Optimizing androgen deprivation therapy (ADT) in advanced prostate cancer

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Understanding the efficacy and safety profiles of GnRH agonists and GnRH antagonists

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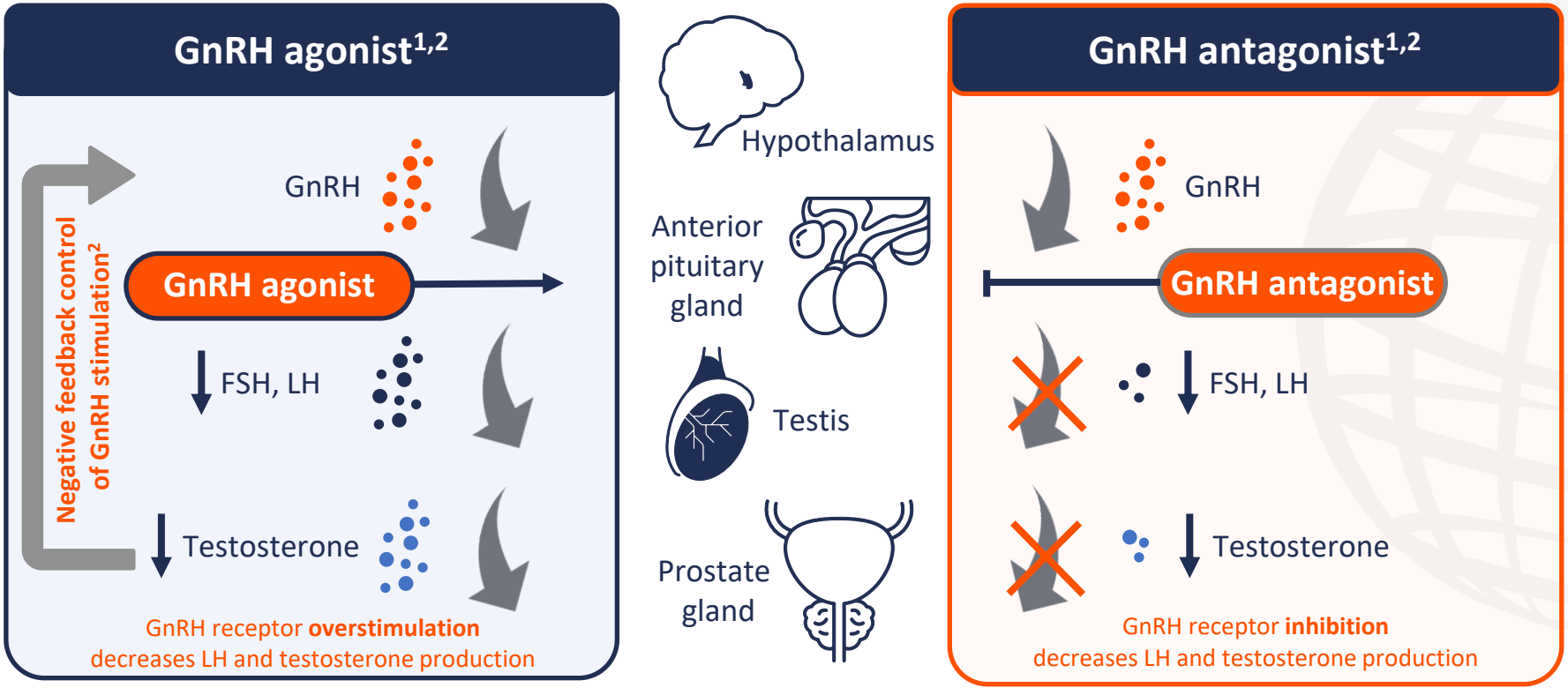
What is the difference between GnRH agonists and antagonists?

Mechanism of action of ADTs differ significantly



ADT, androgen deprivation therapy; FSH, follicle-stimulating hormone; GnRH, gonadotropin-releasing hormone; LH, luteinizing hormone.

1. Van Poppel H, Abrahamsson PA. *Int J Urol.* 2020;27:830–37; 2. Rosario DJ, et al. *World J Urol.* 2016;34:1601–9.

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How should we interpret the key efficacy data for GnRH antagonists and agonists?

