

# Medical management of chronic orchialgia

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**Abstract:** Chronic idiopathic orchialgia is a urologic disease process that is as frustrating as it is common. While no consensus exists on management for otherwise-unexplained testicular pain, most providers would agree that once other treatable organic causes are ruled out, initial management should be symptom focused, and should be medical rather than surgical. This chapter presents a review of the evidence available for a variety of pharmacotherapies commonly employed in the treatment of idiopathic chronic orchialgia.

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## Introduction

This chapter will focus on the medical management of idiopathic orchialgia that cannot be attributed to any identifiable organic cause, including structural irregularities, torsion, trauma, post-operative pain, infection, or referred pain from another site (e.g., ureteral stone). Chronic orchialgia of this type is commonly thought to be a part of the more complex picture of chronic genitourinary pain syndromes (1), and is also termed chronic epididymitis, chronic testicular pain, chronic orchidynia, and chronic scrotal pain syndrome (CSPS) (2). As is detailed in other chapters in this series, there is evidence that neural inflammation, as in other complex regional pain syndromes, may play a role in chronic orchialgia; this is reflected in some of the treatment options detailed below. There is also an established but poorly understood relationship between such chronic pain syndromes and mental illness, primarily depression, and this relationship can also occasionally be exploited therapeutically (1). Generally, however, the exact mechanism by which each of the therapeutic classes of drugs listed below is not fully understood. However, it is the opinion of these authors that in the treatment of idiopathic chronic orchialgia, despite our incomplete understanding

of the pathophysiology, medical management in multiple forms should be employed prior to consideration of more invasive measures.

## Antibiotics

While discussion of antibiotics in a chapter regarding management of *idiopathic* testicular pain may seem counterintuitive, we have opted to mention it here due to the frequency with which they are used as first-line therapy in the absence of clinical infection. Strebel *et al.* found that up to 82% of polled urologists in Switzerland prescribed a trial of antibiotics of various types for men presenting with chronic scrotal pain (2) without an obvious clinical infection. This was termed a presumed “post-infectious” etiology of the pain. In a later study by the same group, patients with CSPS were prospectively evaluated, and only 22% of these cases were found to demonstrate evidence of an infectious etiology. Thus, they conclude that widespread empiric use of antibiotics in patients with CSPS is not indicated (3).

## Non-steroidal anti-inflammatory drugs (NSAIDs)

Most urologists would likely include NSAIDs within the

first-line group of pharmacotherapy for CSPA (4). In fact, within the same Swiss cohort described above, the prevalence of the use of antibiotics as a first-line therapy was superseded only by that of NSAIDs, with 92% of patients receiving NSAID therapy for idiopathic scrotal pain. The mechanism of action of NSAIDs is well established, as are their analgesic and anti-inflammatory properties. While various authors have postulated specific areas of neural or intrascrotal inflammation that may respond to NSAIDs, there is no strong evidence proving such postulates. In any case, however, the analgesic properties and the generally favorable safety profile of NSAIDs make them a simple first-choice (especially in combination with non-pharmacologic therapy including supportive undergarments or heat/cold pack application) for the treatment of CSPA.

### Tricyclic antidepressants (TCAs)

The association between chronic pain of various types and depression was first published in 1983 (5). Some of the earliest work establishing the role for TCAs in the treatment of chronic pain was done shortly thereafter, but the majority of the pain treated in the study by Tollison *et al.* was chronic back pain (6). It was published in 1991 by Costabile *et al.* that there appeared to be a role for TCAs in the management of CSPA (7), and since that time, TCAs, including amitriptyline and doxepin, have become part of the CSPA treatment paradigm. More recently, Sinclair *et al.* published a prospective trial of nortriptyline in the treatment of CSPA, and they found that 66.6% of patients had a greater than 50% reduction in their scrotal pain after three months of therapy. Based on an 11-point numerical pain scale, the average reduction in pain was 51.8%. The dosage of nortriptyline was started at 10mg/day and titrated up to 150mg/day as needed based on response. Of note, all patients in this study had previously failed therapy with empiric antibiotics and NSAIDs (8).

