

2018

Do Oral Probiotics in Conjunction with Fluconazole Reduce Symptoms Among Patients Suffering from Vulvovaginal Candidiasis?

Kayla McDaid

Philadelphia College of Osteopathic Medicine

Follow this and additional works at: https://digitalcommons.pcom.edu/pa_systematic_reviews

 Part of the [Medicine and Health Sciences Commons](#)

Recommended Citation

McDaid, Kayla, "Do Oral Probiotics in Conjunction with Fluconazole Reduce Symptoms Among Patients Suffering from Vulvovaginal Candidiasis?" (2018). *PCOM Physician Assistant Studies Student Scholarship*. 331.
https://digitalcommons.pcom.edu/pa_systematic_reviews/331

This Selective Evidence-Based Medicine Review is brought to you for free and open access by the Student Dissertations, Theses and Papers at DigitalCommons@PCOM. It has been accepted for inclusion in PCOM Physician Assistant Studies Student Scholarship by an authorized administrator of DigitalCommons@PCOM. For more information, please contact library@pcom.edu.

Do Oral Probiotics in Conjunction with Fluconazole Reduce Symptoms Among Patients Suffering from Vulvovaginal Candidiasis?

Kayla McDaid, PA-S

A SELECTIVE EVIDENCED BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements For

The Degree of Master of Science

In

Health Sciences- Physician Assistant

Department of Physician Assistant Studies
Philadelphia College of Osteopathic Medicine
Philadelphia, Pennsylvania

June 13, 2018

ABSTRACT

Objective: The objective of this selective EBM review is to determine whether or not “Do oral probiotics in conjunction with fluconazole reduce symptoms among patients suffering from vulvovaginal candidiasis (VVC)?”

Study design: Systematic review of three randomized controlled trials published in 2009 and 2012.

Data sources: Three randomized controlled trials published in peer-reviewed journals comparing the effects of fluconazole in conjunction with probiotics in the treatment of VVC. Data sources found using Embase, EMBScost, and CINAHL

Outcomes measured: Outcomes were measured based on patients reporting of: decrease in dysuria symptoms at 5-7 days post treatment, resolution of abnormal odorless cheese like vaginal discharge, dyspareunia, dysuria, and localized vulvovaginal irritation with VVC at 7 days post treatment, and decrease in vaginal discharges associated with at least one of the following (itching and burning vaginal feeling, dyspareunia and dysuria) at 4 weeks post treatment. All results were examined to determine whether or not oral probiotics in conjunction with fluconazole resulting in a significant difference in symptom reduction of VVC.

Results: In both Nouraei et al. and Martinez et al., oral probiotics in conjunction with fluconazole showed a statistically significant difference and proved to be an effective treatment in reducing the symptoms associated with VVC ($p= 0.02$ and 0.03 respectively). Due to issue faced by the study design in the RCT by Anukam et al., a statistically significant difference was unable to be found when determining a reduction of VVC symptom ($p=0.28$).

Conclusions: Results of these RCT showed conflicting results. While both Nouraei et al. and Martinez et al. indicated that oral probiotics in conjunction with fluconazole was an effective treatment in the reduction of VVC symptoms Anukam et al. was unable to show a statistically significant difference due to loss of follow up. Further studies with more strict protocol and a larger sample size need to be explored in the future in order to reach more definitive answers.

Keywords: Vulvovaginal Candidiasis; Probiotics; Fluconazole

INTRODUCTION

Vulvovaginal candidiasis (VVC) is a vaginal infection caused by the overgrowth of naturally occurring *Candida* species due to a fluctuation in the normal environment and flora of the vagina.¹ Probiotics are supplements containing living microorganisms which are naturally found in the body.² It is thought that the use of these products may be beneficial in restoring the body's natural environment to base line. This systematic review evaluates three double blind, randomized, controlled trials comparing the efficacy of oral probiotic use in combination with fluconazole for the treatment of VVC in comparison to those being treated with fluconazole alone.

With the high incidence of VVC it is important that physician assistants have a firm understanding of this disorder and functional treatment methods to provide the best patient outcomes. Statistics show that 75% of women suffer from VVC at least once during their lives, 45% of those women experience VVC twice or more annually and 5% are diagnosed with chronic and recurrent infections.² Recurrent VVC is defined as ≥ 4 episodes of VVC in a 12 month period.³

Diagnosis and treatment of VVC in addition to the lost wages accrued by decreased work productivity resulted in a total cost of around \$1.8 billion in 1995 and rose to \$3.1 billion in 2014.⁴ While an exact estimate pertaining to VVC alone is not available, it has been determined that roughly 5 to 10 million office visits per year are attributed to vaginitis.⁵ With VVC being the second most common documented cause of vaginitis, after bacterial vaginosis,⁴ one can imagine this number is quite high.

