

# Expert Consensus on Wenxin Granule for Treatment of Cardiac Arrhythmias

Heart Rhythm Society of the Chinese Society of Biomedical Engineering, Nao Xin Tong Zhi Committee of the Chinese Association of Integrative Medicine

**Key words:** Cardiac Arrhythmias; Treatment; Wenxin Granule

## INTRODUCTION

Antiarrhythmic drugs remain a critically important component of the approach to therapy of cardiac arrhythmias. Over the past 20 years, despite their antiarrhythmic efficacy in many pathological settings, Class I and III antiarrhythmic drugs have been shown to be associated with the development of proarrhythmias and an increase in the likelihood of causing higher mortality by inducing torsade de pointes ventricular tachycardia and other serious adverse reactions. Consequently, the development of safe and effective antiarrhythmic regimens remains a primary focus of contemporary cardiovascular research.

The clinical application and study of Wenxin Granule have been ongoing for three decades. Numerous studies, including a randomized, placebo-controlled, double-blind, and multicenter trial, have shown that Wenxin Granule is effective and safe for the treatment of cardiac arrhythmias.<sup>[1]</sup> With respect to the mechanisms of antiarrhythmic action, Wenxin Granule has a clear theoretical basis for the treatment of cardiac arrhythmias underlying traditional Chinese medicine (TCM) and multiple antiarrhythmic mechanisms of actions which have been confirmed by studies using modern clinical and cardiac electrophysiological research techniques.<sup>[2-4]</sup>

Evidence from basic and clinical researches has been advanced in support of the use of Wenxin Granule for the treatment of cardiac arrhythmias, including atrial and ventricular premature beats. This expert consensus statement was drafted by domestic and foreign experts organized by the “Heart Rhythm Society of the Chinese Society of Biomedical Engineering” and the “Nao Xin Tong Zhi Committee of the Chinese Society of Integrative Medicine” in an attempt

to standardize clinical application, to promote in-depth researches into mechanisms underlying Wenxin Granule, and to enhance the evidence base of Chinese medicines. This expert consensus document reviews the available data concerning the use and the mechanism of antiarrhythmic action of Wenxin Granule. We expect this expert consensus to help physicians using both TCM and western medicine to understand the status of the current research and application of TCM antiarrhythmic medicines.

## HISTORY OF RESEARCH AND DEVELOPMENT

In the early 1980s, Dr. Yu-Ping Zhou, together with other TCM doctors from Guang'anmen (GAM) Hospital affiliated with the China Academy of Chinese Medical Sciences (formerly the China Academy of TCM), initiated the research and development of Wenxin Granule (Heart-stabilizing Granule). The ingredients were finalized as five Chinese herbs: Dangshen (Codonopsis root, *Radix Codonopsis*), Huangjing (Siberian Solomon's seal rhizome, *Rhizoma Polygonati*), Sanqi (Pseudoginseng root, *Radix et Rhizoma Notoginseng*), Hupo (Amber, *Succinum*), and Gansong (Nardostachys root, *Radix et Rhizoma Nardostachys*). The composition of this formula was determined under the treatment principle of pattern identification in TCM from the prescriptions of

**Address for correspondence:** Dr. Ji-Hong Guo,

Department of Cardiology and Electrophysiology, Peking University  
People's Hospital, No. 11, Xizhimen South Street, West District,  
Beijing 100034, China  
E-Mail: zlpku@126.com

This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 3.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as the author is credited and the new creations are licensed under the identical terms.

**For reprints contact:** reprints@medknow.com

© 2017 Chinese Medical Journal | Produced by Wolters Kluwer - Medknow

**Received:** 12-10-2016 **Edited by:** Ning-Ning Wang

**How to cite this article:** Heart Rhythm Society of the Chinese Society of Biomedical Engineering, Nao Xin Tong Zhi Committee of the Chinese Association of Integrative Medicine. Expert Consensus on Wenxin Granule for Treatment of Cardiac Arrhythmias. Chin Med J 2017;130:203-10.

### Access this article online

#### Quick Response Code:



**Website:**  
www.cmj.org

**DOI:**  
10.4103/0366-6999.198003

Zhigancao Decoction (prepared licorice root decoction) in the book, *Treatise on Cold Damage*: “Zhigancao Decoction is mainly used in patients with palpitations due to irregular or intermittent pulses,” and from the personal clinical experience of physicians in GAM Hospital. Then, the preparation form of this formula was changed from decoction to granule.

In 1987, Wenxin Granule for the treatment of arrhythmia became a research project of the Institute of Chinese Medical Sciences. In 1991, it was included in “The 8<sup>th</sup> Five-Year Plan,” the National Key Science and Technology Project of TCM. In 1996, the outcomes were reviewed and approved. In 1995, this product received new drug certification issued by the Ministry of Health of the people's Republic of China and was officially marketed.

Since then, further in-depth studies on its antiarrhythmic mechanisms of action were carried out at different levels ranging from clinical studies to basic studies and from myocardial tissues to animals.<sup>[1,5,6]</sup> The results confirmed the significant preventive and therapeutic efficacy of Wenxin Granule on arrhythmias induced by aconitine, barium chloride, and epinephrine.<sup>[5]</sup> Studies on the mechanisms of action then were performed at the cellular and molecular levels. The application of the whole-cell patch-clamp technique proved the followings: Wenxin Granule significantly inhibited sodium, potassium, and calcium channels on myocardial cell membrane in a dose-dependent manner,<sup>[2,3]</sup> and it was found to possess activities of Class I, III, and IV antiarrhythmic drugs.

Foreign scholars began to investigate the Wenxin Granule in 2005. Benefiting from the advanced basic research technologies and previously developed equipment, a number of internationally renowned scholars became involved in the study on Wenxin Granule and three important achievements were quickly achieved.

The first is the study conducted by Xue *et al.*<sup>[4]</sup> This study confirmed that Wenxin Granule significantly inhibited late sodium currents to reduce early after-depolarization, delayed after-depolarization, and T-wave alternate, thus to prevent and reduce the occurrence of malignant ventricular arrhythmia.

