Published in final edited form as:
J Urol. 2013 April ; 189(4): 1415–1420. doi:10.1016/j.juro.2012.10.002.

Safety and Toxicity of Saw palmetto in the Complementary and Alternative Medicine for Urological Symptoms (CAMUS) Trial

Andrew L. Avins, M.D., M.P.H.[a,b], **Jeannette Y. Lee, Ph.D.**[c], **Catherine M. Meyers, M.D.**[d], and **Michael J. Barry, M.D.**[e] **For the Complementary and Alternative Medicine for Urologic Symptoms (CAMUS) Study Group**

[a]Northern California Kaiser-Permanente Division of Research, Oakland, CA

[b]Departments of Medicine and Epidemiology & Biostatistics, University of California, San Francisco, San Francisco, CA

[c]Department of Biostatistics, University of Arkansas for Medical Sciences, Little Rock, AR

[d]National Center for Complementary and Alternative Medicine, National Institutes of Health, Bethesda, MD

[e]General Medicine Division, Massachusetts General Hospital, Boston, MA

Abstract

Purpose—Extracts of the saw palmetto berry are used by many men in the U.S. as self-treatment for lower urinary tract symptoms due to benign prostatic hyperplasia. While the most recent data from double-blind clinical trials do not support efficacy superior to that of placebo, there are few data on the toxicity of saw palmetto.

Materials and Methods—369 patients were randomized in the Complementary and Alternative Medicine for Urological Symptoms (CAMUS) trial; 357 participants are included in this modified intention-to-treat analysis. Participants were randomized to 320mg, 640mg, and 960mg daily of an ethanolic saw palmetto extract or an identical-appearing placebo, in an escalating manner at 6-month intervals, for a total of 18 months follow-up. Adverse-event assessments, vital signs, and blood and urine laboratory tests were obtained at regular intervals.

Results—There were no statistically significant differences between groups in rates of serious or non-serious adverse events, changes in vital signs, digital prostate exam findings, or study withdrawal rates. Overall, there were no significant inter-group differences in the occurrence of laboratory-test abnormalities; differences in individual laboratory tests were uncommon and small in magnitude. No evidence of significant dose-response phenomena were identified.

Conclusions—The saw palmetto extract used in the CAMUS trial showed no evidence of toxicity at doses up to three times the usual clinical dose over a period of 18 months.

Keywords

Serenoa; Drug Toxicity; Phytotherapy

Author contact information: Andrew L. Avins, M.D., M.P.H., Northern California Kaiser-Permanente Division of Research, 2000 Broadway, 3rd Floor, Oakland, CA 94612, Tel: 510-891-3557, Fax: 510-891-3606, andrew.avins@ucsf.edu.

INTRODUCTION

Extracts of the saw palmetto (SP) berry have consistently ranked among the most commonly used dietary supplements in the United States [1]. They are taken primarily by men to treat lower urinary tract symptoms (LUTS), most frequently due to benign prostatic hyperplasia (BPH) [2,3]. Earlier clinical studies suggested that SP had modest efficacy for relieving LUTS [4,5], an assertion challenged by the Saw palmetto Treatment for Enlarged Prostates (STEP) trial, a single-center study that found no evidence of benefit of SP, at a dose of 160mg twice daily, for any subjective or objective outcome [6]. Importantly, the STEP study also found no evidence of toxicity associated with this typical dose of the extract over the one-year study period [7].

In order to help resolve the inconsistency of the reported findings and address the issue of dose-response, the National Institutes of Health initiated a multicenter, dose-ranging double-blind clinical trial of SP for men with LUTS [8]. Doses up to three times that employed in the STEP trial were used in a graduated manner over an 18-month period, providing a unique opportunity to assess potential SP toxicity under more challenging clinical conditions. This study, the Complementary and Alternative Medicine for Urinary Symptoms (CAMUS) trial (clinicaltrails.gov #NCT00603304) again found no evidence of benefit of SP over placebo for any outcome [9].

Though the efficacy results from these two studies suggest that SP is not superior to placebo, many men who perceive benefit from the supplement will likely continue to take it, despite these negative studies [10]. Therefore, it remains important to better define any potential toxicities associated with its use. We report here the adverse-event data from the CAMUS trial with an emphasis on dose-related observations.