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Pivotal trials for approved GnRH antagonists

GnRH antagonist	Degarelix	Relugolix
Study	Phase III; CS21 trial (NCT00295750)[1]	Phase III; HERO (NCT03085095)[3]
Study details	Patients with any stage adenocarcinoma of the prostate Degarelix (n=) vs leuprolide (N=201)[1]	Patients with advanced prostate cancer Relugolix (n=622) vs leuprolide (n=308)
Key results	**Primary endpoint:** • **Testosterone suppression (≤50 ng/dL) day 28 to 364:**[1,2] **Degarelix 240/80 mg: 97.2%** (95% CI 93.5–98.8) **Leuprolide 7.5 mg: 96.4%** (95% CI 92.5–98.2) • **Testosterone levels ≤50 ng/dL at day 3:** **Degarelix 240/80 mg: 96.1%** **Leuprolide 7.5 mg: 0%** • Median testosterone levels **increased by 65%** from baseline by day 3 in leuprolide group (median testosterone 630 ng/dL; p<0.001) • Median testosterone levels remained >50 ng/dL until day 28 in the leuprolide group	**Primary endpoint:** • **Sustained testosterone suppression (<50 ng/dL) day 29 to 48 weeks:** **96.7%** (95% CI 94.9–97.9) **vs 88.8%** (95% CI 84.6–91.8) **Key secondary endpoints:** • **Sustained castration rate in relugolix group non-inferior to that in leuprolide** **Between group difference, 7.9 pp** (95% CI 4.1–11.8) • **Cumulative probability of castration on day 4:** **56.0% vs 0%** • **Cumulative probability of testosterone suppression (<20 ng/dL) on day 15: 78.4% vs 1.0%**

Direct comparisons between trials should not be made due to differences in trial design.

CI, confidence interval; GnRH, gonadotropin-releasing hormone; pp, percentage points.

1. Klotz L, et al. *BJU Int*. 2008;102:1531–8; 2. FDA. Degarelix PI. Available at: www.accessdata.fda.gov/drugsatfda_docs/label/2020/022201s016lbl.pdf (accessed 19 July 2023); 3. Shore ND, et al. *N Engl J Med*. 2020; 382:2187–96.

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What are the key adverse effects associated with ADT?

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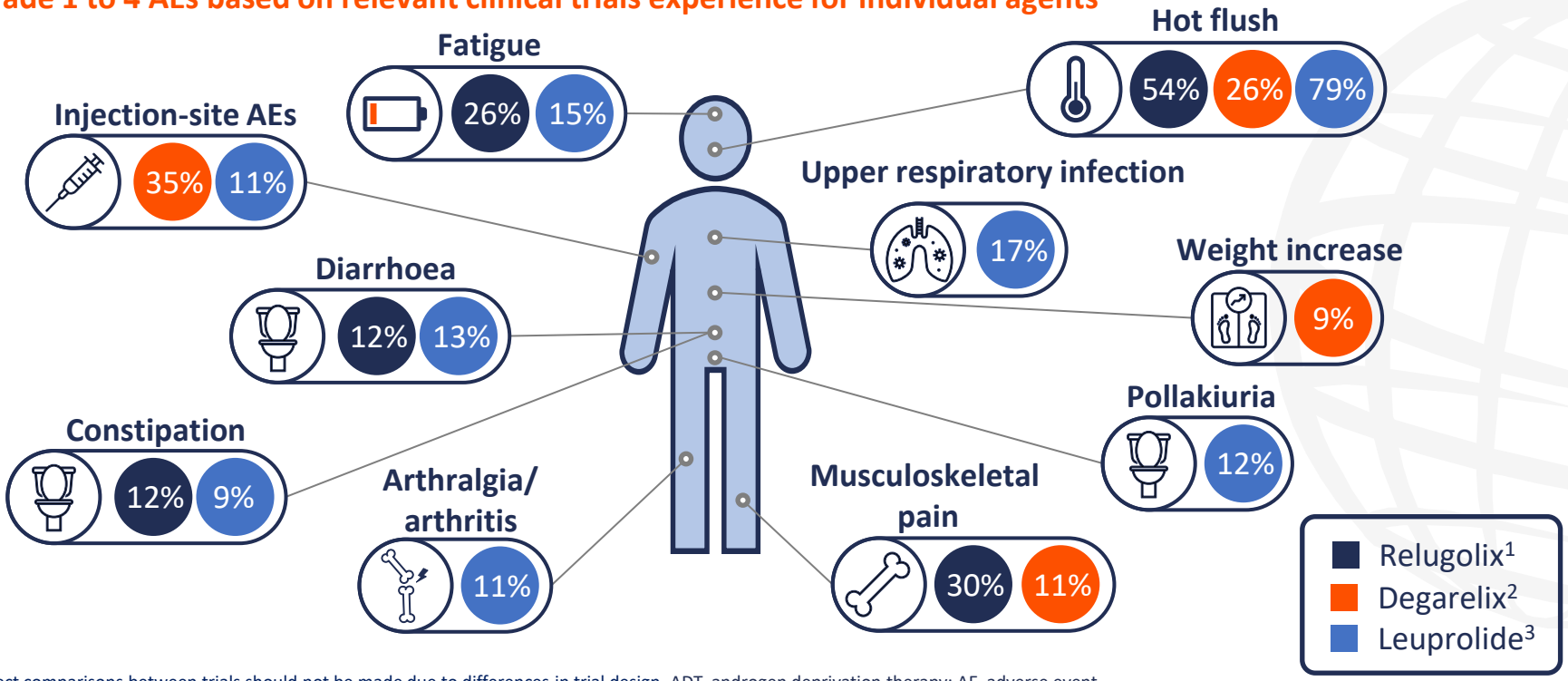
AE profiles play a role in ADT selection

