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Antidepressant Use Trajectories and Risk of Discontinuation After Adolescents and Young Adult Cancer Diagnosis

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Keywords: adolescents and young adults | antidepressants | cancer survivorship | group-based trajectory modeling | mental health

ABSTRACT

Background: Little is known about the continuity of antidepressant treatment after adolescent and young adult (AYA) cancer diagnosis. Clinical guidelines recommend that past antidepressant use trajectories should inform decisions on discontinuation after cancer diagnosis.

We characterized AYAs' antidepressant adherence trajectories before incident cancer diagnosis and assessed any association between their past adherence trajectory and the risk of antidepressant discontinuation up to 1 year afterward.

Methods: We conducted a retrospective, longitudinal cohort study of AYAs receiving ≥ 2 antidepressant fills 9 months before incident cancer diagnosis (index date). Group-based trajectory modeling was used to estimate latent subgroups of antidepressant adherence before cancer diagnosis, using monthly proportions of days covered (PDC) over the nine-month baseline; IQVIA PharMetrics Plus for Academics US claims, 2006–2020. Discontinuation was defined as ≥ 60-days gap without antidepressants within 1 year post-index date.

Results: We observed three distinct antidepressant adherence trajectory groups before cancer diagnosis: *recent start* (17% of cohort, mean PDC [range]: 0.25 [0.03–0.49]); *gradually increasing* (36%, mean PDC [range]: 0.57 [0.22–0.81]); and *consistently high* (47%, mean PDC [range]: 0.90 [0.62–1.00]). Compared with AYAs exhibiting prior *consistently high* adherence trajectories, those with *recent start* (HR, [95% CI] 1.96, [1.46–2.63]) and *gradually increasing* (HR, [95% CI] 1.52, [1.20–1.93]) trajectories experienced about 2 times the higher risk of antidepressant discontinuation over the year following cancer diagnosis.

Conclusion: Past antidepressant trajectory is associated with antidepressant discontinuation after AYA cancer diagnosis. Attention is needed in the psycho-oncologic care of AYAs who recently started antidepressants before cancer diagnosis.

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Summary

- Depression and anxiety are common among adolescents and young adults. In our sample, 11% were treated with antidepressants prior to cancer diagnosis across cancer types.
- Our study demonstrates that antidepressant adherence trajectories prior to cancer diagnosis predict the discontinuation of antidepressant treatment after diagnosis. The risk of discontinuation was highest among those initiating antidepressants in the 3 months prior to cancer diagnosis.
- Further exploration of the determinants, benefits, and harms of discontinuing antidepressant treatment, as well as potential effects on cancer outcomes and survivorship care, is warranted.

1 | Introduction

About 6%–41% of adolescents and young adults (AYAs) diagnosed with cancer have comorbid depression or anxiety [1–3]. Little is known about the continuity of depression treatment after a cancer diagnosis, which represents an important gap in the management of AYAs with these comorbid conditions. A cancer diagnosis may precipitate worsening of AYAs' mood symptoms and increase the need for antidepressants [4–6]. For such AYAs, concerns about CYP2D6 drug–drug interactions between antidepressants and common antineoplastic agents [7–11] (see Table S1) may hasten antidepressant discontinuation. Clinical oncology guidelines recommend considering past trajectories of antidepressant use and treatment response when contemplating antidepressant discontinuation in individuals newly diagnosed with cancer [7, 11]. However, there is limited evidence on how these recommendations are implemented in real-world oncology practice.

Evidence suggests that AYAs with a history of low or disrupted adherence to antidepressants face a higher risk of depression relapse, increased healthcare utilization, and health-related costs [12]; all of which may worsen survivorship after cancer diagnosis. Among AYAs without cancer, abrupt antidepressant discontinuation has been associated with an increased risk of antidepressant discontinuation syndrome [13], mood symptoms relapse [14], and suicide attempts [15].

Antidepressant discontinuation may compromise new cancer survivors' adherence to oral antineoplastics, as has been observed with discontinuation of other chronic medications for example, oral antidiabetics and antilipidemics [16, 17]. Despite these important clinical consequences of antidepressant discontinuation, there is limited evidence on the relationship between AYAs' past trajectories of antidepressant adherence and their risk of antidepressant discontinuation after cancer diagnosis. Thus, we aimed to estimate the prevalence of antidepressant use and to identify antidepressant adherence trajectory subgroups, using antidepressant utilization patterns observed among AYAs 9 months before incident cancer diagnosis. Secondly, we aimed to estimate antidepressant discontinuation in the year after cancer diagnosis, comparing AYAs with distinct adherence trajectories before cancer diagnosis.

2 | Methods

2.1 | Study Design and Data Source

We conducted a retrospective cohort study using a 10% random sample of enrollees within the IQVIA PharMetrics Plus for Academics claims database from September 2006 through December 2020 [18]. PharMetrics Plus for Academics is a health plan claims database of fully adjudicated medical and pharmacy claims for over 110 million unique enrollees since 2006. Data contributors to the database are largely commercial health plans. It is representative of the commercially insured US population for patients under 65 years of age. It contains a longitudinal view of inpatient and outpatient services, prescription and office/outpatient administered drugs, costs, and detailed enrollment information. Diagnoses are captured via International Classification of Diseases, Revision (ICD-9/10) codes. Procedures are recorded using International Classification of Diseases Revision procedure codes (ICD-9/10-PCS), Current Procedural Terminology (CPT), and Healthcare Common Procedure Coding System (HCPCS) codes. Pharmaceutical products and treatments are captured via National Drug Codes (NDC) or HCPCS codes.

2.1.1 | Participants and Eligibility Criteria

Based on the AYA definition by the National Cancer Institute, we identified individuals 15–39 years old with an incident diagnosis claim for any of the most common cancers among this population in the US, for example, thyroid, testicular germ cell, breast, cervical, melanoma, colorectal, uterine, lymphomas, leukemias, others (Table S2) [19, 20]. Incident cancer diagnosis was defined based on observing no cancer claims in the 9 months before a new claim with an ICD-9/10 diagnosis code in the primary position (index date) [21]. Each AYA with a new cancer diagnosis claim was further required to have a second claim for the same cancer within 60 days of the index date [21]. We included AYAs who had filled 2 or more antidepressant prescriptions in the baseline 9 months and who had at least 1 day of antidepressant use within the 60 days immediately preceding the index date. We excluded AYAs with noncontinuous health insurance coverage during the 9 months' baseline. We also excluded those who had been using bupropion previously but were now diagnosed with incident brain or other nervous system (ONS) cancer, as this is an absolute contraindication for bupropion continuation [7, 11].