MATERIALS AND METHODS

The design of the CAMUS trial has been described previously [8,9]. Briefly, eligible men were ≥45 years old, had an American Urological Association Symptom Index (AUASI [11]) score between 8 and 24, with a peak urinary flow rate ≥4 mL/s with a voided volume ≥125 mL. Between June 2008 and May 2009, 369 men were randomized at 11 centers in the U.S. and Canada, of whom 357 are included in this modified intention-to-treat analytic sample (12 participants did not take any doses of study medication and/or did not have at least one follow-up visit).

Men randomized to active therapy took one 320mg gelcap of SP daily for the first 24 weeks (weeks 1–24), two gelcaps for the second 24 weeks (weeks 25–48), then three gelcaps for the third 24-week period (weeks 49–72). Placebo participants received the same escalating number of identical-appearing placebo gelcaps. The primary outcome for the study was change in the AUASI; several secondary outcomes (both symptomatic and objective measures of urine flow and post-void residual volume) were also defined [8,9].

The active preparation used was an ethanolic extract of SP berries (*Serenoa repens* (W. Bartram) Small (Arecaceae)) manufactured by and supplied to the trial by Rottapharm/ Madaus (Cologne, Germany). This extract is sold commercially as PROSTA-URGENIN UNO and was standardized to a reference chromatogram with 85%–95% fatty acids. The placebo consisted primarily of polyethylene glycol.

Adverse-event assessments were conducted at 12-week intervals and at 4 weeks after the initiation of each dose increase. In addition to open-ended questions about adverse experiences, participants also completed questionnaires assessing erectile and ejaculatory function, continence, prostatitis, and sleep; vital signs were obtained at each clinic visit. In

this report, laboratory tests are generally reported dichotomously as normal or abnormal since these measurements were performed locally at each clinical site (with differing normal ranges) so these data could not be combined across sites on a continuous scale. For each laboratory test, Fisher's exact test was used to compare treatment groups with respect to the proportions of patients who had abnormal results at each dose level, and the Cochran-Mantel-Haenszel test was used to compare the treatment arms across dose levels with respect to the proportions with abnormal results. Prostate-specific antigen (PSA) levels were measured at baseline, 24, 48, and 72 weeks and a urinalysis was obtained at baseline and closeout. Serious and non-serious adverse events (as defined by the Food and Drug Administration (17)) were categorized by organ system.

All participants gave written informed consent; the study was approved by the institutional review boards of all clinical sites and the Data Coordinating Center at the University of Alabama, Birmingham.

For dichotomous outcomes measured only at baseline and closeout, inter-group differences were assessed with Fisher's Exact Test. For other outcomes with multiple measurements over the follow-up period, overall comparisons were conducted with generalized estimating equations (GEE) to assess the relationship between treatment groups over time, adjusting for intra-patient variation [12]. For adverse-event categories where at least 5% of study participants experienced an event, the proportions of study participants who experienced an adverse event were calculated by treatment arm and dose level and compared with GEE to assess the relationship between the frequency of adverse events with treatment arm and dose level, adjusting for intra-patient variation. A test for overall dose-response was also conducted for the total of all adverse events by treatment arm. No missing data were imputed. Analyses were conducted with SAS software, v9.2 [13]

RESULTS

The two treatment groups were well-matched at baseline (Table 1). Overall, 176 men were randomized to the SP arm and 181 men to placebo.

Serious Adverse Events

As previously reported, a total of 36 serious adverse events (SAEs) were identified among CAMUS participants, with 18 SAEs occurring in 17 participants in the SP group and 17 SAEs occurring in 17 participants in the placebo group ($p = 1.00$, two-sided Fisher's exact test) (the table from the main publication can be accessed at http://jama.jamanetwork.com/article.aspx?articleid=1104439 [9]). The most common category of serious adverse events in both groups was hospitalization for surgery or trauma (6 events in the active-treatment arm and 8 events in the placebo group).

No deaths occurred in either treatment group.

Non-Serious Adverse Events

As previously reported, 1006 non-serious adverse events (NSAEs) occurred among all CAMUS participants [9]. The most common NSAEs were minor gastrointestinal symptoms, genitourinary problems, musculoskeletal complaints, and upper respiratory tract infections. Overall, there was a slightly, but non-significantly, greater frequency of NSAEs among those participants randomized to the SP group, with an observed NSAE rate among the active-treatment group of 3.01 per participant vs. a rate of 2.63 among placebo-allocated participants ($p = 0.16$). Overall, 136 participants in the active-treatment group and 137 participants in the placebo group experienced at least 1 NSAE ($p = 0.80$).

