

# World Journal of *Clinical Cases*

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**ABOUT COVER**

Editor-in-Chief of *World Journal of Clinical Cases*, Bao-Gan Peng, MD, PhD, is Professor and Director of the Department of Orthopedics at The Third Medical Center of PLA General Hospital. Professor Peng's research interest is spinal surgery. His career work has generated a multitude of new academic viewpoints and theories, and more than 200 academic papers, published both at home and abroad. In practice, he has systematically elucidated the pathogenesis of discogenic low back pain and established a new minimally invasive treatment method: The intradiscal methylene blue injection. He also revealed and characterized a new pathogenesis of Schmorl's nodes, which is a now a famous concept. Finally, he was the first to discover that ingrowth of Ruffini corpuscles into degenerative cervical disc is related to dizziness of cervical origin. (L-Editor: Filipodia)

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## Expert panel's guideline on cervicogenic headache: The Chinese Association for the Study of Pain recommendation

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## Abstract

Cervicogenic headache (CEH) has been recognized as a unique category of headache that can be difficult to diagnose and treat. In China, CEH patients remain managed by many different specialties, and the treatment plans remain controversial. Therefore, there is a great need for comprehensive evidence-based Chinese experts' recommendations for the management of CEH. The Chinese Association for the Study of Pain asked an expert panel to develop recommendations for a series of questions that are essential for daily clinical management of patients with CEH. A group of multidisciplinary Chinese Association for the Study of Pain experts identified the clinically relevant topics in CEH. A systematic review of the literature was performed, and evidence supporting the benefits and harms for the management of CEH was summarized. Twenty-four recommendations were finally developed through expert consensus voting for evidence quality and recommendation strength. We hope this guideline provides direction for clinicians and patients making treatment decisions for the management of CEH.

**Key Words:** Cervicogenic headache; Expert recommendation; Expert panel's guideline; Chinese Association for the Study of Pain; Chronic pain

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**Core Tip:** Cervicogenic headache (CEH) was recognized as a unique category of headache. The treatments of CEH remain controversial among different disciplines. The Chinese Association for the Study of Pain asked a multidisciplinary expert group identified the clinically relevant topics in CEH. Twenty-four recommendations were finally developed through expert consensus voting for evidence quality and recommendation strength. This guideline provides direction for clinicians and patients making treatment decisions for the management of CEH.

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## INTRODUCTION

Cervicogenic headache (CEH), characterized by pain starting in the neck or occipital area that can move to other areas of the head, is a relatively common clinical challenge<sup>[1,2]</sup>. However, controversies related to the management of CEH continue to exist between different disciplines<sup>[3]</sup>. In China and other developed countries, patients with CEH are typically managed by doctors of several different specialties, including general practitioners, neurologists and pain and rehabilitation physicians. Doctors from different disciplines are only rarely concentrated in highly specialized centers<sup>[4]</sup>. In addition, patients with CEH are likely to be treated with several different pharmacological and nonpharmacological interventions, often in combination. Therefore, the Chinese Association for the Study of Pain (CASP) has organized an expert group to develop guidelines for the management of CEH<sup>[4]</sup>.

## CEH DEFINITION AND DIAGNOSIS

The two conflicting viewpoints when defining CEH are as follows: (1) Relying on the clinical features, CEH is said to be characterized by unilateral head pain of fluctuating intensity that is increased by movement of the head, and the pain radiates from the occipital to the frontal regions; and (2) Relying on establishing the diagnosis involves demonstrating a cervical source of head pain and confirming the diagnosis by using anesthetic blocks that pinpoint the sources of pain in the upper cervical joints<sup>[5-7]</sup>. In accordance with the current International Headache Society criteria, the CASP expert group defines CEH as any headache caused by a disorder of the cervical spine or its components, such as bone, disc and/or soft tissue elements that is usually but not invariably accompanied by neck pain.

