

A physician survey of poststroke aphasia diagnosis and treatment in China

SPEECH study

Yuying Zhou, BS^a, Xiaoxia Du, MD^b, Jun Xiao, BS^c, Yunpeng Cao, MD^d, Qihao Guo, MD^e, Aihong Zhou, MD^f, Jiong Zhou, MD^g, Nan Li, MD^h, Yinhua Wang, MS^{i,*}, Lifei Jiao, MS^j

Abstract

The current status of the diagnosis and management of poststroke aphasia (PSA) in China is unknown.

To analyze the physicians' strategy and knowledge about the management of PSA in clinical practice and the needs for standardization of diagnosis and treatment.

This survey was conducted in March–August 2019 at 32 tertiary hospitals in 16 provinces/municipalities in China. The attending physicians from the Neurology and Neuro-rehabilitation/Rehabilitation Departments were included. The online questionnaire inquired about patient information, physicians' diagnosis and treatment behavior for PSA, and physicians' understanding of PSA.

A total of 236 physicians completed the survey. Regarding PSA assessment, 99.2% of the physicians reported using medical history and physical examination, 93.2% reported using neuroimaging, and 76.3% reported using dedicated scales. Most physicians used a combination of drug and non-drug treatment. Neuro-regenerators/cerebral activators and anti-dementia drugs were the most common pharmacotherapies; butylphthalide, edaravone, and memantine were most frequently prescribed. Six months poststroke was rendered as a spontaneous language recovery period, and a ≥6-month treatment for PSA was suggested by many physicians. The lack of standardized treatment regimen/clinical guidelines and the limited number of approved drugs for PSA were the primary challenges encountered by physicians during practice. The majority of the physicians agreed with the necessity of guidelines or consensus for the diagnosis and treatment of PSA.

The knowledge gaps exist among physicians in China regarding the assessment and management of PSA. The improved awareness of the available guidelines/consensus could improve the performance of the physicians.

Abbreviations: ABC = aphasia battery of Chinese, BNT = Boston naming test, CIAT = constraint-induced aphasia therapy, CRRCAE = China rehabilitation research center aphasia examination, CT = computed tomography, MRI = magnetic resonance imaging, MRA = magnetic resonance angiography, PET = positron emission tomography, PSA = poststroke aphasia, SPECT = single-photon emission computed tomography, VFT = verbal fluency test, WAB = Western aphasia battery.

Keywords: aphasia, diagnosis, stroke, survey, treatment

1. Introduction

Poststroke aphasia (PSA) is the loss or impairment of language caused by brain damage and is one of the most devastating cognitive impairments of stroke. The presence of PSA is common, occurring in 15% to 42% of the patients with acute stroke^[1,2]

and 25% to 50% of the patients in the chronic setting.^[3,4] PSA is associated with poor prognosis and outcomes such as death,^[5,6] increased length of hospital stay,^[5,7] greater use of rehabilitation services,^[8] poor quality of life,^[9] and increased health care costs.^[10]

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The present study involving human participants was reviewed and approved by the Medical Ethics Committee of Tianjin Huanhu Hospital. The patients/participants provided written, informed consent before recruitment in this study.

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All data generated or analyzed during this study are included in this published article [and its supplementary information files].

^a Department of Neurology, Huanhu Hospital, Tianjin, ^b Department of Neurorehabilitation, School of Rehabilitation Medicine, Capital Medical University, Beijing Bo'AI Hospital, China Rehabilitation Research Center, Beijing, ^c Department of Neurology, Sichuan Academy of Medical Sciences & Sichuan Provincial People's Hospital, Chengdu, Sichuan Province, PR, ^d Department of Neurology, First Affiliated Hospital of China Medical University, Shenyang, Liaoning Province, ^e Department of Gerontology, Shanghai Jiao Tong University Affiliated Sixth People's Hospital, Shanghai, ^f Innovation Center for Neurological Disorders and Department of Neurology, Xuanwu Hospital, Capital Medical University, National Clinical Research Center for Geriatric Diseases, Beijing, ^g Department of Neurology, Second Affiliated Hospital, School of Medicine, Zhejiang University, Hangzhou, ^h Research Center of Clinical Epidemiology, Peking University Third Hospital, ⁱ Department of Neurology, the First Hospital of Peking University, ^j Drug Development Organization, Lundbeck China, Beijing, China.

