PAIN

# Itraconazole Improves Vulvodynia in Fungus Culture-Negative Patients Post Fluconazole Failure

Rodger Rothenberger, MD,[1] Wendy Jones, CRNP,[2] and Colin MacNeill, , MD[2,3]


## ABSTRACT

**Introduction:** Vulvodynia is a difficult condition to treat due to both the uncertain etiology of the disorder and poorly available therapies. This difficulty leads to a disproportionately high prevalence and cost of treatment for this condition. Candida vulvovaginitis is a frequent co-present diagnosis in vulvodynia patients. Whether through treatment of co-present, candida vulvovaginitis or by systemic interaction, itraconazole has been proposed as a treatment for vulvodynia.

**Aim:** To describe objective change in vulvodynia pain in a cohort of patients treated with itraconazole.

**Methods:** This study was a retrospective cohort study comprised of women diagnosed with vulvodynia who were treated with itraconazole between January 1, 2011 and October 17, 2017. Patients had failed fluconazole treatment and had negative fungus cultures for >2 months before itraconazole treatment. All other vulvovaginal disorders were excluded.

**Main outcome measure:** The main outcome measure was the change in pain before and after treatment as measured by cotton swab testing.

**Results:** 106 patients met inclusion criteria. Average pain reduction for the entire cohort was 60.7%. Patients who continued itraconazole for 5 to 8 weeks demonstrated a 69.6% reduction in cotton swab test pain. Pain reduction as a percentage of total patients showed complete resolution of pain in 37.7% of patients and >50% reduction in 66.0% of patients. Two-sample paired T-tests for means analysis of pain scores disproved the null hypothesis ($P < .01$, $\alpha = 0.01$) and showed a 50% reduction in pain to be significant ($P = 0.043$, $\alpha = 0.05$). Two-tailed Wilcoxon signed rank test also demonstrated rejection of the null hypothesis ($\alpha = 0.05$).

**Conclusions:** Itraconazole therapy is associated with a significant reduction in vulvovaginal pain in patients with negative fungus cultures and no other identifiable disease in this pilot study. A randomized placebo-controlled trial is warranted. **Rothenberger R, Jones W, MacNeill C. Itraconazole Improves Vulvodynia in Fungus Culture-Negative Patients Post Fluconazole Failure. Sex Med 2021;9:100383**




**Key Words:** Vulvodynia; Vulvovaginitis; Itraconazole; Fluconazole; Azole; Antifungal

## INTRODUCTION

Vulvodynia, vulvar pain of undetermined origin of 3 or more months duration,[1] is a difficult condition to treat due the uncertain etiology of the disorder and to poorly available therapies. With a prevalence of 7-8% and an estimated cost per patient of greater than $8800, the estimated an annual cost of vulvodynia is $102-$117 billion per year in the United States[2–4] Vulvodynia should be differentiated from chronic vulvovaginal candidiasis (CVVC), a chronic vulvovaginal pain related to a vulvar or vaginal Candida.[5] The distinction is clouded by the frequently found

*Abbreviations:* CVV, Candida vulvovaginitis; CVVC, Chronic vulvovaginal candidiasis

Received December 20, 2020. Accepted April 22, 2021.

[1]Penn State University College of Medicine Hershey, PA, USA;

[2]Department of Obstetrics and Gynecology – Penn State University College of Medicine, Hershey, PA, USA;

[3]Harvard Vanguard Medical Associates, Burlington, MA



https://doi.org/10.1016/j.esxm.2021.100383

history of CVVC in vulvodynia patients, the overlapping symptom of vulvar vestibule burning in patients with vulvodynia and with CVVC, and the frequently found history in CVVC patients of symptomatic improvement with fluconazole that diminishes over the course of the condition and leads the clinician to suspect the diagnosis is now vulvodynia. Indeed, a study of clinic discharge diagnoses in vulvovaginal specialty clinics reported a large proportion of patients were discharged with 2 diagnoses: vulvodynia and vaginal candidiasis. It has been proposed that studies considering vulvodynia should include fungal cultures or some other test for fungal infection in the inclusion/exclusion criteria and the data analysis.[6–8]

