

Impact of androgen receptor pathway inhibitors (ARPIs) on mental health in Veterans with metastatic androgen pathway modulation-naïve prostate cancer (mAPMN)

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Background:

Androgen deprivation therapy (ADT), the backbone treatment for mAPMN, is associated with depression and anxiety due to testosterone loss and its negative impacts on quality of life. ARPIs, when added to ADT, are now standard of care for mAPMN. Given ARPIs further alter the testosterone axis, we sought to understand the impact of ARPIs on mental health compared to ADT alone.

Methods:

We used national Veterans Health Administration data and a validated natural language processing algorithm to identify Veterans diagnosed with mAPMN between 2018-2022. Veterans receiving care for a second malignancy and those with preexisting mental health conditions were excluded. We conducted a target trial emulation, implementing a clone-censor-weight approach with a 4-month grace period to compare the incidence of depression, anxiety, and other mental health diagnoses within one year of starting ADT in those who received ADT alone v. ADT + ARPI. We modeled the time-to-event outcomes using a pooled logistic regression and adjusted for covariates (age, race, marital status, income, education, comorbidity burden, de novo v. recurrent mAPMN, baseline prostate specific antigen [PSA], baseline pain score, year of ADT start, and home VA facility) using inverse probability censoring weights.

Results:

We identified 3692 Veterans without a preexisting mental health diagnosis who received ADT for mAPMN. At the end of the 4-month grace period, 2119 were receiving ADT alone and 1109 ADT + ARPI. Those who received ADT alone were older (77 v. 76 years, standardized mean difference [SMD] 0.17), started ADT earlier in the study time period (2017-2019, 45% v. 29%, SMD 0.40), had less income (<\$40,000, 25% v. 22%, SMD 0.11), more comorbidities (NCI Charlson comorbidity index ≥ 2 , 41% v. 36%, SMD 0.11), lower baseline PSAs (0-19 ng/mL, 41% v. 33%, SMD 0.36), more recurrent mAPMN (46% v. 39%, SMD 0.15), and lower baseline pain scores (0-3, 51% v. 49%, SMD 0.16). After adjusting for covariates, the 1-year cumulative incidence of depression in the ADT alone arm (9%) was similar to the ADT + ARPI arm (9%; cumulative incidence ratio [CIR] 1.02, 95% CI 0.83-1.21). Likewise, there was no difference in 1-year cumulative incidence of anxiety (5% v. 5%; CIR 1.07, 95% CI 0.78-1.37) or other mental health diagnoses (10% v. 9%; CIR 0.94, 95% CI 0.78-1.13).

Conclusions:

Veterans who received ADT + ARPI as first-line treatment for mAPMN did not receive more incident mental health diagnoses compared to those who received ADT alone. This argues that further altering the testosterone axis with ARPIs does not incrementally increase the risk of mental health symptoms over that of ADT alone. Further work to understand the impact of ARPIs in those with preexisting mental health conditions as well as the impact of specific ARPIs on mental health is underway.

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Conflicts of Interest: None

Table 1. Demographics and clinical characteristics.