2.2 | Study Variables

2.2.1 | Antidepressants Trajectory of Adherence

We calculated the prevalence of antidepressant use before AYA cancer diagnosis as the proportion of all AYAs with 9 months' continuous enrollment before the index date who had ≥ 2 antidepressant fills during the same period. A lookback period of 9 months was selected as this is the recommended length of continuous treatment to reduce the risk of relapse [22] To identify adherence trajectories, group-based trajectory modeling (GBTM) was used to identify meaningful trajectory groups representing patterns of drug use over time [23, 24]. This approach

accounts for both the extent and time-varying nature of adherence, thus potentially capturing more heterogeneity in adherence behavior [23, 24].

Using GBTM, we estimated latent trajectory groups of adherence to antidepressants 9 months before the incident cancer diagnosis. First, we measured each AYA's monthly proportion of days covered (PDC) for each baseline month before the index date. We adjusted for stockpiling by carrying forward any overlapping days of antidepressant supply until after medication from the last refill was exhausted. Next, we successively tested 2-group to 6-group models for classifying the AYAs by their measured adherence into distinct, longitudinal polynomial trajectories, noting the model fit in each case as represented by the Bayesian Information Criterion (BIC). We used the censored-normal group-based trajectory model as our adherence measure (PDC) was continuous [23–25] and we examined permutations up to third-order polynomials for each model. Leveraging guidance from prior literature [26, 27], we chose the best model as that with the highest (i.e., least negative) BIC where at least 10% of the cohort was represented in each identified trajectory group and where groups were parsimonious and clinically relevant. The posterior probabilities and odds of correction classification for each trajectory group were assessed, and results are presented in Table S9 (Supporting Information).

Covariates: We measured AYAs' age group (i.e., 15–24, 25–34, and 35–39 years) at cancer diagnosis, sex, US census region and antidepressant class(es) used before cancer diagnosis (Table S3). To account for antidepressants' CYP2D6 inhibitory strength [28, 29] and its possible influence on discontinuation risk after cancer diagnosis, we classified AYAs as receiving strong, weak-to-moderate, or non-CYP2D6 inhibitor antidepressants. Using the Food and Drug Administration's classification [28, 29], we classified AYAs into mutually exclusive groups based on the antidepressant they used most frequently in the 90 days preceding the index date. We also determined whether AYAs had used other (non-antidepressant) CYP2D6 inhibitors, enzyme inducers or substrates (Table S4) concurrently with antidepressants in the 90 days preceding the index date; as such use could exacerbate the inactivation of common antineoplastics [28, 30, 31] and thus may have contributed to antidepressant discontinuation. We assessed baseline psychotropic polypharmacy and psychotherapy use since receipt of either of these mental health treatments may be indicative of AYAs' mental health severity, which could influence antidepressant discontinuation rates after cancer diagnosis. Psychotropic polypharmacy was defined as baseline fill of ≥1 anxiolytic-sedative hypnotic, psychostimulant, mood stabilizer, or antipsychotic in addition to antidepressants. Psychotherapy use was defined based on CPT or ICD-9/10 procedural codes from previous claims-based studies (Table S3) [32, 33]. Using ICD-9/10 codes from the Chronic Condition Warehouse (CCW) Classification system [34], we assessed mental health disorders (i.e., depressive anxiety, bipolar and psychotic disorders) which are common indications for antidepressant use (Table S5) [35, 36]. Mental health multimorbidity was defined as having ≥2 mental health disorders in the 9 months preceding the index date. We assessed primary cancer type and metastatic status at diagnosis using ICD 9/10 codes (see Table S2). Lastly, we classified the year of cancer diagnosis into three periods: 2006–2009—the period immediately after the first clinical trial highlighted CYP2D6 drug–drug interactions between antidepressants and tamoxifen [37–39]; 2010–2015—the period when evidence first suggested that antidepressant-tamoxifen interactions could be associated with increased breast cancer mortality [40]; 2016–2020—A period of wide dissemination of this evidence and scientific controversy, as other studies began disputing the mortality association [41, 42].

2.2.2 | Outcomes Following Antidepressant Trajectories

The primary outcome was antidepressant discontinuation after an incident cancer diagnosis, defined as a 60 or more days' gap in antidepressant supply over the first year of follow-up. To measure this outcome, we created a daily antidepressant supply diary for each AYA after the index date, based on observed fills, corresponding service dates and days' supply per fill. We then assessed discontinuation by tracking the diary until the earliest observed ≥60-day gap. AYAs were censored upon lapse of their insurance enrollment or completion of 1 year of study follow-up; whichever occurred earlier. Since current practice guidelines allow switching within and between antidepressant classes to prevent antidepressant and antineoplastic agent drug–drug interactions [11, 43, 44], we did not censor our daily tracking of antidepressant supply if antidepressant classes were switched [45].

2.3 | Statistical Analyses

Baseline characteristics were compared across trajectory groups using 2-sided χ^2 tests for categorical variables. Multinomial logistic regression was used to estimate the association between baseline characteristics and trajectory group membership [15, 46], with the group showing the best adherence trajectory set as the referent. Cumulative incidence curves were plotted to estimate and describe the rate of antidepressant discontinuation by trajectory group over a 1-year follow-up. Multivariable Cox regression was used to estimate the adjusted hazard ratio (HR) of antidepressant discontinuation among trajectory group(s) with worse antidepressant adherence trajectories before cancer diagnosis, relative to the group showing the best adherence trajectory.

2.4 | Sensitivity Analyses

Sensitivity analyses were used to estimate the potential misclassification bias using a ≥60-day gap in antidepressant supply, that is, too long or too short to connote discontinuation. We therefore varied the antidepressant supply gap to ≥45, ≥90, and ≥180 days.

All statistical analyses were two-sided, with $\alpha = 0.05$ as the threshold for statistical significance, and were performed using SAS 9.4 (SAS Institute Inc., Cary, NC). The University of Maryland Baltimore Institutional Review Board deemed this study exempt. The reporting of this study conforms to the STROBE statement.