There are several etiological variations of *Candida* which result in VVC. 80-90% of cases have been found to be due to *Candida albicans*, 5-15% are due to *Candida glabrata*,² and a small

percentage are due to *Candida tropicalis*.⁵ The overgrowth of these *Candida* species results in varying symptoms including: thick, white, vaginal discharge, vulvovaginal itching, burning, and dysuria.⁴

Standard treatment of symptomatic disease includes either oral medications or topical vaginal suppositories and creams. For women with infrequent VVC, over the counter preparations of miconazole or clotrimazole for 3-10 days are first line treatment.⁵ Although topical treatments have traditionally been first line treatment, they are slightly hindered by decreased compliance due to longer treatment courses and the discomfort caused by the manner in which they are absorbed.¹ Based on this, oral treatment with fluconazole 150 mg PO for 1 day⁵ is becoming increasingly more common. Azole antifungal medications have been proven to relieve symptoms and result in a negative culture in 80-90% of cases.¹ The use of oral probiotics in conjunction with traditional treatment methods, like fluconazole, may be used to reduce the symptoms associated with VVC and increase the effectiveness of antifungal treatment.

Researchers believe that VVC and its traditional forms of treatment may lead to a destruction of existing vaginal flora.^{2,4} This may result in prolonged symptoms and secondary opportunistic vaginal infections. Due to the known benefits of probiotics, it is thought that they may be quite valuable in the treatment of VVC. Previous studies have proven the benefit of intravaginal probiotic usage in the prevention of VVC and other vaginal infections by strengthening the natural vaginal flora.² *Lactobacillus* and *Bifidobacterium* are two prevalent microorganisms within the vaginal and are the focus of many probiotic treatments. Due to the high incidence of VVC and frequent use of traditional treatments, oral probiotics are being proposed as an adjunctive measure to treating VVC in a hope to improve the therapeutic efficacy.

OBJECTIVE

The objective of this selective EBM review is to determine whether or not “Do oral probiotics in conjunction with fluconazole reduce symptoms among patients suffering from vulvovaginal candidiasis (VVC)?”

METHODS

Three randomized, double blind, placebo controlled clinical trials with specific population, intervention, comparison, and outcomes were selected for this systematic review. All studies focused on a population of non-pregnant women diagnosed with symptomatic VVC. The intervention which was studied was the use of oral probiotics in combination with fluconazole in comparison to the use of a placebo pill in combination with fluconazole. These variants were used to measure the outcome of reduced symptoms associated with VVC.

All articles were published in English written peer-reviewed journals and found by myself using the Embase, EBSCOhost, and CINAHL databases. All studies were discovered using the keywords “vulvovaginal candidiasis”, “probiotics” and “fluconazole”. All studies were selected based on their relevance to the topic and whether or not they included patient oriented evidence that matters (POEMs). The inclusion criteria used for this review were RCTs published after 2007 that discussed the efficacy of oral probiotics in combination with fluconazole as a treatment method for VVC. Exclusion criteria included pregnant patients suffering from VVC as well as patients suffering from a combination of vaginal infections at the same time as a VVC infection. The statistical significance of the study outcomes were determined using relative benefit increase (RBI), absolute benefit increase (ABI), number needed to treat (NNT), number needed to harm (NNH) and p-value. The specific studies demographics and characteristics are outlined in Table 1.

TABLE 1: Demographics and characteristics of included studies

Study	Type	# Pts	Age (yrs)	Inclusion Criteria	Exclusion Criteria	W/ D	Intervention
Nouraei (2012) ²	RCT, double blind, placebo-controlled	102	18-40	<ul style="list-style-type: none"> ▪ women ages 18–40 ▪ married; in a monogamous relationship ▪ receiving clotrimazole without improvement ▪ positive KOH samples in culture ▪ diagnosed VVC with itching, cheesy vaginal discharge, dysuria, pH <4.5, dyspareunia, vulvar erythema, or vulvar edema 	<ul style="list-style-type: none"> ▪ pregnant, lactating, or menstruating ▪ using any vaginal medication, antibiotics, immunosuppressive drugs, or exogenous hormones during the 2 weeks prior to the study ▪ intercourse or vaginal douche in the previous 24 hr ▪ positive trichomonal or bacterial vaginosis infections ▪ known systemic disease 	12	Treatment of vulvovaginal candidiasis with a combination of fluconazole and oral Protexin for 10 days
Anukam (2009) ³	RCT, double blind, placebo-control	59	18-50	<ul style="list-style-type: none"> ▪ Women between 18-50 ▪ History of VVC with ≥3 episodes over the previous 12 months ▪ symptomatic at presentation 	<ul style="list-style-type: none"> ▪ Women with evidence of other urogenital infections ▪ pregnant women 	33	Lactobacillus rhamnosus GR-1 and Lactobacillus reuteri RC-14 with fluconazole treatment for 3 months
Martinez (2009) ⁴	RCT, double blinded, placebo-controlled	55	16-46	<ul style="list-style-type: none"> ▪ Women suffering from vaginal discharge associated itching and burning, dyspareunia or dysuria ▪ Positive Candida culture 	<ul style="list-style-type: none"> ▪ Pregnant or menstruating ▪ Positive for HIV, BV, or trichomoniasis ▪ Use of antibiotic/ anti-fungal agents within 2 weeks ▪ fluconazole allergy 		Fluconazole with two probiotic capsules (containing Lactobacillus rhamnosus GR-1 & Lactobacillus reuteri RC-14) for 4 weeks

