

Transdermal estradiol for prostate cancer: how do patients compare it to other options for androgen deprivation therapy?

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Backgrounds: The PATCH/STAMPEDE trial [NCT00303784] in the UK has established that transdermal estradiol (tE2) offers equally effective cancer control for systemic prostate cancer (PCa) as standard androgen deprivation therapy (ADT) with luteinizing hormone-releasing hormone agonists alone or combined with androgen receptor pathway inhibitors. ADT with tE2 provides significantly better quality of life. However, there are no tE2 products specifically licensed for PCa patients and little evidence on whether PCa patients would be interested in using tE2 for ADT compared to other ADT options. Given that background, we used an online survey to explore PCa patients' reservations versus enthusiasm for tE2 as an option for ADT compared to standard ADT. We also assessed patient preferences for various forms of tE2 administration. The objective of this exploratory study was therefore to assess PCa patients' interest in and concerns about alternative forms of ADT.

Methods: From 13 March–26 May 2025, we conducted a cross-sectional online survey of men diagnosed with PCa, who were accrued via PCa support organizations in Canada and

the USA. The survey included both multiple-choice and an open-ended question.

Results: Eight hundred and twenty-seven PCa patients completed the survey: 45% from the USA, 41% from Canada, 14% from outside North America. Overall, interest in tE2 was high, with >95% of patients wanting tE2 to be a standard of care option for ADT in their country. In terms of positive versus negative comments on ADT, out of 86 comments on standard ADT, 80% were negative. In contrast, out of 23 comments on tE2, none was negative. The great majority (72%) of participants were willing to pay for tE2 off-label and even more (76%) said they would be willing to consult with more than one physician for an off-label prescription. The highest interest in tE2 came from PCa patients who have never been on ADT. Older patients had significantly less concern about gynecomastia, but this did not predict interest in tE2. About 2.8 times more men reported a preference for daily topical tE2 cream/gel products versus multiple tE2 patches changed twice a week.

Conclusions: Our survey establishes that men with PCa believe that tE2 products should be among the standard of care options for ADT and that tE2 side effects are more manageable than those of standard ADT drugs. For administering E2, patients preferred daily topical application of a gel or cream to wearing multiple patches.

Key Words: prostate cancer, transdermal estradiol, androgen deprivation therapy, quality of life

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Introduction

Increased PSA screening in recent decades has led to earlier detection of prostate cancer (PCa), and longer survival for PCa patients on androgen deprivation therapy (ADT). This has, in turn, brought to

the forefront concern about the adverse effects of the standard Luteinizing Hormone-Releasing Hormone (LHRH) agonists and antagonists used for ADT. The search for an ADT treatment with better quality of life (QoL) led to the PATCH/STAMPEDE trial [NCT00303784], which compared transdermal estradiol (tE2) against standard ADT therapies. That trial was a two-armed, head-to-head comparison of tE2 against standard ADT in men with advanced PCa, with overall survival as the primary outcome. The tE2 was administered via transdermal patches currently marketed for women to manage perimenopausal symptoms.

The PATCH/STAMPEDE trial established that tE2 provides as good survival as standard ADT for PCa patients with both MO and M1 disease, when used as monotherapy or when combined with androgen receptor pathway inhibitors (ARPIs).¹ Over the last 20 years, the options for androgen suppressing treatments have expanded, with the addition of LHRH antagonists. The side effect profiles of LHRH agonists and antagonists are largely the same. These include hot flashes, fatigue, metabolic syndrome, loss of sexual function and libido, increased risk of depression, sleep disturbance, and cognitive impairment.²⁻⁵ Prolonged use of ADT results in loss of bone mineral density and a resultant increased incidence of fractures.^{6,7}

Increasingly, ADT is combined with other therapies, including radiation therapy and ARPIs (i.e., enzalutamide, apalutamide, darolutamide and abiraterone).^{8,9} These combinations often provide better oncological control, although with greater adverse effects.¹⁰

To limit these side effects, intermittent ADT—in effect, a “drug holiday”—was assessed in a non-inferiority trial.¹¹ However, we know of no studies examining the impacts of multiple “ADT holidays” on long-term QoL. Full recovery of testosterone (T) back to baseline is rare when patients discontinue ADT after having been on ADT for a prolonged time.¹² Before the PATCH/STAMPEDE trial began, it was recognized that transdermal administration would reduce the thromboembolic risks associated with oral estrogens, such as diethylstilbestrol (DES). When ingested, estrogens are transported via the portal venous system directly to the liver, where clotting factors are up-regulated. When the estrogens are administered parenterally, the increased thromboembolic risk disappears.¹³

The present study was predicated on the well-known fact that many of the side effects of ADT are due to the loss of estradiol (E2), not the loss of T.¹⁴ In women at menopause, supplemental E2 can stop

hot flashes, improve sleep, protect cognitive function, and protect against osteoporosis.^{15,16} Even before the PATCH/STAMPEDE trial was completed, it was established that patients on the tE2 arm reported significantly better QoL than patients taking the standard ADT agents.¹⁷ Despite these positive results, there are currently no officially approved tE2 products for men with PCa in the USA or Canada. Our study is built upon the PATCH/STAMPEDE findings, and explores PCa patients’ interest in and concerns about alternative forms of ADT. We focus not only on the standard depot-injected LHRH agonists and antagonists, but also on the oral LHRH antagonist, relugolix, and on tE2 administered either via cutaneous patches (following the PATCH/STAMPEDE protocol) or via daily topical gels/creams. This survey study was exploratory in nature and was not intended to test a specific primary hypothesis. However, we tested several hypotheses that we thought might influence patients’ preference for one form versus another of ADT. Those hypotheses are detailed in Supplementary Material S1.

Materials and Methods

We used an online questionnaire directed at men diagnosed with PCa in Canada and the USA, although it was not closed to men in other countries. Qualtrics, Inc. survey software (<https://www.qualtrics.com/>) hosted our questionnaire. The survey queried patients’ interest in, and potential acceptance of, various ADT options (Supplementary Material S2). A range of questions explored patients’ attitudes toward various aspects of treatment with tE2, including potential drawbacks—such as the fact that tE2 for ADT is an off-label use. These questions address an array of specific hypotheses presented in a supplemental table (Supplementary Material S1). The research protocol, invitation to the survey, and questionnaire were assessed by the Institutional Review Board of Pearl IRB™ (www.pearlirb.com) and received official approval (Pearl IRB ID: 2025-0067).

Recruitment

Invitations to participate were targeted at PCa patients who were comfortable reading and writing in English. Emails were sent to several major non-profit PCa support organizations in Canada and the USA, in which it was requested that the invitation to our study be shared with their members. Snowball recruitment was encouraged. As a result, some patients from other countries discovered the survey and completed it. Participants were not required to

have had any PCa treatment history to be eligible. However, we sought participation from a range of patients; i.e., from those on active surveillance (AS) to those who had been exposed to multiple treatments for both localized and systemic disease.

To discourage false and multiple responding input, no compensation was provided; further, each participant could only complete the survey once per IP address.