3 | Results

Of 6541 AYAs with an incident cancer diagnosis, 11% ($n = 731$) had past antidepressant use in the 9 months preceding the cancer diagnosis (see Figure 1, Table S8). Of these 731 AYAs, 603 met the study eligibility criteria and were included in the final study cohort (mean age [SD]: 33 [6] years; females: 76%) (see Table 1, Table S7). The most common primary cancer types were thyroid (21%), breast (15%) and melanoma (13%). Selective serotonin reuptake inhibitors (SSRIs [68%]), selective serotonin and noradrenaline reuptake inhibitors (SNRIs [20%]) and bupropion (15%) were the most common antidepressants used. In the 90 days prior to their cancer diagnosis (index) date, 34% and 10% of the cohort were exposed to strong CYP2D6 inhibitors and enzyme inducers, respectively. One-third had a baseline diagnosis of depression (35%) and anxiety (33%). Eleven percent (11.4%) of the cohort experienced an inpatient admission in the 9 months preceding the index date. Mean (SD); median (IQR) of baseline hospitalizations was 0.2 (0.8); 0 (0).

3.1 | Antidepressant Adherence Trajectory Groups

The three-group GBTM best fits the adherence pattern in our data over the 9 months before cancer diagnosis (Figure 2, Figure S1). The first trajectory group comprised 17% of the cohort who displayed a *recent start* of antidepressants about 6 months before cancer diagnosis (mean [range] PDC = 0.25 [0.03–0.49]). The second group comprised 36% of the cohort and followed a *gradually increasing* antidepressant adherence trajectory (mean [range] PDC = 0.57 [0.22–0.81]). The third group comprised 47% of the cohort who exhibited *consistently high* antidepressant adherence (mean [range] PDC = 0.90 [0.62–1.00]). Multinomial logistic regression indicated that the *recent start* adherence trajectory group was more likely to be younger (i.e., 25–34 vs. 35–39 years) and to have baseline anxiety disorders relative to the *consistently high* group (Table S6).

3.2 | Antidepressant Discontinuation After Cancer Diagnosis

Thirty-eight percent ($n = 226$) of AYAs discontinued antidepressants within 1 year after cancer diagnosis (Table 2). About one-third of the entire cohort had discontinued antidepressant use within 90 days after cancer diagnosis (Figure 3). A significantly greater proportion of members of the *recent start* adherence trajectory group discontinued antidepressants after cancer diagnosis (59%), compared to the *gradually increasing* (41%) and *consistently high* (27%) trajectory groups ($p < 0.01$). Although AYAs diagnosed with cancer in the 2016 to 2020 era constituted the smallest fraction (15%) of the overall study cohort (see Table 1), about a third of them discontinued antidepressants within 1 year after cancer diagnosis (see Table 2).

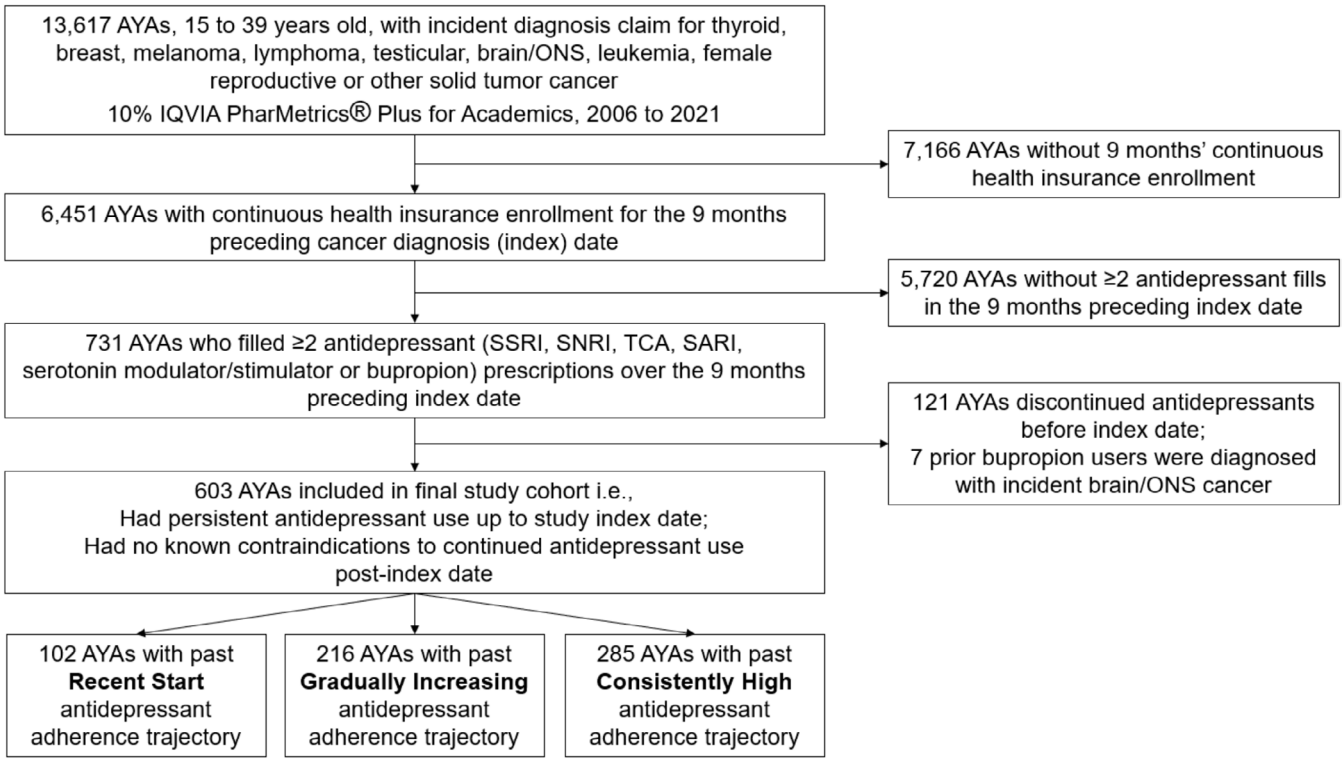


FIGURE 1 | Flow diagram showing selection of cohort of AYAs with 9 months of antidepressant use before new cancer diagnosis Claim, IQVIA PharMetrics plus for academics, 2006–2021. AYA, adolescents and young adults; brain/ONS, brain and other nervous system; NDRIs, norepinephrine dopamine reuptake inhibitors; SARIs, serotonin antagonist and reuptake inhibitors; SD, standard deviation; SNRIs, selective serotonin and noradrenaline reuptake inhibitors; SSRIs, selective serotonin reuptake inhibitors; ONS, other nervous system; TCAs, tricyclic antidepressants, tetracyclics e.g., mirtazapine; 5HT antagonists/agonists, serotonin modulators/stimulators.

