a 4-week washout period
Goadsby PJ (2009)	Randomized, double-blind, placebo-controlled, proof-of-concept study	160	18 – 55	baseline 2 to 6 migraine attacks per month	Tonabersat: 220 mg daily for 2 weeks and 40 mg daily for a further 10 weeks. Placebo: 20 mg daily for 2 weeks and 40 mg daily for a further 10 weeks	12 weeks

Table 3. *Characteristics of studies considered for exclusion.*

Manuscript Author(s)	Reason for Exclusion
Dahlof et al (2009)	The study is about migraine treatment, not migraine prophylaxis.
Tvedskov JF et al (2004)	The study is not complete.

used. The placebo tablets were identical in number and appearance to the tonabersat tablets. Patients were informed of the inclusion of placebo but not of the precise schedule of the study. Patients and all personnel involved in the trial were blinded to treatment with the exception of the washout period, during which only patients were blinded. Data were not unblinded until data from the last patient to complete the trial had been recorded. We judged the study to have a low risk.

## 2.4 Meta-analysis

There were 2 trials included for tonabersat for migraine prophylaxis. Consequently, no meta-analysis was feasible.

## 2.5 Effects of Interventions

### 2.5.1 Change in Mean Number of Migraine Headache Days

The 2 studies (14,15) both reported the primary outcome measure, but the study by Goadsby et al (14) reported the change in mean number of migraine headache days, 1.0-day (95% confidence interval [CI] -0.33, 2.39;  $P = 0.14$ ), the study by Hauge et al (15) reported the median number of migraine headache days,  $P = 0.09$ . So no significant difference was found.

### 2.5.2 Change in Attacks

The study by Goadsby et al (14) reported that the reduction in mean monthly migraine attacks comparing baseline to month 3 of treatment was  $-2.4 - 0.4$  for the tonabersat group and  $-1.4 - 0.5$  for the placebo group (difference 1.0, 95% CI -0.29, 2.20;  $P = 0.13$ ). The median number of attacks of aura (with or without a headache) per 12 weeks of the other study by Hauge et al (15) was 3.2 (IQR 1.0 – 5.0) during placebo treatment and 1.0 (0 – 3.0) during tonabersat treatment. The difference between treatment periods was significant ( $P = 0.01$ ). For this outcome, they have different  $P$  value, one study by Goadsby et al (14) was not significant and the other by Hauge et al (15) was significant.

### 2.5.3 Responder Rates

In the study by Goadsby et al (14), the overall 50% responder rate comparing the number of headache days during baseline with month 3 of treatment for tonabersat was 59% compared with placebo at 49% ( $P = 0.22$ ). However, the other study by Hauge et al (15) did not present the results.

### 2.5.4 The Reduction of the Consumption of Rescue Medication

For the overall treatment period, the study by Goadsby et al (14) reported the reduction in the tonabersat group was  $-2.9 - 0.5$  compared with  $-2.1 - 0.4$  in the placebo group (difference 1.0, 95% CI -0.08, 2.05;  $P = 0.07$ ). It was reported that median days with intake of rescue medication was 2.9 (IQR 0 – 6.6) during placebo treatment and 0 (0 – 6.1) during tonabersat treatment ( $P = 0.2$ ) in the study by Hauge et al (15). No significant difference was found.

### 2.5.5 Adverse Events

The study by Goadsby et al (14) reported that the most commonly occurring adverse events were nausea (11% of patients), upper respiratory tract infection (7% of patients), and dizziness and urinary tract infection (each reported in 7% of patients). A higher proportion of patients in the tonabersat group compared with the placebo group reported nausea (17% vs 6% of patients), dizziness (9% vs 5% of patients), and headache (7% vs 2% of patients). Only one patient in each

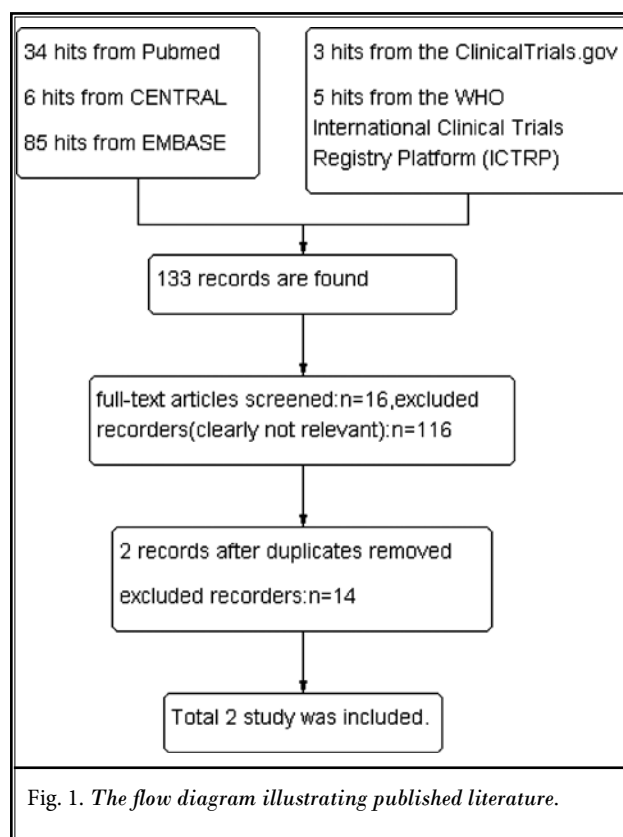


Fig. 1. The flow diagram illustrating published literature.

treatment group was reported with at least one serious treatment-emergent adverse event. Hauge et al (15) reported commonly occurring adverse experience in both treatment groups were infection, dizziness and vertigo, tiredness, and nausea. No serious adverse events were reported. Only one patient dropped out during tonabersat treatment owing to an adverse event, whereas 3 patients dropped out during placebo treatment owing to adverse events.

