

# BuNaoGao in the management of Amyotrophic Lateral Sclerosis/Motor Neuron Disease-A review of our experience with Western patients during March 2003-Nov. 2007

MengQi Xia<sup>a</sup>, MD., Ph.D., Stephen Byer<sup>b</sup>, YongChao Xia<sup>c</sup>, MD.

<sup>a</sup>TianHe Bioscience, Inc, Lexington, MA 02421, USA, <sup>b</sup>Stephen Byer & Associates, Madison, WI 53703, USA

<sup>c</sup>Department of Neurology, GanSu Provincial Hospital of Chinese Medicine, Lanzhou, P.R. China

## INTRODUCTION

The relentlessly progressive course of ALS leads to death or tracheotomy of most ALS patients within 2-5 years after symptom onset. Past clinical trials have repeatedly failed to improve the median tracheotomy-free survival rate at 15-18 month follow-up<sup>1-7</sup>. Riluzole is thus far the only FDA approved drug for ALS that extends survival by 3-5 months during the first 15-18 months of its initiation. To support the desperate need of ALS/MND patients, BuNaoGao (BNG), a unique cocktail of Chinese medicine consisting essentially of Radix angelica sinensis, Ligusticum chuansiong, Polygonatum sibiricum, Astragalus membranaceus and additional ingredients, was supplied through a collaborative effort. The neuronal health benefit of BNG<sup>8-13</sup> has already been approved by a peer-reviewed process in China. BNG is classified as dietary supplement in USA.

According to the theory of Chinese medicine, ALS/MND belongs to the category of Qi deficiency, "liver" and "kidney" weakness (Wei Zheng or Wei Syndrome). The Chinese medicine definition of "liver" includes liver, part of the CNS, autonomic nervous system, blood and visual systems; the definition of "kidney" includes urinary system, reproductive system, parts of the endocrine system and nervous system. BuNaoGao was designed to achieve its neuronal supporting effect through the nourishment of "liver" and "kidney", and the nourishment, mobilization and harmonization of "Qi" and "blood". Experimental studies of BNG in animal models had revealed its effects in improving blood circulation, reducing blood viscosity and in immune regulation and anti-inflammation<sup>9,15</sup>. Its potent beneficial effects in patients with head or spinal cord injuries (both acute and chronic injuries) also implicated a role of BNG in promoting neuronal regeneration and tissue repair. Apparently the mechanism behind BNG in managing ALS/MND is through systemic regulation.

## MATERIAL AND METHOD

BuNaoGao were made available in two types, the mixture of dry ingredients for self-brewing at home or the concentrated extract from the concoction in the form of lozenge. The mixture of dry ingredients was provided by TianHe Bioscience, Inc, MA, USA. Lozenge form was manufactured and provided by the GanSu Provincial Hospital of Chinese Medicine, P.R. China. Most BNG were distributed through Stephen Byer & Associates (WI, USA). Before July 2004, only BNG dry ingredients were available. After July 2004, when lozenge became available, most patients used lozenge, only a small number of patients continue to use the self-brewing type of BNG. BNG is consumed orally at 1-1.25 fold of standard adult dosage.

BNG users came from over 20 countries, with American and European patients in predominance. 435 ALS/MND patients at various stages of the disease were supplied with BNG for duration ranging from 1mth to continuous use. 396/435 (91%) patients have ALS <5 year duration, 39/435 (9%) had ALS >5 years; 45/435 (10%) cases were in advanced stage and had feeding tube or tracheotomy before BNG; 70/435 (16%) had significant breathing compromise (FVC confirmed or expected to be <60%). Vast majority (424 cases) are either confirmed or probable ALS. 8 cases were suspicious of ALS/MND.