Only 12 NSAEs (1.2%) were considered by the site investigator to be at least probably related to the blinded study intervention while 841 (83.6%) were considered unlikely to be related or definitely unrelated to the intervention. The remaining 153 events (15.2%) were considered possibly related to the study medication.

Laboratory Data

Extensive laboratory testing was conducted throughout the trial and few significant differences between treatment arms were detected (Table 2). Significant between-group differences were found for the hemoglobin level at the highest dose level, and for sodium at the lowest dose level. Across dose levels, the proportions of participants with abnormal hemoglobin levels was higher in the placebo arm than in the SP arm, and sodium abnormalities were reported more frequently in the SP arm, though the magnitude of the differences in both measurements were small (0.6 g/dL for the hemoglobin level and 0.5 mEq/dL for sodium). **It should be noted that these differences may not have achieved levels of statistical significance had adjustments been made for multiple comparisons.** No differences were detected with respect to urine dipstick levels at week 72 (Table 3).

Vital Signs

Assessments of systolic blood pressure, diastolic blood pressure, and heart rate showed small declines over the course of the study in both study groups (Figure 1). None of the inter-group tests of changes over time were significant.

Digital Prostate Exam

No evidence of an increased rate of palpable prostate abnormalities was observed and there were no significant inter-group differences (Table 4).

Discontinuation Rates

The CAMUS study experienced a low rate of study withdrawal. Overall, 335 of the originally randomized 369 participants completed the study (93.8% of the modified intention-to-treat subset and 90.8% of all randomized participants). While the crude discontinuation rate was slightly higher among participants in the active-treatment group (7.5% vs. 5.0%), this difference was not significant ($p = 0.39$, Table 5). Only 2 participants withdrew from the study for perceived adverse events and both of these were in the SP group. However, this inter-group difference was also non-significant ($p = 0.25$).

Dose-Response Data

Potentially important toxicities associated with higher doses of SP may be obscured by grouping response data for all three doses together. Therefore, we analyzed all NSAEs that occurred with a frequency ≥5% for evidence of dose-response phenomena in their frequency (Table 6). Only upper respiratory tract infections and oral/dental problems showed evidence of a significant dose-response relationship but for both of these NSAEs, the trend was toward a reduced frequency of events with increasing doses of study medication. An overall test of dose-related differences in the frequency of NSAEs was non-significant ($p > 0.2$).

Other Outcomes

As previously reported, there were no significant differences between treatment groups in changes over time for the International Index of Erectile Function, the Male Sexual Health Questionnaire - Ejaculatory Dysfunction Scale, the National Institutes of Health Chronic Prostatitis Symptom Index, the International Continence Society Male Incontinence Scale, and the Jenkins Sleep Dysfunction Scale [9].

DISCUSSION

Consistent with the results of the STEP study [7], the multicenter CAMUS trial found no evidence of important toxicity associated with higher-than-usual SP doses in a larger patient cohort with dose escalation and an 18-month period of product exposure.

While there was a higher rate of NSAEs among SP-allocated participants than in placebo-treated participants, the difference was not significant, and the absolute difference between the rates in the two study groups was small. The great majority of these NSAEs were not thought to be related to the study medication by the local site investigators. The rates of SAEs were nearly identical between the study groups. There were also few clinically important between-group differences in rates of laboratory abnormalities, as well as no differences in vital signs or palpable prostate abnormalities. Finally, overall and cause-specific withdrawal rates were low and not significantly different between the two study arms.

Taken together, the evidence from the two large NIH-funded clinical trials of SP are highly consistent in suggesting that, for periods up to 18 months, there are no serious safety concerns associated with use of this dietary supplement, even at a dose of nearly 1 gm/day, three times the typical dose. In addition, no other common or serious toxicity has been noted in any of the prior trials of SP, though most of these studies did not routinely report extensive data on safety and toxicity in a standardized manner [14]. Recent reviews of reported toxicities associated with the use of herbal supplements have generally concluded that SP appears to be relatively safe [3,14–17]. Importantly, these data, as well as additional published data, strongly suggest that SP does not alter PSA values [7,18].