Itraconazole is a potent antifungal agent that, by the same mechanism as fluconazole, inhibits ergosterol synthesis (causing a fungicidal effect). Though Itraconazole and fluconazole both are triazole antifungals, they are structurally distinct and elicit different reactions systemically. The question posed in this paper involves whether itraconazole, thus far unstudied in vulvodynia, can be used in the treatment of vulvodynia. Itraconazole has been utilized in the treatment of non-fungal conditions before, with active study being undertaken in its treatment of basal cell carcinoma, prostate, non-small cell lung cancer, triple-negative breast cancer, and ovarian cancers.[9] The mechanism by which it acts systemically is unclear with numerous possibilities suggested but none confirmed. These authors favor a mechanism of mTOR pathway modulation and thereby changes in angiogenesis and nerve growth.[10] Within the realm of pain indications, however, with the exception of a clinical trial being undertaken in the treatment of chronic pain,[11] there has been, as of yet, very little study. Does itraconazole decrease fungal culture-negative vulvodynia pain?

## METHODS

This study is a retrospective cohort study which specifically examined women diagnosed with vulvodynia and who were treated with itraconazole. The primary outcome was defined as an objective reduction in cotton swab test of the vulvar vestibule for pain. Cotton swab testing was performed as described by Bergeron et al. in 2001. The labia majora and labia minora were palpated (right, left, and midline) followed by six vestibular sites in a clockwise fashion: 12 o'clock, then 12-3, 3-6, 6, 6-9, and 9-12 o'clock.[12] Pain score was recorded as the maximal pain value in a 10 point pain scale during this testing (10 being the greatest pain and 0 being no pain). We postulated that pain reduction scores of >50%, if achieved, would outperform all previously reported placebo effects in vulvodynia.[13] This cohort of patients was selected from patients who had first been treated with up to 200 mg daily of fluconazole for 6 to 8 weeks with insufficient reduction in vulvar pain and subsequently desired further treatment for continued vulvovaginal pain and elected to initiate treatment with itraconazole. This cohort of patients was obtained through a search of the electronic medical record pharmacy records for all patients prescribed itraconazole at Penn State Hershey Medical Center. Both providers prescribed itraconazole at a dose of 400 mg per day[14] to all patients involved in this study.

Inclusion criteria comprised of all patients who were administered itraconazole by the second and third authors between the dates of January 1, 2011 and October 17, 2017. All subjects were over 18 years of age, female in gender, and carried the diagnosis of vulvodynia using the ISSVD definition of vulvodynia.[1] From this cohort of patients treated with itraconazole, all patients with both negative fungus cultures for >2 months before itraconazole initiation and previous treatment with up to 200 mg daily of fluconazole for 6 to 8 weeks were selected. It was this cohort of fungus culture-negative, fluconazole refractory, vulvodynia patients who were treated with itraconazole that was examined in this study.

Exclusion criteria included patients with any identifiable vulvovaginal disease, such as lichen sclerosis or lichen planus and lichen simplex chronicus. Antibiotic therapy during the itraconazole treatment period and the lack of pain with cotton swab examination at the initiation of itraconazole treatment were also treated as an exclusion criterion. Baseline liver disease was treated as an exclusion criterion as well. All patients under the age of 18 were excluded. Patients whom received other treatments for vulvodynia such as alternative oral and/or topical medications, physical therapy, and surgery were excluded.

Data on pain, as determined through maximal pain score on cotton swab palpation of the vulvar vestibule before and after treatment with itraconazole was collected from medical record entries at clinic visits, following up every 3 to 4 weeks with liver function tests (LFTs) at each visit. These before and after pain data points for each treatment were contrasted to create a percent reduction in pain. Data regarding the duration of treatment with itraconazole and discontinuation of itraconazole due to side effects were also collected.

Statistical analysis utilized the two-tailed Wilcoxon signed rank test to determine the significance of the change in pain scores with itraconazole administration. The two-sampled paired *t*-test for means was also completed to both reject the null hypothesis and to demonstrate significance to a 50% reduction in pain scores. Statistics performed using the Microsoft Excel Software (version 2019 16.0.6742.2048. Redmond, WA. Microsoft Corp.)

Of the patients studied, not reported in the above figures are 3 patients who discontinued itraconazole due to gastrointestinal side-effects (frequent bowel movements), 1 patient who discontinued treatment due to elevated LFTs, and 1 patient who discontinued itraconazole after a seizure during the treatment period. It should be noted that liver function testing was conducted for all patients prior to initiation of itraconazole treatment and at follow up appointment(s). Elevated LFTs normalized after itraconazole discontinuation.