OUTCOMES MEASURED

All selected RCT examined the effectiveness of oral probiotics in conjunction with fluconazole in the treatment of VVC by measuring a reduction in reported symptoms. This systematic review evaluates the outcomes that matter to patients in each RCT.

In all three RCT participants improvement was measuring based on patients subjective impression and their reporting of a decrease in symptoms.

Study outcomes in the RCT by Nouraei et al. were measured 5-7 days after the start of treatment based on patient reporting reduced dysuria associated with VVC when comparing the fluconazole + placebo group to the fluconazole + protexin group.

Anukam et al. focuses on the resolution of symptoms by day 7 of treatment through the use of a questionnaire which asked participants to log the day on which they obtained symptom relief. Symptoms in this study were defined as abnormal, odorless, vaginal discharge, dyspareunia, dysuria, and localized irritation or discomfort to the vulvovaginal area.

Martinez et al. measured resolution of vaginal discharge associated with at least one of the following symptoms: dyspareunia, dysuria and itching or burning vaginal sensation on day 28 of treatment based on patient report.

RESULTS

This systematic review examined three RCT comparing the effectiveness of oral probiotics in conjunction with fluconazole in the treatment of VVC. Each RCT studied non-pregnant women suffering from symptomatic VVC who had not been diagnosed with any other vaginal infection. Specific inclusion and exclusion criteria are outlined in Table 1. All three studies compared a placebo control to an oral probiotic group. The probiotic used in the RCT by

Nouraei et al. was protexin. Anukam et al. and Martinez et al. both used *Lactobacillus rhamnosus* GR-1 and *Lactobacillus reuteri* RC-14 as the probiotics treatment. All three studies contained dichotomous data that could be used to calculate RBI, ABI, and NNT.

In the RCT by Nouraei et al., 90 women who had been diagnosed with VVC were randomly assigned to either the fluconazole + placebo group (n= 45) or the fluconazole + protexin group (n= 45) to determine the effectiveness of oral probiotics in conjunction with fluconazole in the treatment of VVC symptoms. Patients received two 150 mg fluconazole and twenty placebo or protexin capsules, depending on their assigned group. Two protexin or placebo capsules were administered per day, one in the morning and one in the evening, after meals. Medications were distributed in a double-blinded manner. On days 5-7 after the start of treatment patients were reevaluated for cure rate. Of the expressed symptoms (itching, cheesy vaginal discharge, dysuria, dyspareunia, vulvar erythema and edema), a significant difference in the reduction of dysuria symptoms ($P = 0.02$) were found. The fluconazole-protexin combination proved to be more effective in the treatment of VVC associated dysuria than the fluconazole-placebo group. Relative benefit increase (RBI) was calculated to be 69.5% and absolute benefit increase (ABI) was calculated to be 33.2% (Table 2). Numbers needed to treat (NNT) was calculated to be 4 (Table 2), meaning that for every 4 patients with VVC who were treated with fluconazole in combination with Protexin, 1 more will have a resolution in dysuria symptoms than the control group. All patients who entered into the study successfully completed all treatments and none were lost to follow up. While the majority of patients reported no adverse drug reactions, 6.7% of the fluconazole + placebo group reported nausea associated with their treatment.² Number needed to harm (NNH) was calculated to be -15, meaning that for every 15

patients treated with fluconazole + Protexin, one fewer patients will have side effects than compared to the control group (Table 3).