While reassuring, these data do not preclude the occurrence of rare and potentially serious toxicities of SP, since such events would be too uncommon to be recognized in trials of this size. Indeed, there are a handful of case reports implicating SP in a disparate set of adverse events including hepatotoxicity [19], coagulopathy [20], pancreatitis [2122], and intraoperative floppy-iris syndrome [23]. However, the causal relationship between the use of SP and each of these adverse events is not firmly established for most of these, as these reports are complicated by concomitant use of other drugs or supplements, absence of re-challenge, and missing information about temporal relationships. Nonetheless, as with most herbal therapies, SP contains many organic compounds and individuals may be at risk for idiosyncratic toxicities. The potential for significant herb-drug interactions has been described for other widely used products, such as St. John's Wort, but has not been explored for most marketed supplements [24].

Reliable data on the safety of dietary supplements are critical since current U.S. regulatory policy permits distributing and marketing of supplements without governmental pre-market review of clinical data on safety and efficacy [25]. Despite lack of safety and efficacy data on dietary supplements, use of these products by the public is widespread, with regular use by approximately 20% of the public [1]. In view of extensive public use, large trials such as CAMUS provide much-needed safety data. Reports indicate that negative results of large trials of dietary supplements do impact product sales and patterns of use by the public [1,26,27]. It is also recognized that even when efficacy data demonstrate no clear superiority of a supplement over placebo, many people will continue to take these over-the-counter supplements because they perceive a benefit, despite the average null effect observed in the studies [10]. Hence, even if published data do not support the efficacy of a dietary supplement, many individuals will continue to self-medicate with these substances. Toxicity data remain vital for patients' informed decision making regarding how they manage their health care, as well as for healthcare providers in counseling patients.

While the CAMUS trial was the largest clinical study of SP that included detailed and repeated structured assessments of symptomatic adverse effects and asymptomatic physical and laboratory abnormalities, its limitations should be acknowledged. As noted above, the size of the trial was too small to rule out uncommon but potentially serious SP-related toxicity. While we examined a large set of laboratory tests, there are many more measurements which were not assessed that might have revealed unrecognized toxicity. Though our safety data (and those of the STEP study) are reassuring for those supplements used in these trials, they may not generalize to all other manufacturers or extraction techniques [28]. **We did not have analyses relevant to the issue of potential interactions between SP and prescription medications or other dietary supplements. We conducted a large number of statistical tests without adjustment for multiple comparisons and the potential for false positives must be considered.** Finally, the CAMUS trial lasted only 18 months and these results may not generalize well to longer time frames (a particular concern since men often use SP supplements for many years).

CONCLUSIONS

Our data suggest that SP is unlikely to be associated with important and common toxicity for a period up to 18 months. While the most recent clinical evidence does not support the superiority of SP over placebo, it appears that those men who elect to try the supplement are unlikely to suffer substantial adverse medical consequences from its short-term use. This information should help the many men who suffer from LUTS and their care providers make more informed and personally appropriate decisions for managing this common and bothersome condition.

Acknowledgments

This study was funded by cooperative agreements from the National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases: U01 DK63795, U01 DK63797, U01 DK63825, U01 DK63835, U01 DK63866, U01 DK63833, U01 DK63862, U01 DK63840, U01 DK63883, U01 DK63831, U01 DK63778 and U01 DK63788. Support was also provided by the National Center for Complementary and Alternative Medicine and the Office of Dietary Supplements, NIH. Saw palmetto extract and matching placebo were donated by Rottapharm/ Madaus, Cologne, Germany.

Glossary

AUASI	American Urological Association Symptom Index
BPH	Benign Prostatic Hyperplasia (BPH)
CAMUS	Complementary and Alternative Medicine for Urinary Symptoms trial
LUTS	Lower Urinary Tract Symptoms
NSAE	Non-Serious Adverse Event
PSA	Prostate Specific Antigen
SAE	Serious Adverse Event
SP	Saw palmetto
STEP	Saw palmetto Treatment for Enlarged Prostates (STEP) trial