* Correspondence: Yinhua Wang, Department of Neurology, the First Hospital of Peking University, Beijing, China (e-mail: wyh2nd@163.com).

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The long-term assessment of the poststroke patients is necessary to diagnose PSA because of variability in the patients' condition over time.^[11,12] In addition, since multiple brain regions are involved in language, a variety of manifestations of PSA are produced, complicating diagnosis.^[12] Nevertheless, patients with PSA might benefit from careful diagnosis and development of a treatment plan to maximize recovery.^[12] The diagnosis for PSA includes interviews with the patient and family, assessment of behavioral language, assessment of motor speech abilities, assessment of other cognitive faculties, and screening for depression.^[12] The most common treatments for PSA are behavioral therapy^[13–14] and speech therapy.^[15,16] Moreover, drugs that enhance neuronal plasticity, including piracetam,^[17] acetylcholinesterase inhibitors,^[18] and memantine,^[19] have been tested, but limited evidence is obtained.^[12]

All treatments and general care for PSA aim at improving the patients' quality of life, and hence, it is necessary to select timely and effective treatment options. PSA is relatively well-studied in western countries, but the real-world characteristics and deficiencies in the diagnosis and management of PSA in China, and whether the drug and non-drug treatments are appropriately selected, are currently unknown as no large-scale survey or study examined this question in China. Therefore, we designed the cross-sectional study—the physician survey of PSA diagnosis and treatment in China (the SPEECH study). This study aimed to analyze the physicians' knowledge about the diagnosis, treatment strategy, and the actual needs for the standardization of diagnosis and treatment of PSA. The findings could eventually help in establishing a national strategy for the comprehensive management of PSA in China and improve the patients' quality of life.

2. Methods

2.1. Study design and participants

This survey was conducted from March 20–August 18, 2019, at 32 hospitals in 16 provinces/municipalities in China.

The inclusion criteria were as follows:

1. attending physician (experience ≥ 3 years);
2. physician from the Department of Neurology or Rehabilitation/Neurorehabilitation;
3. involvement in the treatment and management of patients with PSA within the past 6 months.

2.2. Survey sampling

In this study, the participants were obtained through two-stage sampling. In the first stage, cities in China were selected by a typical sampling method; 18 cities were selected from the northeast, north, central, east, south, northwest, and southwest China. In the second stage, 32 hospitals with PSA diagnosis and treatment capacity were selected from the 18 cities. All physicians of 32 hospitals who met the requirements of this study were selected as subjects.

In this study, it was critical to identify and determine whether the physicians had PSA experience. Therefore, after the completion of sampling, the physicians were required to answer a series of questions to determine whether the inclusion criteria were fulfilled. In order to reduce the workload of the survey, we chose the medical information service platform MedLive, which is widely used among Chinese physicians, to hand out the

screening questionnaire and conduct the survey. During the study, we invited physicians from relevant hospitals to participate in this survey by sending invitations online and recruiting from relevant departments to fill in the MedLive questionnaire.

2.2.1. Object screening and survey implementation. The survey consists of 2 sections, the screening section, and the main section. The screening section was to understand the profiles of the physicians and screen for the eligible physicians. The main section gathered the patient information, physicians' diagnosis and treatment behavior for PSA, and physicians' understanding of PSA.

The survey was carried out online via the MedLive platform. It is a comprehensive platform for providing professional medical information services for physicians, with >2 million doctor members, and also the largest online research platform for doctors in China. The survey required 20 to 30 minutes. In order to increase the number of completed surveys, the participating physicians received a consultant fee from the investigator. The link to the survey was sent by text message or email. The physicians willing to participate could participate in the survey by clicking on the link.

The survey was written in the Decipher system (a dedicated platform for survey programming by Focus Vision), and the answer logic was checked by a Python-based program. A pre-test with a small sample was conducted in the initial stage. The survey was amended based on the test feedback. The effective surveys were those with all responses completed.