Grade 1 to 4 AEs based on relevant clinical trials experience for individual agents*



*Direct comparisons between trials should not be made due to differences in trial design. ADT, androgen deprivation therapy; AE, adverse event.

1. FDA. Relugolix PI. Available at: www.accessdata.fda.gov/drugsatfda_docs/label/2023/214621s004lbl.pdf (accessed 17 July 2023);
2. FDA. Degarelix PI. Available at: www.accessdata.fda.gov/drugsatfda_docs/label/2020/022201s016lbl.pdf (accessed 17 July 2023);
3. FDA. Leuprolide PI. Available at: www.accessdata.fda.gov/drugsatfda_docs/label/2023/205054s004lbl.pdf (accessed 17 July 2023).

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Based on the current evidence, are GnRH agonists or antagonists associated with CV risk?

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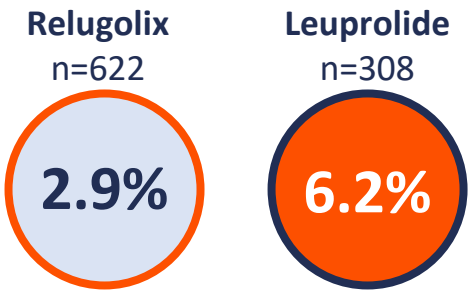
CV risk for GnRH antagonists vs agonists

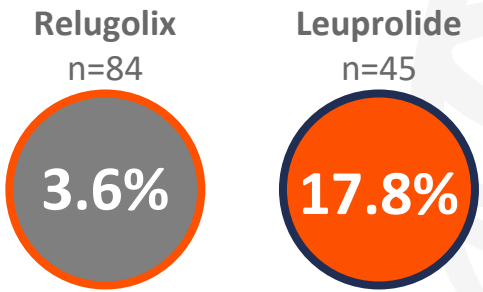
Phase III RCT investigating the effect of relugolix on testosterone suppression compared to leuprolide[1]

Incidence of MACEs:*
Whole population[1]



54% lower risk in the relugolix group
(HR 0.46, 95% CI 0.24–0.88)

Incidence of MACEs:*
Patients with reported medical history of MACEs[1]



Odds of CV event were 4.8 times higher with leuprolide compared with relugolix

Murine studies suggest **destabilization of pre-existing atherosclerotic plaques** may explain the **increased CV risk** in patients with prostate cancer treated with GnRH agonists[2]

*MACE defined as non-fatal myocardial infarction, non-fatal stroke, and death from any cause. CI, confidence interval; CV, cardiovascular; GnRH, gonadotropin-releasing hormone; HR, hazard ratio; MACE, major adverse cardiovascular event; RCT, randomized controlled trial.

1. Shore ND, et al. *N Engl J Med.* 2020;382:2187; 2. Knutsson A, et al. *Sci Rep*. 2016;6:26220.

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Does recent evidence indicate a potential link between ADT and dementia in patients with prostate cancer?