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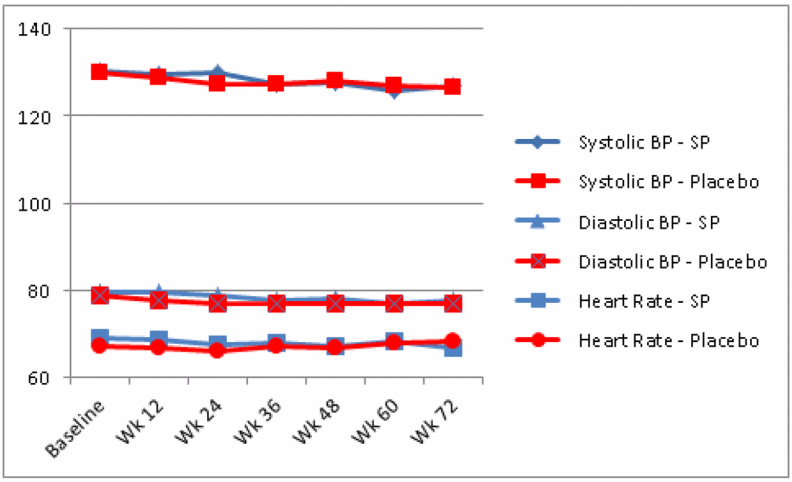

Figure 1.
Changes in vital signs among CAMUS participants, stratifed by treatment group

Table 1

Demographics of CAMUS study participants

Characteristic (units, [summary statistics])	Saw palmetto N = 176	Placebo N= 181
Categorical characteristics [N (%)]		
Age (years [N (%)])		
50–59 years	45 (40%)	42 (37%)
60–69 years	46 (41%)	48 (42%)
70–79 years	21 (18%)	23 (20%)
Race [N (%)]		
African-American	4 (4%)	8 (7%)
Asian or Pacific Islander	7 (6%)	8 (7%)
White	94 (84%)	89 (79%)
Hispanic	6 (5%)	5 (4%)
Other	1 (1%)	2 (2%)
Continuous characteristics [mean (SD)]		
American Urological Association Symptom Index (score)	15.7 (5.7)	15.0 (5.3)
Maximum urinary flow rate (ml/sec)	11.4 (3.5)	11.6 (4.3)
Post-void residual bladder volume (ml)	80.0 (51.9)	84.5 (63.8)
BPH Impact Index (score)	3.4 (2.2)	3.7 (2.8)
PSA (ng/ml)	2.2 (1.9)	2.3 (1.1)

Table 2

Proportion of study participants who had an abnormal lab test value by treatment arm and dose level

Lab Test	Dose Level	Saw palmetto (%)	Placebo (%)	*p*-value for comparing treatment arms at each dose level*	*p*-value for comparing treatments across dose levels**
Bicarbonate	1	14.9	14.5	1.00	0.19
	2	14.8	13.7	0.88	
	3	18.3	11.0	0.07	
Chloride	1	13.2	7.8	0.12	0.08
	2	11.2	7.4	0.27	
	3	10.4	9.9	1.00	
Creatinine	1	7.5	6.7	0.84	0.69
	2	8.3	7.4	0.84	
	3	7.9	7.6	1.00	
GGT	1	11.5	8.5	0.46	0.10
	2	10.2	8.6	0.71	
	3	12.2	7.6	0.20	
Glucose	1	35.1	38.0	0.58	0.14
	2	33.1	38.3	0.37	
	3	37.8	43.0	0.37	
Hemoglobin	1	12.7	19.4	0.11	0.001
	2	12.4	19.4	0.08	
	3	11.0	19.2	0.048	
Potassium	1	9.2	8.4	0.85	0.39
	2	8.3	8.0	1.00	
	3	7.3	4.1	0.24	
RBC	1	16.8	20.6	0.41	0.31
	2	18.9	20.6	0.79	
	3	17.8	19.8	0.68	
SGOT	1	11.3	7.9	0.35	0.84
	2	10.1	12.0	0.61	
	3	9.8	9.9	1.00	

Lab Test	Dose Level	Saw palmetto (%)	Placebo (%)	*p*-value for comparing treatment arms at each dose level*	*p*-value for comparing treatments across dose levels**
SGPT	1	13.2	11.0	0.61	0.46
	2	14.2	17.0	0.55	
	3	12.2	16.3	0.35	
Sodium	1	14.9	7.8	0.04	0.01
	2	13.6	8.0	0.12	
	3	9.8	8.1	0.70	
WBC	1	7.5	6.7	0.84	0.57
	2	4.1	5.7	0.62	
	3	6.8	8.7	0.55	

*Fisher's exact test

**Cochran-Mantel-Haenszel test

Table 3

Proportion of study participants who had abnormal* urine dipstick values at week 72