TABLE 1 | Characteristics of 603 adolescent and young adult cancer survivors with prior antidepressant use before cancer diagnosis, by past antidepressant adherence trajectory group, PharMetrics Plus for academics, 2006–2020.

	All prior AD users, 603 (100%)	Recent start adherence, *n* (%) 102 (16.9%)	Gradually increasing adherence, *n* (%) 216 (35.8%)	Consistently high adherence, *n* (%) 285 (47.3%)	*p*
Demographics					
Age group at diagnosis, *n* (%)					0.17
35–39 years	293 (48.6)	39 (38.2)	106 (49.1)	148 (51.9)	
25–34 years	250 (41.5)	52 (51.0)	86 (39.8)	112 (39.3)	
15–24 years	60 (10.0)	11 (10.8)	24 (11.1)	25 (8.8)	
Sex, *n* (%)					
Females	457 (75.6)	73 (71.6)	170 (78.7)	214 (75.1)	0.35
Males	146 (24.4)	29 (28.4)	46 (21.3)	71 (24.9)	
Region, *n* (%)					0.57
South	157 (26.0)	29 (28.4)	62 (28.7)	66 (23.2)	
Midwest	176 (29.2)	23 (22.5)	63 (29.2)	90 (31.6)	
West	144 (23.9)	24 (23.5)	52 (24.1)	68 (23.9)	
North-East	112 (18.6)	22 (21.6)	36 (16.7)	54 (19.0)	
Missing	14 (2.3)	NR (NR)	NR (NR)	7 (2.5)	
Antidepressants and other psychosocial treatments					
Antidepressants used, by CYP2D6 enzyme activity					0.36
Strong inhibitors	204 (33.8)	32 (31.4)	76 (35.2)	96 (33.7)	
Weak or moderate inhibitors	279 (46.3)	49 (48.0)	106 (49.1)	124 (43.5)	
Non-Inhibitors	120 (19.9)	21 (20.6)	34 (15.7)	65 (22.8)	
Antidepressants used, by class					
SSRIs, *n* (%)	408 (67.7)	66 (64.7)	155 (71.8)	187 (65.6)	0.27
SNRIs, *n* (%)	120 (19.9)	15 (14.7)	39 (18.1)	66 (23.2)	0.13
NDRIs, *n* (%)	**92 (15.3)**	**5 (4.9)**	**27 (12.5)**	**60 (21.1)**	**< 0.01**
TCAs, tetracyclics, *n* (%)	60 (9.9)	10 (9.8)	16 (7.4)	34 (11.9)	0.24
SARIs; 5HT antagonists/agonists, *n* (%)	31 (5.1)	5 (4.9)	8 (3.7)	18 (6.3)	0.42
Psychotropic polypharmacy, *n* (%)	177 (29.4)	29 (28.4)	57 (26.4)	91 (31.9)	0.39
Received psychotherapy, *n* (%)	96 (15.9)	19 (18.6)	27 (12.5)	50 (17.5)	0.22
Past 90 days' concurrent medications					
Other CYP2D6 inhibitors, *n* (%)	37 (6.1)	5 (4.9)	13 (6.0)	19 (6.7)	0.81

(Continues)

TABLE 1 | (Continued)

	All prior AD users, 603 (100%)	Recent start adherence, *n* (%) 102 (16.9%)	Gradually increasing adherence, *n* (%) 216 (35.8%)	Consistently high adherence, *n* (%) 285 (47.3%)	*p*
Enzyme inducers, *n* (%)	61 (10.1)	6 (5.9)	18 (8.3)	37 (13.0)	0.07
CYP2D6 substrates, *n* (%)	54 (9.0)	10 (9.8)	17 (7.9)	27 (9.5)	0.78
Mental health comorbidities					
Depressive disorder, *n* (%)	208 (34.5)	36 (35.3)	71 (32.9)	101 (35.4)	0.82
Anxiety disorder, *n* (%)	**202 (33.5)**	**48 (47.1)**	**60 (27.8)**	**94 (33.0)**	**< 0.01**
Mental health multimorbidity, *n* (%)					0.16
≥ 2 MH disorders	175 (29.0)	32 (31.4)	56 (25.9)	87 (30.5)	
1 MH disorder	163 (27.0)	34 (33.3)	53 (24.5)	76 (26.7)	
0 MH disorders	265 (44.0)	36 (35.3)	107 (49.5)	122 (42.8)	
Prescriber factors					
Clinical specialty of last prescriber before cancer diagnosis, *n* (%)					
Psychiatrist	55 (9.1)	8 (7.8)	14 (6.5)	33 (11.6)	0.13
Primary care	183 (30.4)	24 (23.5)	70 (32.4)	89 (31.2)	0.25
Other specialist	88 (14.6)	15 (14.7)	34 (15.7)	39 (13.7)	0.81
Unknown	277 (45.9)	55 (53.9)	98 (45.4)	124 (43.5)	0.55
Cancer and cancer treatment factors					
Primary cancer type, *n* (%)					
Thyroid	128 (21.2)	25 (24.5)	48 (22.2)	55 (19.3)	0.49
Breast	92 (15.3)	13 (12.8)	29 (13.4)	50 (17.5)	0.33
Melanoma of the skin	80 (13.3)	7 (6.7)	34 (15.7)	39 (13.7)	0.09
Lymphomas (Hodgkin's and non-hodgkin's)	59 (9.8)	13 (12.8)	25 (11.6)	21 (7.4)	0.16
Testicular germ cell	29 (4.8)	8 (7.8)	8 (3.7)	13 (4.6)	0.26
Brain, ONS	31 (5.1)	9 (8.8)	12 (5.6)	10 (3.5)	0.11
Leukemias	16 (2.7)	NR (NR)	NR (NR)	8 (2.8)	0.89
Cervix, uterus, ovaries	53 (8.8)	11 (10.8)	16 (7.4)	26 (9.1)	0.59
Other (Solid) tumors	115 (19.1)	14 (13.7)	38 (17.6)	63 (22.1)	0.14
Metastatic cancer at diagnosis, *n* (%)	36 (6.0)	9 (8.8)	11 (5.1)	16 (5.6)	0.40
Time trends					
Era of cancer diagnosis, *n* (%)					0.14
2016–2020	111 (14.8)	20 (19.6)	30 (13.9)	61 (21.4)	

(Continues)

TABLE 1 | (Continued)