The second is the study conducted by Burashnikov *et al.*<sup>[3]</sup> in 2012. This study showed that Wenxin Granule produced atrial-selective inhibition of peak sodium current ( $I_{Na}$ ) and was thus capable of prolonging postrepolarizing refractoriness and prevented or terminated atrial fibrillation induced by acetylcholine and burst pacing. The conclusion was affirmed by a commentary article.<sup>[7]</sup>

The third is another study conducted by Minoura Y *et al.*,<sup>[8]</sup> in which Wenxin Granule was found to inhibit the transient outward current  $I_{to}$ . Using experimental models of Brugada syndrome generated with the  $I_{to}$  agonists (NS5806), Wenxin Granule, particularly in combination with quinidine, was shown to suppress the electrocardiographic and arrhythmic manifestations of Brugada syndrome, with the inhibition

rate of 60% and 100% by 5 and 10 g/L Wenxin Granule, respectively, suggesting a therapeutic effect of Wenxin Granule on Brugada syndrome.<sup>[8]</sup>

In 2010–2012, a randomized, double-blinded, placebo-controlled, and multicenter clinical study<sup>[1]</sup> on Wenxin Granule for the treatment of atrial premature beats and ventricular premature beats was conducted. This study, involving 60 Grade-III medical institutions in China, was led by researchers at Beijing Fuwai Cardiovascular Hospital and enrolled 2400 participants. The results showed that the total effective rate of Wenxin Granule for the treatment of atrial premature beats and ventricular premature beats was 83.6% and 83.0%, respectively. It was also reported to improve heart palpitations, chest tightness, fatigue, and other symptoms. No proarrhythmia was observed; the incidence of adverse reactions was not statistically different from those of the placebo group.

In summary, recent studies have advanced our understanding of the mechanisms of action of Wenxin Granule and its clinical effectiveness.

## FEATURES OF FORMULA IN THE DESCRIPTION OF TRADITIONAL CHINESE MEDICINE

Wenxin Granule consists of Dangshen, Huangjing, Sanqi, Hupo, and Gansong. Among them, Dangshen is the “monarch” medicinal herb of this regimen. Characterized by a moderate and nourishing nature with a neutral property and sweet flavor, it supplements the middle energizer, boosts *qi* (nutrients), tranquilizes the mind, and relieves palpitations. Huangjing is the “minister” herb of this regimen, helping Dangshen tonify *qi* and generate blood; it also has a neutral property and sweet flavor and fortifies the spleen *qi* to nourish the heart and lungs. The other three ingredients are all assistant medicinal herbs. Sanqi has a slightly bitter flavor and a warm property. It can remove blood stasis, relieve pain, and tonify weakness. Hupo is neutral and sweet with the effects of activating blood, removing stasis, pacifying the liver, and tranquilizing the mind. Gansong is warm and sweet and can relieve depression, remove stagnation, and regulate the liver and spleen *qi*.

Simple but carefully formulated, this formula has effects of supplementing *qi*, nourishing *yin*, tranquilizing the mind, restoring pulses, activating the blood, and removing stasis. Its indication is dual *qi* and *yin* deficiency and its stasis pattern manifests as palpitations, shortness of breath, listlessness, dizziness, vexation, insomnia, chest distress, and chest pain.

This formula has the following three features. First, it targets the key mechanism of the *qi-yin* deficiency pattern in palpitations. Zhong-Jing Zhang was the first to elaborate on the cause of palpitations as interior deficiency and formulated the Zhigancao Decoction for it. His book, “Essential Prescriptions from the Golden Cabinet”, described the observation of weak and thready radial pulse in palpitations. Based on these findings, palpitations are often

considered to be caused by a deficiency of both *qi* and *yin* with obstructed heart meridians. Wenxin Granule is on target for the treatment of palpitations by supplementing the *qi* and *yin*, tranquilizing the mind, restoring vessels, activating the blood, and removing stasis.

Second, it also protects the spleen and stomach. The Yellow Emperor's Internal Classic stated, "When food is ingested and then digested in stomach, turbid *qi* will flow to the heart and circulate the essence in the meridians," therefore fortifying the spleen and stomach that reinforce the heart *qi* and blood. In this formula, Huangjing and Danshen replenish the spleen and stomach.

Finally, this formula regulates both *qi* and blood aspects. The majority of deficiency patterns are often accompanied by blood stasis caused by *qi* deficiency, and insufficient blood in the meridians. Following the TCM theory of "blood generating *qi* and *qi* directing blood", Sanqi and Hupo are thus selected to activate the blood, maintain the blood flow in vessels fluent, and relieve palpitations effectively.

## PHARMACODYNAMICS AND TOXICOLOGY

Wenxin Granule has been studied in several models of induced arrhythmias to assess its antiarrhythmic efficacy and potential toxicity. Subsequent researches focused on its effects on ion channels in single cardiomyocytes as well as electrophysiological parameters in isolated cardiac tissues and wedge preparations. In recent years, researches have focused on the selective inhibition of late sodium current and atrial selectivity for fast (peak) sodium current.

### Pharmacodynamic study

#### Inhibition of ventricular arrhythmias induced by aconitine, barium chloride, myocardial ischemia, and reperfusion

Rats were used as an experimental animal model for the early pharmacodynamic study of Wenxin Granule. Ventricular arrhythmic models were developed using aconitine, barium chloride, and myocardial ischemia-reperfusion methods. Wenxin Granule was administered in progressively higher doses. The results showed that Wenxin Granule could significantly delay the onset arrhythmias, shortened its duration, and also reduced ischemia-reperfusion-mediated arrhythmias.<sup>[5]</sup>

#### Inhibition of isoproterenol-induced ventricular arrhythmias following myocardial infarction

Wenxin Granule, amiodarone, and placebo were evaluated in rats subjected to ischemia followed by infusion of isoproterenol. Wenxin Granule reduced the development of ventricular arrhythmia when compared with placebo.<sup>[4]</sup>

### Toxicological study

#### Acute toxicity test

Mice were given a single-dose of Wenxin Granule by intragastric gavage; the dosing volume was 0.04 ml/g and the dose was 80 g/kg (equivalent to 88.9-fold, the dose for adult patients). During the 7-day observation period

after administration, the mice were quiet and ate, urinated and defecated normally with smooth fur. No deaths were reported, suggesting that Wenxin Granule had no significant acute toxicity (unpublished data).