The diagnostic criteria recommended by the International Classification of Headache Disorders 3<sup>rd</sup> edition<sup>[8,9]</sup> are as follows: (1) Any headache fulfilling criterion (3); (2) Clinical, laboratory and/or imaging evidence of a disorder or lesion within the cervical spine or soft tissues of the neck that can cause headache; (3) Evidence of causation demonstrated by at least two of the following findings: (a) Headache developed in temporal relation to the onset of cervical disorder or appearance of the lesion; (b) Headache that significantly improved or resolved along with an improvement in or the resolution of cervical disorder or lesion; (c) The cervical range of motion is reduced, and the headache is significantly aggravated by provocative maneuvers; and (d) Headache disappears after diagnostic block to the suspected cervical spine structure or its supply nerve; and (4) Headache that is not better accounted for by another International Classification of Headache Disorders-3 diagnosis.

## ANATOMY AND PATHOPHYSIOLOGY

The anatomic locus for CEH is the trigeminocervical nucleus in the upper cervical spinal cord, the convergence between the upper cervical nociceptive afferents and the trigeminal nociceptive afferents in the trigeminocervical complex<sup>[10]</sup>. This approach allows for pain arising from the upper cervical nerves to be referred to the regions of the head innervated by trigeminal afferents, such as the orbital, frontal and parietal regions<sup>[11,12]</sup>.

CEH is believed to be caused by referred pain from the cervical nerves and upper cervical joints<sup>[13]</sup>. Pathological changes in the cervical zygapophyseal joints can generate pain in the areas innervated by the trigeminal nerve (*e.g.*, the frontal and periorbital regions) or the upper three cervical spinal nerves (*e.g.*, the occipital and auricular regions). Involvement of the C2-3 zygapophyseal joint and atlantoaxial joint is the most frequent source of CEH. Impairment of the C2-3 zygapophyseal joint reportedly caused CEH in 70% of all patients, of whom 27% could be diagnosed with third occipital neuropathic headache<sup>[14]</sup>.

## CLINICAL FEATURES AND EXAMINATION

CEH is a chronic unilateral head pain of fluctuating intensity that is increased by movement of the head and radiates from occipital to frontal regions<sup>[15]</sup>. The pain is

typically nonthrobbing, nonlancinating, of moderate to severe intensity and of variable duration. Patients with CEH may have restricted neck range of motion and may have ipsilateral neck, shoulder or arm pain. Most patients also show concomitant symptoms of nausea, tinnitus, dizziness, phonophobia, photophobia, blurred vision or disordered sleep<sup>[16]</sup>.

A detailed history and examination should be the starting point for the clinicians. Patients with CEH are more likely to have myofascial trigger points on the transverse processes of the second cervical vertebra that can spread to the head and splenius capitis, trapezius, sternocleidomastoid and suboccipital muscles<sup>[6]</sup>. Additional maneuvers on physical examination should include movement tests of the cervical spine, such as passive flexion, extension and rotation and segmental palpation of the cervical facet joints. Imaging (through X-rays, computed tomography and magnetic resonance imaging) is considered useful to evaluate cervical disc degeneration, herniation and the degenerative changes in the atlantoaxial, zygapophyseal and uncovertebral joints. Although imaging can be employed to exclude certain diseases from probable diagnosis, it should not be considered a diagnostic modality for CEH<sup>[17]</sup>.

## MANAGEMENT

Despite the availability of several different treatment modalities, no proven effective treatment for CEH has yet been established. By using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) methods<sup>[18]</sup>, a group of 19 experts worked on questions that are considered essential for daily clinical management of patients with CEH and have developed recommendations accordingly.

### Methods

This method consists of the identification of clinically relevant questions, followed by a systematic literature search and summary of the evidence with final recommendations being moderated by feedback from experts.

**Multidisciplinary expert panel:** The CASP organized an expert panel consisting of 19 professionals working in the field of pain medicine, neurology, neurosurgery and rehabilitation from China. Fourteen of them were pain physicians, two were neurologists, one was a rheumatologist, one was an orthopedist and one was a neuroscientist.