	All prior AD users, 603 (100%)	Recent start adherence, *n* (%) 102 (16.9%)	Gradually increasing adherence, *n* (%) 216 (35.8%)	Consistently high adherence, *n* (%) 285 (47.3%)	*p*
2010–2015	268 (44.4)	43 (42.2)	95 (44.0)	130 (45.6)	
2006–2009	224 (37.2)	39 (38.2)	91 (42.1)	94 (33.0)	

Note: Bold values represent statistically significant differences between groups with alpha set to < 0.05.
Abbreviations: AYA, adolescents and young adults; CYP2D6, cytochrome P450 family 2 subfamily D member 6 enzyme; MH, mental health; NDRIs, norepinephrine dopamine reuptake inhibitors; NR, not reported due to cell suppression; SARIs, serotonin antagonist and reuptake inhibitors; SD, standard deviation; SNRIs, selective serotonin and noradrenaline reuptake inhibitors; SSRIs, selective serotonin reuptake inhibitors; ONS, other nervous system; TCAs, tricyclic antidepressants, tetracyclics e.g., mirtazapine; 5HT antagonists/agonists, serotonin modulators/stimulators.

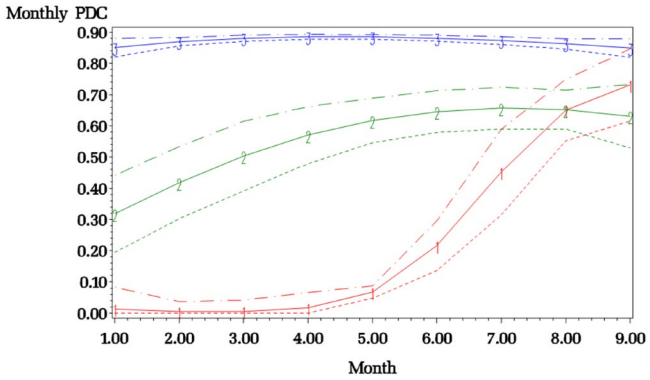


FIGURE 2 | Trajectory groups according to the best fitting prediction model of antidepressant adherence over the 9 Months before an incident cancer diagnosis among 603 adolescents and young adults, PharMetrics Plus for Academics, 2006–2020. Censored normal group-based trajectory model with Bayesian information criterion (BIC) = −4296.82. Key: Group 1: Recent start (17% of cohort), Group 2: Gradually increasing (37%), Group 3: Consistently high (47% of cohort). Dotted lines represent estimated trajectories; solid lines represent observed trajectories.

3.3 | Association Between Past Antidepressant Adherence Trajectory and Antidepressant Discontinuation After Cancer Diagnosis

We observed a significantly higher hazard of antidepressant discontinuation after cancer diagnosis within the *recent start* (HR, [95% CI] 1.96, [1.46–2.63]) and *gradually increasing* (HR, [95% CI] 1.52, [1.20–1.93]) adherence trajectory groups, relative to the *consistently high* adherence trajectory group (see Table 2). The risk of antidepressant discontinuation after cancer diagnosis was highest among AYAs diagnosed with cancer during the 2016–2020 period (HR, [95% CI] 1.71, [1.28–2.29]), relative to the 2006–2009 period. The association between prior antidepressant adherence trajectory group and discontinuation after cancer diagnosis remained robust in magnitude and direction across sensitivity analyses where the duration of the antidepressant supply gap was varied to ≥45, ≥90, and ≥180 days (see Table 2).

4 | Discussion

About one in ten AYAs (11%) diagnosed with incident cancer in the US were using antidepressants before cancer diagnosis. AYAs who recently started or gradually increased their adherence to antidepressants before cancer diagnosis face an almost doubled risk of antidepressant discontinuation once cancer is diagnosed, compared to AYAs with histories of consistently high adherence to antidepressants. These findings have important survivorship care implications, as they highlight the need to identify and care for distinct subgroups of AYAs treated with antidepressants prior to their cancer diagnosis. A new cancer diagnosis is associated with psychosocial and emotional stress, particularly at a crucial developmental life stage [47]. Some AYAs may present with long-standing mental health disorders for which long-term psychotropic treatment is needed. Others may present with recent-onset mood disorders which could require long-term treatment [48]. Continuing psychotropic prescriptions after cancer diagnosis may be essential to preventing relapse or exacerbation of mental health symptoms within certain AYA subgroups, as deterioration in mental health status could worsen their chances of successfully tolerating cancer treatment [49]. Our study observed a higher antidepressant use prevalence (11%) among adults aged 18–39 years compared to other studies [50, 51], likely due to differences in study periods, differences in study populations, and cancer types. Moreover, in our cohort, 56% of patients had at least one mental health diagnosis, where 34.5% and 33.5% had a diagnosis of depression or anxiety, respectively. However, antidepressants are widely used in psychiatric conditions other than depression and anxiety, and it is possible that many AYAs may have been prescribed antidepressants for other conditions such as obsessive-compulsive disorder, post-traumatic stress disorder, pain, insomnia, or smoking cessation [52].

Our findings are comparable to prior evidence of antidepressant utilization patterns, including discontinuation, before and after AYA cancer diagnosis. In a Swedish study including adults (median age = 69 years) with multiple types of cancer between 2001 and 2010, the authors observed a 12.2% prevalence of any psychiatric medication use and about 8% prevalence of antidepressant medication use 2 months before cancer diagnosis [53]. Another study that measured new purchases of antidepressants after cancer diagnosis among Finnish children and AYAs found 6% had antidepressant use before cancer diagnosis [6]. The lower prevalence of antidepressant use in this study compared to ours may be due to the inclusion of children in the Finnish cohort, since antidepressants are less commonly prescribed to children than adolescents. Portteus et al. [54] and Valluri et al. [55] reported the prevalence of antidepressant initiation at or within 24 months of cancer diagnosis as 10.2% and 8.8%, respectively, among US children and adolescents. Our

TABLE 2 | Cox regression of the association between the trajectory of adherence to antidepressants before cancer diagnosis and the risk of antidepressant discontinuation after cancer diagnosis, Pharmetrics Plus for academics, 2006–2020.

