

## Excessive Antibiotic Use in Men with Prostatitis

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### ABSTRACT

**BACKGROUND:** Prostatitis accounts for 2 million outpatient visits annually. The majority of prostatitis cases fit the definition of chronic pelvic pain syndrome, for which routine antibiotic use is not indicated.

**METHODS:** Inpatient, outpatient, and pharmacy datasets from the Veterans Health Administration were used to quantify the magnitude of antibiotic use attributable to chronic pelvic pain syndrome. Specifically, men with a diagnosis of infectious/acute prostatitis or a urinary tract infection were excluded, and the remaining men with a diagnosis of prostatitis were defined as having chronic pelvic pain syndrome.

**RESULTS:** The annual prevalence of chronic pelvic pain syndrome was 0.5%. Prescriptions for fluoroquinolone antibiotics were filled in 49% of men with a diagnosis of chronic pelvic pain syndrome compared with 5% in men without chronic pelvic pain syndrome. Men with chronic pelvic pain syndrome were more than 7 times more likely to receive a fluoroquinolone prescription independently of age, race/ethnicity, and comorbid conditions. Increased use of other antibiotics also was observed. High use was similar in men with either infectious/acute prostatitis or chronic pelvic pain syndrome.

**CONCLUSION:** Despite evidence that antibiotics are not effective in the majority of men with chronic pelvic pain syndrome, they were prescribed in 69% of men with this diagnosis. Some increased use is probably due to uncontrolled confounding by comorbid conditions or inaccurate diagnostic coding. However, a 7-fold higher rate of fluoroquinolone usage suggests that strategies to reduce unnecessary antibiotic use in men with prostatitis are warranted.

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**KEYWORDS:** Antibiotics; Drug utilization; Male; Prostatitis

Prostatitis refers to several clinical syndromes and has been categorized in 4 types: acute bacterial infection, chronic

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bacterial infection, poorly defined chronic pelvic pain syndrome, and asymptomatic prostate inflammation.<sup>1</sup> Acute and chronic bacterial prostatitis account for approximately 5% to 10% of all cases of prostatitis.<sup>2</sup> Both are clearly associated with bacterial infection (often recurrent) and a urine culture that grows uropathogens. However, most men diagnosed with prostatitis have pelvic pain without evidence of infection.

Because antibiotics are not effective for treatment of abacterial chronic prostatitis, their use should be limited to individuals with confirmed positive cultures on expressed prostatic fluid or associated urinary tract infection.<sup>3</sup> Recent efforts have been made to disseminate this information and implement appropriate antibiotic prescribing for several common conditions, including prostatitis.

In the United States, chronic pelvic pain syndrome accounts for the majority of all prostatitis diagnoses, totaling almost 2 million outpatient visits and 1% of primary care visits annually.<sup>4</sup> Associated symptoms are common, bothersome, and burdensome in terms of health-related quality of life<sup>5,6</sup> and economic costs.<sup>7</sup> Because there are no reliable physical or laboratory findings, diagnosis of chronic pelvic pain syndrome is based on the exclusion of other causes, particularly infection.

Although fluoroquinolones are a Food and Drug Administration-approved treatment for prostate infections,<sup>8</sup> the majority of prostatitis cases are not infectious but instead comprise a syndrome of chronic pelvic pain.<sup>2,4</sup> The cause of this condition is unclear, but a systematic review<sup>9</sup> and subsequent randomized trials<sup>10,11</sup> of the efficacy of treatments have demonstrated that routine antibiotics, including fluoroquinolones, are not effective. Furthermore, previous research has found that, after excluding men with urinary tract infection, diagnosed cases of chronic pelvic pain syndrome have similar detection rates for uropathogenic and non-uropathogenic bacterial species when compared with asymptomatic controls.<sup>12</sup> Fluoroquinolone use has substantially increased during the past decade, driven by the increasing use of newer broader-spectrum fluoroquinolones.<sup>8,13</sup> In 2002, fluoroquinolones accounted for 24% of all antibiotics prescribed, and family practice doctors, internal medicine providers and urologists accounted for 31%, 21%, and 10% of all fluoroquinolones, respectively.<sup>8</sup> Overuse of antibiotics is a serious public health issue leading to antimicrobial drug resistance, drug-related adverse effects, and increased costs of medication.<sup>13</sup>

To estimate antibiotic use, the current study uses data from male veterans receiving care at the Veterans Health Administration (VHA) between 1999 and 2003 to calculate the increased likelihood of antibiotic use, particularly fluoroquinolones, for the treatment of chronic pelvic pain syndrome.

