Research Article

Gabapentin for Phonasthenia: A prospective Cohort Study

Effat A. Zaki
Department Phoniatrics, Minia University

Abstract
Purpose: The aim of the current study was: (1) to quantify the response rate and efficacy of gabapentin in treating patients with phonasthenic symptoms and (2) to describe an efficient treatment protocol (dose and duration). Study Design. This study is a prospective controlled study.
Methods: Patients diagnosed with phonasthenia, non-organic voice disorders during a 6 months period were potentially study candidates. Upon diagnosis of phonasthenia, all patients were treated with gabapentin 300 mg/day for 3-6 months. Data collection included the patient demographics, dose and duration of the Gabapentin, and degree of improvement as evaluated by the voice handicap index pre and post medication. Results: 60 patients met the diagnostic and inclusion criteria and had a complete data set. 85% (34 of 40) of the patients responded well to the medication after 6 months regimen. Patients reported symptom relief 57.5% (23 of 40) after 3 months of medication and reached to 85% after 6 months.
Conclusion: gabapentin appear to vary in its effectiveness for individual cases of phonasthenic symptoms; across a whole cohort, symptom relief was with average dose 300 mg daily.
Key words: Phonasthenia, Gabapentin, non-organic voice disorder

Introduction
Kotby reported that phonasthenia is a dysphonia that is felt in the neck and throat rather than heard by patients and their listeners. Hegazi reported that phonasthenia is frequently experienced by individuals with high vocal demands. It may also be described by the patients as status in which voice is not coping with demands of daily life activities but patients typically report worsening of symptoms with extended voice use. Relative incidence of phonasthenia was 45% among non-organic dysphonia in a one-year study from the Ain Shams, Unit of Phoniatrics (N= 148). Yiu also found that the five most common symptoms, as reported by at least half of the practicing teachers who complained of voice problems, were dry throat, change of voice shortness of breath, inability to sing high pitch and vocal tiredness.

Phonasthenia is expected to develop more readily in individuals whose laryngeal musculature and mucous membranes are usually sensitive. In these cases, only a small departure from optimal phonatory conditions may lead to vocal fatigue. Vocal fatigue is used to denote negative vocal adaptation that occurs as a consequence of prolonged voice use, indicating undesirable or unexpected changes in the functional status of the laryngeal mechanism.

Phonasthenia, like all functional voice disorders, is considered as multifactorial in origin. Long standing vocal abuse, misuse, smoking and exposure to environmental pollution are common predisposing factors. Also, Phonasthenia may result from psychological stress or anxiety. In addition, poor physical condition, improper hydration, chronic disease or illness, generalized fatigue and allergies have been associated etiologically with phonasthenia. Also frequent upper respiratory tract infections, subacute and chronic cough also have been associated etiological factors.

It is hypothesized that two distinct types of vocal fatigue occur: muscle fatigue and tissue fatigue. Muscle fatigue happens when the muscles of the vocal system are overused. Tissue fatigue is caused by excessive
destruction of the cells in the vocal fold tissues\(^7\). Auditory perceptual assessment of voice is generally normal, but it may be strained or breathy. Laryngeal examination is normal, but it may reveal increased vascular marking in the mucosa. Subtle stroboscopic deviations in the form of asymmetries of the glottal mucosal wave may be observed\(^1\).

Titze\(^{10}\) hypothesized a number of physiological and biomechanical mechanisms that may be important contributors to vocal fatigue; these are neuromuscular fatigue, increased vocal fold viscosity, non-muscular tissue strain, reduced blood circulation, and respiratory muscle fatigue. Kotby\(^9\) attributed the pharyngeal and throat sensations of soreness to the shared sensory supply of the vocal folds with the pyriform fossae and the anterior wall of the hypo- pharynx. Yoshida\(^{11}\) explained that those feelings are representing a laryngeal referred pain.