Characteristics	*N* (%) Discontinuing antidepressants after cancer diagnosis, by baseline category	Primary cox regression model HR (95% CI)	SA 1 Discontinuation equals ≥ 45-day gap in supply, HR (95% CI)	SA 2 Discontinuation equals ≥ 90-day gap in supply, HR (95% CI)	SA 3 Discontinuation equals ≥ 180-day gap in supply, HR (95% CI)
All 603 prior antidepressant users, *n* (%)	226 (37.5%)				
Prior adherence trajectory group, *n* (%)					
Recent start adherence	60 (58.80)	1.96 (1.46–2.63)	1.91 (1.43–2.55)	1.92 (1.41–2.59)	1.68 (1.19–2.35)
Gradually increasing adherence	89 (41.20)	1.52 (1.20–1.93)	1.72 (1.37–2.17)	1.46 (1.14–1.88)	1.45 (1.10–1.90)
Consistently high adherence	77 (27.02)	1.00 [Ref]	1.00 [Ref]	1.00 [Ref]	1.00 [Ref]
Demographics					
Age group at diagnosis, *n* (%)					
15–24 years	27 (45.00)	1.09 (0.74–1.60)	1.12 (0.77–1.62)	1.14 (0.76–1.70)	1.16 (0.75–1.81)
25–34 years	98 (39.20)	1.07 (0.86–1.34)	1.06 (0.85–1.31)	1.13 (0.89–1.42)	1.07 (0.83–1.39)
35–39 years	101 (34.47)	1.00 [Ref]	1.00 [Ref]	1.00 [Ref]	1.00 [Ref]
Sex, *n* (%)					
Males	54 (36.99)	1.18 (0.89–1.57)	1.17 (0.89–1.55)	1.20 (0.89–1.61)	1.27 (0.92–1.74)
Females	172 (37.64)	1.00 [Ref]	1.00 [Ref]	1.00 [Ref]	1.00 [Ref]
Region, *n* (%)					
South	65 (41.40)	1.09 (0.80–1.51)	1.21 (0.89–1.66)	1.05 (0.76–1.45)	0.96 (0.67–1.37)
Midwest	72 (40.91)	1.16 (0.85–1.59)	1.16 (0.85–1.57)	1.03 (0.75–1.42)	0.90 (0.64–1.29)
West	48 (33.33)	0.89 (0.64–1.25)	0.92 (0.66–1.28)	0.76 (0.54–1.08)	0.75 (0.52–1.09)
Missing	5 (35.71)	NA	NA	NA	NA
North-East	36 (32.14)	1.00 [Ref]	1.00 [Ref]	1.00 [Ref]	1.00 [Ref]

(Continues)

TABLE 2 | (Continued)

Characteristics	*N* (%) Discontinuing antidepressants after cancer diagnosis, by baseline category	Primary cox regression model HR (95% CI)	SA 1 Discontinuation equals ≥ 45-day gap in supply, HR (95% CI)	SA 2 Discontinuation equals ≥ 90-day gap in supply, HR (95% CI)	SA 3 Discontinuation equals ≥ 180-day gap in supply, HR (95% CI)
Antidepressants and other psychosocial treatments					
Antidepressants used, by CYP2D6 enzyme activity, *n* (%)					
Strong inhibitors	72 (35.3)	0.88 (0.63–1.22)	0.89 (0.65–1.23)	0.95 (0.67–1.35)	0.97 (0.66–1.42)
Weak or moderate inhibitors	113 (40.5)	0.93 (0.67–1.28)	0.93 (0.68–1.28)	1.02 (0.72–1.43)	1.14 (0.78–1.66)
Non-inhibitors	41 (34.2)	1.00 [Ref]	1.00 [Ref]	1.00 [Ref]	1.00 [Ref]
Antidepressants used, by class					
SNRIs, *n* (%)	36 (30.00)	0.80 (0.58–1.10)	0.78 (0.57–1.07)	0.84 (0.60–1.16)	0.98 (0.69–1.40)
No SNRIs, *n* (%)	190 (39.34)	1.00 [Ref]	1.00 [Ref]	1.00 [Ref]	1.00 [Ref]
NDRI (Bupropion), *n* (%)	**23 (25.00)**	0.95 (0.67–1.37)	0.93 (0.66–1.31)	0.94 (0.64–1.36)	1.18 (0.79–1.74)
No NDRI (Bupropion), *n* (%)	**203 (39.73)**	1.00 [Ref]	1.00 [Ref]	1.00 [Ref]	1.00 [Ref]
Psychotropic polypharmacy, *n* (%)	58 (32.77)	0.86 (0.67–1.11)	0.87 (0.68–1.11)	0.91 (0.70–1.18)	0.85 (0.64–1.13)
No Psychotropic polypharmacy, *n* (%)	168 (39.44)	1.00 [Ref]	1.00 [Ref]	1.00 [Ref]	1.0 [Ref]
Past 90 Days' concurrent medications					
Other CYP2D6 Inhibitors, *n* (%)	17 (45.95)	1.09 (0.72–1.66)	1.15 (0.77–1.73)	0.78 (0.49–1.27)	0.86 (0.52–1.44)
No Other CYP2D6 Inhibitors, *n* (%)	209 (36.93)	1.00 [Ref]	1.00 [Ref]	1.0 [Ref]	1.00 [Ref]
Enzyme inducers, *n* (%)	17 (27.87)	**0.65 (0.44–0.97)**	0.68 (0.46–1.00)	**0.58 (0.38–0.89)**	**0.57 (0.35–0.92)**
No enzyme inducers, *n* (%)	209 (38.56)	1.00 [Ref]	1.00 [Ref]	1.00 [Ref]	1.00 [Ref]
CYP2D6 substrates, *n* (%)	17 (31.48)	1.12 (0.77–1.64)	1.06 (0.73–1.55)	1.18 (0.80–1.75)	1.45 (0.97–2.17)
No CYP2D6 substrates, *n* (%)	209 (38.07)	1.00 [Ref]	1.00 [Ref]	1.00 [Ref]	1.00 [Ref]

(Continues)

TABLE 2 | (Continued)