	Baseline (N = 3,692)	Uncensored at End of Grace Period ¹		
		ADT alone (N = 2,119)	ADT + ARPI (N = 1,109)	SMD ²
Age, years (mean, range, standard deviation)	77 (48 – 102; 8.8)	77 (48 – 102; 9.1)	76 (51 – 97; 7.9)	0.17
Race (n, %)				0.03
<i>White</i>	2,625 (71.1%)	1,492 (70.4%)	795 (71.7%)	
<i>Black</i>	978 (26.5%)	570 (26.9%)	288 (26.0%)	
<i>Other</i>	89 (2.4%)	57 (2.7%)	26 (2.3%)	
Marital status (n, %)				0.05
<i>Married</i>	2,006 (54.3%)	1,131 (53.4%)	620 (55.9%)	
<i>Not married</i>	1,686 (45.7%)	988 (46.6%)	489 (44.1%)	
Income				0.11
<i>More than \$100,000</i>	692 (18.7%)	390 (18.4%)	222 (20.0%)	
<i>\$70,000 - \$99,999</i>	828 (22.4%)	485 (22.9%)	240 (21.6%)	
<i>\$40,000 - \$69,999</i>	1,167 (31.6%)	644 (30.4%)	375 (33.8%)	
<i>Less than \$40,000</i>	892 (24.2%)	529 (25.0%)	247 (22.3%)	
<i>Unknown</i>	113 (3.1%)	71 (3.4%)	25 (2.3%)	
Education				0.03
<i>Completed High School</i>	1,345 (36.4%)	772 (36.4%)	402 (36.2%)	
<i>Completed College</i>	1,096 (29.7%)	631 (29.8%)	341 (30.7%)	
<i>Completed Grad School</i>	345 (9.3%)	195 (9.2%)	107 (9.6%)	
<i>Attended Vocational/Technical School</i>	24 (0.7%)	15 (0.7%)	8 (0.7%)	
<i>Unknown</i>	882 (23.9%)	506 (23.9%)	251 (22.6%)	
ADT start year				0.40
<i>2017, 2018</i>	699 (18.9%)	478 (22.6%)	134 (12.1%)	
<i>2019</i>	760 (20.6%)	477 (22.5%)	188 (17.0%)	
<i>2020</i>	628 (17.0%)	397 (17.9%)	181 (16.3%)	
<i>2021</i>	730 (19.8%)	382 (18.0%)	259 (23.4%)	
<i>2022, 2023</i>	875 (23.7%)	403 (19.0%)	347 (31.3%)	
NCI Charlson comorbidity index (n, %)				0.11
<i>0</i>	1,255 (34.0%)	701 (33.1%)	420 (37.9%)	
<i>1</i>	971 (26.3%)	560 (26.4%)	292 (26.3%)	
<i>≥2</i>	1,466 (39.7%)	858 (40.5%)	397 (35.8%)	
Baseline PSA ³ , ng/mL (n, %)				0.36
<i>0-19</i>	1,338 (36.2%)	863 (40.7%)	368 (33.2%)	
<i>20-49</i>	506 (13.7%)	261 (12.3%)	175 (15.8%)	
<i>50-99</i>	379 (10.3%)	202 (9.5%)	128 (11.5%)	
<i>≥100</i>	1,043 (28.3%)	478 (22.6%)	364 (32.8%)	
<i>No measurements</i>	426 (11.5%)	315 (14.9%)	74 (6.7%)	
De novo v. recurrent mAPMN				0.15
<i>De novo</i>	2,146 (58.1%)	1,139 (53.8%)	678 (61.1%)	
<i>Recurrent</i>	1,546 (41.9%)	980 (46.2%)	431 (38.9%)	
Baseline pain score				0.16
<i>Low: 0-3</i>	1,793 (48.6%)	1,082 (51.1%)	541 (48.8%)	
<i>Moderate: 4-6</i>	577 (15.6%)	315 (14.9%)	192 (17.3%)	
<i>High: 7-10</i>	1,070 (29.0%)	548 (25.9%)	323 (29.1%)	
<i>Unknown</i>	252 (6.8%)	174 (8.2%)	53 (4.8%)	

¹Censoring occurred during the 4-month grace period for 1) death or 2) experiencing the outcome of interest. Table 1 represents those who were uncensored at the end of the 4-month grace period when a depression diagnosis was the outcome of interest.

²Standardized mean difference represents the magnitude of difference between two groups measured in units of standard deviation. A SMD ≥0.10 represents imbalance, suggesting a statistically significant difference between the two groups.