Lee and Woo\(^{12}\) had presented 28 patients who had chronic cough or throat-clearing as a manifestation of sensory neuropathy involving the superior or recurrent laryngeal nerve. They had been identified as having sudden-onset cough, laryngospasm, or throat-clearing after viral illness, surgery, or an unknown trigger. Seventy-one percent of the patients had concomitant superior laryngeal nerve or recurrent laryngeal nerve motor neuropathy documented by laryngeal electromyography or video stroboscopy. These patients were treated with gabapentin at 100 to 900 mg/d. Symptomatic relief was achieved in 68% of the patients. The authors claimed that sensory neuropathy of the recurrent laryngeal nerve or superior laryngeal nerve should be considered in the workup for chronic cough or laryngeal irritability. Moreover, they added that symptomatic management of patients with cough and laryngospasm due to a suspected sensory neuropathy may include the use of anti-seizure medications such as gabapentin.

Also, Norris and schweinfurth\(^{13}\) mentioned that patients with suspected neuropathy of the recurrent laryngeal nerve frequently appear to have better outcomes with neuromodulator therapy.

Chung\(^{14}\) mentioned that chronic cough is a neuropathic condition that could be secondary to sensory nerve damage caused by inflammatory, infective and allergic factors. They reported that recent success in the treatment of chronic cough with agents used for treating neuropathic pain such as gabapentin and amitryptiline would also support this concept. Greene and Simpson\(^{15}\) stated that although gabapentin was approved for use in 1993 as adjunctive therapy for partial seizures, but also, it is currently estimated that gabapentin is prescribed for off-label uses in 80% of cases. Gabapentin given the limited therapeutic options in patients with severe idiopathic chronic cough, it was believed reasonable to try gabapentin because it is well tolerated, has a wide margin of safety, and has no significant drug interactions. Although gabapentin was designed as a GABA-mimetic agent capable of crossing the blood–brain barrier, the effects of gabapentin in epilepsy do not seem to be mediated through interaction with GABA receptors and the exact mechanism of action remains controversial.

To the best of our knowledge no research work was carried out on the effect of gabapentin as a neuromodulator on phonasthenia and other non-organic voice disorders.

**Subjects and Method**

**Patients:**
This study included 60 patients complained of phonasthenic symptoms and were diagnosed as non-organic voice disorders (phonasthenia).

**This group study was divided into subgroups:**

**Group A:** Included 40 patients complained of phonasthenic symptoms and received medical treatment in the form of gabapentin 300 mg capsule daily for 3-6 months. They were 18 males (45%) and 22 females (55%),

---

159

**Gabapentin for Phonasthenia: A prospective cohort study**
with a mean age of 35.4 ±13.3 and a range of 19 years to 51 years.

**Group B:** Included 20 patients (control group) complained of phonasthenic symptoms and received placebo capsule daily for 6 months in the form of gelatin capsule filled with sugar. This group included 18 patients. They were 9 males (45%) and 11 females (55%), with a mean age of 37.4 ±12.8 and a range of 22 years to 48 years.

These patients were selected from outpatient's clinic of Phoniatrics and ENT, Minia University hospital, in the period from January 2014 to July, 2014.

**Methods:**
Each individual of both groups was subjected to the following protocols of assessment and all the patients signed consent to be enrolled in the study.

[A] The full voice evaluation protocol in the Phoniatric Unit, Minia University Hospital\(^{(1)}\) which includes:

**I- Elementary Diagnostic Procedures:**

i) **Patient Interview:**
This includes personal data of the patients, then, analysis of the patient’s complaint as regards the onset, course and duration followed by asking about the phonasthenic symptoms (Voice fatigue, frequent throat clearing, globus sensation and tenderness at the larynx). Predisposing factors for voice disorders were reported for all patients, they include type of job, excessive use of voice, temperament, emotional stress, smoking, spirits, repeated upper respiratory tract infection and its frequency, allergic tendencies, hyperacidity, reflux, medications, surgical interference and trauma.

ii) **Auditory Perceptual Assessment (APA):**
After careful listening to the patient’s voice by three trained phoniatrician, for the presence or absence of dysphonia, the grade of dysphonia, character of voice, pitch changes, loudness, glottal attack and affection of associated laryngeal functions could be determined using the modified GRBAS scale\(^{(16)}\).