Characteristics	*N* (%) Discontinuing antidepressants after cancer diagnosis, by baseline category	Primary cox regression model HR (95% CI)	SA 1 Discontinuation equals ≥ 45-day gap in supply, HR (95% CI)	SA 2 Discontinuation equals ≥ 90-day gap in supply, HR (95% CI)	SA 3 Discontinuation equals ≥ 180-day gap in supply, HR (95% CI)
Mental health comorbidities					
Depressive disorder, *n* (%)	69 (33.17)	0.83 (0.65–1.05)	**0.78 (0.61–0.99)**	0.84 (0.65–1.09)	0.82 (0.62–1.09)
No depressive disorder, *n* (%)	157 (39.75)	1.00 [Ref]	1.00 [Ref]	1.00 [Ref]	1.00 [Ref]
Anxiety disorder, *n* (%)	81 (40.10)	1.02 (0.80–1.30)	1.10 (0.87–1.40)	0.94 (0.73–1.22)	0.89 (0.67–1.19)
No anxiety disorder, *n* (%)	145 (36.16)	1.00 [Ref]	1.00 [Ref]	1.00 [Ref]	1.00 [Ref]
Cancer and cancer treatment factors					
Primary cancer type, *n* (%)					
Brain, ONS	10 (32.26)	0.88 (0.51–1.49)	0.86 (0.51–1.45)	0.87 (0.50–1.49)	0.92 (0.50–1.67)
Breast	31 (33.70)	1.06 (0.74–1.52)	1.06 (0.75–1.51)	1.11 (0.76–1.61)	0.88 (0.58–1.35)
Melanoma of the skin	33 (41.25)	1.02 (0.71–1.47)	1.09 (0.77–1.55)	0.92 (0.62–1.36)	0.99 (0.65–1.50)
Lymphomas (Hodgkin's, Non-Hodgkin's)	15 (25.42)	0.89 (0.58–1.37)	0.91 (0.60–1.37)	1.00 (0.65–1.54)	0.94 (0.58–1.52)
Testicular germ cell	12 (41.38)	1.08 (0.63–1.87)	0.97 (0.57–1.68)	1.02 (0.57–1.81)	1.23 (0.68–2.23)
Leukemias	9 (56.25)	**1.97 (1.03–3.79)**	1.71 (0.89–3.26)	1.95 (0.99–3.84)	1.84 (0.88–3.87)
Cervix, uterus, ovaries	25 (47.17)	1.44 (0.97–2.14)	**1.57 (1.07–2.30)**	1.42 (0.94–2.15)	1.31 (0.83–2.06)
Other (Solid) tumors	45 (39.13)	0.98 (0.70–1.38)	0.96 (0.69–1.34)	0.98 (0.69–1.40)	0.94 (0.64–1.39)
Thyroid	46 (35.94)	1.00 [Ref]	1.00 [Ref]	1.00 [Ref]	1.00 [Ref]
Metastatic cancer at diagnosis, *n* (%)	18 (50.00)	1.15 (0.75–1.75)	1.18 (0.79–1.78)	0.91 (0.57–1.46)	0.91 (0.55–1.52)
No metastases at diagnosis, *n* (%)	208 (36.68)	1.00 [Ref]	1.00 [Ref]	1.00 [Ref]	1.00 [Ref]
Time trends					
Era of cancer diagnosis, *n* (%)					
2016–2020	29 (32.58)	**1.71 (1.28–2.29)**	**1.59 (1.19–2.12)**	**2.05 (1.52–2.77)**	**2.09 (1.51–2.89)**

(Continues)

TABLE 2 | (Continued)

Characteristics	*N* (%) Discontinuing antidepressants after cancer diagnosis, by baseline category	Primary cox regression model HR (95% CI)	SA 1 Discontinuation equals ≥ 45-day gap in supply, HR (95% CI)	SA 2 Discontinuation equals ≥ 90-day gap in supply, HR (95% CI)	SA 3 Discontinuation equals ≥ 180-day gap in supply, HR (95% CI)
2010–2015	103 (38.43)	1.19 (0.93–1.51)	1.21 (0.95–1.52)	**1.32 (1.03–1.70)**	1.19 (0.90–1.58)
2006–2009	89 (39.73)	1.00 [Ref]	1.00 [Ref]	1.00 [Ref]	1.00 [Ref]

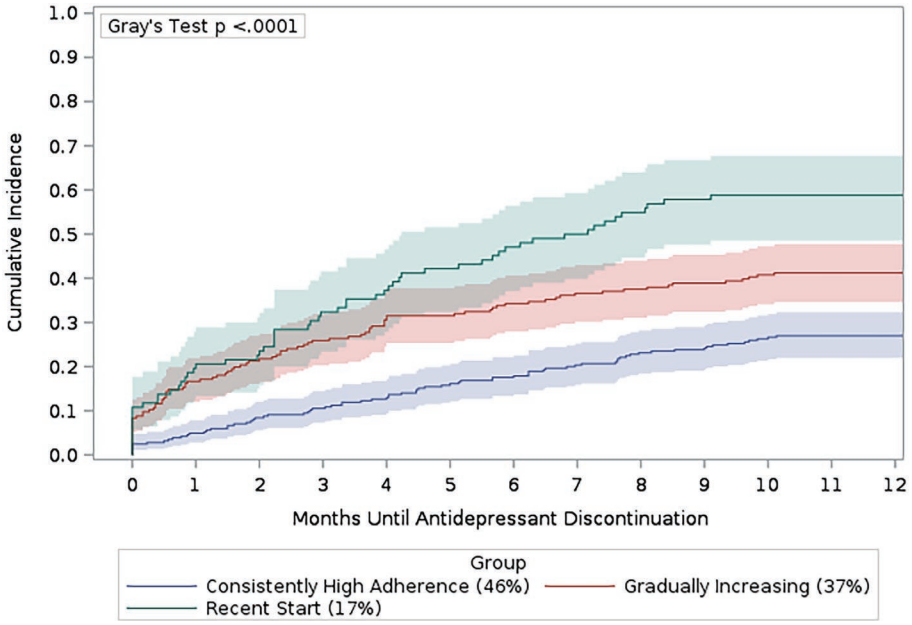
Note: Bold values represent statistically significant between-group differences (column 2) or hazard ratios (columns 3 to 6), with alpha set to 0.05.

Abbreviations: AYA, adolescents and young adults; CYP2D6, cytochrome P450 family 2 subfamily D member 6 enzyme; MH, mental health; NDRIs, norepinephrine dopamine reuptake inhibitors; NR, not reported due to cell suppression; SARIs, serotonin antagonist and reuptake inhibitors; SD, standard deviation; SNRIs, selective serotonin and noradrenaline reuptake inhibitors; SSRIs, selective serotonin reuptake inhibitors; ONS, other nervous system; TCAs, tricyclic antidepressants, tetracyclics e.g., mirtazapine; 5HT, antagonists/agonists, serotonin modulators/stimulators; 95% CI, 95% confidence interval.

study design precludes an assessment of antidepressant initiation at the time of AYA cancer diagnosis, which remains a gap in the current literature. Our finding of an association between past antidepressant adherence trajectory and risk of antidepressant discontinuation has important implications for the American Society of Clinical Oncology guideline [56], which recommends assessment of past antidepressant treatment and treatment response (e.g., adherence) history when making decisions about prescribing antidepressants after cancer diagnosis [11, 56].