**Organizers and experts' coordinators:** Yan-Qing Liu, Hui Liu, Hong Xiao, Bao-Gan Peng.

**Organizational committee:** The CASP.

**CASP experts:** Hong Xiao, Bao-Gan Peng, Ke Ma, Dong Huang, Xian-Guo Liu, Yan Lu, Qing Liu, Li-Juan Lu, Jin-Feng Liu, Yi-Mei Li, Song Tao, Tao Wei, Wen Shen, Xiao-Qiu Yang, Lin Wang, Xiao-Mei Zhang, Zhi-Gang Zhuang, Hui Liu, Yan-Qing Liu.

**Scope determination:** A modified Delphi method was employed to establish the guideline related to the target topics in the management of CEH using the population, intervention, comparator and outcomes method<sup>[19]</sup>. The scope of these recommendations includes different treatments for CEH. The users are expected to be physicians (mainly pain physicians) and other healthcare professionals who care for patients with CEH. The core leadership team supervised and coordinated the project and established the following clinical questions: (1) What is the role of pharmacological therapy for CEH? Among nonsteroidal anti-inflammatory drugs (NSAIDs), muscle relaxants, antiepileptic drugs and antidepressants, which of the drugs have shown efficacy in the long-term treatment of CEH? (2) Should nerve block, minimally invasive intervention and surgical procedures be considered if the medical treatment is not effective or tolerated? What are the outcomes of invasive operation under the guidance of imaging technologies such as ultrasound, X-ray and computed tomography? What are the indications, therapeutic effects, and complications of joint injections or nerve blocks such as atlantoaxial joint injection, C2-3 zygapophyseal joint injection, cervical spinal nerve root block, third occipital nerve block and occipital nerve block? What are the indications, therapeutic effects and complications of minimally invasive interventions or surgical techniques such as radiofrequency thermocoagulation and pulse radiofrequency, ozone injection and percutaneous laser disc decompression?; and (3) Can nonpharmacological and nonsurgical therapies, such



as physical therapy, traditional Chinese medicine, health education and psychological treatment, be considered as complementary management modalities for CEH?

**Literature search:** The literature review group members were assigned topics based on expertise, and 3-4 experts were responsible for 2-3 clinical questions. Papers published in peer-reviewed journals were identified using the PubMed/MEDLINE, Embase, Cochrane, China National Knowledge Infrastructure and WanFang Library. Systematic reviews, randomized and nonrandomized controlled trials, observational cohorts and case series limited to English or Chinese language publications were included. GRADE method was used to separately determine the quality of available evidence (rated as high, moderate, low or very low) based on the risk of bias, imprecision and inconsistency (Table 1). One or more recommendations were drafted for each topic.

**Recommendation making:** The expert panel assessed the feedback on the recommendations and evidence provided from the literature review group, and they rated the necessity for each item and selected recommendations in the first-round meeting. Recommendations due to poor-quality or conflicting evidence were eliminated, rephrased or combined. During the second round, according to the GRADE approach, the expert voting panel made recommendations (strong or weak/for or against) on the basis of the balance between desirable and undesirable effects, quality of evidence, values and preferences and costs (Table 2). To achieve consensus, an a priori decision was made to conduct up to three rounds of anonymous voting or until consensus was achieved (defined a priori as consensus agreement at  $\geq 70\%$  with a minimal response rate of 70%) for each draft recommendation, whichever came first<sup>[18]</sup>. Much of the evidence proved to be indirect, given that it did not specifically address the population, intervention, comparator and outcomes question as written and was of low-to-moderate quality.

## Recommendations

After the synthesis of our experts' work and the implementation of the GRADE method, 24 recommendations were formalized by the organizational committee (Table 3).

**Pharmacologic management:** Pharmacologic treatment is recommended as the first-line therapy for CEH (Evidence quality: moderate; Recommendation strength: strong).

Pharmacologic treatments for CEH are largely based on case reports and a lack of convincing clinical evidence on effective medications for CEH. Despite that, pharmacotherapy remains among the best available treatments<sup>[6,20]</sup>. The medications used include NSAIDs, muscle relaxants, antiepileptic drugs and antidepressants<sup>[2,21]</sup>. Before using analgesic therapy for CEH, the patients require comprehensive education around safe limitations for medication use and prevent medication-induced headache.