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ADT increases the risk of a dementia diagnosis

Real-world study into the association between ADT and the risk of dementia

N=627,025
US EHR collected data
Males >50 years old with
no prior dementia, stroke or TIA

ADT
n=73,933
Mean age=70.8

Non-ADT
n=57,005
Mean age=70.4

	ADT group patients with dementia	Non-ADT group patients with dementia	Adjusted HR (95% CI), p value
All ADT categories	3.12%	2.19%	1.60 (1.49–1.73), <0.0001
GnRH agonist	3.33%	2.12%	1.69 (1.56–1.83), <0.0001
GnRH antagonists	2.75%	2.11%	1.92 (1.47–2.52), <0.0001

ADT exposure associated with **statistically higher dementia risk** among **White patients than non-ADT** (78.6% vs 77.7%, p<0.001), but **no significant difference** among **African American patients**

- Risk of dementia is **significantly higher** in patients on ADT – **60% increased risk**
  - Highest risk reported in GnRH antagonists (degarelix) – **92% increased risk**

ADT, androgen deprivation therapy; CI, confidence interval; EHR; electronic health records; GnRH, gonadotropin-releasing hormone; HR, hazard ratio; TIA, transient ischaemic attack.

Elantably D, et al. *J Clin Oncol*. 2023;41(16_Suppl.):5086.

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ADT increases the risk of a dementia diagnosis

Retrospective analysis into the association between cumulative ADT exposure and the onset of dementia after primary treatment – nationwide longitudinal registry of men with prostate cancer

N=13,570
CaPSURE registry data
Males ≥50 years old

Diagnosis of dementia in all patients

2.3% (after a median of 7.0 years of follow-up; IQR 3.0–12.0)

ADT **54%**

Non-ADT **46%**

Subset analysis where propensity score matched by whether or not patients received ADT (n=8,506)

Association between ADT and dementia (HR 1.59, 95% CI 1.03–2.44; p=0.04)

- **Cumulative ADT** use **significantly associated with dementia** (HR 2.02, 95% CI 1.40–2.91; p<0.01)
- No association between primary treatment type and onset of dementia in patients who did not receive ADT (n=8,489; HR 1.4, 95% CI 0.9–2.18; p=0.14)

ADT, androgen deprivation therapy; CaPSURE, Cancer of the Prostate Strategic Urologic Research Endeavor; CI, confidence interval; HR, hazard ratio; IQR, interquartile range.

Longeran PE, et al. *J Urol*. 2022;207:832–40.

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Overcoming disparities and barriers in prostate cancer: How can we give all patients the opportunity to access appropriate care?

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How does race impact prostate cancer outcomes?

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Race impacts outcomes less when care is equal

Meta-analysis of 47 studies evaluating the association of social determinants of health with prostate cancer-specific mortality and OS in Black and White patients with prostate cancer

N=1,019,908

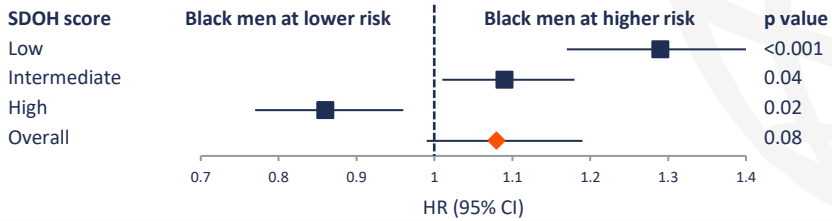
Social determinants of health covariables studied

- Age
- Comorbidities
- Insurance status
- Income status
- Extent of disease
- Geography
- Standardized treatment
- Insurance benefits

RESULTS

No significant differences among Black men vs White men for overall prostate cancer-specific mortality (p=0.08)

SDOH score	Studies (n)	Black patients (n)	White patients (n)	HR (95% CI)
<5	5	16,986	86,012	1.29 (1.17–1.41)
5–9	15	94,391	508,036	1.09 (1.01–1.18)
≥10	5	23,167	53,689	0.86 (0.77–0.96)
Overall	25	134,544	647,737	1.08 (0.99–1.19)



When accounting for disparities in SDOH, Black men with prostate cancer had similar or improved survival outcomes compared with White men with prostate cancer

CI, confidence interval; HR, hazard ratio; OS, overall survival; SDOH, social determinants of health.

Vince RA, et al. *JAMA Netw Open*. 2023;6:e2250416.

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What other social factors influence outcomes in prostate cancer?

