

Use of Herbal Supplements for Overactive Bladder

Bilal Chughtai, MD,¹ Elizabeth Kavalier, MD,² Richard Lee, MD,¹ Alexis Te, MD,¹ Steven A. Kaplan, MD,¹ Franklin Lowe, MD³

Department of Urology, ¹New York-Presbyterian Hospital, Weill Cornell Medical College, ²Lenox Hill Hospital, ³St. Luke's-Roosevelt Hospital Center, Columbia University College of Physicians and Surgeons, New York, NY

Anticholinergics, specifically antimuscarinic agents, are the most common medications prescribed for overactive bladder (OAB). The most common side effects of these agents are dry mouth and constipation, although other more concerning effects include changes in blood pressure, pulse rate, or heart rhythm when treatment is initiated. Herbal treatments are an increasingly popular alternative for treating OAB. A 2002 survey of US adults aged ≥ 18 years conducted by the Centers for Disease Control and Prevention indicated that 74.6% of those with OAB had used some form of complementary and alternative medicine. The World Health Organization estimates that 80% of the world's population presently uses herbal medicine for some aspect of primary health care. Women were more likely than men to use complementary and alternative medicine. The authors review the most commonly used herbal medications for OAB.

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KEY WORDS

Overactive bladder • Herbal medicine • Gosha-jinki-gan • Hachi-mi-jio-gan • Buchu (*Barosma betuline*) • Cleavers (*Galium aparine*) • Cornsilk (*Zea mays*) • Horsetail (*Equisetum*) • *Ganoderma lucidum* • Resiniferatoxin • Capsaicin

Overactive bladder (OAB) is defined by the International Continence Society as a syndrome that includes urgency, with or without urge incontinence, frequency, and nocturia. The prevalence of OAB is estimated to range between 9% and 16%, depending on the population studied.¹⁻³ As symptoms of OAB increase with age, they can negatively impact quality of life (QoL).

The cost of treating OAB is estimated to be approximately \$12 billion annually in the United

States.⁴ This estimate accounts for the direct cost of management, including protective undergarments, bedside commodes, and medical treatment, as well as indirect costs, such as those resulting from urinary tract infections and falls due to urgency and nocturia. There are also additional intangible costs that cannot be estimated such as pain, suffering, and poor QoL.

The negative impact on health and the sense of well-being as well as the impairment in the ability

Drs. Chughtai and Kavalier contributed equally to this work.

to perform activities of daily living, has been well-documented. For example, elderly patients with OAB and subsequent incontinence are more likely to be admitted to nursing homes. Thom and colleagues reported a twofold increased risk of admission to a nursing facility for patients with incontinence.⁵ Urinary incontinence can also lead to anxiety, negative self-image, and isolation.⁴ Other problems associated with OAB include skin ulcer-

the most common medications prescribed for OAB. The most common side effects are dry mouth and constipation.^{9,10} Other more concerning side effects include changes in blood pressure, pulse rate, or heart rhythm when treatment is initiated. Additional adverse events (AEs) include memory loss, cognitive impairment, and balance problems. Thus, alternative therapies not involving standard medications and their associated risks

radix (5.0 g), *Achyranthis radix* (3.0 g), *Corni fructus* (3.0 g), *Moutan cortex* (3.0 g), *Alismatis rhizome* (3.0 g), *Dioscorea rhizoma* (3.0 g), *Plantaginis semen* (3.0 g), *Hoelen* (3.0 g), processed *Aconiti tuber* (1.0 g), and *Cinnamomi cortex* (1.0 g).¹² GJG has been studied in both preclinical as well as clinical models. Gotoh and colleagues reported on the inhibition of activated spinal κ opioid receptors by GJG. The inhibition of bladder sensation leads to decreased urinary frequency in rats.¹³ Suzuki and colleagues reported on the impact of GJG on detrusor contraction in anesthetized dogs. Bladder contraction mediated by pelvic nerve stimulation and induced by acetylcholine administration was significantly inhibited by administration of 100 mg/kg GJG; effects were similar to that seen with atropine administered at 0.1 mg.^{14,15}

Human data on the use of GJG has also been reported. Kajiwara and Mutaguchi reported on a prospective study of 44 women with OAB treated with 7.5 g/d of GJG. Significant improvements in International Prostate Symptom Scores (IPSS) (14.2-10.0), QoL