2.3. Statistical analysis

All analyses were carried out using SPSS 20.0 (IBM, Armonk, NY, USA). Only descriptive statistics were used. The continuous variables (years of experience with PSA, numbers of PSA patients, numbers of stroke patients, self-reported percentages, and scores for the difficulty in diagnosis and treatment) were presented as means \pm standard deviations or median (1st Quartile, 3rd Quartile). Categorical variables (department, job title, PSA assessment method, neuroimaging used, scales used, PSA treatment protocol, medications, recovery, and recommended treatment course) were expressed as frequencies (percentages).

3. Results

3.1. Survey process

The survey was sent to 3135 physicians, and 430 responded. Among them, a total of 194 physicians were excluded: 156 were not eligible, and 38 were eligible but did not complete all questions. Finally, a total of 236 physicians completed the survey.

3.2. Characteristics of the physicians

Table 1 presents the characteristics of the included physicians. The majority of the physicians were from the Neurology Department (94.5%) and were attending physicians (48.7%). They had been working with patients with PSA for an average of 8.4 years, with 21.7 patients managed each month.

3.3. Diagnosis of PSA

Table 2 presents the diagnostic tests for PSA. Regarding the PSA assessment methods, 99.2% of the physicians reported using medical history and physical examination, 96.6% used patients' complaints and statements from the family, 93.2% used

Table 1
Characteristics of the physicians.

Variables	Physicians (n = 236)
Department, n (%)	
Neurology	223 (94.5)
Rehabilitation/neurorehabilitation	13 (5.5)
Job title, n (%)	
Attending physician (>3yr)	115 (48.7)
Deputy chief physician	91 (38.6)
Chief physician	30 (12.7)
Years in diagnosis and treatment of PSA, median (1st Quartile, 3rd Quartile)	8 (5, 12)
Monthly number of PSA patients treated and managed in the last 6 mo, self-reported, median (1st Quartile, 3rd Quartile)	10 (5, 23)
The number of patients with PSA who were treated or managed for stroke in the past 6 mo, self-reported, median (1st Quartile, 3rd Quartile)	8 (5, 15)

PSA = poststroke aphasia.

neuroimaging, and 76.3% used dedicated scales. Regarding neuroimaging, all the physicians used magnetic resonance imaging, 92.3% used magnetic resonance angiography, 85.0% used computed tomography, 10.9% used single-photon emission computed tomography (SPECT), and 10.0% used positron emission tomography. Regarding the scales, 66.7% used the verbal fluency test, 59.4% used the Boston naming test, 56.1% used the aphasia battery of Chinese, 47.8% used the China rehabilitation research center aphasia examination, and 26.1% used the Western aphasia battery.

3.4. Treatment of PSA

Table 3 presents the treatments for PSA. Most physicians used a combination of drug and non-drug treatment (94.6%); the most common drugs were neuro-regenerators/cerebral activators

Table 2
Diagnosis of poststroke aphasia.

Variable	Physicians (n = 236)
PSA assessment method, n (%)	–
Medical history/examination of patients	234 (99.2)
Patient complaint/family member statement	228 (96.6)
Neuroimaging	220 (93.2)
Dedicated scales	180 (76.3)
Others	5 (2.1)
Neuroimaging used, n (%)	–
Magnetic resonance imaging (MRI)	236 (100)
Magnetic resonance angiography (MRA)	218 (92.3)
Computed tomography (CT)	201 (85.0)
Single-photon emission computed tomography (SPECT)	26 (10.9)
Positron emission tomography (PET)	24 (10.0)
Others	6 (2.7)
Scales used, n (%)	
Verbal fluency test (VFT)	157 (66.7)
Boston naming test (BNT)	140 (59.4)
Aphasia battery of Chinese (ABC)	132 (56.1)
China rehabilitation research center aphasia examination (CRRCAE)	113 (47.8)
Western aphasia battery (WAB)	62 (26.1)
Others	5 (2.2)

Table 3
Treatment of poststroke aphasia.