**II- Clinical Diagnostic Aids:**
All patients included in the study underwent Telescopic rigid laryngoscopy (Henke-Sass Wolf angle 90) in the Phoniatrics unit at Minia University Hospital. The voices of all patients were recorded and analyzed auditory by 3 expert phoniatricians to assess the grade of dysphonia.

[B] The Voice Handicap Index (VHI): Malki et al.,\(^{(17)}\)
All individuals included in the study completed the questions of VHI with or without the researcher’s help. The Arabic VHI is reliably applied to the Arabic-speaking population, as it can help in estimating the degree of voice disorder severity. The Arabic version of the VHI is a valid and reliable tool for assessment of patients’ self-perception of voice handicap. It has also been shown to be sensitive for a wide variety of voice disorders. This self-administered questionnaire consists of 30 questions; the patient responds according to the appropriateness of each item (0 = none to 4 = always). The Arabic VHI is scored from 0 to 120 with the latter representing the maximum perceived disability due to voice difficulties based on the patient response.

- Functional scale: mild if >10, moderate if >12, severe if >18.
- Physical scale: mild if >15, moderate if >18, severe if >22.
- Emotional scale: mild if >8, moderate if >13, severe if >20.

So the VHI total score can be divided into mild if >33, moderate if >44 and severe if >61.

(C) Treatment protocol for sensory neuropathic cough
All the patients of group A were asked to receive medical treatment in the form of 300 mg oral gabapentin according to the following protocol. Ethics approval (protocol #5460) for case neuropathy was obtained from the institutional review board of Advocate Healthcare. Consent was waived for this retrospective study, Bastian;\(^{(18)}\)Table (1).
Table (1): Treatment protocol for sensory neuropathic

<table>
<thead>
<tr>
<th>Treatment protocol for sensory neuropathic</th>
</tr>
</thead>
<tbody>
<tr>
<td>To make sure gabapentin is safe for patient, these investigation was done before start Gabapentin kidney function (UREA and CREATININE); RANDOM blood SUGER; liver functional SGOT SGPT complete blood picture</td>
</tr>
</tbody>
</table>

Known side effects were explained to patients who had a diagnosis of non-organic voice disorder- phonathenia patients willing to accept the risks participated.

Step 1: First-line medication trial
Day1: 100 mg orally with the evening meal
Day2: 200 mg orally with the evening meal
Days3 for 6 months: 300 mg orally with the evening meal

Step 2: Phone follow-up, either 14 days after starting the medication.
At every phone follow-up, the patient must supply: name of current medication, dose, and duration of use; percent reduction of symptoms globally; side effects, if any; questions, if any; and best contact information.

Results

Methods of statistical analysis:
Data were collected, revised, verified, coded, then entered PC for statistical analysis done by using SPSS statistical package version 22.

1) Demographic data:
The (study group) consisted of 60 patients complaining of phonasthenia. This group was divided to subgroups:
Group A: Included 40 patients complained of phonasthenic symptoms and had received medical treatment in the form of Gabapentin 300 mg daily for 3-6 months according to the response of treatment.
Group B: Included 20 patients complained of phonasthenic symptoms and revived placebo Capsule once daily for 3-6 months. Both groups were statically matched in comparative data age and sex distribution.

Non-statistical significant difference was obtained between patients of the group (A) and group (B) as regards the age and gender (P≥0.05). The patients included in group A were 18 males (45%) and 22 females (55%), with mean age of 35.4 ±13.3 and a
range of 19 years to 51 years, while individuals in group B were 9 males (45%) and 11 females (55%), with a mean age of 37.4 ±12.8 and a range of 22 years 48 year (Tables2-3).