Survey design & hypotheses

The invitation to participate linked to a “Consent to Participate” page, the completion of which opened the full survey. Informed consent was established when those who opened the survey completed the informed consent page and clicked through to the survey questions. The survey was active from 13 March to 26 May 2025, and took on average of 9.3 min to complete.

Throughout the survey, a conscious effort was made to present neutral information and to not bias the survey toward one treatment over another. In several sections, background text explained why certain questions were asked. In presenting information on the various treatments, we strove not to preemptively bias the survey for one treatment option over another. To minimize any influence, we narrowly adhered to risks (such as more blood tests) and benefits (such as improved QoL, lower osteoporosis risk) that were specific to that treatment versus the other options and confirmed in well-designed RCTs. While most questions were motivated by research hypotheses (listed in Supplementary Material S1), to avoid bias, the hypotheses were not explicitly stated in the survey proper.

The first section of the survey asked for the patient’s age and prostate cancer treatment history. One hypothesis was that younger patients and those who had never been on ADT (i.e., those on AS, or whose treatment had not included hormone therapy) might avoid tE2 because of its most conspicuous side effect, gynecomastia. Conversely, we hypothesized that older patients and those who had been previously on standard ADT, would be enthusiastic about tE2, given their experience with adverse ADT side effects.

The next section explored PCa patients’ comparative interest in various ADT treatments, in light of their side effects and QoL. The intent was to explore concerns that might limit patients’ interest in tE2 compared to standard ADT agents. The alternatives mentioned were tE2 patches, topical E2 gel/cream, and the oral LHRH antagonist, relugolix.

We hypothesized that twice-weekly administration of tE2 (i.e., following the PATCH protocol) or daily administration (i.e., oral relugolix or daily topical E2 products), might appeal to those with concerns about depot injections. Also, because fewer PSA blood tests are typically used when the ADT is delivered via longer term depot injections, we hypothesized that those who disliked blood draws would prefer the less-frequent depot injections vs. the more frequent blood draws associated with starting patients on tE2 and relugolix.

We next explored concerns about osteoporosis, which is a major adverse effect of ADT with LHRH agonists and antagonists. Although osteoporosis can’t be immediately sensed or observed like hot flashes or gynecomastia, it is directly associated with an elevated risk of fractures.⁷ A major benefit of tE2 compared to standard ADT is that it reduces the risk of osteoporosis and even increases net bone mineral density by ~8% after 2 years.¹⁸ Therefore, we hypothesized that patients with osteoporosis concerns would look more favourably on tE2 options.

We also inquired about patients’ preferences for tE2 delivery methods: patches versus topical gels and creams. The PATCH/STAMPEDE trial used 2–4 simultaneous patches to suppress T to castrate levels, with the requirement to change the patches twice per week. Daily administration of tE2 topical gels and creams can also achieve castrate levels of T. We hypothesized that the PATCH protocol might be perceived as cumbersome, compared to a daily topical gel or cream.

The next section included questions related to costs. tE2 products in North America are prescription drugs, and none are specifically licensed for men. For ADT use, they must be prescribed off-label, which typically requires out-of-pocket payment and negotiations between patients and their physicians. Therefore, the survey investigated patient willingness to seek off-label access and to personally pay for them.

We expected that in Canada, with its universal healthcare system, patients would be less willing to pay out-of-pocket for medications than Americans. We also hypothesized that higher self-reported income would be associated with a greater willingness to pay.

We also sought insight into how badly patients wanted access to tE2 options. To do so, we asked about the number of physicians patients might be willing to approach if they were first declined an off-label prescription.

The survey closed with standard socioeconomic questions. We expected to find that better-educated

individuals would be more open to using tE2, and that those in larger urban centres, who may have higher socio-economic status and access to more medical options, might show more interest in alternatives to standard ADT drugs.

We also included a question about the various sources of information that patients trusted most when it came to ADT. We were curious to know where patients learned about ADT, and whether their preferred sources influenced their potential interest in tE2. Because we do not expect uro-oncologists or medical oncologists to promote off-label use of tE2, we hypothesized a positive association between less reliance on medical professionals for information and higher interest in tE2.

Supplementary Material S1 provides a complete list of hypotheses and associated results. The survey ended with an open-ended question in which patients were asked, "Is there anything else you'd like to share about your views on alternative options for ADT?"

Statistical analysis

Data were analyzed using SPSS software (version 30.0, IBM Corp., Armonk, NY, USA). Patients' degree of interest in tE2 as an option for ADT was ranked from 1, highest interest to 4, lowest interest. For purposes of analyses, this variable was re-coded so 4 = highest interest, etc. Assumptions of normality were not met. This variable was thus treated as ordinal in subsequent analyses. Non-parametric tests were conducted to explore potential associations between interest in tE2 and other variables. Guided by our hypotheses, Kruskal-Wallis tests (categorical variables with >2 categories), Mann-Whitney U tests (binary variables), and Spearman Rank-Order Correlation (continuous variables) were run to test associations. Data are presented as Means (Standard Deviation, Range), with p -values specified in text and tables as $p < 0.05$ or $p < 0.001$.

Generally, all data were pooled for analyses; however, if a statistically significant effect was found, analyses were repeated to assess significance according to country/region (i.e., analyses were re-run among sub-samples from each country/region separately).

Comments from the final open-ended question were reviewed and sorted into four primary categories: (1) positive reflections about standard ADT; (2) negative reflections about standard ADT; (3) positive reflections about tE2; and (4) negative reflections about tE2. We had not specifically asked about orchiectomy, but in their comments two patients mentioned that they had undergone orchiectomies for ADT, and reflected on their experiences. After review

and discussion, subcategories were added to include positive and negative comments about both relugolix and orchiectomy.

Two authors independently reviewed all comments and conferred until all coding discrepancies were resolved.

Results

Participant demographics

While 909 males started the survey, 82 completed less than 5% of questions and were deleted from the data set, for a final sample size of 827. Most patients reported residing in the United States (45%, $n = 376$) or Canada (41%, $n = 339$). One hundred and twelve (14%) did not state a place of residence and were coded as "other". According to the qualitative comments, some of the "other" places of residence were the United Kingdom ($n = 5$), Australia ($n = 1$), Denmark ($n = 1$), Finland ($n = 1$), and Thailand ($n = 1$).

Most patients self-identified as white (93%, $n = 721$) and married (76%, $n = 589$), but there was more diversity in terms of age ($Mean = 71.60$, $SD = 8.19$, range = 44–99), education, income level, and PCa history (Table 1 & Supplementary Material S3).

Significant differences between Canadian, American, and non-North American participants were found for a number of variables (Tables 1–3). Canadian participants were slightly older ($Mean = 72.67$, $SD = 7.80$, range = 45–99) than American participants ($Mean = 70.61$, $SD = 8.28$, range = 44–93, $p < 0.001$).

Canadian and American participants also differed significantly in ethnicity, education level, and income level (all $p < 0.05$). Participants from Canada were more likely to live in an urban centre vs. those in the United States. A larger proportion of Canadians paid for their health care via government funding (86% of Canadians vs. 73% of Americans; $p < 0.001$) and out of pocket (33% of Canadians vs. 19% of Americans, $p < 0.001$). Interestingly, there were no significant differences in the number of participants from each country who cited private insurance as a method of payment (Table 1).