In the study by Anukam et al., 59 women who had been diagnosed with acute VVC were randomized into two groups based on age and previous history of VVC. One group received fluconazole + placebo (n= 20) and the remaining received fluconazole + *L. rhamnosus* GR-1 and *L. reuteri* RC-14 (n= 39) to determine to effectiveness of oral probiotics in combination with fluconazole in the treatment of VVC symptoms. Patients received one 150mg oral dose of fluconazole plus either a daily placebo capsule or a daily probiotic capsule consisting of 5 billion *L. rhamnosus* GR-1 and *L. reuteri* RC-14 live organisms depending on their treatment group.³ Treatments were distributed in a double blinded manner for 3 months. Patients were reassessed at day 7 to document proof of cure and continued to follow up at 1 month, 2 months, and 3 months to assess their status. At each visit symptoms and cure rate were assessed based on patient answered questionnaires, which focused on the day the patient felt as though they obtained relief of symptoms (day 1 to day 7) and report of any side effects or recurrent infections during the 90 day study period, as well as 2 vaginal swabs that were tested for yeast microscopically and by culture. The final vaginal swabs, taken at 3 months, were further assessed using bacterial and fungal DNA extraction and species specific primers for PCR.

The results of this study were severely hindered by a lack of full compliance by the subjects. At the conclusion of the study 56% of patients were lost to follow up. Of the original 59 patients, 47 reported on day 7 (33 in the probiotic group and 14 in the placebo) and only 26 patients returned on day 30 and 90 (19 in the probiotic group and 7 in the placebo group). All results were calculated using the data collected on day 7 from the patients who remained in the study on day 90. Unfortunately, due to challenges faced by the study design, the research was

unable to show a significant reduction of symptoms between the placebo and probiotic group. On day 7 of the study 47% of the probiotic group reported a resolution of symptoms as compared to 14% of the placebo group³ ($p=0.2794$). The data demonstrated a relative benefit increase (RBI) of 231.5% and an absolute benefit increase of 33.1% (Table 2). The number needed to treat (NNT) was 4, meaning that 4 patients needed to be treated with fluconazole + *L. rhamnosus* GR-1 and *L. reuteri* RC-14 in order for 1 more patient to experience a resolution of VVC symptoms (Table 2).

Of the patients who followed up for the extent of the study, few reported side effects of treatment. While the reported symptoms could not be directly correlated to the treatments, a few patients in each group reported a single episode of headache and nausea during the 90 day treatment window.³ Because the exact number of patients who reported side effects was not disclosed, a number needed to harm (NNH) statistic could not be calculated.

In the study Martinez et al., 55 women who had been diagnosed with VVC by a positive *Candida* culture were randomly divided into two groups, the fluconazole + placebo ($n= 26$) and the fluconazole + *L. rhamnosus* GR-1 and *L. reuteri* RC-14 ($n=29$), to determine to effectiveness of oral probiotics in combination with fluconazole in decreasing the symptoms associated with VVC. Participants received a single 150mg dose of fluconazole plus either 2 capsules of *L. rhamnosus* GR-1 and *L. reuteri* RC-14 (each capsule containing 1×10^9 viable cells⁴) or 2 placebo pills, depending on their treatment group. Treatments were distributed every morning in a double blinded manner for 28 days. Patients were reassessed at day 28 based on patient report of symptom resolution. A statistically significant difference was seen between the two groups; 26 patients in the probiotic group ($n= 29$) reported resolution of vaginal discharge and at least one symptom (itching, burning, dyspareunia, and dysuria) where as only 17 on the control group

(n=26) reported a resolution of symptoms⁴ (p= 0.03). The dichotomous data in this study displays a relative benefit increase (RBI) of 37.2% and an absolute benefit increase (ABI) of 24.3% (Table 2). The number needed to treat (NNT) was found to be 5 (Table 2), meaning that 5 patients with VVC need to be treated with Fluconazole + *L. rhamnosus* GR-1 and *L. reuteri* RC-14 in order for 1 to have a relief from symptoms.

While side effects could not be directly correlated to any treatment methods within the study, two subjects in the fluconazole- probiotic group reported an increase in appetite, one reported a single episode of light stool and another reported one headache during treatment.⁴ Based on reported side effected the number needed to harm (NNH) is 8, meaning that for every 8 patients treated with Fluconazole + *L. rhamnosus* GR-1 and *L. reuteri* RC-14 , 1 more will experience an adverse reaction than compared to the control group(See Table 3).