Social factors and prostate cancer outcomes

Socioeconomic status[1]

Multilevel data from two multiethnic, US population-based case-control studies (N=2,008 with advanced prostate cancer)

Increased risk of death ($p<0.05$) associated with:*

- **Lower socioeconomic housing** (HR 1.56, 95% CI 1.11–2.19)
- **Lower education** (HR 1.32, 95% CI 1.05–1.67)

African American men had **worse survival** than non-Hispanic White men†

Insurance[2]

Data obtained from self-reported measures in the National Health Interview Survey (2019)

US patients aged 18–64 years **without insurance** were:

- **More likely to delay or not receive medical care**
- **More likely to have advanced disease at diagnosis and worse survival**

Proportion aged <65 years **without insurance** was:

- **Higher among Black** (14.3%), **American Indian/Alaska Native** (25.9%) and **Hispanic** (30.2%) people than among White (10.2%) or Asian (7.1%) people
- **Higher** among people with **lower income** or **education levels,** or in **the South** region

*Study underpowered to look at prostate cancer-specific mortality; †attenuated by neighbourhood SES.
CI, confidence interval; HR, hazard ratio; SES, socioeconomic status.

1. DeRouen MC, et al. *Cancer Epodemiol*. 2018;53:1–11; 2. Islami F, et al. *CA Cancer J Clin*. 2022;72:112–43.

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Impact of social factors on prostate cancer outcomes

Geography[1]

Relationship between rural residence,* stage and treatment in the US

N=51,049 prostate cancer diagnosis between 2009 and 2015†

- **Non-urban residents are less likely to receive any treatment** even when stratified by low-, intermediate- and high-risk disease
- Difference in receipts of treatment between urban and rural residents was **largest in men with high-risk disease** (aOR 0.68; 95% CI 0.53–0.89)

Differences in treatment between urban and rural populations may be due to:

- **Socioeconomic status**
- **Environment**
- **Access to care**

Transgender population[2]

Cancer stage at diagnosis, treatment and survival in transgender vs cisgender patients in the US‡

N=11,776,699 (n=589 transgender patients)

Transgender patients were more likely to have **poorer survival** after diagnosis with prostate cancer (HR 1.91, 95% CI 1.06–3.54)

For many cancer types, transgender patients may be:

- **Diagnosed at a later stage**
- **Less likely to receive treatment**
- **Have worse survival for many cancer types**

*Rurality of residence defined based on the Agriculture Rural-Urban Commuting Area codes from the United States Department of Agriculture; †patients identified from the Pennsylvania Cancer Registry; ‡data taken from the National Cancer Database. aOR, adjusted odds ratio; CI, confidence interval; HR, hazard ratio.

1. Maganty A, et al. *J Urol*. 2020;203:108–14; 2. Jackson SS, et al. *J Natl Cancer Inst*. 2021;113:1221–7.

What are some of the barriers to accessing equitable care in prostate cancer?

Individual barriers to equitable care in prostate cancer

Personal patient views

18% of all men in the US did not have a healthcare provider*[1]

1/3 of men believed they didn't need annual check-ups†[2]

Transgender population

1/3 experienced negative healthcare-related events in the previous year‡[3]

May avoid healthcare settings due to **anticipation of mistreatment**[3–6]

Black American population§[7]

7/10 say they were treated unfairly by the healthcare system

55% do not trust the healthcare system

Patients may feel undervalued in the healthcare system, embarrassed by their diagnosis, and reluctant to seek help or discuss their disease[8]

*2021 survey, data based on the Behavioral Risk Factor Surveillance System, a state-based, random-digit-dialled telephone survey of non-institutionalized civilian adults aged ≥18 years; †survey for the US population commissioned by Orlando Health; ‡2015 survey examining experiences of transgender people in the US (N=27,715); §2020 KFF survey data. Survey of over 1,700 US adults including nearly 800 African Americans. 1. KFF. 2022. Available at: https://bit.ly/44jPecY (accessed 25 August 2023); 2. Orlando Health. 2022. Available at: https://bit.ly/3NNpqih (accessed 25 August 2023); 3. National Center for Transgender Equality. 2015. Available at: https://bit.ly/3D5tRA2 (accessed 25 August 2023); 4. Mikulak M, et al. *Br J Gen Pract*. 2021;71:e941–7; 5. Warner DM 2nd, Mehta AH. *J Gen Intern Med*. 2021;36:3559–61; 6. Safer JD, et al. *Curr Opin Endocrinol Diabetes Obes*. 2016;23:168–71; 7. KFF. 2020. Available at: https://bit.ly/47jR1As (accessed 25 August 2023); 8. Chambers SK, et al. *BMJ Open*. 2018;8:e019917.

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What are some strategies that may help to improve outcomes in those who are at high risk of prostate cancer?