Variable	Physicians (n = 236)
PSA treatment protocol, n (%)	N = 202
Drug + non-drug treatment	191 (94.6)
Drug treatment alone	5 (2.5)
Non-drug treatment alone	5 (2.5)
Medication options, n (%)	N = 196
Drugs for nerve repair and brain activation	173 (88.3)
Anti-dementia drugs	166 (84.7)
Others	105 (53.6)
What percentage of patients will be selected when prescribing the following drugs	–
Anti-dementia drugs of self-reported percentage (via scroll bar), %, median (1st Quartile, 3rd Quartile)	N = 166
Memantine	50 (25, 70)
Donepezil	20 (15, 40)
Ginko Biloba preparation	10 (0, 30)
Rivastigmine	0 (0, 10)
Drugs for nerve repair and brain activation of self-reported percentage (via scroll bar), %, median (1st Quartile, 3rd Quartile)	N = 173
Butylphthalide	50 (20, 70)
Edaravone	30 (10, 50)
Nimodipine	10 (0, 20)
Others	0 (0, 5)
Concerns for drug selection, n (%)	N = 236
Symptom improvement	222 (93.9)
Recommendations by guidelines/consensus	210 (88.8)
Mechanism	207 (87.8)
Good safety	193 (81.8)
Evidence-based medicine	191 (81.1)
Health insurance directory	119 (50.5)
Others	2 (1.0)
Non-drug treatment options, n (%)	N = 236
Speech and language training	225 (95.4)
Cognition treatment (attention, memory training)	194 (82.1)
Family training	172 (73.0)
Acupuncture and moxibustion therapy	94 (39.8)
Computer-based therapy	73 (31.1)
Others	2 (1.0)

(88.3%) and anti-dementia drugs (84.7%). The most frequently prescribed anti-dementia drug was memantine (50%, Q1 = 25%, Q3 = 70%), followed by donepezil (20%, Q1 = 15%, Q3 = 40%), Ginko biloba preparation (10%, Q1 = 0%, Q3 = 30%), and rivastigmine (0%, Q1 = 0%, Q3 = 10%). The most frequently prescribed neuro-regenerator/cerebral activator was butylphthalide (50%, Q1 = 20%, Q3 = 70%), followed by edaravone (30%, Q1 = 10%, Q3 = 50%), and nimodipine (10%, Q1 = 0%, Q3 = 20%). The primary considerations for selecting a specific drug were the improvement of the symptoms (93.9%), recommendations by guidelines/consensus (88.8%), mechanism of action (87.8%), safety (81.8%), and health insurance coverage (50.5%). The non-drug treatments included speech and language training (95.4%), cognition training (82.1%), family training (73.0%), acupuncture and moxibustion (39.8%), and computer-based therapy (31.1%).

3.5. Knowledge of PSA

Table 4 presents the data about the physicians' knowledge of PSA. Most of the physicians believe that patients with PSA can achieve partial spontaneous recovery (88.1%), that spontaneous recovery occurs within 6 months of stroke (47.9%), and that the

Table 4
Knowledge of poststroke aphasia.

Variable	
Spontaneous recovery of language function in PSA patients, n (%)	
Unable to recover spontaneously	19 (8.1)
Partial spontaneous recovery	208 (88.1)
Complete spontaneous recovery	9 (3.8)
Spontaneous recovery time, n (%)	
Within 1 mo after stroke	10 (4.6)
Within 3 mo after stroke	65 (30.0)
Within 6 mo after stroke	104 (47.9)
Within 12 mo after stroke	33 (15.2)
More than 12 mo after stroke	5 (2.3)
Recommended course of treatment by physicians, n (%)	
1 mo	0
3 mo	26 (11.0)
6 mo	93 (39.4)
12 mo	57 (24.2)
More than 12 mo	60 (25.4)
Difficulties in the diagnosis and treatment of PSA (1–7 points), mean \pm SD	
Lack of standardized treatment protocols and clinical guidelines for PSA	5.8 \pm 1.2
Lack of approved drugs for PSA indications	5.8 \pm 1.3
Patients don't know how to find specialists for PSA treatment	5.6 \pm 1.4
Uncertainty on evaluation of effectiveness and outcome of PSA treatment	5.4 \pm 1.3
Patients and family members don't know much about PSA	5.3 \pm 1.5
Clinicians lack opportunities to communicate with PSA patients	5.2 \pm 1.4
Lack of diagnostic criteria for PSA diagnosis	5.1 \pm 1.6
Poor adherence in PSA patients	5.0 \pm 1.5
Clinicians lack experience in identifying PSA	5.0 \pm 1.6
Lack of method to prevent PSA	4.8 \pm 1.7
High cost for PSA diagnosis	4.2 \pm 1.6
Understand that there are guidelines or consensus for diagnosis and treatment of PSA, n (%)	84 (35.6)
Agree with the necessity of guidelines or consensus for diagnosis and treatment of PSA, n (%)	147 (99.3)
Which of the following is the best clinical practice for PSA? n (%)	
Drugs+rehabilitation	139 (58.9)
Rehabilitation	72 (30.5)
Drugs	15 (6.4)
Comprehensive treatment	8 (3.4)
Others	2 (0.8)