## MATERIALS AND METHODS

### Study Population

This study was conducted as part of the Urologic Diseases in America project, whose aim was to quantify the burden of urologic diseases.<sup>14-17</sup> The study population consisted of all male patients aged 18 years and more who used inpatient acute care or outpatient care in the VHA between 1999 and 2003. The institutional review boards of both the Minneap-

olis and Edward Hines Jr VA Hospitals approved the study, including a Health Insurance Portability and Accountability Act waiver of authorization.

### Data Collection

VHA Inpatient and Outpatient datasets and Pharmacy Benefits and Management files from October 1, 1998, to September 30, 2003, were merged to assess prostatitis prevalence and antibiotic use. The *International Classification of Diseases, 9th Version, Clinical Modification* (ICD-9-CM) diagnostic codes for inpatient and outpatient records were used to detect diagnoses of prostatitis and other potential confounding conditions. The majority of cases of prostatitis are not confirmed as either bacterial or abacterial, and there is no specific code for abacterial prostatitis. Therefore, men were defined as either having a diagnosis of "chronic pelvic pain syndrome" or "infectious/acute prostatitis." "Chronic pelvic pain syndrome" was defined by either the

ICD-9 codes for chronic prostatitis (601.1x) or prostatitis, unspecified (601.9x). "Infectious/acute prostatitis" was defined by the ICD-9 codes for "acute prostatitis" (601.0x), "abscess of prostate" (601.2x), "prostatocystitis" (601.3x), "prostatitis in diseases classified elsewhere, actinomycosis, blastomycosis, syphilis, tuberculosis" (601.4x), or "other specified inflammatory diseases of prostate, prostatitis: cavitory, diverticular, granulomatous" (601.8x). To further identify men with chronic prostatitis unlikely to benefit from antibiotics, men with any diagnosis of urinary tract infection in the same fiscal year were excluded.

Medication data were obtained from the Pharmacy Benefits and Management national database Version 3.0. The database for this project contains information from the time frame defined. For the current project, unique patient counts were determined for specific antibiotics frequently used for treatment of bacterial prostatitis or urinary tract infections, including fluoroquinolones, cephalosporins, penicillins, sulfonamides, and tetracycline within the fiscal years 1999 to 2003. Patients were only counted once in each year.

In addition, diagnoses of the following conditions were used as comorbidities that might affect antibiotic use: cerebrovascular disease, cardiovascular disease, congestive heart failure, chronic lung disease, dementia, alcohol abuse, diabetes, and hypertension. ICD-9 codes used to define each condition can be obtained from the authors.

Age was categorized into 5 groups (<50, 50-59, 60-69, 70-79, and 80+ years). Race/ethnicity data were obtained

### CLINICAL SIGNIFICANCE

- Efforts have been made to reduce unnecessary antibiotic prescribing in several common conditions.
- Antibiotics are not effective for treatment of abacterial chronic prostatitis.
- The findings from this study indicate that antibiotic use is common in men with chronic abacterial prostatitis.
- Efforts to reduce inappropriate antibiotic use in men with abacterial prostatitis are needed and could decrease unnecessary and potentially harmful antibiotic prescribing in a large number of men.

from the VHA data and when missing were supplemented by those in the Medicare Denominator files. Details on the completeness and validity of the self-reported race/ethnicity data have been published for these data.<sup>18</sup>

### Statistical Analysis

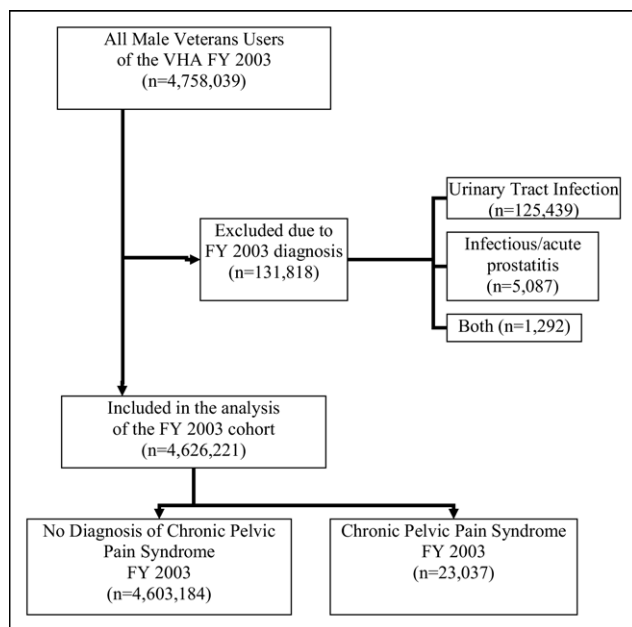
Comparisons of differences in age, race/ethnicity, number of comorbid conditions (0, 1, or ≥ 2), and prescription of any oral antibiotic or a specific prescription for a fluoroquinolone were calculated for men with and without a diagnosis consistent with chronic pelvic pain syndrome. For all of the primary analyses, men with a diagnosis of urinary tract infection were excluded from that year’s analysis. The association between chronic pelvic pain syndrome and fluoroquinolone use was calculated as a prevalence ratio (PR) adjusted for age, race/ethnicity, and number of comorbid conditions, using published log binomial regression methods.<sup>19</sup> Adjusted population attributable risks were then calculated from the adjusted PR and prevalence of chronic pelvic pain syndrome. The population attributable risk estimates the number of men with fluoroquinolone prescriptions who might be expected to have received prescription(s) for their chronic pelvic pain syndrome after accounting for age, race/ethnicity, and comorbidities. These methods were repeated to estimate the number of men with an antibiotic prescription other than fluoroquinolone.