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Strategies to improve outcomes in high-risk groups

Community-focused education

- **Educate community leaders** to increase knowledge and advocacy intentions[1]
- Prostate cancer screening education:
  - **Locate** where the audience feels **comfortable,** e.g. **churches** and **barbershops**[2]
  - **Increase educator appeal**[3]
    - Prostate cancer survivor educators had significantly more appeal with audiences than health educators (p=0.03)

Transgender population

- Ensure clinical practices are **welcoming and respectful to all** gender identities and expressions[4]
- Ask HCPs to attend training or skills-building workshops to **increase understanding and comfort** of treating transgender people[5]
- **Acknowledge authenticity** of transgender individuals' identities, lives and experiences[6]

Increase clinical trial participation[7]

- Recommend **all demographic groups** to consider trials
- **Increase telehealth appointments** to reduce need to travel to clinical trial appointments
- **Reimburse** travel expenses
- Include trial sites with **higher percentages of underrepresented patients**

HCP, healthcare professional; LGBTQIA+, lesbian, gay, bisexual, transgender, queer/questioning, intersex, asexual and more.

1. Aristizabal C. *Cancer Res*. 2020;80(Suppl. 16):4346; 2. Fu J, et al. *Curr Oncol Rep*. 2023;25:699–708; 3. Vijaykumar S, et al. *J Cancer Educ*. 2013;28:623–8; 4. Squires LR, et al. *LGBT Health*. 2022;9:8–17; 5. Quinn GP, et al. *JCO Oncol Pract*. 2020;16:309–16; 6. Lombardi E. *Am J Public Health*. 2001;91:869–72; 7. Cackowski FC, et al. *Am Soc Clin Oncol Educ Book*. 2021;41:1–12.

Supporting adherence in prostate cancer treatment: Incorporating patient preferences and shared decision making

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How do treatment adherence rates compare between clinical trials and clinical practice and how does this impact patient outcomes?

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Adherence to oral prostate cancer treatments is higher in clinical trials vs real-world settings

HERO trial[1]
Phase III randomized trial of relugolix or leuprolide for 48 weeks

N=934

	Treatment adherence*	Completed 48 weeks of treatment
Relugolix	>99%	90.2%
Leuprolide	>99%	89.0%

Retrospective analysis of large prescription claim database from October 2014 to September 2019 for apalutamide, enzalutamide, or abiraterone[2,3]

N=27,262

	Medication possession ratio ≥80%	Proportion of days covered ≥80%
6 months	92.2%	57.5%
12 months	86.1%	42.8%

Direct comparisons between trials should not be made due to differences in trial design.
*Defined as the percentage of expected doses actually taken.
1. Shore ND, et al. *N Engl J Med.* 2020;382:2187–96; 2. Fleshner NE, et al. *Ther Adv Med Oncol*. 2023;15:1–22; 3. Pilon D, et al. *Future Oncol*. 2021;18:231–43.

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Non-adherence rates are similar between oral and injectable therapies

Non-adherence rates of therapy[1]

Systematic review of non-adherence rates to prostate cancer treatments in real-world practice

Oral therapies
Mean non-adherence rates:
25–51%

Injections
Overall non-adherence rates:
>27%

Injection delays (dosing non-adherence)[2]

22,860 US patients treated with LHRH agonists

84% LHRH injections **administered later than scheduled***

60%
Injections
>1 week late

29%
Injections
>2 weeks late

Groups with low adherence rates[3]

- Black men
- Older patients (≥75 years)
- Prior chemotherapy
- Higher prescription costs

*In a 28-day month. Late injections were defined as dosing after day 28, 84, 112 and 168 for the 1-, 3-, 4- and 6-month formulations, respectively.[2]
LHRH, luteinizing hormone-releasing hormone.

1. Higano CS, Hafron J. *J Urol*. 2023;209:485–93; 2. Crawford ED, et al. *J Urol*. 2020;203:743–50; 3. Pilon D, et al. *Future Oncol*. 2021;18:231–43.