recommended treatment is for ≥ 6 months (86.4%). The highest-rated (on a 7-point scale) difficulties in diagnosing/treating PSA were: lack of standardized treatment protocols and clinical guidelines for PSA (5.8 \pm 1.2), lack of approved drugs for PSA indications (5.8 \pm 1.3), and patients do not know how to find specialists for PSA treatment (5.6 \pm 1.4). Although only 35.6% of the physicians were aware of the guidelines or consensus for the diagnosis and treatment of PSA, 99.3% agree with the necessity of guidelines or consensus for the diagnosis and treatment of PSA. Among the surveyed physicians, 58.9% considered that the combined use of drugs and rehabilitation is the best course of action, followed by 30.5% who considered that rehabilitation alone is the best course of action for the treatment.

4. Discussion

The SPEECH study aimed to investigate the physicians' actual strategy, knowledge, and needs with respect to the management

of PSA. The current results showed a high level of unawareness regarding the existence of clinical guidelines and a high level of confusion concerning appropriate pharmacotherapies for PSA. Hence, there is an urgent need for standardized diagnostic criteria and management guidelines for patients with PSA in China.

In the present study, neuroimaging was used by 93.2% of the physicians for the diagnosis of PSA, albeit associated with several issues. Interestingly, language processing involves a large number of brain regions, many of which have not been fully characterized yet. In addition, previous studies present limitations, especially about the choice of the tasks for neuroimaging and the selection of patients.^[20] A wide range of clinical measures and assessments are used to test language function of post-stroke patients.^[21] Nevertheless, the wide variety of available language tests might be an impediment for the reliable and consistent diagnosis of PSA, especially since none of them is specific to PSA or has been validated for PSA.^[21] Although the Western aphasia battery can be used to distinguish between aphasic and non-aphasic test performance,^[21] it is used by only 26% of the physicians in the SPEECH study. Further, the Aphasia battery of Chinese test has been validated as a screening tool for PSA in Chinese patients,^[22] but is only used by 56.1% of the physicians. The best approach could lie in the use of multiple scales for the screening of PSA because of the wide variety of types and manifestations of PSA. Additional studies are essential to determine the best scales for the screening and diagnosis of PSA.

The available guidelines of PSA recommend early rehabilitation and the development of alternative or complementary means of communication, as reviewed by Shrubsole et al^[23] and Berthier et al.^[24] In patients with moderate or severe PSA, rehabilitation alone could be insufficient. Several drugs that might help in the management of PSA are available. One of the mechanisms responsible for the pathogenesis of PSA is the disruption of major neurotransmitters pathways connecting the language centers.^[24] Memantine is an uncompetitive N-methyl-D-aspartate glutamate receptor antagonist that improves the activity of salvaged neural networks by improving glutamatergic transmission.^[25] A previous trial showed that the addition of memantine to constraint-induced aphasia therapy improves aphasia severity in PSA as compared to constraint-induced aphasia therapy alone with good tolerability and safety.^[19] In addition, the efficacy of memantine can be maintained for the long-term.^[19] Similarly, butylphthalide has been shown to be beneficial in the management of ischemic stroke, including PSA, partially by modulating glutamatergic transmission.^[26] Nootropic drugs have also been reported to improve the manifestations of PSA.^[24,27] Nevertheless, the available guidelines on stroke management do not provide clear recommendations on the use of pharmacological management but consider the use of cholinesterase inhibitors (donepezil, rivastigmine, and galantamine) or memantine.^[28] In the present study, only a subset of physicians was aware of the guidelines for the management of PSA, and most physicians utilize a combination of drugs (memantine and butylphthalide) and rehabilitation. The current ambiguity in the guideline recommendations for drug therapy is partially due to the limited number of high quality randomized controlled trials. Thus, extensive studies on drug therapy for PSA, as well as the dose and timing of drug administration, are needed in the future.