Medical backgrounds

More Canadians (55.8%, $n = 187$) than Americans (38.2%, $n = 143$) reported previous prostatectomy ($p < 0.001$), while more Americans (71.1%, $n = 266$) than Canadians (62.3%, $n = 210$) reported previous radiation therapy (Table 1). Similarly, more Americans reported having been on ADT (previous and/or current), with 76.3% of Americans ($n = 287$) and

TABLE 1. Sociodemographic characteristics and treatment history of participants

	USA (n = 376)		Canada (n = 339)		Outside of North America (n = 112)		All participants (n = 827)	
	Mean (SD)	Range	Mean (SD)	Range	Mean (SD)	Range	Mean (SD)	Range
Age (years)**	70.61 (8.28)	44–93	72.67 (7.80)	45–99	71.68 (8.66)	50–91	71.60 (8.19)	44–99
Age at diagnosis (years)¹	64.05 (7.86)	42–90	64.36 (7.63)	40–96	65.27 (9.12)	45–89	64.34 (8.00)	40–96
	Number (N)	Percent%	Number (N)	Percent %	Number (N)	Percent %	Number (N)	Percent%
Ethnicity*								
White	357	95.5	311	92.3	53	82.8	721	92.9
Black or African American	6	1.6	2	0.6	4	6.3	12	1.5
Asian	3	0.8	14	4.2	5	7.8	22	2.8
Other	8	2.1	10	3.0	2	3.1	21	2.7
Marital status								
Married	275	73.9	266	78.9	48	76.2	589	76.3
Widowed	7	1.9	13	3.9	2	3.2	22	2.8
Divorced	43	11.6	19	5.6	4	6.3	66	8.5
Separated	4	1.1	3	0.9	2	3.2	9	1.2
Never married	22	5.9	16	4.7	3	4.8	41	5.3
Partnered	16	4.3	17	5.0	3	4.8	36	4.7
Prefer not to answer	5	1.3	3	0.9	1	1.6	9	1.2
Highest level of education*								
Less than high school	0	0	5	1.5	1	1.6	6	0.8
High school graduate	13	3.5	21	6.2	5	7.9	39	5.0
Some college	43	11.5	66	19.6	6	9.5	115	14.9
2-year degree	22	5.9	42	12.5	7	11.1	71	9.2
4-year degree	124	33.2	78	23.1	13	20.6	215	27.8
Professional degree	136	36.4	105	31.2	30	47.6	271	35.0
Doctorate	36	9.6	20	5.9	1	1.6	57	7.4
Household income (USD) for last 12 months, before taxes⁴¹								
Less than \$25,000	8	2.2	9	2.7	4	6.8	21	2.7
\$25,000–\$50,000	37	9.9	31	9.3	9	15.3	77	10.1
\$50,000–\$75,000	37	9.9	39	11.6	10	16.9	86	11.2
\$75,000–\$100,000	51	13.7	64	19.1	6	10.2	121	15.8
\$100,000–\$125,000	44	11.8	47	14.0	10	16.9	101	13.2
\$125,000–\$150,000	35	9.4	28	8.4	6	10.2	69	9.0
More than \$150,000	91	24.5	52	15.5	6	10.2	149	19.5
Prefer not to answer	69	18.5	65	19.4	8	13.6	142	18.5
Country of residence								
United States	376	100.0	0	0	0	0	376	45.5
Canada	0	0	339	100	0	0	339	41.0
Other	0	0	0	0	112	100	112	13.5
Size of community of residence**								
Rural location (less than 1000 people)	28	7.5	18	5.4	5	8.3	51	6.6
Town (1000 to 30,000 people)	81	21.7	27	8.0	10	16.7	118	15.3
Small city (30,000–50,000 people)	60	16.0	24	7.1	7	11.7	91	11.8
Large city (Over 50,000 people)	205	54.8	267	79.5	38	63.3	510	66.2
Payment method for healthcare (select all that apply)								
Government funding (Public health insurance via Medicare in the USA or Provincial Healthcare in Canada)**2	276	73.4	293	86.4	55	49.1	624	75.5
Private insurance ²	161	42.8	148	43.7	16	14.3	325	39.3
Out of pocket**1	72	19.1	112	33.0	15	13.4	199	24.1
Currently on active surveillance for PCa								
Yes	25	6.6	24	7.1	3	2.8	52	6.3
No	351	93.4	314	92.9	105	97.2	770	93.1

(Continued)

TABLE 1. (Continued)

	USA (n = 376)		Canada (n = 339)		Outside of North America (n = 112)		All participants (n = 827)	
	Mean (SD)	Range	Mean (SD)	Range	Mean (SD)	Range	Mean (SD)	Range
Prostatectomy**								
Yes	143	38.2	187	55.8	40	37.4	370	45.3
No	231	61.8	148	44.2	67	62.6	446	54.7
Radiation therapy in the past*								
Yes	266	71.1	210	62.3	72	66.7	548	66.9
No	108	28.9	127	37.7	36	33.3	271	33.1
Androgen deprivation therapy (ADT) in the past*								
Yes	273	73.0	210	62.3	73	68.2	556	68.0
No	101	27.0	127	37.7	34	31.8	262	32.0
Currently on ADT*								
Yes	170	45.5	128	37.9	41	38.0	339	41.3
No	204	54.5	210	62.1	67	62.0	481	58.7
Ever on ADT (past/current)**								
Yes	287	76.3	220	64.9	75	68.8	582	70.6
No	89	23.7	119	35.1	34	31.2	242	29.4
Currently used ADT medication (pick one)**								
Leuprolide acetate (Lupron, Abbvie)	57	31.0	32	21.9	7	14.0	96	25.3
Leuprolide acetate (Eligard, Tolmar)	41	22.3	37	25.3	11	22.0	90	10.9
Goserelin (Zoladex, TerSera)	3	1.6	43	29.5	9	18.0	57	6.9
Triptorelin pamoate (Trelstar, Verity)	0	0	4	2.7	0	0	4	1.1
Degarelix	5	2.7	6	4.1	2	4.0	14	1.7
Relugolix (Orgovyx, Sumitomo)	51	27.7	4	2.7	10	20.0	65	17.1
Triptorelin (Decapeptyl, Ipsen)	0	0	1	0.7	1	2.0	2	0.5
Other ⁺	27	14.7	19	13.0	10	20.0	56	14.7
Chemotherapy in the past								
Yes	34	9.1	29	8.6	10	9.3	73	8.9
No	339	90.9	309	91.4	98	90.7	746	91.1
Currently on chemotherapy								
Yes	5	1.3	11	3.3	1	.9	17	2.1
No	367	98.7	326	96.7	108	99.1	801	97.9

Note. *Significant difference between Canadian and American participants ($p < 0.05$); **Significant difference between Canadian and American participants ($p < 0.001$); ¹Significant difference between North American and Non-North American participants ($p < 0.05$); ²Significant difference between North American and Non-North American participants ($p < 0.001$); + Participants provided written comments pertaining to the “Other” medication category. Responses included Abiraterone Acetate/Zytiga: $n = 13$; Bicalutamide/Casodex: $n = 4$; Enzalutamide/Xtandi: $n = 4$; Apalutamide/Erleada: $n = 3$; Darolutamide/Nubeqa: $n = 6$; Orchiectomy: $n = 3$; Estradiol/Estrogen: $n = 11$; USA: United States of America; ADT: Androgen Deprivation Therapy; USD: United States Dollar.