#### Maximum dose test

Mice were given three doses within 24 h by intragastric gavage; the first dosing volume was 0.04 ml/g and the dose was 80 g/kg (equivalent to 88.9-fold, the dose for an adult patient); the second and third doses were 80% of the first dose. During the 7-day continuous observation, the treated mice showed reduced activities and became quiet. Some animals developed diarrhea and recovered within 24 h. No deaths occurred. No other obvious adverse effects were observed (unpublished data).

#### Chronic toxicity test

Mice received  $13.3 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$  of Wenxin Granule by intragastric gavage. The administered dose was equivalent to 40-, 25-, and 10-fold, the clinical dose for adult patients. The control group was given an equal volume of tap water. The treatment lasted for 90 successive days. When compared with the control group, no abnormalities were observed in the Wenxin Granule group, suggesting that it had no significant chronic toxicity (unpublished data).

## MECHANISMS OF ACTION

### Effects on myocardial ion channels

Domestic and foreign experts used the patch-clamp technique to study the electrophysiological action in individual myocardial cells. The results confirmed that Wenxin Granule inhibited multiple ion channels.

### Sodium channel blockade

#### Inhibition of fast sodium current ( $I_{\text{Na}}$ )

When individual rabbit ventricular myocytes were examined using whole-cell patch-clamp, *Nardostachys chinensis* Batal extract (main ingredient of Wenxin Granule, concentration = 5 and 10 g/L) significantly reduced the peak  $I_{\text{Na}}$  ( $I_{\text{Na,max}}$ ) and slowed down the recovery from inactivation, with no change in steady-state activation or reversal potential.<sup>[9]</sup> Furthermore, in rabbit ventricular myocytes and Purkinje cells, the half maximal inhibitory concentration ( $\text{IC}_{50}$ ) of Wenxin Granule on fast sodium currents was  $10.6 \pm 0.9 \text{ mg/ml}$  and  $13.3 \pm 0.9 \text{ mg/ml}$ , respectively.<sup>[10]</sup>

#### Inhibition of late sodium current

Slow inactivated and late reopenings of the sodium channel give rise to late  $I_{\text{Na}}$ . Although its amplitude is a small fraction (merely one-thousand) that of the fast sodium current in normal myocardial cells, the late  $I_{\text{Na}}$  is known to increase under various pathological conditions (e.g., hereditary ion channel diseases, ischemia, or heart failure), which would result in prolonged repolarization and increased repolarization heterogeneity, promoting the occurrence of malignant arrhythmias. In recent years, the role of the late sodium current in the pathogenesis of arrhythmia has

attracted increasing attention.<sup>[11]</sup> Studies employing rabbit ventricular myocytes and Purkinje cells showed that Wenxin Granule selectively inhibited late  $I_{Na}$ . The median effective concentration inhibiting late  $I_{Na}$  in rabbit ventricular myocytes and Purkinje cells was  $3.8 \pm 0.4$  mg/ml and  $4.3 \pm 0.5$  mg/ml, respectively. Therefore, the concentration of Wenxin Granule needed to inhibit the late sodium current is 2.8–3.1-fold lower than that needed to inhibit the peak sodium current.<sup>[4,10]</sup>

### Calcium channel blockade

*Nardostachys chinensis* Batal extract (5 and 10 g/L) inhibits L-type calcium currents and shifts the current-voltage relationship upward without changing its activation potential or reversal potential. The effect is increased with higher concentrations.<sup>[9]</sup>

### Potassium channel blockade

#### Inhibition of slow-activating delayed rectifier potassium current ( $I_{Ks}$ )

A dose of 5 or 10 g/L *Nardostachys chinensis* Batal extract, the main ingredient of Wenxin Granule, inhibits the  $I_{Ks}$  tail current ( $I_{K-tail}$ ) by 20.9% and 41.6%, respectively.<sup>[6]</sup> However, it has no significant effect on the inward rectifier potassium current ( $I_{K1}$ ).

#### Inhibition of transient outward potassium current ( $I_{to}$ )

Wenxin Granule (10 g/L) reduced the  $I_{to}$  peak in ventricular myocytes of adult rats by 57.9%.<sup>[9]</sup> In canine ventricular myocytes, 5 and 10 g/L of Wenxin Granule decreased the  $I_{to}$  amplitude by 41.9% and 69.8%, respectively. This result was consistent with inhibition of the Brugada wave and polymorphic ventricular tachycardia at the tissue level, suggesting that Wenxin Granule may be effective in the treatment of J-wave syndromes, including Brugada syndrome.<sup>[8]</sup>

### Effects of Wenxin Granule on myocardial electrophysiological properties

#### Effects of Wenxin Granule on ventricular sodium current and conductivity

Low concentrations of Wenxin Granule inhibit late sodium current with little effect on fast sodium current, leading to abbreviation of action potential duration (APD), reduction of T-wave peak-to-end interval (Tp-e, related to the dispersion of repolarization),<sup>[4]</sup> and suppression of early and delayed after-depolarization. Higher concentrations of Wenxin Granule inhibits fast sodium current, leading to mild increase of QRS duration without significant rate dependence, which means very little change in QRS wave duration with varying heart rate, such characteristics are significantly different from Class Ic antiarrhythmic drugs but similar to the class Ib drug lidocaine. The mechanism of action may be related to the quick dissociation of Wenxin Granule from sodium channel proteins.<sup>[3]</sup>

#### Characteristics of action on atrial electrophysiology

Because Wenxin Granule inhibits peak sodium current to a greater extent in atrial myocardium than in ventricular myocardium,<sup>[8,12,13]</sup> consequently, it abbreviates the atrial

APD but prolongs atrial effective refractory period, resulting in a significant postrepolarization refractory period, being capable of suppressing atrial arrhythmias.