Table (2): Comparison of age distribution between group A and B

<table>
<thead>
<tr>
<th>Age (in years)</th>
<th>Group A (n=40)</th>
<th>Group B (n=20)</th>
<th>t</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean ± SD (Range)</td>
<td>35.4 ±13.3 (19-51)</td>
<td>37.4 ±12.8 (22-48)</td>
<td>0.058</td>
<td>0.23</td>
</tr>
</tbody>
</table>

Non- significant (P≥0.05), significant (p< 0.05), highly significant (p< 0.01)

Table (3): Comparison of gender distribution between group A and B

<table>
<thead>
<tr>
<th>Gender</th>
<th>Group A (n=40)</th>
<th>Group B (n=20)</th>
<th>t</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Freq.</td>
<td>%</td>
<td>Freq.</td>
<td>%</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>18</td>
<td>45</td>
<td>9</td>
<td>45</td>
</tr>
<tr>
<td>Female</td>
<td>22</td>
<td>55</td>
<td>11</td>
<td>55</td>
</tr>
</tbody>
</table>

No statistical significant difference was obtained between the 2 groups as regarding VHI grading before start medical treatment in the first visit (P≥0.05) (Table4).

Table (4): Comparison of VHI between 2 groups before stat medication

<table>
<thead>
<tr>
<th>VHI grading</th>
<th>Group A (n=40)</th>
<th>Group B (n=20)</th>
<th>t</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>VHI</td>
<td>69 ± 22</td>
<td>65 ± 18</td>
<td>0.046</td>
<td>&lt;0.001*</td>
</tr>
</tbody>
</table>

Non- significant (P≥0.05), significant (p< 0.05), highly significant (p< 0.01)

Dose of Gabapentin/Result of Therapy in group A
Twenty three patients resolved completely of phonasthenic symptoms after 3 months on regimen dose 300 mg/day of Gabapentin and the patients followed up for 6 months period. Five patients resolved completely of phonasthenic symptoms after 4 months on regimen dose 300 mg/day of Gabapentin and they followed up for 6 months. Six patients resolved completely of phonasthenic symptoms after 6 months on regimen dose 300 mg/day of Gabapentin. Two patients reported partial symptoms relieve and they thought it was ineffective after 3 months use, however, they got more worse after stopping of the drug. Two patients stopped medication after 4 weeks because of fatigue. Two patients had completed the course of treatment for 3 months without any improvements and they discontinued medication use. Table (5):
Table (5): Dose of Gabapentin/Result of Therapy in group A

<table>
<thead>
<tr>
<th>No of patient/40</th>
<th>Dose of Gabapentin</th>
<th>Result of Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>23 (57.5%)</td>
<td>300 mg/ day / for 3 months</td>
<td>Symptoms completely resolved</td>
</tr>
<tr>
<td>5 (12.5%)</td>
<td>300 mg/ day / for 4 months</td>
<td>Symptoms completely resolved</td>
</tr>
<tr>
<td>6 (15%)</td>
<td>300 mg/ day / for 6 months</td>
<td>Symptoms completely resolved</td>
</tr>
<tr>
<td>2 (5%)</td>
<td>300 mg/ day / for 3 months</td>
<td>Two patients reported partial symptoms relieve and they thought it was ineffective after 3 months use, however, they got more worse after stopping of the drug</td>
</tr>
<tr>
<td>2(5%)</td>
<td>300 mg/ day / for 4 weeks</td>
<td>Stopped medication after 4 weeks because of fatigue.</td>
</tr>
<tr>
<td>2(5%)</td>
<td>300 mg/ day / for 3 months</td>
<td>Two patients had completed the course of treatment for 3 months without any improvements and they discontinued medication use.</td>
</tr>
</tbody>
</table>

There was high statistically significant difference as regards VHI between patients in group A. However, there was non-significant difference as regards VHI between patients in group B after 3 months of medication (table 6).