64.9% of Canadians ($n = 220$) reporting current/past ADT treatment.

We found that a subset of patients said they were on AS but also had a history of treatment with ADT. We reserved the “AS” category for those who had never received any active treatments. Thus, patients who indicated both AS and previous/current ADT use were recoded as “not on AS”.

Healthcare funding and willingness to pay for tE2

Here, we anticipated national differences between Canadians and Americans, as Canadians are covered by provincial healthcare. However, the differences in patients’ willingness to pay out of pocket for off-label tE2 products were small: 70.3% of Canadians ($n = 230$), 75.2% of Americans ($n = 276$), and 67.1% of non-North Americans ($n = 49$) reported willingness

TABLE 2. Sources of ADT-related information

	USA (n = 376)		Canada (n = 339)		Outside of North America (n = 112)		All participants (n = 827)	
	Number (N)	Percent%	Number (N)	Percent %	Number (N)	Percent%	Number (N)	Percent%
Trusted source of ADT-related information (choose 1–2)								
Scientific literature**1	185	49.2	117	34.5	36	32.1	338	40.9
Physicians ²	219	58.2	184	54.3	29	25.9	432	52.2
Webinars ¹	74	19.7	67	19.8	10	8.9	151	18.3
Online support groups**2	208	55.3	127	37.5	29	25.9	364	44.0
In-person support groups**1	38	10.1	95	28.0	10	8.9	143	17.3
Family or friends on ADT**1	17	4.5	39	11.5	6	5.4	62	7.5
Books (e.g., Androgen Deprivation Therapy: An Essential Guide)*	72	19.1	87	25.7	11	9.8	170	20.6

Note. *Significant difference between Canadian and American participants ($p < 0.05$); **Significant difference between Canadian and American participants ($p < 0.001$); ¹Significant difference between North American and Non-North American participants ($p < 0.05$); ²Significant difference between North American and Non-North American participants ($p < 0.001$); USA: United States of America; ADT: Androgen Deprivation Therapy.

TABLE 3. Summary of patients’ positive versus negative comments about different ADT options

	Total comments	Positive comments	Negative comments
Standard ADT depot injections	74	12 (16%)	62 (84%)
Oral relugolix	12	5 (42%)	7 (58%)
Transdermal estradiol (tE2)	23	23 (100%)+	0
Orchiectomy	2	2 (100%)	0

Note. +Of the 23 people who discussed tE2, 5 people mentioned a concern alongside something positive (e.g., hard to find a doctor to prescribe it). One person simply stated, “Have been unable to get tE2 from a local doctor.” There were no complaints about tE2. ADT: Androgen Deprivation Therapy.

to pay. There were, however, significant differences in the amounts they were willing to pay; more Americans than Canadians were willing to pay between \$35–\$70 USD per month ($p < 0.05$). Similar proportions of Canadians (13.6%) and Americans (14.0%) were willing to pay more than \$70 USD. Americans (83.7%, $n = 304$) were more likely than Canadians (68.0%, $n = 222$) to consult at least one other physician if initially denied off-label tE2 ($p < 0.001$). See [Figure 1](#) for pooled results.

North Americans differed from non-North American participants in their payment methods. Significantly fewer non-North Americans (49.1%, $n = 55$) reported government funding for healthcare,

compared to 73.4% ($n = 276$) in the United States and 86.4% ($n = 293$) in Canada. Similarly, fewer non-North Americans reported private insurance (14.3%, $n = 16$) and paying out-of-pocket (13.4%, $n = 15$) as their payment methods.

Support for tE2

Interest in using tE2 as an option for ADT was overwhelmingly positive, with 96.8% and 94.0% of Americans and Canadians, respectively, wanting some form of tE2 to be “approved as an option for ADT” in their country. Outside of North America, 90.8% also felt that tE2 should be an approved option for ADT in their country.

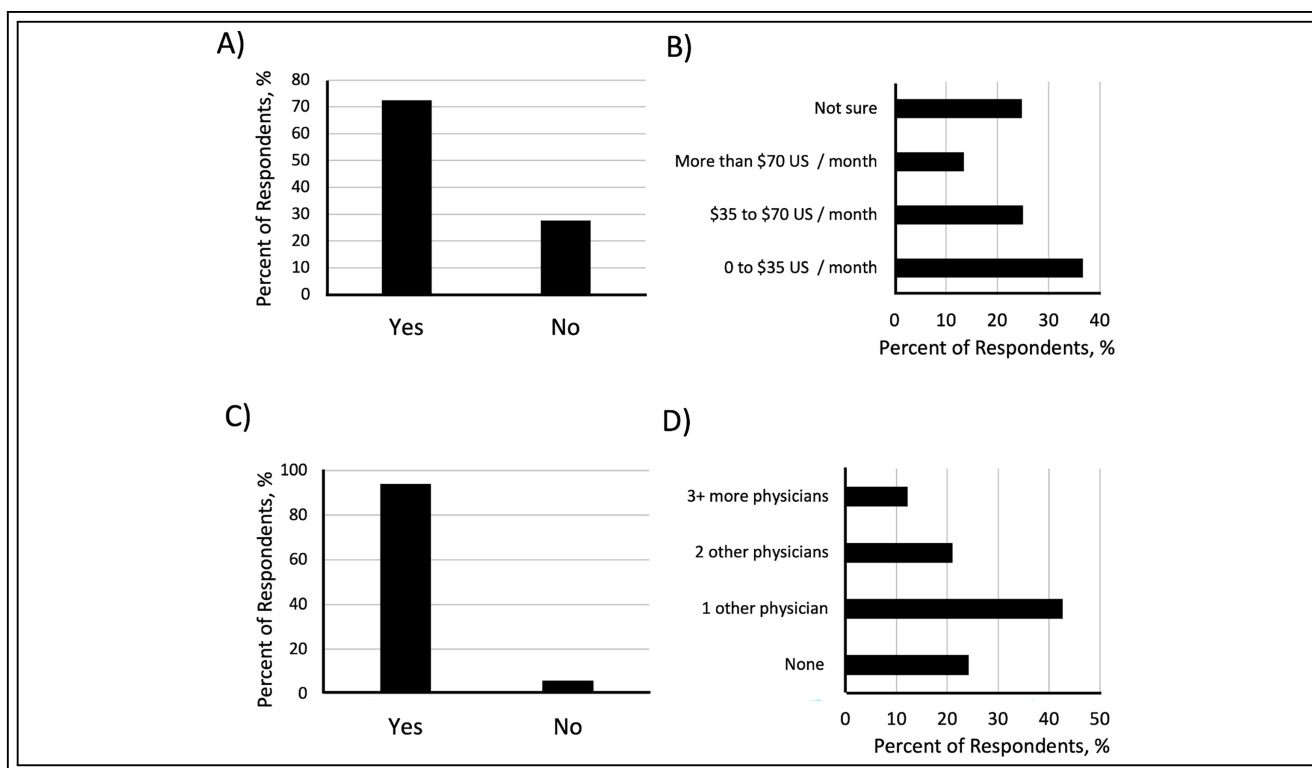


FIGURE 1. Respondents' willingness to pay out of pocket and to seek additional physicians for consult about tE2. (A) Willingness to pay out of pocket for tE2. (B) Amount willing to pay out of pocket for tE2. (C) Willingness to have more frequent blood tests. (D) Number of physicians willing to consult about tE2. tE2: transdermal estradiol

Does PCa history affect patient interest in tE2?