### Neuromodulating drugs

In keeping with the theory that CSPA represents a subtype of complex regional pain syndrome in the genitourinary organs, it stands to reason that treatment of such a syndrome could include neuromodulating drugs that are used to treat other such conditions (9). The archetypal and best-studied of these in this context is gabapentin. Originally prescribed as an antiepileptic, gabapentin is a

drug that is thought to limit neural excitation and enhance inhibition by blocking calcium voltage-gated ion channels in the central nervous system (8). Since its introduction in the 1990s, gabapentin and its derivatives have proven effective for a variety of neuropathic conditions including post-herpetic neuralgia and diabetic neuropathic pain (10). In a study related to that involving nortriptyline referenced above, Sinclair *et al.* also demonstrated that in a similar group of patients previously treated with NSAIDs and antibiotics, gabapentin produced a >50% reduction in pain in 61.5% of treated patients. When combined with those treated with nortriptyline and excluding patients with post-vasectomy pain, these drugs resulted in a >50% reduction in pain in 80% of patients treated (8). The gabapentin dosage described in the study was 300 mg/day titrated up to 1,800 mg/day as needed based on response.

### Vitamin B12 and testosterone

In a recently published study, Cui and Terlecki were the first to examine the relationship between vitamin B12 and/or testosterone deficiency and CSPA. Citing the established relationship of B12 deficiency to neuropathy and testosterone deficiency to increased inflammation, they retrospectively examined the levels of each in men presenting with CSPA. They found that 76% of patients had a deficiency in one or both levels. Also interesting is that of those who elected for repletion of the deficient biochemical(s), 65% of patients reported “a significant improvement” in their CSPA syndromes while an additional 16% reported “some improvement” (11). While these findings have not been studied by others or in a prospective fashion, they provide an interesting new direction that could help guide CSPA treatment refractory to other pharmacologic therapies.

### Alpha-adrenergic blockade

A variety of basic science research projects have elucidated that the alpha-adrenergic receptor, especially the alpha-1 and alpha-2 receptor subtypes, is present and active in the vas deferens and epididymis in both rodents and humans. It has been hypothesized that over-sensitivity to alpha-adrenergic action could result in increased neural activity and/or spasms of associated smooth muscle that could result in perceived pain (1). While at the time of this writing the clinical application of alpha blockade in the treatment of

CSPS remains theoretical and unstudied, it may provide a new direction for future CSPS therapy studies.

## Conclusions

As reviewed above, there exist a variety of pharmacologic therapies in the clinician's arsenal to help combat idiopathic orchialgia. The evidence supporting the efficacy of these therapies is variable, but a few reasonable conclusions can be drawn. First, in the absence of clinical or radiologic evidence of infection of scrotal structures, antibiotics are not an effective treatment for orchialgia. Second, a number of agents have been proven useful in the treatment of this condition for many patients. It is the opinion of these authors that with regard to pharmacotherapy, a trial of NSAIDs (with or without hot/cold compresses and scrotal support) is almost always a reasonable first step due to their wide availability and relatively low side effect profile. If the desired relief is not achieved, either gabapentin or TCAs can be used as second-line therapy, potentially in combination. Third, there are other treatments that may have some efficacy in certain patients, but that the evidence is not as strong as for the aforementioned therapies. However, in patients who are not ideal surgical candidates, a trial of B12 and/or testosterone supplementation may be worthwhile in patients deficient in either. Finally, there is much room for development of novel medical therapies using existing drugs, e.g., the use of the anxiolytic drug buspirone in unpublished data from Liaw and Lowe, which show promise. Medical management of chronic orchialgia remains the first step in the treatment of the condition; only after the failure of multiple medical agents should any invasive therapy be considered.

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## Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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