Table (6): Comparison of VHI between groups A and B after stat medication with 3 months

<table>
<thead>
<tr>
<th>VHI grading</th>
<th>Group A (n=38)</th>
<th>P-value</th>
<th>Group B (n=20)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>VHI</td>
<td>before</td>
<td>after</td>
<td>before</td>
<td>after</td>
</tr>
<tr>
<td>VHI</td>
<td>69 ± 22</td>
<td>20±28</td>
<td>&lt;0.001*</td>
<td>65 ± 18</td>
</tr>
</tbody>
</table>

Non-significant (P≥0.05), significant (p< 0.05), highly significant (p< 0.01)

After 6 months follow up, there was high statistically significant difference as regards VHI score in group A. While, there was non-significant difference as regards VHI score in group B (table 7)

Table (7): Comparison of VHI score in groups A and B after 6months follow up:

<table>
<thead>
<tr>
<th>VHI grading</th>
<th>Group A (n=34)</th>
<th>P-value</th>
<th>Group B (n=20)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>VHI</td>
<td>3 Months</td>
<td>6 months</td>
<td>3 Months</td>
<td>6 months</td>
</tr>
<tr>
<td>VHI</td>
<td>20±28</td>
<td>5±13</td>
<td>&lt;0.001*</td>
<td>60±45</td>
</tr>
</tbody>
</table>

Non-significant (P≥0.05), significant (p< 0.05), highly significant (p< 0.01)
Discussion

In the current study, the patients diagnosed with phonasthenic manifestations were followed up for symptomatic improvement after initiation of treatment with a neuromodulator (Gabapentin). Treatment outcome was defined by improvement or resolution of symptoms on an objective self-assessment by with voice handicap index.

Sixty patients was identified and exhibited evidence of phonasthenia (non-organic voice disorder) according to protocol of voice assessment. Forty patients were treated with neuromodulator therapy (Gabapentin) over a mean follow-up period of 6 months. The median dose of Gabapentin was 300 mg once daily for 3-6 months period. The control group (20 patients) with phonathenic symptoms was received placebo for the same duration.

We found that, there were high statistically significant differences as regards VHI between group A patients in comparison to group B patients after 3 months of medical treatment with gabapentin 300 mg daily. Moreover, after 6 months of follow up, there was high statistically significant difference as regards VHI between group A patients in comparison to group B patients.

In the current study, 23(57.5%) of the patients completely resolved of phonasthenic symptoms after 3 months on regimen of 300mg Gabapentin and about 85% of patients in group A have been resolved completely of phonasthenic symptoms after 6 months treatment by 300mg Gabapentin. This marked improvement in patients symptoms might be explained by the fact that vocal focal fatigue and other phonasthenic manifestations namely, globus sensation and frequent throat clearing are the results of neuropathy that affects the superior laryngeal nerve and/or recurrent laryngeal nerve that could responded well to neuromodulator. However in group B (Placebo group) slight improvement occurs but it was non-significant. These results proved the effectiveness of gabapentin in alleviating patient's complaints in comparison to the placebo effect. Also the present results highly suggestive of the etiological background of phonasthenia as a neuropathy that might affect the superior and/or recurrent laryngeal nerve. Some patients did not respond well to the current medication and few patients did not respond at all to the current medication this might highlight the presence of comorbid factors associated with the occurrence of phonasthenia as misuse and abuse of voice or other factors that need more investigations.

The current findings in an agreement to the study done by Kotby[9] who attributed the pharyngeal and throat sensations of soreness to the shared sensory supply of the vocal folds with the pyriform fossae and the anterior wall of the hypo-pharynx. Moreover, Yoshida[11] claimed that those feelings are representing a laryngeal referred pain because of involvement of superior laryngeal nerve neuropathy.