A central question in the survey was: How does PCa treatment history influence patient interest in having tE2 as a treatment option for ADT? Patients ranked their interest using a 1 to 4 Likert-scale, with 4 representing the lowest level of interest. We found a significant ($p < 0.05$) relationship, where the highest interest was among patients with no previous ADT experience. Similarly, higher interest in tE2 among current AS patients approached significance ($p = 0.095$). This level of interest may imply that patients with no previous experience of ADT were (1) worried about the plethora of side effects of the standard ADT agents, and (2) consequently interested in tE2 as an alternative.

When looking at current versus past use of traditional ADT, a significant association between ADT status and interest in tE2 was found only for those who reported past use of ADT ($p < 0.05$). Among current users of ADT, the relationship approached significance ($p = 0.080$). Preference rankings skewed toward higher interest in tE2 among those who had never been on ADT ($Mean = 2.84$, $SD = 1.20$) vs. those with previous exposure ($Mean = 2.58$, $SD = 1.15$).

Ranked interest in tE2 was higher among those not currently on ADT ($Mean = 2.73$, $SD = 1.19$) vs. those currently on ADT ($Mean = 2.53$, $SD = 1.14$). It may be the case that men currently on ADT were satisfied with treatment-induced reductions in PSA and thus less interested in alternatives. In contrast, men on AS may only have been able to speculate about potential effects, without the lived experience and reinforcement of treatment-related PSA reductions.

tE2 interest among patients experienced with other forms of ADT

Results also indicate that patients who preferred long-duration (3–6 months) depot injections with standard ADT agents had less interest in tE2 for ADT ($p < 0.001$). Contrary to the hypothesis that the adverse side effects of standard ADT might motivate patients to try tE2, this group showed a reluctance to change from their standard ADT treatments. Presumably this was because their current treatment was effective in cancer control, and they were willing to endure the side effects of standard ADT. This was further underscored by comments left by some patients,

who expressed a willingness to stay with their current treatment if it was successful in controlling their cancer.

The survey explored patients' interest in degarelix, the fast-acting LHRH antagonist administered as a depot injection. Degarelix requires monthly injections, after two starter injections. Here there was a significant ($p < 0.001$) association between higher ranked preference for degarelix and lower interest in tE2. There was also a significant difference ($p < 0.001$) in interest level according to ranked preference for relugolix, the oral LHRH antagonist. Surprisingly, patients who ranked relugolix as their second treatment preference had the highest average interest in tE2. Of those who rated relugolix as their second choice ($n = 93$), 71% indicated tE2 as their first choice.

Canadians and Americans differed in their current use of relugolix. This drug was available in the USA for more than a year before it was available in Canada. Because it is the most expensive ADT agent, provincial health agencies were slow to commit to funding it; fewer Canadian patients have therefore used it. This is reflected in the percentage of patients using relugolix (3% in Canada versus 28% in the USA), and in the observed discrepancies in ranked preference for relugolix among Canadian versus American patients.

Associations between interest in tE2 and various treatment-related concerns

The survey also explored questions related to patients' concerns about (1) differences in ongoing monitoring associated with various ADT options, in terms of treatment safety and oncological control, and (2) specific side effects of the different treatments. For example, tE2 ADT ideally requires more frequent blood tests vs. standard ADT agents. This is because (as shown in the PATCH/STAMPEDE trial),¹ men vary in the tE2 patch application schedules that can give them the best testosterone control. Serum E2 levels also varied considerably (90–580 pg/mL, median = 230 pg/mL).^{1,19} Although not statistically significant, there was an increased interest in tE2 among those willing to have more frequent blood tests ($p = 0.080$).

One of tE2's important benefits is protection of bone mineral density. Interestingly, though, treatment-related reduction in the risk of osteoporosis was not significantly associated with interest in tE2 ($p = 0.353$). This finding may point to a general lack of understanding amongst patients in terms of the significant silent morbidity of event-fractures 5–10 years after starting ADT.^{6,18} Given the heightened incidence of fractures for men on standard ADT, one might expect greater concern. This suggests

that patients are inadequately educated about the silent morbidity associated with osteoporosis and the increased risk of hip fractures for men on standard ADT drugs.⁶ This should be a prime area of concern for patients on traditional ADT.

Impacts of age and potential mediators

A statistically significant positive, though weak (as per R^2 value), association was found between age and interest in tE2, with higher interest among older patients ($R^2 = 0.117$, $p = 0.019$).

We aimed to assess the potential for concerns about gynecomastia—a key side effect of tE2—to mediate the association between age and interest in tE2. Although older patients had significantly less concern about gynecomastia (Beta = -0.033 , $p < 0.001$), this level of concern did not significantly predict interest in tE2 (Beta = -0.004 , $p = 0.941$). Therefore, concerns about gynecomastia did not mediate or account for the slightly higher interest in tE2 among older patients.

Preference of mode of administration and associations with overall tE2 interest

When we examined a potential association between patients' degree of interest in tE2 and their preference for the form of tE2 (i.e., patches, topical gel/cream, or no preference), the association approached significance ($p = 0.093$). Interest was highest among those who preferred daily gel/cream ($M = 2.74$, $SD = 1.19$), followed by patches ($M = 2.60$, $SD = 1.06$), and no preference ($M = 2.43$, $SD = 1.18$) (See Supplementary Material S1). Interestingly, 2.8 times more men said they would prefer daily topical tE2 products versus tE2 patches that are changed twice a week (Figure 2). This preference was strongest among Canadian patients, with 3.75 times more Canadians than Americans preferring daily tE2 gel/cream products.