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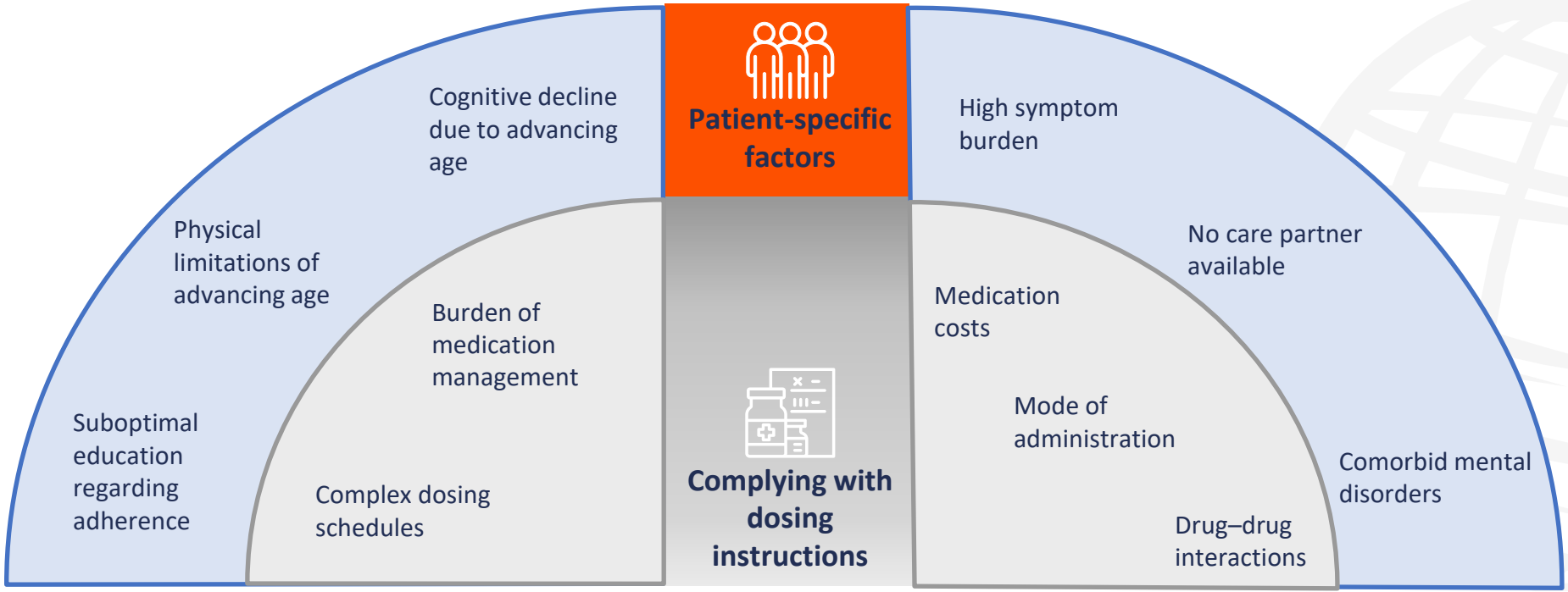
What factors can affect patient adherence to treatment regimens?

Barriers to treatment adherence



Higano CS, Hafron J. *J Urol*. 2023;209:485–93.

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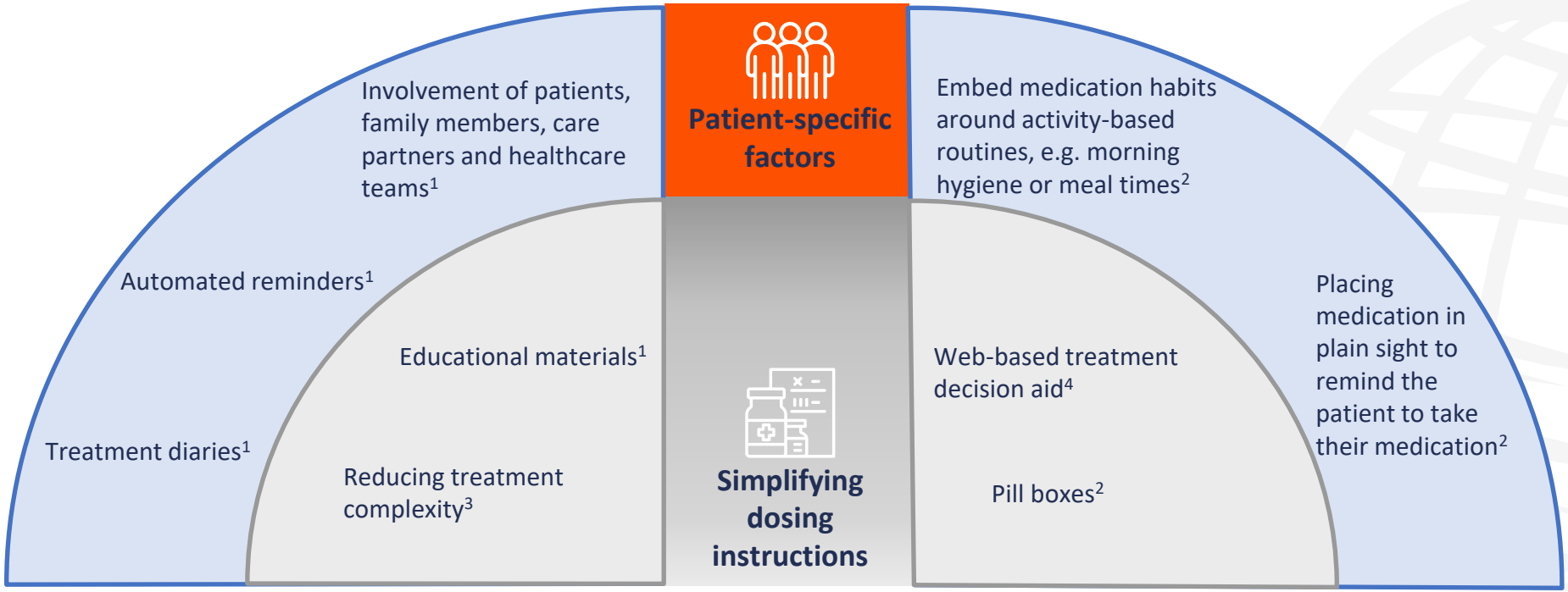
How can patient adherence be improved?