## RESULTS

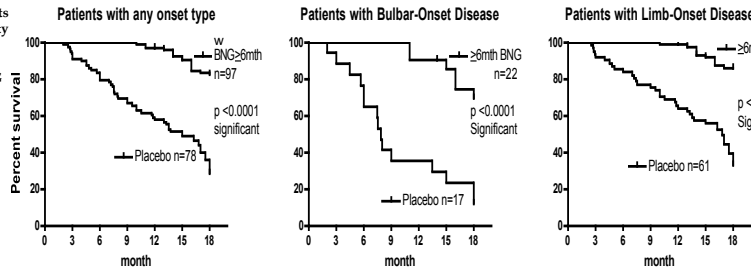
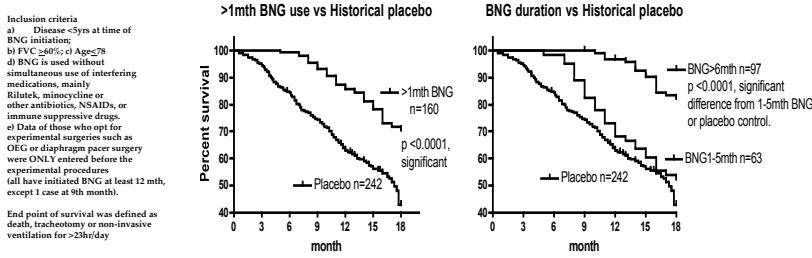
### 1. Slope of ALSFRS-R change during BNG use

Inclusion criteria: a) Disease <5yrs at time of BNG initiation; b) FVC >60%, no feeding tube; c) Age <75; d) BNG is used without simultaneous use of interfering medications, such as Riluzole, minocycline or other antibiotics, NSAIDs or other anti-inflammatory drugs, beta blocker >5mg).

Cases	Baseline ALSFRS-R (SD)	Slope of Change unit/month (SE)	p value
6mth BNG use	n=96 39.6 (+/-6.1)	-0.27 (0.04)	<0.0001
Historical placebo(a)	n=99 37.9 (+/-5.2)	>-1.00 (<0.09)	
9mth BNG use	n=53 39.2 (+/-6.8)	-0.33 (0.05)	<0.0001
Historical placebo(b)	n=206 37.9 (+/-5.2)	-1.04 (0.07)	
12mth BNG use	n=32 40.8 (+/-5.6)	-0.33 (0.06)	<0.0001
Historical placebo(c)	n=99 37.9 (+/-5.2)	-1.08 (0.09)	

SD: Standard Deviation; SE: standard error  
p value was calculated using two-tailed t test  
a) placebo data from 12mth celebrex trial used<sup>12</sup>  
b) placebo data from 9 mth minocycline trial used<sup>14</sup>.

### 2. Tracheotomy-free survival at 18mth follow up-160 cases (Kaplan-Meier analysis)



Of the 6 cases in BNG group who reached end point within 18mth, 3 were on BNG, 3 cases stopped BNG for 2mth.  
Of the 10 cases in BNG group who reached end point within 18mth, 2 were on BNG, 2 stopped BNG for 2mth, 1 tried an experimental drug for 3mth before reaching end point, 3 stopped BNG for 4-5mth, 2 stopped BNG for 9-10mth.

Table 2 Patient baseline characteristics

Group	Race				Age distribution										Onset location				ALS duration at time of BNG initiation																	
	Case	Female	Male	%	Average age±SD	Youngest	1st	2nd	3rd	4th	5th	6th	7th	8th	9th	10th	11th	12th	13th	14th	15th	16th	17th	18th	19th	20th	21st	22nd	23rd	24th	25th	26th	27th	28th	29th	30th
>6mth BNG use	47	298	8%	54±10.8	37.8	14.0%	21.0%	24.0%	24.0%	16.0%	5.0%	22.0%	44.0%	23.0%	10.0%	2	8	21	22%	4	43%	19	13%	6	6%	9	9%									
>9mth BNG use	43	238	8%	53±8.49	37.1	3.0%	23.0%	23.0%	23.0%	10.0%	5.0%	13.0%	28.0%	20.0%	11.0%	4	7	15	25%	15	24%	13	20%	7	11%	6	9%									
All >6mth BNG use combined	140	538	9%	54±10.1	37.7	7.0%	24.0%	24.0%	24.0%	10.0%	5.0%	17.0%	36.0%	21.0%	10.0%	6	15	37	27%	19	31%	18	13%	13	9%	15	14%									

### 3. Tracheotomy-free survival at 24 mth follow-up & at 5 year disease duration-137 cases

Inclusion criteria: Similar to Result section 1 or 2, except all patients included in this analysis are participants who initiated BNG on or prior Nov 2005 (completed at least 24 month follow up).