Overall, this study's finding of a lower risk of antidepressant discontinuation among AYAs with a prior trajectory of consistently high adherence to antidepressants suggests clinical practice compliance with guidelines recommending careful evaluation of antidepressant use history before discontinuation post-cancer diagnosis. However, the observed higher risk of antidepressant discontinuation among AYAs in the *recent start* or *gradually increasing* antidepressant trajectory groups is concerning. This finding raises pertinent questions about present-day antidepressant management practices for AYAs who *recently started* or were *gradually increasing* antidepressant adherence right before their cancer diagnosis. In our study, the *recent start adherence* trajectory group was more likely comprised of younger AYAs and those with anxiety disorders. Little is known about how anxiety and other indications for antidepressant use are managed after antidepressants are discontinued, especially among young people newly diagnosed with cancer. Additionally, about 10% of AYAs in this cohort were concurrently using enzyme inducers with antidepressants within 90 days before cancer diagnosis. Evidence suggests that such concurrent use is associated with a decrease in CYP2D6 enzyme activity [31] and consequent marked reductions in plasma concentrations of antineoplastics like tamoxifen [30]. Each identified trajectory group in this study represents clusters of AYAs who share both observed and latent characteristics, as defined by the trajectory group membership based on similar antidepressant adherence patterns.

Strengths of this research include its (i) longitudinal measurement of baseline antidepressant adherence and identification of latent trajectory groups; (ii) study design which excludes AYAs' whose incident brain or ONS cancer diagnosis constitutes a contraindication to continued antidepressant (bupropion) use, (iii) sensitivity analyses assessing the potential for misclassification bias in our outcome definition of antidepressant discontinuation. However, this study is not without limitations. First, our measures of antidepressant adherence and discontinuation rely on observing AYAs' filled prescriptions but not actual antidepressant consumption. Secondly, as with all observational studies, our findings could be limited by unmeasured confounders associated with both membership in adherence trajectory groups and the risk of antidepressant discontinuation. Furthermore, the status of cancer diagnosis was not validated in the study population, although we applied a claims-based algorithm for identifying cancer which has been previously validated, albeit in an older cancer population, with high positive predictive value and specificity, but moderate sensitivity [21, 57]. Lastly, we were unable to assess the use of over-the-counter medications with relevant CYP2D6 activity.



Trajectory Group	Event Status	Months				
		0	3	6	9	12
Recent Start	Discontinuation (n)	11	33	48	59	60
	At risk (n)	**102**	**63**	**42**	**29**	**25**
Gradually Increasing	Discontinuation (n)	18	56	74	84	89
	At risk (n)	**216**	**147**	**112**	**91**	**75**
Consistently High	Discontinuation (n)	7	30	51	69	77
	At risk (n)	**285**	**239**	**189**	**156**	**133**

FIGURE 3 | Cumulative incidence curves with 95% confidence intervals, depicting the 1-year risk of antidepressant discontinuation after cancer diagnosis among 603 adolescents and young adults with prior antidepressant use, by prior antidepressant adherence trajectory group. PharMetrics Plus for academics, 2006–2020.

5 | Conclusion

Our findings suggest that past adherence trajectory is associated with antidepressant discontinuation after AYA cancer diagnosis. Subgroups with baseline trajectories of poor adherence may be disproportionally at a higher risk of antidepressant discontinuation after cancer diagnosis. Given that about one in ten AYAs use antidepressants before cancer diagnosis, a better understanding of the determinants, benefits, and harms of discontinuing antidepressant treatment and its potential effects on cancer outcomes and survivorship care is warranted. Further evidence is needed on how cancer treatment affects antidepressant treatment continuation as well as its impact on survivorship outcomes and mental health burden.

5.1 | Plain Language Summary

Among AYAs, we explored how differences in adherence to antidepressant treatment use before a cancer diagnosis could predict if they continue using antidepressants after being diagnosed. Using information from health insurance, we looked at records of over 6500 AYAs. If they used an antidepressant prior to being diagnosed with cancer, we measured if they adhered to the treatment in the year after cancer diagnosis. Based on how consistent they were in filling their prescriptions for antidepressants, we used a novel methodology to classify them into adherence groups: recent start, gradually increasing, and consistently high adherence. We then explored which of these adherence groups were more likely to discontinue using antidepressants after cancer diagnosis. We found that 1 in 10 individuals used antidepressants prior to being diagnosed with cancer. Of those, one-third had discontinued antidepressant treatment in the first 90 days after cancer diagnosis. The majority of those who discontinued belonged to the recent start group. AYAs in the consistently high adherence group had the lowest risk of discontinuing antidepressant treatment. Our research highlights the need to better understand the determinants, potential benefits, and harms of discontinuing antidepressant treatment that can impact cancer outcomes and survivorship care.

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Disclosure

The content expressed in this paper is solely the responsibility of the authors and does not necessarily represent the official view of the University of Maryland Baltimore ICTR, NCATS, or NIH. The statements, findings, conclusions, views, and opinions contained and expressed in this manuscript are based in part on data obtained under license from IQVIA. The statements, findings, conclusions, views, and opinions contained and expressed herein are not necessarily those of IQVIA or any of its affiliated or subsidiary entities. *Source:* IQVIA PharMetrics Plus for Academics, January 2006—December 2020. All Rights Reserved. All authors contributed equally to the work and have approved the manuscript and its submission. This manuscript has not been published elsewhere, accepted for publication elsewhere, or is under consideration for publication elsewhere.

Ethics Statement

This study was deemed exempt by the University of Maryland Baltimore Institutional Review Board. The reporting of this study conforms to the STROBE statement.

Conflicts of Interest

All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Oluwadamilola Onasanya and Udim Damachi have no conflicts to disclose at the time this work was conducted. Susan dos Reis receives funding from GSK for work unrelated to the content of the manuscript. She also consults for Alexion Pharmaceuticals. Wendy Camelo Castillo was supported in part by a research grant from the Investigator-Initiated Studies Program of Merck Sharp & Dohme Corp, unrelated to this work.

Data Availability Statement

The data underlying this article was provided by IQVIA with permission under a data use agreement. Per the data use agreement, data will not be shared, but IQVIA PharMetrics Plus for Academics data are available to investigators for research purposes and can be requested from IQVIA at https://www.iqvia.com/locations/united-states/library/fact-sheets/iqvia-pharmetrics-plus-for-academics-enhanced-with-mortality-data.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.