NSAIDs are recommended for patients with CEH (Evidence quality: low; Recommendation strength: weak).

NSAIDs such as nonselective COX and selective COX-2 inhibitors can be effective treatment modalities for CEH<sup>[1]</sup>; however, owing to the low quality of evidence, the recommendation for NSAID administration is relatively weak. Clinical considerations aimed at risk mitigation for the safe use of NSAIDs include appropriate patient selection, regular monitoring for the development of potential adverse gastrointestinal, cardiovascular and renal side-effects and potential drug interactions.

Muscle relaxants are recommended for patients with CEH (Evidence quality: moderate; Recommendation strength: strong).

Muscle relaxants such as tizanidine, baclofen, and eperisone hydrochloride have central action mechanisms aimed at providing analgesic effects in the acute phase and for prevention<sup>[22,23]</sup>. Tizanidine can be combined with NSAIDs due to its gastro-protective effect and good safety profile.

Antiepileptic drugs are conditionally recommended for patients with CEH (Evidence quality: low; Recommendation strength: weak).

Common antiepileptic drugs include gabapentin and pregabalin, which can be used in patients with neuropathic pain<sup>[24]</sup>.

Antidepressants are recommended for CEH patients with severe anxiety and depression. (Evidence quality: low; Recommendation strength: strong).

The evidence for these drugs is limited. However, considering its clinical efficacy in the treatment of headache, patients also presenting with severe anxiety and depression are recommended to use amitriptyline, venlafaxine or duloxetine<sup>[25]</sup>. When used alone or in combination with other drugs, the tolerability and side effects should be

**Table 1 Grading of Recommendations, Assessment, Development and Evaluation system for rating quality of evidence**

Quality of evidence	Definition
High quality	Further research is very unlikely to change confidence in the estimate of effect
Moderate quality	Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate
Low quality	Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate
Very low quality	Any estimate of effect is very uncertain

**Table 2 Grading of Recommendations, Assessment, Development and Evaluation system for strength of recommendations**

Recommendation strength	Definition
Strong	When the desirable effects of an intervention clearly outweigh the undesirable effects or clearly do not
Weak (“conditional” or “discretionary”)	When the trade-offs are less certain either because of low-quality evidence or because evidence suggests that desirable and undesirable effects are closely balanced

considered.

**Anesthetic blockade:** Anesthetic joint injections or nerve blocks are often used both diagnostically and therapeutically (Evidence quality: moderate; Recommendation strength: strong).

Anesthetic injections of the lateral atlantoaxial joint, the C2-3 zygapophyseal joint (and the overlying third occipital nerve) and/or the C3-4 zygapophyseal joint can temporarily reduce or relieve pain and may allow greater participation in physical treatments<sup>[26]</sup>. Patients with suboccipital or occipital pain aggravated by cervical rotation or pain due to inflammatory stimuli are expected to benefit from atlantoaxial joint injection (Evidence quality: low; Recommendation strength: weak). One study showed that injection to the atlantoaxial joint was effective in 81.2% of all cases<sup>[27]</sup>. C2-3 zygapophyseal joint injection can be considered for patients with upper neck pain spreading to the occipital region or pain that increases when the neck is rotated or when the back is stretched (Evidence quality: low; Recommendation strength: weak). Selective nerve root injection reportedly showed 50% pain relief after 12 mo<sup>[28]</sup>; therefore, it can be used in patients with cervical spondylotic radiculopathy (Evidence quality: low; Recommendation strength: strong). The third occipital nerve block can be used to diagnose CEH and predict the efficacy of radiofrequency treatment (Evidence quality: low; Recommendation strength: strong). The occipital nerve injection is used to diagnose and treat occipital pain (Evidence quality: low; Recommendation strength: strong). In addition, imaging technologies (ultrasound<sup>[29]</sup>, X-ray and computed tomography) are recommended for guiding invasive therapies (Evidence quality: high; Recommendation strength: strong).

Administration of glucocorticoid injections is recommended for CEH (Evidence quality: low; Recommendation strength: strong).