Table 3a. 24mth & 5 yr survival of patients with onset at any location					Table 3b. Longer term survival rate of limb onset patients						
Historical data (ref 2, 17-22)	death/ trach of within patients	living trache-free beyond 24mth	Already & Expected living trach-free above 5yr	Median Survival	Historical data	death/ trach of within patients	living trache-free beyond 24mth	Already & Expected living trach-free above 5yr	Median Survival		
1-5mth BNG	62	39	23 (37%)	≥12 (≥19%, <31%)	47.5mth	1-5mth BNG	48	28	20 (40.8%)	≥11 (≥23%, <37%)	55mth
6-8mth BNG	25	10	15 (60%)	≥9 (≥36%, <52%)	Has yet reached expected to be >50.5mth	6-8mth BNG	17	5	12 (71%)	≥8 (≥47%, <53%)	Has yet reached expected to be >50mth
>9mth BNG	50	15	35 (70%)	≥26 (≥52%, <59%)	Has yet reached expected to be >50mth	>9mth BNG	38	7	31 (81%)	≥23 (≥60%, <71%)	Has yet reached expected to be >50mth
≥6 mth BNG combined	75	25	50 (67%)	≥36 (≥48%, <55%)	Has yet reached expected to be >48mth	≥6 mth BNG combined	55	12	43 (78%)	≥31 (≥56%, <65%)	Has yet reached expected to be >50mth

Inclusion: FVC >60%, can have bi-pap, ALS FRs can be <30  
exclusion: ALSFRS-R <30, on bi-pap, and bulbar onset patients

Among the >6mth BNG user (table 3a), 36 patients have so far reached 5 year duration and beyond, (upper range at 7 yrs 9mth by Nov 07). No tracheotomy or death has been reported in this group of patients per last updates of last 6mth. A higher 10-year survival rate is expected among this group of BNG users.

### 4. Patients with disease duration >5 years at time of BNG initiation

#### -Tracheotomy-free survival at 18mth follow up

Inclusion criteria: no feeding tube when BNG started. No restriction on FVC was set. A higher rate of stabilization by BNG was observed. For the 19 cases ≥5 mth BNG users who completed 18mth follow-up (excluding those who opt for experimental surgeries during the follow-up period), the tracheotomy-free rate at the 18<sup>th</sup> month were 94.7%.

## SUMMARY & CONCLUSIONS

BNG has demonstrated significant positive impact in the following categories

- 1) Reduced ALSFRS-R monthly decline rate: When patients were on standard dosage BNG, the ALSFRS-R monthly decline rate is significantly slower than historical control (p<0.0001).
- 2) Improved Survival at 18mth follow-up: 18mth follow-up of 97 cases of >6mth BNG users, the rate of tracheotomy-free survival at 12mth, 15mth and 18mth month was 97%, 90% and 82% respectively (significantly different from historical controls, P < 0.0001). The survival rate of the 63 cases 1-5mth BNG users was not significantly different from historical controls, P=0.3).
- 3) Tracheotomy-free survival at 5th year of disease duration from onset
  - a) If Inclusion criteria at BNG initiation: FVC ≥60%, no feeding tube; ALSFRS-R can be at any level

Historical data (all onset types): 10-20% (30% referral bias)  
>6mth BNG users (all onset types): ≥ 48% but <55%  
>9mth BNG users (all onset types): ≥ 52% but <59%

  - b) If Inclusion criteria at BNG initiation: limb onset only, FVC ≥60%, no feeding tube; ALSFRS-R 30

Historical data (limb onset only): 15-30%  
>6mth BNG users (limb onset only): ≥56% but <65%  
>9mth BNG users (limb onset only): ≥60% but <71%
- 4) Further, a higher 10-year survival rate is expected among these >6mth BNG users who have now reached above 5 year disease duration. Historically only 4%-10% survive beyond the 10th year tracheotomy-free.
- 5) Even better survival rate is expected if BNG is initiated at early stage of the disease and is used at continuous manner without extended break.

Our outcome analyses indicate a highly significant impact of BNG at slowing down ALS progression and improving tracheotomy-free survival and strongly support further evaluation of BNG's positive impact on ALS/MND on a larger scale.

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