Secondary analyses were conducted to assess the effect of excluding men with infectious/acute prostatitis from the analyses. The primary methods were repeated, and the magnitude of effect for infectious/acute prostatitis diagnosis on fluoroquinolone use was compared with that of chronic pelvic pain syndrome.

### RESULTS

In the entire cohort of 4,758,039 male users of the VA health care system during 2003, 6379 men (0.13%) had a diagnosis of infectious/acute prostatitis and 126,731 men (2.7%) had a diagnosis of urinary tract infection. The 131,818 men with a diagnosis of either infectious/acute prostatitis or urinary tract infection were excluded from all of the other results, leaving 4,626,221 men as the denominator. In 2003, 23,037 men (0.50%) had a diagnosis consistent with chronic pelvic pain syndrome, meaning they had a diagnosis of prostatitis with no corresponding diagnosis of either urinary tract infection or infectious/acute prostatitis (Figure). Distributions of diagnoses were similar in each of the 4 previous years (data not shown).

Chronic pelvic pain syndrome prevalence varied by age, number of comorbidities, and race/ethnicity. Men with chronic pelvic pain syndrome were substantially more likely to be prescribed an antibiotic, particularly a fluoroquinolone, during the same year as their diagnosis than men without chronic pelvic pain syndrome. Among men with a diagnosis of chronic pelvic pain syndrome in 2003, 49% received a prescription for a fluoroquinolone within the same year compared with only 5% of men without chronic



**Figure** Study patient flow chart for fiscal year 2003. A similar process of inclusion and exclusion was conducted for the years 1999 to 2002.

pelvic pain syndrome, despite the exclusion of men with infectious/acute prostatitis or urinary tract infection (Table 1). These associations were similar in each of the 4 previous years (data not shown).

In unadjusted models, men with chronic pelvic pain syndrome had a 10-fold higher prevalence of fluoroquinolone use (PR = 10.3; 95% confidence interval [CI], 10.1-10.4) in 2003. This association was attenuated only modestly by adjustment for age group, race/ethnicity, and number of comorbidities (PR = 7.9; 95% CI, 7.8-8.0). From 1999 to 2003, an estimated 32,562 men with a diagnosis of chronic pelvic pain syndrome received a fluoroquinolone attributable to their chronic pelvic pain syndrome diagnosis, even though they lacked a diagnosis of infectious/acute prostatitis or urinary tract infection during the corresponding year (Table 2). Although the adjusted percentage attributable risk for all fluoroquinolone use remained stable over time, ranging from 3.54% to 3.30% per year, the total number of men who were estimated to have been prescribed a fluoroquinolone to treat their chronic pelvic pain syndrome increased 50% from 5091 in 1999 to 7635 in 2003 because of the larger number of men receiving care at the VHA and the increased use of fluoroquinolones.

Men with a diagnosis of chronic pelvic pain syndrome were also more likely to have been prescribed other classes of antibiotics (PR = 3.57; 95% CI, 3.51-3.63) independently of age, race/ethnicity, and number of comorbid conditions (Table 3). During the 5-year period, we estimated 14,153 men were prescribed an antibiotic other than a fluoroquinolone to treat their chronic pelvic pain syndrome.