The atrial-selective inhibition of sodium channel parameters is related not only to the differential electrophysiological properties between atrial myocardium and ventricular myocardium but also to Wenxin Granule-mediated inactivation of sodium channels in atrial myocytes. When compared with ventricular myocardium, a relatively low concentration of Wenxin Granule inhibited the fast sodium current in the atrial myocardium, increasing the diastolic stimulation threshold, decreasing atrial excitability, and thus terminating or preventing the acetylcholine-mediated atrial fibrillation.<sup>[3]</sup>

#### Effects on myocardial contractility

Studies involving myocardial cells have shown that Wenxin Granule inhibits calcium channel current and reduces contractility.<sup>[8]</sup> However, in ventricular myocardial tissue wedges, Wenxin Granule increased the contractility of ventricular myocardial tissues in a concentration-dependent manner. The reason for this difference is that Wenxin Granule induced the release of catecholamines from sympathetic nerve endings at the tissue level. Perfusion of the ventricular myocardium with tyramine can also cause the release of catecholamines from the epinephrine nerve endings, potentiating the contractility of the ventricular myocardium. Because the Wenxin Granule's action was similar to changes following the application of tyramine, Wenxin Granule can be considered to exert a tyramine-like effect.<sup>[8]</sup>

## INDICATIONS AND CLINICAL APPLICATIONS

### Indications

Wenxin Granule is mainly used for the treatment of complicated atrial premature beats and ventricular premature beats in symptomatic patients with or without organic heart disease. It has some preventive and therapeutic effects on paroxysmal atrial fibrillation.

### Clinical application

#### Atrial premature beats

It should be noted that the majority of atrial premature beats including frequent atrial premature beats and even atrial bigeminy do not require treatment if the patient has no symptoms. When the symptoms become apparent and affect the hemodynamics or quality of life, treatment can be considered. Clinically, the patients often have a certain degree of anxiety and anxiety-associated systemic symptoms caused by climacteric syndrome or cardiac neurosis. For concomitant atrial premature beats in these patients, Wenxin Granule has therapeutic advantages because it can treat both atrial premature beats and directly or indirectly improves the subjective symptoms.

Results of a single-center study showed that the total efficacy on atrial premature beats was higher with Wenxin Granule than in control group (76.7% vs. 30.0%,  $P < 0.05$ ) but

was similar to that of propafenone (150 mg, 3 times daily) (75% vs. 72%,  $P > 0.05$ ).<sup>[14,15]</sup> However, Wenxin Granule had a lower incidence of adverse reactions and weak sinus bradycardia effects.

A multicenter evidence-based medical study in China showed that the total effective rate of Wenxin Granule for the treatment of atrial premature beats was 83.6%. The incidence of adverse reactions was not statistically different from that of the placebo group.<sup>[5]</sup>

#### Ventricular premature beats

A single-center study showed that the effective rate of Wenxin Granule for the treatment of ventricular premature beats was 68–85%.<sup>[16]</sup>

A multicenter, randomized, double-blind, parallel, placebo-controlled study showed that the total effective rate of Wenxin Granule to reduce ventricular premature beats and nonsustained paroxysmal ventricular tachycardia was 83%.<sup>[1]</sup>

#### Atrial fibrillation

In an experimental acetylcholine-mediated model of AF, 5 g/L Wenxin Granule effectively terminated and prevented the development of atrial fibrillation in 100% preparations. Currently, there are no large-scale multicenter study data for the clinical application of Wenxin Granule for the treatment and prevention of atrial fibrillation. Two single-center studies<sup>[17,18]</sup> have shown that the addition of Wenxin Granule can improve the efficacy of other drugs (including amiodarone and propafenone) in the treatment of patients with paroxysmal atrial fibrillation. For patients with chronic atrial fibrillation, Wenxin Granule in combination with digoxin or metoprolol further decreased the ventricular rate, improved the symptoms, and increased exercise tolerance.<sup>[19,20]</sup>

#### Others

In the elderly<sup>[21]</sup> and in patients with hypertension,<sup>[22]</sup> heart failure,<sup>[23]</sup> pulmonary heart disease,<sup>[24]</sup> acute coronary syndrome,<sup>[25,26]</sup> hyperthyroidism,<sup>[27]</sup> angina pectoris,<sup>[28]</sup> menopausal syndrome, and anxiety disorders,<sup>[29]</sup> Wenxin Granule has been shown to suppress premature beats with a high level of safety profile.

#### Improvement of traditional Chinese medical “syndrome”

In addition to the effective treatment of atrial and ventricular premature beats, Wenxin Granule can significantly improve the specified groups of symptoms or “syndrome” within the scope of TCM. Its indications include *qi* and *yin* deficiency and heart blood stasis, complicated with palpitations, shortness of breath, fatigue, dizziness, chest tightness, chest pain, and insomnia to improve a patient’s quality of life.<sup>[30]</sup>

## METHOD OF ADMINISTRATION

### Conventional application

Wenxin Granule is a prescription preparation formula of proprietary Chinese herbal medicines. The packaging specification is 5 g/bag (sugar-free) or 9 g/bag (with sugar). The conventional usage is to dissolve it in boiled water,

one bag each time, three times daily, or following medical directions.

### Special application

#### Increased dose

For patients with serious disease conditions, the dose can be increased to two bags each time, 3 times daily. After the disease condition becomes stable, the treatment can be changed to a conventional maintenance dose.

#### Long-term use

Depending on the disease conditions, long-term application is possible. It was reported that the continuous administration of Wenxin Granule for 6 months and 12 months resulted in satisfactory efficacy without severe adverse reactions.