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ations and urinary tract infections. Nocturia is common with OAB and ranks among the most bothersome of lower urinary tract symptoms.⁶ In addition to sleep interruption and resulting fatigue, patients with nocturia may be more likely to suffer from falls and fractures, which are associated with high mortality in elderly patients. Approximately 33% of elderly people do not survive beyond 1 year after a hip fracture.⁷

The impact of OAB was clearly reported in the National Overactive Bladder Evaluation (NOBLE) study.⁸ The NOBLE study represented a computer-assisted telephone interview survey that used health-related QoL (HRQoL) questionnaires to compare continent OAB patients, with incontinent OAB patients, and control groups in a nested case-control fashion. In this study, OAB was associated with lower QoL scores, higher scores on depression, and poorer sleep quality when compared with control subjects.⁸ Note that, although the prevalence of OAB increases with age, it should not be considered a normal consequence of aging.

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are sought by patients to alleviate symptoms of OAB.

Herbal treatments represent an increasingly popular alternative for treating OAB. A 2002 survey of US adults aged ≥ 18 years conducted by the Centers for Disease Control and Prevention indicated 74.6% of those with OAB had used some form of complementary and alternative medicine. The World Health Organization estimates that 80% of the world's population

presently uses herbal medicine for some aspect of primary health care. Women were more likely than men to use complementary and alternative medicine.^{10,11} We review the most commonly used herbal medications used for OAB.

Gosha-jinki-gan

Gosha-jinki-gan (GJG) is a traditional Chinese blended herbal medicine composed of 10 different herbs. It is composed of *Rehmanniae*

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(4.2-3.1), and daytime frequency (9.3-7.8) were seen; interestingly, no objective parameters were studied.¹⁶ Adverse reactions were seen in 9% of patients. Ogushi and Takahashi reported on a study of 30 men with one of more episodes of urgency per 24 hours with OAB Symptom Score (OABSS) ≥ 3 and IPSS storage subscores ≥ 2 treated with 2.5 g of GJG mixture three times daily for 6 weeks.¹² Significant improvements in IPSS (15.2 vs 12; $P < .0001$),

OABSS (7.5 vs 4.9; $P < .0001$), and QoL score (4.4 vs 3.3; $P < .0001$) were seen. Peak flow rate (Q_{\max}) and postvoid residual urine (PVR) volume were unchanged after treatment. Mild AEs (nausea, diarrhea, urinary frequency) were seen in three patients.

Hachi-mi-jio-gan

Hachi-mi-jio-gan (HE) represents a Chinese herbal medicine composed of eight natural ingredients. Several of the main ingredients overlap with those of GJG. HE is composed of *Rehmannia radix*, *Cori frunc-tus*, *Dioscorea rhizome*, *Alismalis rhizome*, *Hoelen*, *Moutan cortex*, *Aconitii tuber*, and *Cinnamomi corte*. It is believed to have a relaxant effect on the acetylcholine-induced contraction of smooth muscle.

HE has been studied in the pre-clinical setting. Ito and colleagues studied its use in the ex vivo rat bladder, demonstrating inhibition of acetylcholine-induced contraction of rat bladder strips by HE in a dose-dependent fashion.¹⁷ The binding affinity for HE was found to be greatest for purinergic receptors, followed by muscarinic receptors. Preliminary toxicology studies in an in vivo rat counterpart with orally administered HE showed little perturbation of hepatic function.

Buchu (*Barosma betulina*)

Buchu is an herbal remedy used throughout South Africa. It was first introduced in the 1650s as a medicinal plant. It was traditionally used as an antispasmodic; an anti-pyretic; a liniment; a cough remedy; a general treatment of colds and influenza; a diuretic; as a treatment for kidney and urinary tract infections; for hematuria and prostatitis; for the treatment of cholera and other stomach ailments; for

the relief of rheumatism, gout, and bruises; for the relief of nephrolithiasis; and for antiseptic purposes. No clinical studies have been done regarding Buchu and OAB.

Cleavers (*Galium aparine*)

Cleavers commonly grow in North America and have small hooks that make them sticky. Due to their hooks, they cannot be consumed raw and are typically consumed in teas.¹⁸ They have been used to treat cystitis although no clinical studies have been done regarding cleavers and OAB.¹⁹

Cornsilk (*Zea mays*)

Cornsilk is derived from the female flower of corn. It has been used for indications from jaundice to cystitis.¹⁹ There are no clinical studies that have been done using cornsilk for OAB.