This research was approved by the Penn State Hershey Medical Center Institutional Review Board before data collection with a waiver of informed consent.

**Table 1.** Reduction in pain associated with number of weeks of treatment

| | % Reduction in Pain (standard deviation) | 95% Confidence Interval | Number of Patients |
|---|---|---|---|
| Overall Average | 60.7 (39.0) | 7.52 | 106 |
| Less than 4 Weeks Treatment | 36.6 (43.2) | 36.1 | 8 |
| 4 Weeks of Treatment | 52.0 (44) | 20.0 | 21 |
| 5-6 Weeks of Treatment | 69.6 (31.9) | 10.6 | 37 |
| 8 Weeks of Treatment | 58.4 (44) | 19.1 | 23 |
| 9+ Weeks of Treatment | 66.6 (34) | 17.6 | 17 |

## RESULTS

Patient characteristics of age, weight, BMI, and menopausal status were recorded from the time of itraconazole initiation. Participants ranged from 18 to 86 years of age with an average age of 39.9 years. Of the 106 Participants, 77 patients were premenopausal and 29 patients were postmenopausal. Average weight was 69.9 kg and average BMI was 25.4 kg/m$^2$. Data was normally distributed with a kurtosis of -0.6 and a skewness z value of -0.6.

The 106 patients who received itraconazole were found to have a 60.7% reduction in pain in response to cotton swab testing. Interestingly, we observed that pain reduction increased with duration of itraconazole therapy. In Table 1 one can see the varying duration of itraconazole therapy and change in maximal pain on cotton swab testing. The optimal therapeutic window is 5 to 6 weeks of therapy with a 69.7% reduction in pain. With longer duration of therapy the benefit of maintenance itraconazole continued, with similar reductions in pain observed in the 8 and 9+ week treatment groups. These reductions in pain may be nonsignificant due to the small number of participants and lack of control group, however, they appear to indicate a correlation between these periods of itraconazole therapy and reduction of symptoms.

Two-sample paired T-tests for means were undertaken to examine both pre-treatment and post-treatment objective pain scores, whether the null hypothesis could be rejected and whether significance could be proven to a >50% pain reduction. Null hypothesis was disproven ($P < .01$, $\underline{\alpha} = 0.01$) and a decrease in patients' objective pain score by greater than 3 (correlating with a 50% reduction in pain) was demonstrated ($P = .038$, $\underline{\alpha} = 0.05$). Two-tailed Wilcoxon signed rank test also demonstrated rejection of the null hypothesis ($\underline{\alpha} = 0.05$).

Pain reduction as a percentage of total patients studied can be seen in Table 2. Overall, 37.7% of patients in this study underwent complete resolution of symptoms, and 53.8% of patients had a greater than 60% reduction in pain. A lack of symptom reduction was observed in 9.43% of patients, and in 3.77% of patients, an increase in pain was observed.

**Table 2.** Pain reduction as a percentage of total patients studied

| % Reduction | Percent of total patients |
|---|---|
| 100% | 37.7 |
| 60 % or more | 53.8 |
| >50% | 66.0 |
| <50% | 34.0 |
| 0% | 9.43 |
| Symptoms Worsened | 3.77 |

## DISCUSSION

This study demonstrates that the use of itraconazole in fungus culture-negative vulvodynia patients is associated with a reduction or elimination of vestibular pain as objectively measured by the cotton swab test. Our examination of dose and duration of treatment demonstrated that treatment for 5 or more weeks with a dosage of 400 mg of itraconazole (dispersed as 200 mg twice per day) was deemed the most effective. In this study, the pain scores of patients with chronic vulvar pain were collected before and after initiation of a daily dose of itraconazole. To our knowledge this is the first report of a significant reduction in objectively tested vulvar pain associated with itraconazole treatment and is striking in its complete or almost complete amelioration of pain in a large percentage of patients.

A limitation of this work is the retrospective study design and the lack of a control group causing the palpable placebo effect in the vulvodynia patient population to cloud the impact of this data. An understanding of this placebo effect through the literature on vulvodynia may ameliorate this concern. In the systematic review conducted by Dr. JC Andrews interventions available for vulvodynia were examined and the placebo effect in vulvodynia, defined as an absolute effect of >50% decline in pain score, was found to range from 14% to 33%, with a median of 22%.[13] We applied this benchmark to determine whether the primary outcome has been achieved. Using these median and maximal values of the projected placebo effect, this study offers benefit at this >50% benchmark to 66.0% of patients (see Table 2). This substantial benefit extends well past the placebo effect. The mechanism for this Itraconazole efficacy in vulvodynia is uncertain. It is possible itraconazole is active against a small population of yeast that do not grow in culture; alternatively, itraconazole may reduce vulvodynia pain through an anti-inflammatory or other systemic effect yet undocumented since its synthesis in 1980.