### Combined application

Reported are available that Wenxin Granule can be used in combination with amiodarone,<sup>[17]</sup> digoxin,<sup>[19]</sup> metoprolol,<sup>[20]</sup> and propafenone.<sup>[18]</sup>

## ADVERSE REACTIONS AND TREATMENT

Wenxin Granule-related adverse reactions include dizziness, nausea, dry mouth, and upper abdominal discomfort. A large-sample study showed that the incidence of adverse reactions in the Wenxin Granule treatment group was 0.5% with no statistical difference from the placebo group. The majority of these adverse reactions require no special treatment; if necessary, drug discontinuance is usually sufficient.<sup>[31]</sup>

## PRECAUTIONS

Patients with severe bradyarrhythmia should not use this product; pregnant women should use it with caution.

## CONCLUDING REMARKS

“Expert consensus on Wenxin Granule for the treatment of cardiac arrhythmias” is the first expert consensus on the antiarrhythmic use of a TCM. This consensus is the outcome of conscientious writing by hundreds of national and international experts from medical universities/colleges, hospitals and research institutes worldwide, thorough discussions at dedicated meetings, seeking opinions of experts from relevant subdisciplines/specialties, and repeated argumentation to ensure scientific, professional, accurate, and practical unity. All participants hope that their efforts will make this consensus highly representative and stand the test of time.

The development, application, and postapplication study of Wenxin Granule are the achievements of a successful integration of TCM and western medicine, which has concentrated the wisdom and expertise of Chinese and foreign experts. Wenxin Granule has multiple electrophysiological actions. The main characteristics include selective block of ventricular late sodium current and atrial-selective block of peak sodium current. Further investigations is needed to determine whether the

concentrations used in basic research studies are consistent with the clinical actions of the drug.

Clinical use of Wenxin Granule showed good efficacy and safety as the first-line therapy of ventricular and atrial premature beats; it can be used either alone or in combination with antiarrhythmic agents used in western medicine. Recent studies also indicated that Wenxin Granule may be of benefit in the treatment of other types of arrhythmias, including atrial fibrillation and Brugada syndrome. An understanding of its mechanism of action and characteristics will continue to enhance its use. Certainly, the accumulation and transformation of study achievements will move the application of Wenxin Granule toward a more standardized, scientific, and accurate direction.

### Writing committee

Ji-Hong Guo (Department of Cardiology, Peking University People's Hospital), Gan-Xin Yan (Department of Cardiology, Lankenau Heart Institute, Thomas Jefferson University Hospital, PA, USA), Lin Wu (Department of Cardiology, Peking University First Hospital), Bu-Chang Zhao (Cardiovascular Internal Medicine Department, Buchang Pharma), Yi-Min Wang (Cardiovascular Internal Medicine Department, Buchang Pharma), Fu-Sheng Gu (Department of Cardiology, Beijing Friendship Hospital, Capital Medical University), Yu-Ping Zhou (Department of Cardiology, Guang'anmen Hospital, China Academy of Chinese Medical Sciences), Charles Antzelevitch (Lankenau Institute for Medical Research, Lankenau Heart Institute, PA, USA), Jing-Xuan Guo (Department of Cardiology, Peking University Third Hospital), Jie-Fu Yang (Department of Cardiology, Beijing Hospital, Ministry of Health), Xin-Chun Yang (Department of Cardiology, Beijing Chaoyang Hospital, Capital Medical University), Yan-Sheng Ding (Department of Cardiology, Peking University First Hospital), Ping Zhang (Department of Cardiology, Beijing Tsinghua Changgung Hospital), Hai-Cheng Zhang (Department of Cardiology, Peking University People's Hospital), Hong-Xu Liu (Department of Cardiology, Beijing Hospital of Traditional Chinese Medicine, Capital Medical University), Wei-Xing Lu (Department of Cardiology, Beijing University of Chinese Medicine Third Affiliated Hospital), Yan-Wei Xing (Department of Cardiology, Guang'anmen Hospital, China Academy of Chinese Medical Sciences), Jian-Feng Fan (Cardiovascular Internal Medicine Department, Buchang Pharma), Feng Ze (Department of Cardiology, Peking University People's Hospital), Guang-ping Li (The Second Hospital of Tianjin Medical University), Yi-Gang Li (Xin Hua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine), De-Ning Liao (Shanghai Changzheng Hospital), Xiao-Lin Xue (Xi'an Jiaotong University the First Hospital).

### Acknowledgments

Hai-Chu Yu (Department of Cardiology, Affiliated Hospital of Qingdao University), Shu-Qing Wang (Department of

Cardiology, The First Hospital of Qiqihaer City), Jun-Kui Wang (Department of Cardiology, Shanxi Provincial People's Hospital), Yue-Li Shi (Cardiovascular Internal Medicine Department), Li-Yue Wu (Department of Cardiology, Wuhan Puren Hospital), Yang-Jin Wu (Department of Cardiology, Zhongnan Hospital of Wuhan University), Tian-Song Wang (Department of Cardiology, Sanyan People's Hospital), Mei-Ling Yun (Department of Cardiology, Affiliated Hospital of Hainan Medical College), Hong Kong (Department of Cardiology, Sichuan Provincial People's Hospital), Hua-Gui Mao (Department of Cardiology, Guiyang First People's Hospital), Chun-Feng Niu (Department of Cardiology, The Second Affiliated Hospital of Harbin Medical University), Jin-Long Deng (Department of Cardiology, Guangxi Zhuang Autonomous Region People's Hospital), Yu-Lin Deng (Department of Cardiology, Sanya Branch of Chinese People's Liberation Army General Hospital), Bei Shi (Department of Cardiology, The Affiliated Hospital of Zunyi Medical College), Hua Fu (Department of Cardiology, West China Hospital of Sichuan University), Hong-Liang Cong (Department of Cardiology, Tianjin Chest Hospital), Yan-Wei Xing (Department of Cardiology, Guang'anmen Hospital of China Academy of Chinese Medical Sciences), Xue-Feng Guang (Department of Cardiology, Yan'an Hospital from Kunming), Peng Qu (Department of Cardiology, The Second Affiliated Hospital of Dalian Medical University), Wen-Qing Zhu (Department of Cardiology, Zhongshan Hospital Affiliated to Fudan University), Feng Liu (Department of Cardiology, Guangzhou First Hospital), Li-Na Chen (Xi'an XD Group Hospital), Yi-Wen Liu (Cardiovascular Internal Medicine Department), Li-Ping Liu (Cardiovascular Internal Medicine Department), Tong-Bao Liu (Department of Cardiology, Shandong Provincial Hospital), Jian-Ping Liu (Department of Cardiology, The First Affiliated Hospital of The Third Military Medical University), Xin-Can Liu (Department of Cardiology, The First Affiliated Hospital of Henan University of TCM), Xing-De Liu (Department of Cardiology, The Affiliated Hospital of Guizhou Medical University), Xian-Xia Liu (Department of Cardiology, Hai'nan Province Nongken General Hospital), Xi-Chao Liu (Department of Cardiology, Sanyan People's Hospital), Yi An (Department of Cardiology, The Affiliated Hospital of Qingdao University), De Lu (Department of Cardiology, Linyi Hospital of Traditional Chinese Medicine), Shu-Shan Qi (Department of Cardiology, The Second Xiangya Hospital of Central South University), Jian-Jun Mou (Department of Cardiology, The First Affiliated Hospital of Xi'an Jiaotong University), Jian Sun (Department of Cardiology, The First Affiliated Hospital of Jilin University), Jian-Hui Sun (Department of Cardiology, Changzhou First People's Hospital), Ji-An Yan (Department of Cardiology, Anhui Provincial Hospital), Wei Su (Department of Cardiology, Wuxi Hospital of Traditional Chinese Medicine), Jing-Bo Li (Department of Cardiology, Shanghai Sixth People's Hospital), Xing-Tao Li (Department of Cardiology, The Fourth Hospital of Hebei Medical University), Gong-Xin Li