There are no controlled trials evaluating glucocorticoid injections for CEH. However, the results from small retrospective studies suggested that some patients may achieve pain relief through the administration of intra-articular glucocorticoid injections<sup>[30]</sup>.

**Minimally invasive interventional management:** Radiofrequency intervention is conditionally recommended for patients with intractable CEH (Evidence quality: moderate; Recommendation strength: strong).

Percutaneous radiofrequency neurotomy can be considered for CEH arising from the C2-3 or C3-4 zygapophyseal joint if diagnostic anesthetic nerve blockade is temporarily successful in providing complete pain relief. However, the available evidence is limited and conflicting<sup>[31]</sup>. None of the supplied evidence indicates that radiofrequency ablation or pulsed radiofrequency therapy was effective for CEH. However, three small nonrandomized studies<sup>[32-34]</sup> on radiofrequency ablation and one study<sup>[35]</sup> on pulsed radiofrequency therapy suggested that these techniques were effective for CEH. Pulse radiofrequency is a type of neuromodulation therapy, and it has fewer complications than radiofrequency thermocoagulation<sup>[36]</sup>. Thus, pulse radiofrequency is preferred over ablation as a recommendation for patients with

**Table 3 Chinese Association for the Study of Pain recommendations for the management of cervicogenic headache**

Item	Recommendation	Quality	Strength
Pharmacologic management	Pharmacologic treatment is recommended as the first-line therapy for CEH	Moderate	Strong
	NSAIDs are recommended for patients with CEH	Low	Weak
	Muscle relaxants are recommended for patients with CEH	Moderate	Strong
	Antiepileptic drugs are conditionally recommended for patients with CEH	Low	Weak
	Antidepressants are recommended for CEH patients with severe anxiety and depression	Low	Strong
Anesthetic blockade	Anesthetic joint injection or nerve block are often used both diagnostically and therapeutically	Moderate	Strong
	Atlantoaxial joint injection for patients with suboccipital or occipital pain aggravated by cervical rotation or pain due to inflammatory stimuli	Low	Weak
	C2-C3 zygapophyseal joint injection can be considered for patients with upper neck pain spreading to the occipital region or pain that increases when the neck is rotated or back is stretched	Low	Weak
	Selective nerve root injection could be used in patients with cervical spondylotic radiculopathy	Low	Strong
	Third occipital nerve block can be used to diagnose CEH and predict the efficacy of radiofrequency treatment	Low	Strong
	The occipital nerve injection is used to diagnose and treat occipital pain.	Low	Strong
	Imaging technology (ultrasound, X-ray and CT) are recommended for guidance of invasive therapies	High	Strong
	Glucocorticoid injection is recommended for CEH	Low	Strong
Minimally invasive interventional management	Radiofrequency intervention is conditionally recommended for patients with persistent CEH	Moderate	Strong
	Pulse radiofrequency is preferred over ablation for patients with persistent CEH	Low	Strong
	Ozone injection is recommended for CEH	Low	Weak
	PLDD is conditionally recommended for CEH	Low	Weak
Surgical procedures	Surgery is not recommended for CEH unless there is compelling evidence of a surgically amenable lesion causing the cervicogenic headache that is refractory to all reasonable nonsurgical treatments	Low	Strong
	Nonpharmacological and nonsurgical therapy is recommended as a complementary management for CEH	Low	Strong
Physical therapy	Physical therapy is the preferred initial treatment recommended for CEH	Moderate	Weak
	Cervical manipulation and mobilization are recommended for CEH	Moderate	Strong
TCM	TCM is conditionally recommended for CEH.	Low	Weak
Psychological therapy	Patients with refractory severe CHE need psychological assessment and intervention	Low	Strong
Health education	Health education is recommended for CEH	Low	Strong

CEH: Cervicogenic headache; CT: Computed tomography; NSAIDs: Nonsteroidal anti-inflammatory drugs; PLDD: Percutaneous laser disc decompression; TCM: Traditional Chinese medicine.

persistent CEH (Evidence quality: low; Recommendation strength: strong).

Ozone injection is recommended for CEH (Evidence quality: low; Recommendation strength: weak).