A significant relationship was found between interest in tE2 and concerns about patch visibility ($p = 0.010$). Interestingly, those with the most concern about visibility had the highest interest in tE2. Topical tE2 gel and cream products are applied daily and are invisible once applied. We found a significant association between interest in tE2 and degree of concern about daily application. Those with no concern over daily application of gel/cream had the highest level of interest in tE2; those with moderate concern had the lowest interest in tE2. This seems consistent with concerns about the visibility of patches, although that was not exceptionally high. Indeed, 45% of patients were not concerned about patch visibility, while 44% had some to moderate concern (Figure 3). More

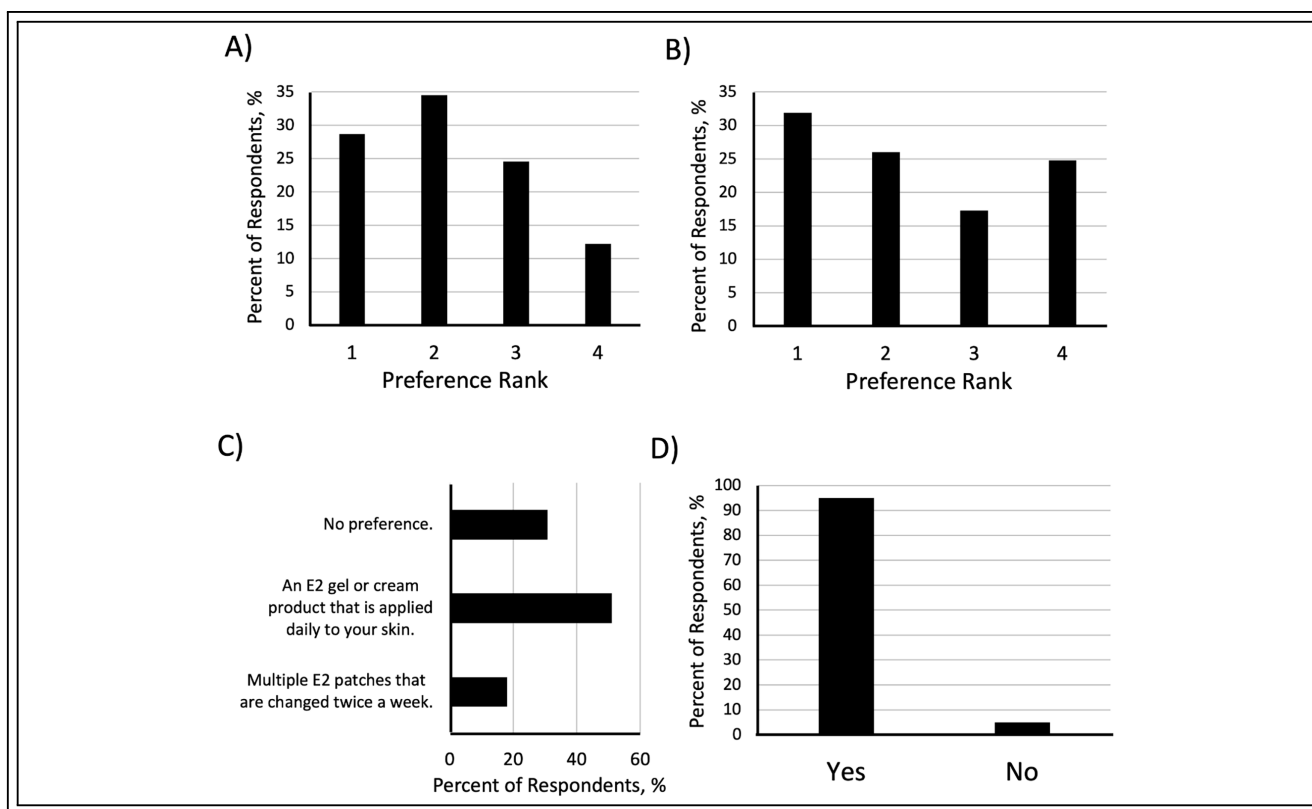


FIGURE 2. Respondent preferences for different forms of ADT. Rank 1 = high preference; Rank 4 = low preference. (A) Preference for choosing relugolix. (B) Preference for choosing tE2. (C) Preference for choosing a tE2 product form. (D) Should tE2 be approved for ADT? tE2: transdermal estradiol; ADT: androgen deprivation therapy

patients (70%) reported some to moderate concern about potential dermatitis from the patches, with 13% reporting no concern.

Associations between interest in tE2 and information source

Of the seven sources from which patients reported receiving their information about ADT (see Table 2), only physician sources were statistically significantly associated with self-reported level of interest in tE2. Receiving information primarily from physicians was associated with lower interest in tE2 (Beta = -0.384 , $p < 0.05$).

Exploring the qualitative results

The survey ended with the open-ended question: "Is there anything else you'd like to share about your views on alternative options for ADT?"

Comments were analyzed specifically to assess patients' opinions (i.e., positive or negative) about standard ADT, relugolix, orchiectomy, and tE2

(Table 3). A sample of comments is provided below in italics, with further examples provided in a supplemental table (Supplementary Material S4).

Seventy-four patients left comments about traditional ADT, 84% of which were coded as negative reflections on ADT experiences. For example:

"I've been on ADT (Eligard and Abiraterone) for 7 years. Most of the common side effects went away within the first year. Muscle mass loss and depression are the two side effects I still struggle with, and depression in particular I have had minimal support for, from either my urologist or family doctor. It's very frustrating."

In contrast, 16% of comments reflected positive experiences with standard ADT. For example: "I am doing very well on standard treatments, Xtandi plus Eligard, so [I] would be very reluctant to switch. [P]resently I think that my oncologist feels the same way. If I am responding so well, why change?"

Twelve patients left comments specifically about relugolix, 42% of which were positive. For example: "I