(Department of Cardiology, Zhujiang Hospital of South Medical University), Xin-Hua Li (Department of Cardiology, Linyi People's Hospital), Chen-Wen Ku (Department of Cardiology, Weifang Hospital of Traditional Chinese Medicine), Bin Wu (Department of Cardiology, Hubei Provincial Hospital of Traditional Chinese Medicine), Tong-Guo Wu (Department of Cardiology, Guangzhou Red Cross Hospital), Zhong Wu (Department of Cardiology, Hainan Provincial People's Hospital), Zheng He (Department of Cardiology, Xijing Hospital of Fourth Military Medical University), Jian-Ping Shen (Department of Cardiology, Jiangsu Provincial Hospital of Integrated Traditional Chinese Medicine and Western Medicine), Chao-Ying Zhang (Department of Cardiology, The Second Affiliated Hospital of Xi'an Jiaotong University), Shu-Long Zhang (Department of Cardiology, The First Affiliated Hospital of Dalian Medical University), Fei-Long Zhang (Department of Cardiology, Fujian Medical University Union Hospital), Ming Zhang (Department of Cardiology, Hainan Provincial Hospital of Traditional Chinese Medicine), Ai-Yuan Zhang (Department of Cardiology, Weifang People's Hospital), Cheng-Jian Yang (Department of Cardiology, The Wuxi Second People's Hospital), Yan-Zong Yang (Department of Cardiology, The First Affiliated Hospital of Dalian Medical University), Shi-Juan Lu (Department of Cardiology, Haikou People's Hospital), Mo-Shui Chen (Department of Cardiology, Haikou People's Hospital), Zhi-Jian Chen (Department of Cardiology, Union Hospital Affiliated to Tongji Medical College of Huazhong University of Science and Technology), Shou-Qiang Chen (Department of Cardiology, The Second Affiliated Hospital of Shandong University of Traditional Chinese Medicine), Bo-Jun Chen (Department of Cardiology, Guangdong Provincial Hospital of Traditional Chinese Medicine), Chao-Gui Lin (Department of Cardiology, Fujian Medical University Union Hospital), Zhi-Hong Ou (Department of Cardiology, Linyi People's Hospital), Xi-Zhen Fan (Department of Cardiology, Anhui Provincial Hospital), Su-Xin Luo (Department of Cardiology, The First Affiliated Hospital of Chongqing Medical University), Zhi-Gang Jin (Department of Cardiology, Wisco General Hospital), Yong Zhou (Department of Cardiology, Zhangjiagang First People's Hospital), Guo-Bao Zhou (Department of Cardiology, Suzhou Municipal Hospital), Xiao-Fang Zhou (Department of Cardiology, Sichuan Provincial People's Hospital), Bai-Ming Qu (Department of Cardiology, Zhejiang Provincial People's Hospital), Shen-Jiang Hu (Department of Cardiology, The First Affiliated Hospital of Zhejiang University), Guo-Qiang Zhong (Department of Cardiology, The First Affiliated Hospital of Guangxi Medical University), Ya-Xi Zheng (Department of Cardiology, Guizhou Provincial People's Hospital), Xiao-Dong Zhao (Department of Cardiology, Suzhou Hospital of Traditional Chinese Medicine), Jiang Hong (Department of Cardiology, The First People's Hospital Affiliated to Shanghai Jiaotong University), Jing-Quan Zhong (Department of Cardiology, Shandong University Qilu Hospital), Ping Hou (Department of Cardiology, The