The present survey identified a number of issues that hinder the management of PSA in China. These factors include a lack of standardized protocols and guidelines, a lack of drugs with clear PSA indication, a lack of patient referral to PSA specialists, a lack

of public knowledge about PSA, a lack of communication between physicians and patients with PSA, a lack of clear diagnostic criteria, and high healthcare costs for the management of PSA. These factors should be considered when PSA management guidelines are designed.

The present study has some limitations. First, only a small proportion of physicians completed the survey and could be included in the analysis. The unsatisfactory knowledge level of PSA and the low awareness of PSA rehabilitation guidelines observed in the present study could be partially attributed to the fact that only 13 (5.5%) physicians from the neuro-rehabilitation department were included. Moreover, the survey was not validated, and all data were self-reported, rendering inevitable bias. However, the present study provides a foundation for future studies on the real-world condition of PSA management in China and the establishment of Chinese guidelines. There is an urgent need for high-quality studies on the concept, assessment, diagnosis, and treatment of PSA to guide clinical practice.

Knowledge gaps exist among physicians in China regarding the assessment and management of PSA. Thus, there is an urgent need for standardized diagnostic criteria and management guidelines for patients with PSA.

Author contributions

Conceptualization: Yuying Zhou.

Data curation: Yuying Zhou, Nan Li, Yinhua Wang, Lifei Jiao.

Resources: Yinhua Wang.

Writing – original draft: Yuying Zhou, Xiaoxia Du, Jun Xiao, Yunpeng Cao, Qihao Guo, Aihong Zhou, Jiong Zhou, Nan Li, Yinhua Wang, Lifei Jiao.

Writing – review & editing: Yuying Zhou, Xiaoxia Du, Jun Xiao, Yunpeng Cao, Qihao Guo, Aihong Zhou, Jiong Zhou, Nan Li, Yinhua Wang, Lifei Jiao.