Ozone possesses strong anti-inflammatory and analgesic effects that can benefit patients in whom the use of glucocorticoid is contraindicated<sup>[37]</sup>. However, there is limited evidence showing that the ozone injection has potential benefits for CEH patients.

Percutaneous laser disc decompression is conditionally recommended for CEH (Evidence quality: low; Recommendation strength: weak).

Percutaneous laser disc decompression is effective in patients with cervical disc herniation, protrusion or disc degeneration along with neck and shoulder pain with nerve root symptoms<sup>[38]</sup>.

**Surgical procedures:** Surgery is not recommended for CEH unless there is compelling evidence indicating the presence of a surgically amenable lesion causing CEH that is refractory to all reasonable nonsurgical treatments (Evidence quality: low;

Recommendation strength: strong).

Numerous surgical interventions have been performed for presumed cases of CEH. Available data are limited to small retrospective studies<sup>[39,40]</sup>, but they suggest that surgery may be beneficial for the following three specific etiologies of CEH: (1) C2 spinal nerve compression by vascular/ligamentous structures; (2) osteoarthritis of the lateral atlantoaxial joint; and (3) upper cervical intervertebral disc pathology.

Nonpharmacological and nonsurgical therapies are recommended as a complementary management for CEH (Evidence quality: low; Recommendation strength: strong).

**Physical therapy:** Physical therapy is the preferred initial treatment recommended for CEH (Evidence quality: moderate; Recommendation strength: weak).

Physical therapy has been shown to provide the most long-term relief of CEH<sup>[41]</sup>. This may include cervical traction, massage and strengthening. A systematic review and meta-analysis revealed that physical therapy led to a statistically significant benefit for reduced pain, frequency and duration of CEH<sup>[42]</sup>.

Cervical manipulation and mobilization are recommended for CEH (Evidence quality: moderate; Recommendation strength: strong).

In a large clinical trial<sup>[43]</sup>, which evaluated 200 patients with CEH, patients assigned to 6 wk of active treatment with either manipulative therapy, low-load endurance exercise therapy or a combination of both therapies showed a significant reduction in headache frequency at 12 mo. The effect size was reported as moderate and clinically relevant<sup>[44]</sup>.

**Traditional Chinese medicine:** Traditional Chinese medicine is conditionally recommended for CEH (Evidence quality: low; Recommendation strength: weak).

Traditional Chinese medicine treatments include acupuncture, silver needle, internal hot needle and other forms of Chinese medicine. However, the relevant research and the evidence are limited<sup>[45]</sup>. The overall quality of the evidence for traditional Chinese medicine in CEH management is generally low and occasionally moderate.

**Psychological therapy:** Patients with refractory severe CHE need psychological assessment and intervention (Evidence quality: low; Recommendation strength: strong).

Studies have indicated that the incidence of depression and generalized anxiety disorder is high in headache patients<sup>[46,47]</sup>. Patients with refractory severe CHE need psychological assessment, including past medical history, psychological status and the risk factors affecting prognosis. Past studies have indicated that the addition of psychological therapy on the basis of regular drug therapy can play a more significant therapeutic effect on headache. Psychotherapy includes listening, headache education, cognitive behavior therapy, biofeedback therapy and relaxation training<sup>[48]</sup>.

**Health education:** Health education is recommended for CEH (Evidence quality: low; Recommendation strength: strong).

Neurophysiological pain education strategy addressing neurophysiology and neurobiology of pain can have a positive effect on pain<sup>[49]</sup>. Health education includes maintaining a good posture, keeping the neck and shoulder warm and appropriate neck exercises (such as neck flexion, neck rotation and Alexander's fitness)<sup>[41]</sup>.

## CONCLUSION

The CASP asked an expert panel to develop recommendations for a series of questions that are essential for daily clinical management of patients with CEH. A systematic review of the literature was performed, evidence supporting the benefits and harms for the management of CEH were summarized. Finally, 24 recommendations were developed through expert consensus voting for evidence quality and recommendation strength. We hope this guideline provides direction for clinicians and patients making treatment decisions for the management of CEH.

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