Affiliated Hospital of Liaoning University of Traditional Chinese Medicine), Bao-Xiang Duan (Department of Cardiology, Nanjing First Hospital), Li-Hong Jiang (Department of Cardiology, The Affiliated Hospital of Changchun University of Traditional Chinese Medicine), Ning Gu (Department of Cardiology, Nanjing Hospital of Traditional Chinese Medicine), Wei-Xia Gu (Department of Cardiology, Wujiang First People's Hospital), Nai-Zhi Geng (Department of Cardiology, The First Affiliated Hospital of Heilongjiang Provincial Hospital of Chinese Medicine), Yue Xia (Department of Cardiology, The First Hospital of Hebei Medical University), Yun-Long Xia (Department of Cardiology, The First Affiliated Hospital of Dalian Medical University), Yin-Jun Li (Department of Cardiology, Shenyang Fourth People's Hospital), Wei Xu (Department of Cardiology, Nanjing Drum Tower Hospital), Gui-Dong Xu (Department of Cardiology, Suzhou Municipal Hospital), Geng Xu (Department of Cardiology, The Second Affiliated Hospital of Zhejiang University), Ren-Hui Xue (Cardiovascular Internal Medicine Department), Min Jia (Department of Cardiology, Zaozhuang Municipal Hospital), Quan-Zhong Yin (Department of Cardiology, Wuxi Jiangyin Municipal People's Hospital), Tao Guo (Department of Cardiology, The First Affiliated Hospital of Kunming Medical University), An-Li Tang (Department of Cardiology, The First Affiliated Hospital of Sun Yat-Sen University), Xia Mei (Department of Cardiology, Chongqing Zhongshan Hospital), Zhao-Quan Huang (Department of Cardiology, Zhejiang Hospital of Traditional Chinese Medicine), Jun-Shan Huang (Department of Cardiology, Fujian Provincial Institute of Traditional Chinese Medicine), Jiu-Rong Huang (Department of Cardiology, Sichuan Provincial People's Hospital), Tao Gong (Department of Cardiology, Chongqing Steel General Hospital), Ming-Hua Han (Department of Cardiology, Yunnan Provincial Second People's Hospital), Zhi-Ming Ge (Department of Cardiology, Qingdao branch of Qilu Hospital), Jing-Tian Peng (Department of Cardiology, The First Affiliated Hospital of Nanchang University), Yu-Xiang Dong (Department of Cardiology, The First Affiliated Hospital of Jilin University), Xiao-Shu Cheng (Department of Cardiology, The Second Affiliated Hospital of Nanchang University), Ying-Jie Chu (Department of Cardiology, Henan Provincial People's Hospital), Hong-Bin Cai (Department of Cardiology, The First Affiliated Hospital of Fujian Medical University), Di-Guang Pan (Department of Cardiology, Guilin People's Hospital), and Xiao-Hua Dai (Department of Cardiology, Anhui Provincial Hospital of Traditional Chinese Medicine).

#### **Financial support and sponsorship**

Nil.

#### **Conflicts of interest**

Expenses for traveling of the committee members to attend the consensus meetings were supported by Buchang Pharmaceutical Co., Ltd., China.