Horsetail (*Equisetum*)

Horsetail is named for its appearance, which resembles a horsetail. This plant looks like a fern and reproduces with spores.¹⁹ In an ex vivo study by Stajner and associates, horsetail demonstrated antioxidant properties.²⁰ There are, however, no clinical data demonstrating efficacy of horsetail in OAB.

Ganoderma lucidum

Ganoderma lucidum (GL) extract has been used in East Asia to cure various ailments including hepatitis, hypertension, hypercholesterolemia, and various cancers. GL has a strong 5 α -reductase inhibitory activity. In a study by Liu and colleagues, GL has been shown to inhibit testosterone-induced growth of the ventral prostate in castrated rats.²¹⁻²³ In a double-blind, placebo-controlled, randomized study, GL was studied in 50 healthy

volunteer men.^{24,25} IPSS scores improved by a mean of 3.22 over 8 weeks. There were no changes in objective parameters such as Q_{\max} or postvoid residual volume.

Resiniferatoxin

Resiniferatoxin (RTX) is derived from the resin of a cactus-like plant called *Euphorbia resinifera*, which is native to Morocco. Because of its application in pain control, efforts at producing a synthetic form resulted in a compound that allowed it to be mass produced. The toxin attaches to the vanilloid receptor in the afferent sensory neurons that transmit pain sensation to the brain. Activation of the vanilloid receptor leads to calcium entry through the neuronal membrane, resulting in desensitization of the nerve and, thus, analgesia. Attempts to translate these desensitization effects have been applied to the bladder. Intravesical RTX theoretically should attach to the vanilloid receptor of C-fiber afferents within the bladder, desensitizing the bladder, leading to increased bladder capacity, and decreased instability;²⁴ however, no studies have been performed to test the effect of RTX on humans with OAB. Studies done in animal models actually demonstrated the opposite—increased pain sensation and more frequency after instillation of RTX into the rat bladders.²⁶

Because RTX works through central nervous system afferent modulation, efforts were made to test its effect on the bladder through intrathecal injections in a rat model. Reduction in the mRNA transcription of pain receptors were found in the rats in whom the RTX was injected centrally, whereas the opposite was found in those in whom RTX was instilled directly into the bladder.²⁷ The theoretical use of RTX in the bladder has not been confirmed in animal models.

Capsaicin

Capsaicin is derived from chile peppers. It is found in the fleshy part of the pepper, not in the seeds. When capsaicin comes in contact with mucus membranes, it causes a burning, pungent sensation. Topically, capsaicin has been used in anesthetic ointments to treat arthritis, backaches, and sprains. Capsaicin binds to the transient receptor potential vanilloid receptor and opens calcium channels in a fashion similar to RTX. Binding of the receptor leads to a reduction in substance P, a major pain neurotransmitter.²⁷ There have been no clinical studies looking at the effect of capsaicin on OAB, but there is interest in studying it for the management of pelvic pain syndrome, in which OAB often presents as a symptom.

Conclusions

The use of complementary medication in the management of OAB has proven elusive. Although anticholinergic medications leave much to be desired, comparable herbal agents have not been found. Several of these agents show some promise for the treatment of OAB but lack definitive studies to prove their efficacy. RTX and capsaicin show more promise for the management of pelvic pain

syndromes than for OAB. Randomized controlled trials need to be conducted in order to know whether any of these agents will benefit those who have OAB. ■

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MAIN POINTS

- Anticholinergics are the most common medications prescribed for overactive bladder (OAB), with side effects including dry mouth and constipation, as well as changes in blood pressure, pulse rate, or heart rhythm. Additional adverse events include memory loss, cognitive impairment, and balance problems. Thus, alternative therapies are sought by patients to alleviate symptoms of OAB.
- Several herbal treatments show some promise for the treatment of OAB but lack definitive studies to prove their efficacy. These include gosha-jinki-gan, hachi-mi-jio-gan, buchu, cornsilk, cleavers, and horsetail. Resiniferatoxin and capsaicin show more promise for the management of pelvic pain syndromes than for OAB.
- The use of complementary medication in the management of OAB has proven elusive. Randomized controlled trials need to be conducted in order to know whether any of these agents will benefit the 33 million Americans who have OAB.