Urine Test	Saw palmetto (%)	Placebo (%)	*p*-value
Glucose	3.1	1.8	0.50
Blood	4.3	3.0	0.57
Ketones	1.8	2.4	1.00
Protein	3.7	5.3	0.60
Leukocyte esterase	1.23	0	0.24

* any abnormality (trace, 1+, 2+, 3+, or 4+)

Table 4

Prostate digital rectal exam findings*

	Baseline	Closeout	Change	*p*-value*
Nodules (%) [N(%)]				1.00
Saw Palmetto	0 (0%)	0 (0%)	0 (0%)	
Placebo	0 (0%)	0 (0%)	0 (0%)	
Asymmetry [N(%)]				1.00
Saw Palmetto	8 (4.6%)	5 (3.1%)	−3 (−1.5%)	
Placebo	12 (6.6%)	8 (4.7%)	−4 (−1.9%)	
Tenderness (%)				1.00
Saw Palmetto	2 (1.1%)	0 (0%)	−2 (−1.1%)	
Placebo	3 (1.7%)	1 (0.6%)	−2 (−1.1%)	

*p-values for comparison of saw palmetto vs. placebo groups by Fisher's exact test

Table 5

Discontinuation rates by treatment group and dose

Treatment Group	Single Dose	Double Dose	Triple Dose	Total	*p*-value*
Discontinuation for Any Reason [N (%)]					
Saw palmetto	4 (2.3%)	8 (4.6%)	1 (0.6%)	13 (7.5%)	0.39
Placebo	2 (1.1%)	6 (3.3%)	1 (0.6%)	9 (5.0%)	
Discontinuation for Adverse Event [N (%)]					
Saw palmetto	1 (0.6%)	1 (0.6%)	0 (0%)	2 (1.2%)	0.25
Placebo	0 (0%)	0 (0%)	0 (0%)	0 (0%)	

* *p*-value for comparison of Saw palmetto vs. placebo groups by Fisher's exact test

Table 6

Proportions of participants who experienced each category of adverse event by dose level *

Adverse Event	Saw palmetto (%)	Placebo (%)	*p*-value for drug	*p*-value (Double vs Single)**	*p*-value (Triple vs single)**
Arrhythmia			0.67	0.41	0.41
Single dose	2.3	2.2			
Double dose	1.1	1.7			
Triple dose	1.1	1.7			
Elevated blood pressure			0.10	0.20	0.12
Single dose	4.0	1.7			
Double dose	2.8	0			
Triple dose	0.6	1.7			
Upper respiratory infection			0.64	0.17	<0.001
Single dose	11.8	15.9			
Double dose	10.6	10.2			
Triple dose	6.3	6.0			
Flu-like symptoms			0.60	0.28	0.45
Single dose	4.5	3.3			
Double dose	3.4	1.7			
Triple dose	2.3	3.3			
Oral/dental			0.10	0.72	<0.001
Single dose	5.7	5.0			
Double dose	6.8	2.8			
Triple dose	1.7	0			
Musculoskeletal			0.44	0.28	0.41
Single dose	15.6	15.5			
Double dose	15.6	9.9			
Triple dose	13.4	13.0			
Genitourinary			0.90	0.98	0.78
Single dose	10.6	8.7			

Adverse Event	Saw palmetto (%)	Placebo (%)	*p*-value for drug	*p*-value (Double vs Single)**	*p*-value (Triple vs single)**
Double dose	9.5	9.7			
Triple dose	8.4	9.3			
Elevated PSA			0.81	0.65	0.35
Single dose	1.1	2.8			
Double dose	2.8	2.2			
Triple dose	4.0	2.2			
Gastrointestinal			0.69	0.72	0.09
Single dose	12.4	10.9			
Double dose	10.1	11.3			
Triple dose	6.2	9.3			
Dermatologic			0.30	0.73	0.56
Single dose	2.8	4.9			
Double dose	3.9	2.7			
Triple dose	2.8	6.6			
Physical injury/trauma			0.02	0.37	0.18
Single dose	4.0	1.1			
Double dose	5.1	2.2			
Triple dose	6.2	2.8			
Abnormal serum chemistry			0.66	0.69	0.07
Single dose	0	1.7			
Double dose	0.6	0.6			
Triple dose	4.5	1.7			

* Includes only those adverse events that occurred in at least 5% of study participants

** *p*-value for comparing dose levels across treatments and time adjusting for intra-patient variation using generalized estimating equations

J Urol. Author manuscript; available in PMC 2014 April 01.