### **3.0 Discussion**

In the current review, we included 2 randomized controlled trials (14,15) involving a total of 199 patients and 2 comparisons (tonabersat versus placebo). Among them, one was a randomized, double-blind, placebo-controlled, proof-of-concept study and the other was a randomized, double-blind, placebo-controlled cross-over trial. All published reports referred to their analyses as being intention to treat. As a result, we were unable to perform a meta-analysis as planned because of the differences in study methodology, statistical method, choice of outcomes, and inadequate reporting of outcome data. Therefore, we analyzed the studies individually using the available data.

According to the results of the overall efficacy analysis, we failed to show a significant difference favoring either tonabersat or placebo according to the outcomes. The difference in effect for the primary outcome measure is negative. Among the secondary outcomes, the change of attacks were negative. One (14) was not significant, and the other (15) was significant. The reasons may be the differences in study methodology, statistical method, and demographic characteristics. Among the 2 studies, for the safety outcomes, there were no available data for analysis, but the only 2 trials included reported that adverse events in the trials were generally mild to moderate in severity when compared with placebo, including the 3 most common adverse effects, nausea, infection, and dizziness. The results of the included studies (14,15) were not in favor of tonabersat for migraine when compared with placebo.

However, we noted that the results for the included outcomes were unsatisfactory due to the fact that they were extracted from only 2 studies.

#### **3.1 Quality of the Evidence**

The reporting quality of the 2 studies (14,15) was good. But the reporting of methodological factors, such as the method of allocation concealment and generating the random sequence, was not described

and was poor in the study by Goadsby et al (14), but it was probably done. However, the study by Hauge et al (15) reported the methodological factors in detail. The extremely short follow-up period (7 days) cannot predict clinical efficacy and tolerability of tonabersat considering a long-term prevention of migraine in the study by Goadsby et al (14), while the other study by Hauge et al (15) did not mention the follow-up period.

The results of tonabersat compared with placebo were only based on 2 trials. Although the methodological qualities of them were rated well, the results in the studies (14,15) should be interpreted cautiously. In the available trials, tonabersat was used at safe doses, but the doses are still clinically useful levels of efficacy. The efficacy and safety of a single 15, 20, 25, 40 or 80-mg doses of tonabersat taken acutely at the onset of migraine with or without aura were examined in 3 multicenter, randomized, double-blind, placebo-controlled, parallel-group trials (17). This may limit the effective treatment to some degree. There were inadequate numbers of patients and events to draw firm conclusions about possible differences among doses or drugs.

It is likely to underestimate the therapeutic effect because the enlistment for the trials was through clinics. Clinics may select participants whose migraines are more severe or resistant to treatment than in the general population. On the other hand, these participants may be more motivated than the population as a whole.

The study by Silberstein (17) reported the mechanisms of tonabersat for migraine prophylaxis. Related research showed that the study by Tvedskov et al (16) was stopped prematurely due to a possible interaction between the induced drug and SB-220453, but the data showed a small reduction in peak headache and accompanying migraine symptoms when SB-220453 was compared with placebo. A comment by Dodick (18) about the prevention of tonabersat reached the same conclusion as this review that tonabersat failed to prevent attacks of migraine and a larger randomized controlled preventive trial in patients with migraine with aura is warranted.

The main limitation of the present analysis was that the differences in study methodology, statistical method, choice of outcomes, and inadequate reporting of outcome data prevented us from doing a meta-analysis. For a systematic review, the number of patients is relatively small. Further studies are needed with large populations or other dosages to monitor tonabersat's

effectiveness when comparing tonabersat to placebo or alternative drugs. And the follow-up should be longer to observe the long-term effects and adverse effects. Long-term studies are required to determine the safety and tolerability.

### 3.2 Potential Biases in the Review Process

The search for trials was based on electronic databases. We searched The Cochrane Pain, Palliative & Supportive Care Trials Register, CENTRAL, Pubmed, and EMBASE. Hand searching was not undertaken. We undertook searches for unpublished trials but none of the studies identified qualified for inclusion. We cannot disregard the possibility that there are unpublished trials we are not aware of. In addition, we have failed

to obtain some important information and data in the included trials from the original investigators and the manufacturer of tonabersat. There are only 2 studies included, we wanted to include observational studies, but there were no available observational studies that met the criteria.

### 4.0 CONCLUSION

Current studies suggest that tonabersat treatment failed to demonstrate a significantly greater reduction in migraine headache days than placebo. But it was well tolerated. Future work should further investigate the utility of tonabersat in the preventive management of migraine.

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