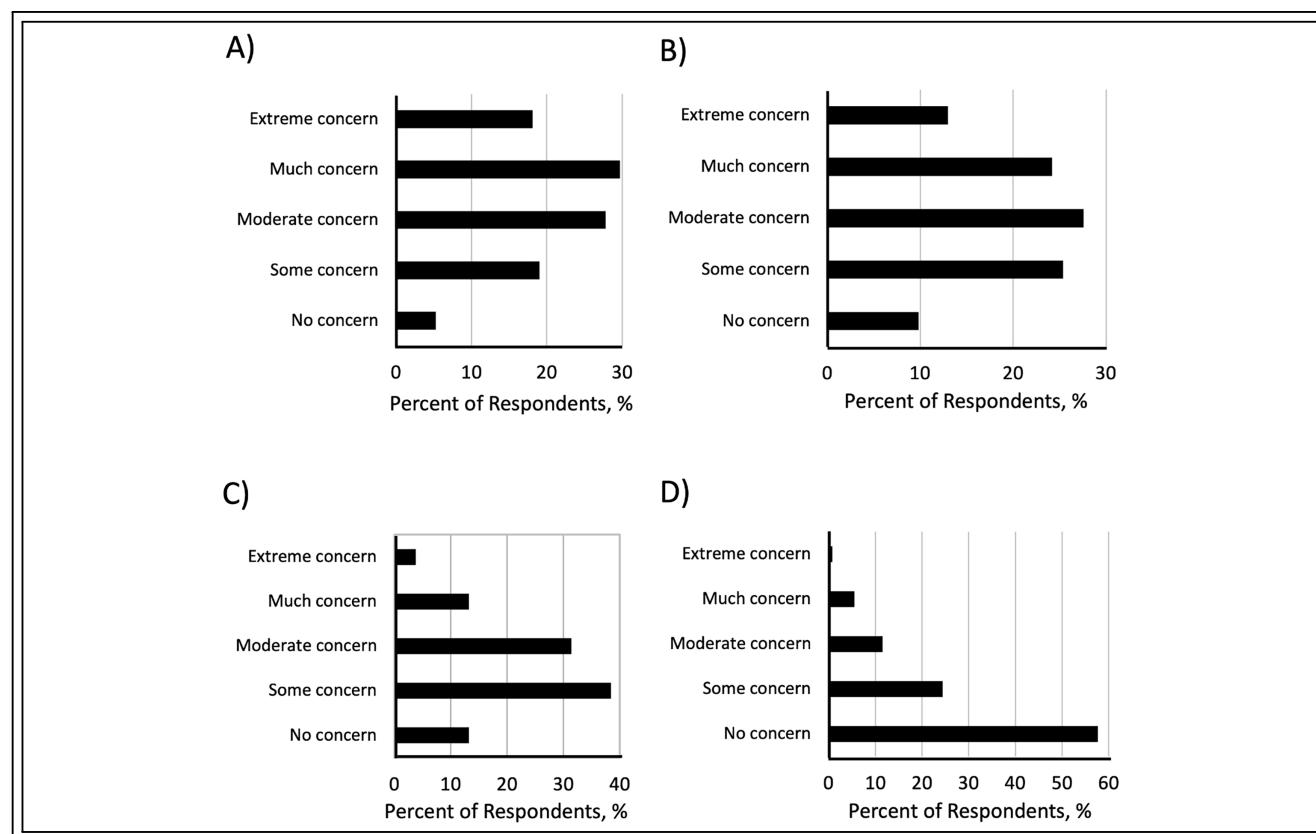


FIGURE 3. Respondent concerns about risks with LHRHa ADT and tE2 ADT. (A) Concern about osteoporotic risk from LHRHa ADT. (B) Concern about gynecomastia risk from tE2 ADT. (C) Concern about dermatitis risk from tE2 patches. (D) Concern about daily application of E2 gels/creams. LHRHa: luteinising hormone releasing hormone agonists; tE2: transdermal estradiol; ADT: androgen deprivation therapy

find relugolix easy to take one pill a day and I tolerate any adverse effects ok. It would remain my treatment of choice"

Similarly, two people commented that orchiectomy was, or would be, their treatment of choice: *"Bilateral orchiectomy was my primary ADT followed with Zytiga for adrenal suppression. Very happy."*

Twenty-three patients left comments in which they supported tE2 as an option for ADT (11 of whom reported current use of tE2). Notably, no patients reported negative experiences with tE2. However, three of the twenty-three patients mentioned concerns with accessing a prescription. One mentioned an openness to trying tE2 should he need to use ADT again, and another noted that he would switch from goserelin to tE2 as long as gynecomastia *"wasn't pronounced"*. Another patient wrote: *"I find that tE2 is a very effective, inexpensive, and painless, form of ADT. I highly recommend it."*

One patient described his experience with tE2 as an *"add-back"* treatment to help with ADT-related side effects: *"I am currently on traditional ADT (Lupron*

+ abiraterone) plus tE2 for symptom management. If I'd been starting my ADT today, I'd have chosen tE2 as the primary ADT."

A more extensive list of patients' comments, coded as positive or negative, for the various ADT treatment options is accessible in Supplementary Material S4 and a full list can be found at: <https://estradiolinitiative.org/2025-survey-of-opinions/>.

Discussion

Our survey indicates that PCa patients strongly desire tE2 options for ADT. Interest in tE2 was higher among men who had never been on ADT. Older patients also had higher interest in tE2 than did younger patients. Although older patients were significantly less concerned about gynecomastia, this did not account for their higher level of interest in tE2.

Similarly, we did not find a significant relationship between a patient's ADT experience and their

concerns about gynecomastia. Furthermore, gynecomastia concerns did not predict interest in tE2.

Results also indicate that men who ranked depot injections more highly had lower levels of interest in tE2, a finding that was further corroborated by comments in which the patients described an unwillingness to change from their current ADT medication. Men, who ranked standard ADT medications as their lowest preferred option, had the highest levels of interest in tE2.

A substantially higher proportion of patients indicated a preference for daily topical tE2 gel/cream products vs. tE2 patches.

tE2 and quality of life

The PATCH/STAMPEDE trial's survival data confirm that tE2 is as effective as the LHRH agonists or antagonists for cancer control.¹ In addition, after six months, patients on tE2 reported significantly better QoL compared to those on standard ADT agents.^{1,17} Although those authors did not explore in depth the mechanisms underlying tE2-related improvements in QoL, both preclinical research with rats and research on the QoL of PCa patients point to the fact that it is the loss of estrogen and not the loss of testosterone that accounts for much of the more bothersome and serious side effects of the standard ADT agents.¹⁴

Given these findings, a critical question arose: why might PCa patients have resistance to trying tE2 options for ADT? In our study, there were no significant associations between interest in tE2 and concerns about frequent blood tests (though it approached significance), gynecomastia, administration route (patch vs. gel/cream; approached significance), or risk of dermatitis with patches. These factors may therefore not represent substantial barriers for patients considering tE2 options. However, there were significant associations between interest in tE2 and concerns about both visibility of patches and daily application of gel/creams. Those who reported no concern with daily application of gel/creams had the highest degree of interest in tE2. Moreover, interest in tE2 was lower among men whose primary source of information about ADT was a physician. This suggests that physicians may not be presenting tE2 as an ADT option to their patients. Given the positive findings of the PATCH/STAMPEDE trials,¹ more effort may be warranted to inform healthcare providers about the safety and QoL benefits of tE2 for ADT, compared to LHRH agonists/antagonists.

Perhaps our most dramatic finding pertaining to patients' interest in tE2 for ADT is the importance of previous or current treatment with standard ADT. Interest in tE2 was statistically significantly higher

among those with no ADT experience, including those on Active Surveillance.

Some patients prefer oral and topical ADT agents over depot injections, particularly the multiple monthly injections of Degarelix. The survey data suggest some resistance to changing the initial ADT agent when it has demonstrated good cancer control.

Factors that have kept transdermal estradiol from being approved option for ADT

In North America, there are a variety of patches, gels, and creams to help women with hot flashes. Some have been on the market for over 40 years.²⁰ In contrast, we know of no tE2 products licensed in North America to treat PCa, and have seen little medical or industrial interest in bringing such products to market. In light of the PATCH/STAMPEDE survival data and PCa patients' desire to have tE2 as an option for ADT, there is an urgent need to identify and, if possible, overcome barriers to making tE2 products standard of care (SOC) options for ADT.