Interventions that can help improve adherence



1. Higano CS, Hafron J. *J Urol*. 2023;209:485–93; 2. Sanders MJ, Oss TV. *Am J Occup Ther*. 2013;67:91–9; 3. Fleshner NE, et al. *Ther Adv Med Oncol*. 2023;15:1–22;
4. Bagshaw HP, et al. *BMC Med Inform Decis Mak*. 2021;21:374.

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What is shared decision making and how does it improve adherence?

What is shared decision making?

"A process in which decisions are made in a collaborative way, where trustworthy information is provided in accessible formats about a set of options, typically in situations where the concerns, personal circumstances, and contexts of patients and their families play a major role in decisions"[1]

Survey of 76 stakeholders, including patients with cancer, potential future patients, oncologists and SDM researchers, found that:[2]

Oncologists should:

- Emphasize the importance of the patient's opinion
- Determine possible treatments
- Provide treatment recommendations
- Provide guidance to patients
- Explain the treatment options
- Get to know patients

Patients should:

- Feel free to ask questions
- Express their thoughts and feelings
- Offer opinions
- Search for information
- Consider their options
- Decide or delegate decisions to the oncologist

Decision aids in prostate cancer

- Improve patient–provider communication[3]
- Educate on the medical information[4]
- Enable comparison of risks of treatments and nature of side effects[4]
- Allow the patient to consider their options[4]

SDM, shared decision making.

1. Elwyn G, et al. *Br Med J*. 2017;359:j4891; 2. Bomhof-Roordink H, et al. *Psychooncology*. 2019;28:139-46; 3. Bagshaw HP, et al. *BMC Med Inform Decis Mak*. 2021;21:374; 4. Hochstenbach LMJ, et al. *Internet Interv*. 2023;31:100606.

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Improving the treatment experience in prostate cancer

Shared decision making

What does shared decision making mean for patients?

- Better identification of patients' needs, perceptions and expectations[1]
- Identification of patient-specific issues, e.g. fear of needles or travel constraints[2]
- Focus on patients' priorities, particularly important in LGBTQIA+ population[3]

How does shared decision making impact outcomes?

- Increased adherence[1,2,4,5]
- Increased patient satisfaction[1,4,5]
- Better persistance[2]
- Increased patient wellbeing and QoL[5]

Decision aids

How do decision aids help patients with prostate cancer?

- Increased comprehension of medical information[4]
- Improved knowledge and accuracy of perceptions[4]
- Greater perceived control of treatment selection[4,5]

How do decision aids impact prostate cancer outcomes?

- Improved treatment compliance[4]
- Reduced decisional regret[6]

LGBTQIA+, lesbian, gay, bisexual, transgender, queer/questioning, intersex, asexual and more; QoL, quality of life.

1. Glatzer M, et al. *Oncology*. 2020;98:370-78; 2. Higano CS, Hafron J. *J Urol*. 2023;209:485–93; 3. Quinn GP, et al. *JCO Oncol Pract*. 2020;16:309; 4. Bagshaw HP, et al. *BMC Med Inform Decis Mak*. 2021;21:374; 5. Driever EM, et al. *Patient Educ Couns*. 2020;103:77-82; 6. Hochstenbach LMJ, et al. *Internet Interv*. 2023;31:100606.

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