References

- [1] Kadojic D, Bijelic BR, Radanovic R, et al. Aphasia in patients with ischemic stroke. *Acta Clin Croatica* 2012;51:221–5.
- [2] Ryglewicz D, Hier DB, Wiszniewska M, et al. Ischemic strokes are more severe in Poland than in the United States. *Neurology* 2000;54:513–5.
- [3] Ee CH, Kwan PE, Tan ES. Stroke rehabilitation of elderly patients in Singapore. *Singapore Med J* 1991;32:55–60.
- [4] Gialanella B, Bertolinelli M, Lissi M, Prometti P. Predicting outcome after stroke: the role of aphasia. *Disability Rehabilitation* 2011;33:122–9.
- [5] Bersano A, Burgio F, Gattinoni M, Candelise L, Group PS. Aphasia burden to hospitalised acute stroke patients: need for an early rehabilitation programme. *Int J Stroke* 2009;4:443–7.
- [6] Di Carlo A, Lamassa M, Baldereschi M, et al. Sex differences in the clinical presentation, resource use, and 3-month outcome of acute stroke in Europe: data from a multicenter multinational hospital-based registry. *Stroke* 2003;34:1114–9.
- [7] Guyomard V, Fulcher RA, Redmayne O, Metcalf AK, Potter JF, Myint PK. Effect of dysphasia and dysphagia on inpatient mortality and hospital length of stay: a database study. *J Am Geriatrics Soc* 2009;57:2101–6.
- [8] Dickey L, Kagan A, Lindsay MP, Fang J, Rowland A, Black S. Incidence and profile of inpatient stroke-induced aphasia in Ontario, Canada. *Arc Physical Med Rehabil* 2010;91:196–202.
- [9] Bullier B, Cassouesalle H, Villain M, et al. New factors that affect quality of life in patients with aphasia. *Ann Phys Rehabil Med* 2020;63:33–7.
- [10] Ellis C, Simpson AN, Bonilha H, Mauldin PD, Simpson KN. The one-year attributable cost of poststroke aphasia. *Stroke* 2012;43:1429–31.
- [11] Flowers HL, Skoretz SA, Silver FL, et al. Poststroke aphasia frequency, recovery, and outcomes: a systematic review and meta-analysis. *Arch Physical Med Rehabil* 2016;97:2188–201. e2188.
- [12] Fama ME, Turkeltaub PE. Treatment of poststroke aphasia: current practice and new directions. *Seminars Neurol* 2014;34:504–13.
- [13] Kelly H, Brady MC, Enderby P. Speech and language therapy for aphasia following stroke. *Cochrane Database Syst Rev* 2010;CD000425.
- [14] Bhogal SK, Teasell R, Speechley M. Intensity of aphasia therapy, impact on recovery. *Stroke* 2003;34:987–93.
- [15] Wertz RT, Weiss DG, Aten JL, et al. Comparison of clinic, home, and deferred language treatment for aphasia. A Veterans Administration Cooperative Study. *Arch Neurol* 1986;43:653–8.
- [16] Brady MC, Kelly H, Godwin J, Enderby P, Campbell P. Speech and language therapy for aphasia following stroke. *Cochrane Database Syst Rev* 2016;2016:CD000425.
- [17] Zhang J, Wei R, Chen Z, Luo B. Piracetam for aphasia in post-stroke patients: a systematic review and meta-analysis of randomized controlled trials. *CNS drugs* 2016;30:575–87.
- [18] Whyte EM, Lenze EJ, Butters M, et al. An open-label pilot study of acetylcholinesterase inhibitors to promote functional recovery in elderly cognitively impaired stroke patients. *Cerebrovascular Dis* 2008;26:317–21.
- [19] Berthier ML, Green C, Lara JP, et al. Memantine and constraint-induced aphasia therapy in chronic poststroke aphasia. *Ann Neurol* 2009;65:577–85.
- [20] Rapp B, Caplan D, Edwards S, Visch-Brink E, Thompson CK. Neuroimaging in aphasia treatment research: issues of experimental design for relating cognitive to neural changes. *NeuroImage* 2013;73:200–7.
- [21] Rohde A, Worrall L, Godecke E, et al. Diagnosis of aphasia in stroke populations: a systematic review of language tests. *PLoS one* 2018;13:e0194143.
- [22] Wu JB, Lyu ZH, Liu XJ, Li HP, Wang Q. Development and Standardization of a New Cognitive Assessment Test Battery for Chinese Aphasic Patients: A Preliminary Study. *Chin Med J (Engl)* 2017;130:2283–2290.
- [23] Shrubsole K, Worrall L, Power E, O'Connor DA. Recommendations for post-stroke aphasia rehabilitation: an updated systematic review and evaluation of clinical practice guidelines. *Aphasiology* 2017;31:1–24.
- [24] Berthier ML, Pulvermuller F, Davila G, Casares NG, Gutierrez A. Drug therapy of post-stroke aphasia: a review of current evidence. *Neuropsychol Review* 2011;21:302–17.
- [25] Lipton SA. Pathologically-activated therapeutics for neuroprotection: mechanism of NMDA receptor block by memantine and S-nitrosylation. *Current Drug Targets* 2007;8:621–32.
- [26] Wang S, Ma F, Huang L, et al. DL-3-n-Butylphthalide (NBP): a promising therapeutic agent for ischemic stroke. *CNS Neurological Disorders Drug Targets* 2018;17:338–47.
- [27] Watanabe K, Tanaka M, Yuki S, Hirai M, Yamamoto Y. How is edaravone effective against acute ischemic stroke and amyotrophic lateral sclerosis? *J Clin Biochem Nutr* 2018;62:20–38.
- [28] Winstein CJ, Stein J, Arena R, et al. Guidelines for adult stroke rehabilitation and recovery: a guideline for healthcare Professionals from the American Heart Association/American Stroke Association. *Stroke* 2016;47:e98–169.