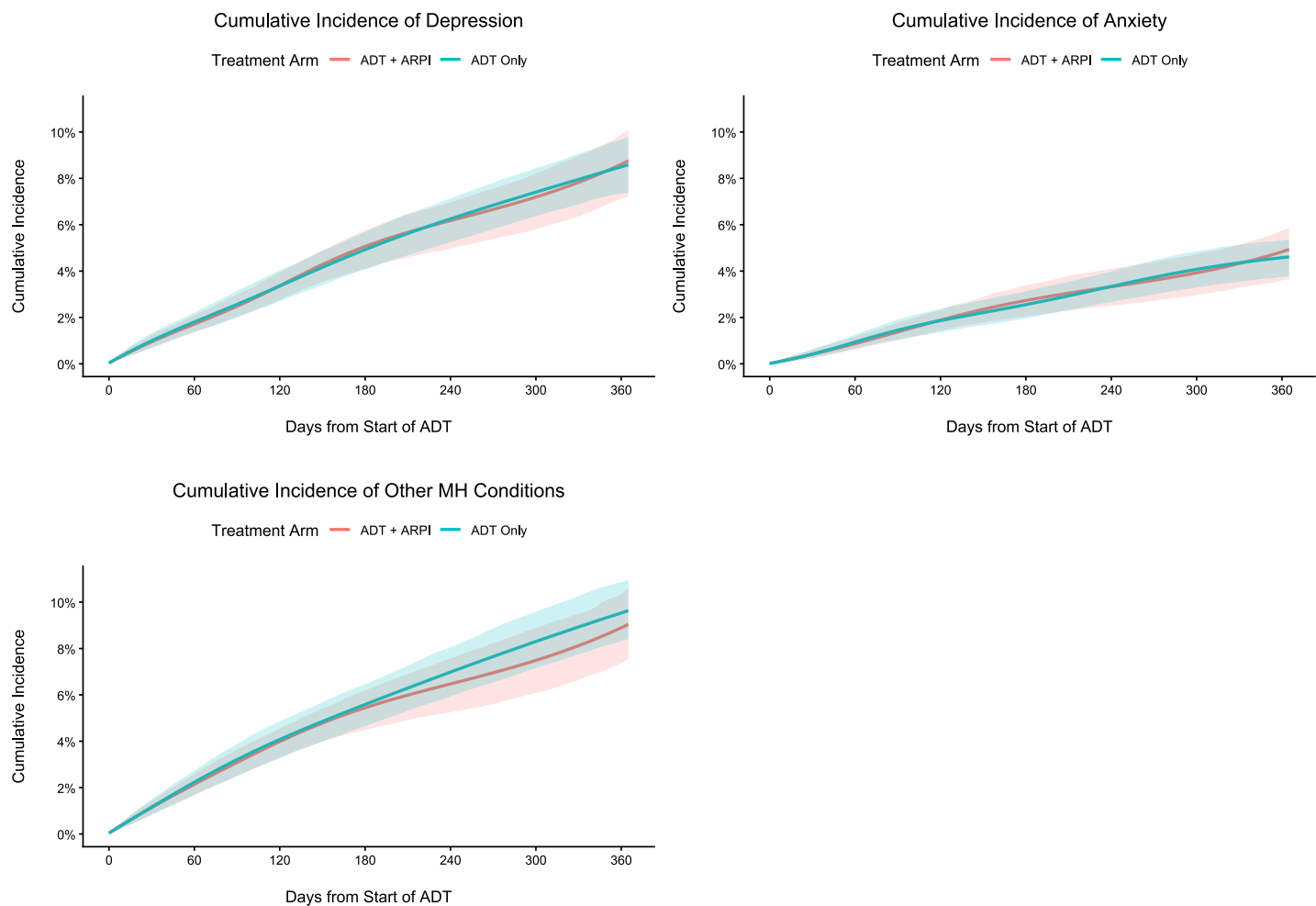
³Baseline PSA was defined as the highest PSA value within a 120-day window centered on the ADT start date

Abbreviations: ADT, androgen deprivation therapy; ARPI, androgen receptor pathway inhibitor; mAPMN, metastatic androgen pathway modulation-naïve prostate cancer; NCI, National Cancer Institute; PSA, prostate specific antigen; SMD, standardized mean difference

Table 2. Adjusted cumulative incidence of new mental health diagnoses at 1-year after ADT start in Veterans receiving ADT v. ADT + ARPI for mAPMN.

Outcome	Adjusted cumulative incidence at 1-year after ADT start (95% CI)			
	ADT alone	ADT + ARPI	Difference	Ratio
Depression	8.6% (7.40, 9.77)	8.8% (7.21, 10.11)	+0.2% (-1.6, +1.7)	1.0 (0.8, 1.2)
Anxiety	4.6% (3.8, 5.4)	4.9% (3.6, 5.9)	+0.3% (-1.1, +1.4)	1.1 (0.8, 1.4)
Other mental health diagnoses	9.6% (8.4, 11.0)	9.0% (7.6, 10.6)	-0.6% (-2.2, +1.2)	0.9 (0.8, 1.1)

Figure 1. Cumulative incidence of new mental health diagnoses in Veterans receiving ADT v. ADT + ARPI for mAPMN.



Note: shaded areas reflect 95% confidence intervals