**Table 1** Fiscal Year 2003 Cohort Characteristics of Male Veterans Affairs Users Excluding Men with a Diagnosis of Infectious/Acute Prostatitis or Urinary Tract Infection

	Chronic Pelvic Pain Syndrome Diagnosis	
	Yes (n = 23,037)	No (n = 4,603,184)
Age, y (%)		
<50	11%	16%
50s	27%	24%
60s	28%	20%
70s	27%	28%
≥80	7%	12%
Race/ethnicity (%)		
White	61.8%	58.1%
Black	12.4%	9.4%
Hispanic	2.9%	2.1%
Other	1.0%	0.9%
Not reported	22.0%	29.4%
No. of comorbid conditions (%)		
0	24%	32%
1	35%	31%
≥2	41%	37%
Fluoroquinolone prescription (%)	49%	5%
Oral antibiotic prescription (%)	69%	14%

## Secondary Analysis Comparing Infectious/Acute Prostatitis with Chronic Pelvic Pain Syndrome

When we included all fiscal year 2003 male VHA users with a diagnosis of prostatitis (n = 34,003), regardless of whether or not it was infectious/acute, we found 28,124 men (0.6% of all VHA users who did not have a diagnosis of urinary tract infection) had at least 1 diagnosis of prostatitis during fiscal year 2003. Approximately 82% (n = 23,037) of these men with prostatitis met our diagnostic criteria for

chronic pelvic pain syndrome. The multivariable-adjusted PRs for fluoroquinolone prescriptions were similar in men with infectious/acute prostatitis and men with chronic pelvic pain syndrome (PRs of 8.60 and 8.66, respectively) compared with men with no prostatitis diagnosis. The observation was similar for all of the years (data not shown).

## DISCUSSION

The findings from this national clinical care database indicate that the majority of men diagnosed with prostatitis lack an appropriate indication for use of antibiotics. Despite this, most men with a diagnosis of prostatitis received an antibiotic, particularly fluoroquinolones. This high percentage of antibiotic use is considerably greater than in men of similar age, race/ethnicity, and number of comorbidities who lack a diagnosis of prostatitis. National Veterans Affairs administrative and clinical datasets do not specify the reason for an antibiotic prescription; therefore, some individual prescriptions may have been for coexisting conditions. However, it is unlikely that there would be a strong (>7-fold) and consistent association in men without urinary tract infection or infectious/acute prostatitis independently of age, race/ethnicity, or comorbidity status. Furthermore, the fact that men with a diagnosis consistent with chronic pelvic pain syndrome had similarly strong associations as men with a diagnosis of infectious/acute prostatitis supports the hypothesis that antibiotic treatment is not restricted to men with prostatitis and a confirmed bacterial infection.

Antibiotic overuse has been identified as 1 of 20 priority areas for improving health care quality.<sup>20</sup> Increased antibiotic use contributes to the development and spread of antibiotic-resistant bacteria. Once confined to the inpatient setting, resistant bacteria are now common community-acquired infections. The increasing prevalence of antibiotic resistant organisms is associated with morbidity and mortality and has led to more expensive and broad-spectrum empiric antibiotic prescribing. Although serious adverse effects are infrequent, nausea, vomiting, diarrhea, headache, dizziness, and skin rash are common and reduce quality of life. Therefore, reducing inappropriate use of antibiotics is a critical step in slowing the progression of current levels of

**Table 2** Association between Chronic Pelvic Pain Syndrome and Fluoroquinolone Use Among Veterans Affairs Users Excluding Men with a Diagnosis of Infectious/Acute Prostatitis or Urinary Tract Infection

Fiscal Year	Prevalence of Chronic Pelvic Pain Syndrome	Adjusted* Prevalence Ratio (95% CI)	Adjusted* PAR	Men with Prescription(s)	Attributable Men with Prescription(s)
2003	0.50%	7.86 (7.76-7.95)	3.30%	231,113	7635
2002	0.51%	7.72 (7.62-7.82)	3.30%	218,276	7214
2001	0.55%	7.29 (7.20-7.39)	3.36%	206,861	6948
2000	0.54%	7.21 (7.11-7.32)	3.24%	174,899	5674
1999	0.56%	7.54 (7.42-7.66)	3.54%	143,945	5091
					Total = 32,562

CI = confidence interval; PAR = population attributable risks.  
\*Adjusted for age, race/ethnicity, and number of comorbidities.