TABLE 2: Treatment effects

RCT	RBI	ABI	NNT	p-value
Nouraei (2012)	69.5%	33.2%	4	0.02
Anukam (2009)	231.5%	33.1%	4	0.28
Martinez (2009)	37.2%	24.3%	5	0.03

TABLE 3: Side effects

RCT	CER	EER	RRI	ARI	Probiotic vs. Control	NNH
Nouraei (2012)	6.7%	0.0%	-1	-6.7	Control group	-15
Martinez (2009)	0.0%	13.8%	Error	13.8%	Probiotic group	8

DISCUSSION

Traditionally VVC has been treated with oral azoles. However, recent studies have shown that the addition of probiotics to treatment regimens may prove to be quite useful. Probiotics are live microorganisms which are similar to those naturally found in the human body, and therefore thought to be beneficial to human health.² Lactobacilli species, such as *L. rhamnosus* and *L.*

reuteri, can found within vaginal flora.² Studies show that these probiotics play an important role in suppressing potential vaginal pathogen.²

The studies in this systematic review analyze probiotic use in combination with fluconazole in the treatment of VVC. Results were deemed significant based on symptom reduction in the probiotic group when compared to the placebo group if the p value was shown to be ≤ 0.05 . While two studies proved to have significant results, the study by Anukam et al. was significant hindered by loss to follow up. After a 37% reduction in patient follow up at day 7, and further reduction of 56% at day 90, the sample size proved too small to provide statistically significant results limiting the validity of this study.

Although some studies have shown probiotics to hold significant benefit in certain health conditions this has not been evaluated by the FDA and is therefore has not been approved as a treatment in any disease.⁶

Due to the lack of FDA recognition, little research has been done regarding the side effects and warnings associated with probiotics. As of now it is believed that they are relatively harmless to healthy individuals and that the majority of patients do not suffer any side effects associated with usage. But because little is known about the actual affects of probiotics it is suggested that immunocompromised patients refrained from using probiotics.⁶

Because probiotics are not considered a treatment for disease approved by the FDA, few health insurance plans are willing to cover the cost. Fortunately probiotics are relatively inexpensive, averaging around \$20 per bottle. Traditional fluconazole treatment tends to be rather inexpensive as well, ranging from \$4-12 on average.⁷ The low costs of these products make treatment much more accessible to patients.

CONCLUSION

Although the majority of the studies in this systematic review supported the proposed hypothesis, the study by Anukam et al. was severely hindered by patient compliance and loss to follow up. Due to personal hardships faced by these patients in their home country of Nigeria, it proved difficult for this population to follow through with the study. The study suggested that patients lacked a great understanding of the condition and the purpose of the study. For significant results to be determined it is essential that larger studies with strict protocols and extensive patient education be conducted in an attempt to prevent such poor results. Because of this, it is necessary to say that results were inconclusive as to whether or not oral probiotics in conjunction with fluconazole reduce symptoms among patients suffering from vulvovaginal candidiasis.

Future study is warranted to test a wider variety of oral probiotics and determine their effect in treating the symptoms of VVC. While all probiotics work in a similar manner, it is important to clarify the treatment outcomes of each probiotic strain so that it is not assumed all hold the same efficacy in VVC symptom reduction.

With the expansion of the medical field and the need for new treatments to battle the rising rate of drug resistance it is likely that this topic will be further explored in future studies

REFERENCES

1. Vaginal Candidiasis. Centers for Disease Control and Prevention.
<https://www.cdc.gov/fungal/diseases/candidiasis/genital/index.html>. Published August 4, 2017.
Accessed September 29, 2017.
2. Nouraei S, Amir Ali Akbari S, Jorjani M, et al.. Comparison between fluconazole with oral protexin combination and fluconazole in the treatment of vulvovaginal candidiasis. *ISRN Obstetrics and Gynecology*. 2012;1-10.
3. Anukam KC, Duru MU, Eze CC, et al.. Oral use of probiotics as an adjunctive therapy to fluconazole in the treatment of yeast vaginitis: A study of nigerian women in an outdoor clinic. *Microbial Ecology in Health & Disease*. 2009;21(2):72-77.
4. Martinez RC, Franceschini SA, Patta MC, et al.. Improved treatment of vulvovaginal candidiasis with fluconazole plus probiotic lactobacillus rhamnosus GR-1 and lactobacillus reuteri RC-14. *Letters in Applied Microbiology*. 2009;48(3):269-274.
5. Carr PL, Felsenstein D, Friedman RH. Evaluation and Management of Vaginitis. *Journal of General Internal Medicine*. 1998;13(5):335-346. doi:10.1046/j.1525-1497.1998.00101.x.
6. 5 Things To Know About Probiotics. National Center for Complementary and Integrative Health. <https://nccih.nih.gov/health/tips/probiotics>. Published September 24, 2015. Accessed December 10, 2017.
7. Fluconazole Prices. GoodRx. <https://www.goodrx.com/fluconazole?drug-name=fluconazole>. Accessed December 13, 2017