## REFERENCES

- Hua W, Gao RL, Zhao BC, Wang J, Chen XH, Cai C, *et al*. The efficacy and safety of Wenxin Keli in patients with frequent premature ventricular contractions: A randomized, double-blind, placebo-controlled, parallel-group, multicenter trial. *Chin Med J (Engl)* 2015;128:2557-64. doi: 10.4103/0366-6999.166026.
- Chen Y, Li Y, Guo L, Chen W, Zhao M, Gao Y, *et al*. Effects of Wenxin Keli on the action potential and L-type calcium current in rats with transverse aortic constriction-induced heart failure. *Evid Based Complement Alternat Med* 2013;2013:572078. doi: 10.1155/2013/572078.
- Burashnikov A, Petroski A, Hu D, Barajas-Martinez H, Antzelevitch C. Atrial-selective inhibition of sodium-channel current by Wenxin Keli is effective in suppressing atrial fibrillation. *Heart Rhythm* 2012;9:125-31. doi: 10.1016/j.hrthm.2011.08.027.
- Xue X, Guo D, Sun H, Wang D, Li J, Liu T, *et al*. Wenxin Keli suppresses ventricular triggered arrhythmias via selective inhibition of late sodium current. *Pacing Clin Electrophysiol* 2013;36:732-40. doi: 10.1111/pace.12109.
- Li G, Yu L, Fu-Jian Z, Peng T. Anti-arrhythmia effect of wenxin granules in rats (In Chinese). *J Beijing Univ Tradit Chin Med* 2013;36:472-5. doi: 10.3969/j.issn.1006-2157.2013.07.010.
- Liu YW, Ji-Hong G, Ping Z, Chun L. Effects of *Nardostachys chinensis* Batal extract in wenxin granule on the activation kinetics of sodium current and transient outward potassium current in rat ventricular myocytes (In Chinese). *Chin J Cardiac Pacing Electrophysiol* 2009;23:533-5.
- Kalifa J, Avula UM. The Chinese herb extract Wenxin Keli: Atrial selectivity from the Far East. *Heart Rhythm* 2012;9:132-3. doi: 10.1016/j.hrthm.2011.11.030.
- Minoura Y, Panama BK, Nesterenko VV, Betzenhauser M, Barajas-Martinez H, Hu D, *et al*. Effect of Wenxin Keli and quinidine to suppress arrhythmogenesis in an experimental model of Brugada syndrome. *Heart Rhythm* 2013;10:1054-62. doi: 10.1016/j.hrthm.2013.03.011.
- Qi-Zhu T, Zheng-Rong H, Xi-Teng S, Teng W, Di-Fei S. Effects of *Nardostachys chinensis* Batal extract on sodium and calcium channels in rabbit ventricular myocytes (In Chinese). *Chin J Cardiol* 2004;32:267-70. doi: 10.3760/j.issn:0253-3758.2004.z2.106.
- Hou JW, Li W, Guo K, Chen XM, Chen YH, Li CY, *et al*. Antiarrhythmic effects and potential mechanism of WenXin KeLi in cardiac Purkinje cells. *Heart Rhythm* 2016;13:973-82. doi: 10.1016/j.hrthm.2015.12.023.
- Noble D, Noble PJ. Late sodium current in the pathophysiology of cardiovascular disease: Consequences of sodium-calcium overload. *Heart* 2006;92 Suppl 4:iv1-5. doi: 10.1136/hrt.2005.078782.
- Guo D, Lian J, Liu T, Cox R, Margulies KB, Kowey PR, *et al*. Contribution of late sodium current (I(Na-L)) to rate adaptation of ventricular repolarization and reverse use-dependence of QT-prolonging agents. *Heart Rhythm* 2011;8:762-9. doi: 10.1016/j.hrthm.2010.12.026.
- Jia S, Lian J, Guo D, Xue X, Patel C, Yang L, *et al*. Modulation of the late sodium current by ATX-II and ranolazine affects the reverse use-dependence and proarrhythmic liability of IKr blockade. *Br J Pharmacol* 2011;164:308-16. doi: 10.1111/j.1476-5381.2010.01181.x.
- Wei-Fu D, Shan-Shan W, Ling Y. Effects of Wenxin granule on heart rate variability in patients with frequent atrial extrasystoles (In Chinese). *Chin J Integr Med Cardio* 2008;6:346-7. doi: 10.3969/j.issn.1672-1349.2008.03.049.
- Hua-Ping W, Hua-Jie Z, Chun-Feng Y. An observation on the efficacy of Wenxin granule combined with small-dose propafenone for the treatment of frequent atrial premature beats (In Chinese). *Mod J Integr Tradit Chin West Med* 2012;21:3489-90. doi: 10.3969/j.issn.1008-8849.2012.31.037.
- Jie-Fu Y, De-Ping L, Jia-Bin T. Efficacy and safety of Buchang's Wenxin granule for the treatment of ventricular premature beats (In Chinese). *Chin J Cardiol* 2004;32:265-6. doi: 10.3760/j.issn:0253-3758.2004.z2.105.
- Min W, Yi-Bo X, Shi-En H, Qiang Y, Jian-Jin S. Clinical observation on effect and safety of combined use of Wenxin granule and amiodarone for conversion of auricular fibrillation (In Chinese). *Chin J Integr Tradit West Med* 2006;26:445-8. doi: 10.3321/j.issn:1003-5370.2006.05.015.8.
- Jianfen H. Clinical observation of Wenxin granule combined with propafenone in the treatment of atrial fibrillation (In Chinese). *Chin J Med Guide* 2013;15:1483-4. doi: 10.3969/j.issn.1009-0959(2013)09-1483-02.
- Li-Li W, Xiao-Dong X, Xing Z. An analysis of the efficacy of wenxin granule combined with digoxin for the treatment of chronic atrial fibrillation (In Chinese). *J Community Med* 2008;6:57-8. doi: 10.3969/j.issn.1672-4208.2008.11.036.
- Ai-Zhen H, Yuan-Yu L, Zhi-Hua W, Jia-Bin H. Wenxin granule combined with metoprolol in the treatment of 42 patients with anxiety and premature beats (In Chinese). *Chin J Integr Med Cardio* 2010;8:13-4. doi: 10.3969/j.issn.1672-1349.2010.01.008.
- Xin-Jun Z, Ning G, Xiao-Li H, Jin-Hui W, Yan-Ling Z, Shuang W, *et al*. The effect of Wenxin Keli on arrhythmia of cardiovascular disease in elderly (In Chinese). *West Chin Med J* 2005;20:263-4. doi: 10.3969/j.issn.1002-0179.2005.02.033.
- Zhi-Qiang Y, Chuan-Yin L, Feng-Fu W, Xue-Qiao W, Min-An P. Effects of wenxin granule on arrhythmia and heart rate variability in patients with essential hypertension (In Chinese). *Pract J Cardiac Cereb Pneum Vasc Dis* 2011;19:248-9. doi: 10.3969/j.issn.1008-5971.2011.02.050.
- Jing-Jie W, Shu-Zhu L, Bao-Long Q, Wei L, Xin G, Ping Z. Effects of wenxin granule on plasma BNP, Ang II and cardiac function in patients with congestive heart failure (In Chinese). *Chin Med Her* 2009;6:106-9. doi: 10.3969/j.issn.1673-7210.2009.16.062.
- Yong W, Gao-Rong L. Clinical study of wenxin granule in treating chronic cor pulmonale complicated by premature ventricular contractions (In Chinese). *Chin Gen Pract* 2012;15:909-10.
- Zhi-Hong L, Xu-Bin W, Ling L, Xu-Ping L, Xiao-Qin Q, Ying-Zhong L, *et al*. A multi-center clinical study of the effects of wenxin granule on acute coronary syndrome complicated with arrhythmia (In Chinese). *J Clin Med Pract* 2010;14:59-62. doi: 10.3969/j.issn.1672-2353.2010.01.020.
- Lei Y, Si-Ning Z, Feng-Yun S, Chao-Jun L, Hai-Feng Z, Li-Min L, *et al*. Effects of wenxin granule on heart rate variability in patients with coronary heart disease (In Chinese). *J Clin Cardiol* 2007;23:472-3. doi: 10.3969/j.issn.1001-1439.2007.06.022.
- Chun-Hua T, Li-Ying Z, Zhi-Jin L, Jing-Zhu Y. Effects of wenxin granule on ventricular rate in patients with hyperthyroidism and rapid ventricular rate (In Chinese). *Chin J Integr Med Cardio* 2012;10:155-6. doi: 10.3969/j.issn.1672-1349.2012.02.017.
- Li-Feng F, Han-Yu C, Ping-Ren W, Pei-Min L, Wen-Bo L. Effect of wenxin keli on hs-CRP, interleukin-6, TNF-alpha and adhesive molecule levels in patients with unstable angina (In Chinese). *Chin J Integr Med Cardio* 2006;4:943-5. doi: 10.3969/j.issn.1672-1349.2006.11.002.
- Lan-Cui W. Wenxin Keli in the treatment of 45 female patients with menopausal arrhythmia (In Chinese). *Chin Pharm* 2011;20:74-5. doi: 10.3969/j.issn.1006-4931.2011.14.045.
- Qian W, Ya-Jun H, Yuan-Hui H, Wei-Xing L, Hong-Xu L, Xiao X, *et al*. Clinical observation on wenxin granules for 199 cases of insomnia with Qi-Yin deficiency syndrome (In Chinese). *J Tradit Chin Med* 2012;53:2115-7.
- Lai-Huan S, Sheng Y, Chao Z, Hong Y, Ling-Xia Z. Efficacy and safety of wenxin granule for treatment of ventricular premature: A meta-analysis (In Chinese). *Chin J Integr Med Cardio* 2013;11:30-3. doi: 10.3969/j.issn.1672-1349.2013.01.016.