**Table 3** Association between Chronic Pelvic Pain Syndrome and Antibiotic Prescriptions Among Veterans Affairs Users Excluding Men with a Diagnosis of Infectious/Acute Prostatitis or Urinary Tract Infection and Excluding Men with a Fluoroquinolone Prescription

Fiscal Year	Prevalence of Chronic Pelvic Pain Syndrome	Adjusted* Prevalence Ratio (95% CI)	Adjusted* PAR	Men with Prescription(s)	Attributable Men with Prescription(s)
2003	0.27%	3.57 (3.51-3.63)	0.68%	412,693	2814
2002	0.28%	3.50 (3.45-3.56)	0.69%	417,411	2896
2001	0.31%	3.28 (3.23-3.33)	0.71%	426,074	3004
2000	0.31%	3.10 (3.06-3.14)	0.66%	427,677	2802
1999	0.34%	2.76 (2.73-2.79)	0.59%	448,646	2636
					Total = 14,153

CI = confidence interval; PAR = population attributable risks.  
 \*Adjusted for age, race/ethnicity, and number of comorbidities.

resistance, preventing the emergence of new strains of antibiotic-resistant bacteria, and improving quality/cost-effective care.

A recent report by the Agency for Healthcare Research and Quality reviewed strategies to improve antibiotic prescribing behavior.<sup>21</sup> Quality improvement strategies were found moderately effective at reducing inappropriate antibiotic prescribing. Although no single quality improvement strategy was clearly superior, active clinician education may be more effective in certain settings. The report by the Agency for Healthcare Research and Quality focused on acute respiratory tract infections. No previous work has been done on trying to improve antibiotic prescribing behavior in men with chronic pelvic pain syndrome. However, our results highlight the importance of this issue, particularly when considering that there is no reason to suppose that the level of inappropriate prescribing in the VHA would be any higher than in other health care facilities.

There are limitations for this study relating to the quantification of inappropriate antibiotic use. Some of the difficulties stem from the fact that fluoroquinolones are approved for the treatment of the small minority of men with bacterial prostatitis, and a specific diagnostic code to separate these patients from those with category III prostatitis or pelvic pain syndrome does not exist.<sup>2</sup> Therefore, although previous research leads us to believe that the majority of men defined in our study as having chronic pelvic pain syndrome did not have identified bacterial infections at rates greater than age-matched controls,<sup>12</sup> it is likely that some small portion of these men had positive bacterial cultures and were not diagnosed with a urinary tract infection or classified as having infectious/acute prostatitis. Efforts to modify the coding for prostatitis to include specific reference to whether or not a positive bacterial culture was obtained would improve future quality assurance measurements and possibly prescribing patterns. Our findings of similarly high rates of fluoroquinolone use in either the chronic pelvic pain syndrome group or infectious/acute group suggest that coding issues do not explain the majority of the association, and instead antibiotics are not being restricted to those with confirmed bacterial infections. Al-

though evidence from a consensus statement<sup>11,22</sup> and an observational study<sup>11,23</sup> have suggested that the use of antibiotics, particularly fluoroquinolones, may have some value in men who have never received antibiotic therapy for chronic pelvic pain syndrome, both of these articles stated that randomized controlled trials were needed to better address this issue. Two such trials have since been completed, and both found no effect beyond that of a placebo.<sup>10,11</sup> Although the lack of benefit could be because many trial participants received previous antibiotics, these trials did not provide stratified results in men with no previous antibiotic exposure. It is likely that many men in our study also had received previous antibiotic treatment. It was not possible within our summary data set to reliably estimate the proportion of men for whom antibiotics were being used the first time to treat their prostatitis. The current study also did not directly connect individual prescriptions to diagnoses at a specific clinical encounter and instead relied on statistical methods to connect an individual's annual antibiotic use with his diagnoses from the same year.

The VHA medical system is the largest fully integrated health care system in the United States,<sup>24</sup> and as such offers advantages in terms of size and completeness of medical and pharmacy data. Because of this, we believe that the results of this study are likely valid and generalizable to many other health care systems in the United States. Because the current study was part of a broad multiyear project to understand general trends in common urologic conditions, we did not attempt to conduct a detailed review of the men diagnosed with prostatitis to determine their history of diagnoses, laboratory findings, and detailed medication history. Future research projects could use more of the available medical record information to educate providers and evaluate and improve antibiotic-prescribing behaviors.

## CONCLUSIONS

Despite evidence that antibiotics are not effective in the majority of men with chronic pelvic pain syndrome, they were prescribed in 69% of men with this diagnosis even after excluding men diagnosed with infectious/acute pros-

tatitis or urinary tract infections. Some increased use is possibly the result of uncontrolled confounding by coexisting conditions or misclassification. However, the multivariable-adjusted 7-fold higher rate of fluoroquinolone use is likely the result of excessive prescribing in a population unlikely to benefit from treatment. Quality improvement strategies to reduce unnecessary antibiotic use in men with chronic prostatitis are warranted.

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