According to the present study, we think that phonasthenia associated with unexplained cough is due to affection of the sensory supply to the larynx as consequences of neuropathic changes that might occur as a result of viral neuritis or other biomechanical factors. This hypothesis is strengthened by the study carried out by Lee and Woo[12], who presented 28 patients with chronic cough and/or throat-clearing as a manifestation of sensory neuropathy involving the superior or recurrent laryngeal nerve. They had been identified as having sudden-onset cough, laryngospasm, or throat-clearing after viral illness. Cough and laryngospasm were the most common complaints. 71% of the patients had concomitant superior laryngeal nerve or recurrent laryngeal nerve motor neuropathy documented by laryngeal electromyography or video stroboscopy. So, we think that sensory neuropathy of the recurrent laryngeal nerve or superior laryngeal nerve should be considered in the workup for patients presented with phonasthenia, chronic cough or laryngeal irritability. Also according to the current study, Symptomatic management of patients with phonasthenia associated with
course of treatment for 3 months without any improvements and they discontinued medication use. Patients partially responded or not responded at all to the current medication might be explained by the fact that not all cases of phonasthenia were due to neuropathy of the mentioned nerves but it may be due to other biomedical factors as misuse and abuse of voice or associated laryngopharyngeal reflux or post nasal drip. These results matched to a study done by Greene and Simpson(15) who reported that among their patients, one patient discontinued gabapentin temporarily because of fatigue. Another patient had transient drowsiness that resolved after one week. This parallels the experience in gabapentin treatment for epilepsy and neuropathic pain in which side effects commonly resolved within 2 weeks of initiating therapy and approximately 10.5% of patients quit controlled studies of gabapentin because of side effects.

In the current study, 23(57.5%) patients resolved completely of phonasthenic symptoms after 3 months on regimen dose of 300 mg/day of Gabapentin and they maintained improvement for a follow up period of 6 months. Five (12.5%) patients resolved completely of phonasthenic symptoms after 4 months on regimen dose 300 mg/day of Gabapentin and continue follow up for 6 months. Six (15%) patients presented by phonasthenia together with throat pain and excessive throat clearing and they needed a longer course of treatment. They resolved completely of phonasthenic symptom after 6 months on regimen dose 300 mg/day of Gabapentin. These results suggested that some patients might need longer course of treatment by gabapentin for 6 months when they not responded well to the 3 months period. Those patients might be associated with, excessive misuse and abuse of voice with excessive muscles tension lead to some degree of neuropathy in the superior laryngeal nerve which presented with excess of throat clearing, throat pain referred to ear. These results are in agreement with that reported by Norris and schweinfurth(13) who conducted a retro-

cough and laryngospasm due to a suspected sensory neuropathy may include the use of ant-seizure medications such as gabapentin.

Symptomatic relief was achieved in 57.5% of the patients after 3 months on gabapentin medications. This might explain the effectiveness of gabapentin to control neuropathy of the affected nerves. Also, Greene and Simpson(15) pointed to post viral sensory neuropathy as a possible cause for refractory chronic cough and vagal neuropathy may affect the sensory branches, inducing chronic cough or laryngospasm.

Gabapentin was approved for use in 1993 as adjunctive therapy for partial seizures. Currently, it is estimated that gabapentin is prescribed for off-label uses in 80% of cases. Although gabapentin was designed as a GABA-mimetic agent capable of crossing the blood–brain barrier, the effects of gabapentin in epilepsy do not seem to be mediated through interaction with GABA receptors and the exact mechanism of action remains controversial. There is no explanation for its effect on chronic cough. It is not surprising that there is variability in the response to gabapentin, because it is probable that there are many different causes for “idiopathic” chronic cough. Also, recent success in the treatment of chronic cough with agents used for treating neuropathic pain such as gabapentin and amitryptiline would also support this concept. Chung(14)

Titze(10) hypothesized a number of physiological and biomechanical mechanisms that may be important contributors to vocal fatigue; these are neuromuscular fatigue, increased vocal fold viscosity, non-muscular tissue strain, reduced blood circulation, and respiratory muscle fatigue.

Our results found that two patients reported partial symptoms relieve and they thought it was ineffective after 3 months use; however, they got more worse after stopping of the drug. Two patients stopped medication after 4 weeks because of fatigue. Two patients had completed the
Gabapentin for Phonasthenia: A prospective cohort study


In the current study, the mean time from the initiation of therapy to get a complete response was 2 months. Patients with suspected neuropathy of the recurrent laryngeal nerve manifested by phonasthenic manifestations frequently respond to neuromodulator therapy.

Conclusion: gabapentin appeared to be effective with varying degrees for individual cases of phonasthenic symptoms; across a whole cohort, symptom relief was with average dose 300 mg daily.

References