Lack of financial incentives is one barrier for pharmaceutical companies in terms of producing tE2 products for men. tE2 is exceptionally inexpensive compared to all the approved drugs for advanced PCa.²¹ Plus, patent protection is unavailable for estradiol itself, since it is a natural hormone.²⁰ The costs and profit for a pharmaceutical company are therefore in the packaging, as can be seen in the different designs of patches available for women. The costs of tE2 patches varies greatly, from \$2/patch to \$35/patch, for the same strength of patch (0.1 mg E2/24 h). That comes out to about \$16/month for the cheapest patch, while tE2 gel costs about \$30/month from a compounding pharmacy. This should be compared to the cost of standard ADT drugs at about \$2000/month. Hence, tE2 drugs are roughly 100 times cheaper than standard ADT drugs, which has huge implications for treating men in low- and lower-middle-income countries.

From the consumer's perspective, tE2 products for menopausal women are quite expensive, given the amount of E2 they contain. However, the excess of choices has led to small profits for the manufactures. This, we believe, is behind the pharmaceutical industry's reticence in developing, testing, and seeking approval for tE2 products for men.

The history of the synthetic estrogen, DES, used to treat PCa, also may be relevant here. Although DES was the first drug treatment for PCa, it carried a high risk of thrombosis, which led to a search for safer drugs to treat PCa. It has now been 40 years since leuporelin received FDA approval as a replacement for DES.

It's of significance here that a multitude of papers, including those from the PATCH/STAMPEDE trial, have proven that the cardiovascular toxicity of estrogens is not intrinsic to their biochemistry.^{22,23} Rather, the problem lies with its oral administration.¹³ Thromboembolic events are rare with parenteral administration, yet the idea that estrogens are toxic for PCa patients persists.

What is ignored in this history is how both the diagnosis and treatments for PCa have changed since the LHRH agonists replaced DES. In the early 1990s, the PSA test became a screening tool.²⁴ Far more men are now diagnosed with PCa than when DES was the SOC. Now, the vast majority of men treated for PCa have few or no symptoms at first presentation and may live symptom-free for decades on ADT. The burden of prostate cancer care has shifted increasingly from survival to QoL.

Limitations

Findings from this web-based, cross-sectional study must be considered in light of several study limitations. The use of exclusively online recruitment, through major PCa care organizations, PCa chat lists, and snowball recruitment, may have introduced selection bias. It may be the case that patients who were more affluent and technologically savvy (i.e., with access to a computer), and those with a higher degree of engagement in their PCa care, were more likely to participate. Indeed, our results indicate that participants were predominantly white, with higher levels of education and socioeconomic status, who were residing in more affluent Western countries (i.e., predominantly USA and Canada). Generalizability is thus affected by the homogeneity of the study sample; results are predominantly derived from PCa patients in North America and may not extend to patients elsewhere.

Participants were not required to have previous PCa treatment history of any kind. Our study sample includes a large proportion of men with no previous exposure to any ADT medications, which may introduce bias in favour of novel treatment options. Few participants had current or prior experience with tE2. Of these, no participants reported negative treatment experiences or side effects. Results must therefore be interpreted in the context of potential selection and responder bias. In addition, statistical analyses did not involve multivariable adjustment.

Conclusions

Our results show that PCa patients strongly support making tE2 available as a SOC option for ADT. Importantly, this sentiment was shared by men in both North America and internationally. Given patients' self-reported willingness to pay out of pocket for tE2 products, there exists a potential for the pharmaceutical industry to profit from tE2 products if they were made available as SOC options for ADT.

In our study, the PCa patients who expressed the highest level of interest in tE2 were those who had no prior ADT experience. Older patients also had higher interest in tE2 than did younger patients. Importantly, concerns about gynecomastia did not limit patients' interest in tE2 products. Conversely, while tE2's bone protective benefit was recognized, it was not seen as a major reason for seeking out tE2. Given the significant silent morbidity of osteoporosis among men on traditional ADT, our findings indicate that more education about the bone-protective effects of tE2 is needed. Men who reported a preference for traditional ADT with longer-duration depot injections had lower interest in tE2, suggesting a reluctance to change once already initiated on a treatment plan with traditional ADT. Men who reported that a physician was their primary source of information about treatment options had the lowest interest in tE2 as an option for ADT. In light of the PATCH/STAMPEDE results, we envision more patients expressing interest in having tE2 options for ADT, even if it is not yet an official SOC. Efficient shared decision-making and informed consent about treatment options will require that both patients and physicians be aware of the perceived pros and cons of alternative forms of ADT.

Survey results suggests that tE2 topical gels or creams are substantially more appealing than are patches. Of import, tE2 gels and creams could be orders of magnitude cheaper than standard ADT agents for both individuals and healthcare systems. More-affordable tE2 products may allow financially-challenged patients to access ADT in combination with more expensive ARPIs, when such combinations are medically warranted. In addition, the fact that estradiol is protective of bone mineral density could reduce patient and healthcare costs, as patients would not need add-on, expensive, bone protective agents such as the bisphosphonate zoledronic acid (Zometa) or the RANKL inhibitor denosumab (Xgeva). Beyond North America, affordable, effective tE2 products could find a global market, especially in regions where traditional therapies are cost prohibitive.

Of the evidence-based options for suppressing testicular androgen production, tE2 provides the best QoL, with equivalent survival rates compared to the standard ADT agents. For that reason alone, both individual physicians and medical societies should prioritize making tE2 options available to PCa patients. Our survey study findings indicate that tE2 should be considered as a SOC option in shared decision-making discussions when ADT is a consideration for the treatment of advanced prostate cancer.

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Author Contributions

Conceptualization: Richard Wassersug, Robert Watson, Paul Schellhammer; data curation: n/a; formal analysis: Carly Sears, Richard Wassersug; funding acquisition: Paul Schellhammer; investigation: Robert Watson, Richard Wassersug, Paul Schellhammer; methodology: Richard Wassersug, Robert Watson, Paul Schellhammer; project administration: Richard Wassersug, Robert Watson, Paul Schellhammer, Carly Sears; resources: n/a; software: n/a; supervision: Richard Wassersug, Robert Watson, Paul Schellhammer; validation: Richard Wassersug, Robert Watson, Paul Schellhammer; visualization: Robert Watson, Wassersug, Paul Schellhammer, Carly Sears; writing—original draft: Carly Sears, Richard Wassersug, Robert Watson, Paul Schellhammer; writing—review & editing: Carly Sears, Eric Brown, Richard Wassersug, Robert Watson, Paul Schellhammer. All authors reviewed and approved the final version of the manuscript.

Availability of Data and Materials

Data available upon reasonable request.

Ethics Approval

The invitation to participate linked to a “Consent to Participate” page, the completion of which opened the full survey. Informed consent was established when those who opened the survey completed the informed consent page and clicked through to the survey questions. The research protocol, invitation to the survey, and questionnaire were assessed by the Institutional Review Board of Pearl IRB™ (www.pearlirb.com) and received official approval (Pearl IRB ID: 2025-0067).

Conflicts of Interest

Richard Wassersug: The ADT Educational Program over the years has received funding in the form of educational grants from Bayer, Astellas, Tolmar. Richard Wassersug has received honoraria for presentation and panel participation from Bayer, Tolmar, J&J Janssen.

Supplementary Materials

The supplementary material is available online at <https://www.techscience.com/doi/10.32604/cju.2026.075285/s1>.

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