The possibility that these patients have a yet unculturable fungus present in their vulvovaginal region status post 4 to 6 weeks

of fluconazole treatment remains present. This possible causative organism remains plausible due to the problematic nature of the universal treatment of CVVC with fluconazole. CVV is most commonly caused by *Candida albicans*, however, non-albicans candida is the causative agent in approximately 10% of CVV and has shown resistance to azole antifungals such as fluconazole.[15] Itraconazole has a similar coverage when compared to fluconazole with the addition of coverage in dimorphic fungal pathogens, dermatophytes, and molds. Itraconazole also tends to concentrate in the skin and nails, accumulating 20 times higher concentrations in these tissues. It has been previously found to not offer clear benefit when compared to fluconazole for vulvovaginal infections and has been deemed to have increased side-effects, variable gastric absorption, and less predictable drug levels causing relegation to use after fluconazole treatment failure. The caveat to these statements is that itraconazole used with this high a dosage and duration has not been previously reported in CVV patients.[16] The possibility that this is a treatment for a yet unculturable pathogen exists.

Alternatively, if one were to consider these patients as having had a negative infectious etiology satisfactorily proven negative cultures before itraconazole initiation, it is reasonable to consider other mechanisms by which itraconazole could reduce vulvodynia pain. Pathologically, hyperinnervation and nociceptor sensitization in the vulva is a well-described characteristic of vulvodynia. It can be hypothesized that it is through a limitation of this mechanism that itraconazole could exert an effect in decreasing or eliminating vulvodynia pain.[6] In murine models, it has been shown that inhibition of angiogenesis in vaginal tissues is likely to inhibit the development of accompanying perivascular nociceptive nerve fibers and hyperinnervation.[17] These findings raise the possibility that inhibition of angiogenesis in the vulva could reasonably be accomplished by itraconazole.

Itraconazole was first identified as an inhibitor of angiogenesis in 2007 by the US food and drug administration and has since been researched as a possible anti-cancer therapy.[9] Itraconazole has been shown to decrease angiogenesis through action on the mTOR signaling pathway, specifically through mTORC1.[10] This same mTORC1 plays an active role in inflammation-related angiogenesis in the body[18] and nerve growth factor protein expression in Schwann cells.[19] The likelihood that modulation of these inhibitory functions by itraconazole is supported by the theorized mechanism for the induction of pain in vulvodynia patients that of infection and/or trauma causing an initial insult which induces inflammation, leading to angiogenesis, nerve fiber proliferation and chronic pain.

Further study in the form of randomized control trials with long-term follow up to 6- and 12-months post-treatment is warranted to detect long-term remission, along with an examination of differing dosages of itraconazole. The implication that an organic and treatable cause exists for vulvodynia with an effective treatment would have substantial practice-altering implications.

**Corresponding Author:** Rodger Rothenberger, MD, University of Cincinnati Medical Center, PO Box 670526, Cincinnati, OH 45267-0526, 231 Albert. Sabin Way, Tel: 6 10 620 3936, Fax: (513) 558-5705; E-mail: rothenrr@ucmail.uc.edu

*Conflict of Interest:* All authors have no conflicts of interest to ?disclose.

*Funding:* No external source of funding was provided. Patient's insurance and the patients themselves purchased itraconazole for treatment of their vulvovaginal pain.

Research approved by the Penn State University College of Medicine Institutional Review Board.

*Patient Consent:* Research was approved by the Penn State College of Medicine Institutional Review Board prior to initiation of chart review with a waiver of informed consent.

## STATEMENT OF AUTHORSHIP

Rodger Rothenberger: Conceptualization, Methodology, Formal Analysis, Investigation, Data Curation, Writing – Original Draft, Writing – Review and Editing; Wendy Jones: Conceptualization, Investigation; Colin MacNeill: Conceptualization, Investigation, Validation, Data Curation, Writing – Review and Editing, Visualization, Supervision.

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