HHS Public Access

Author manuscript

J Cancer Surviv. Author manuscript; available in PMC 2024 December 01.

Published in final edited form as:

J Cancer Surviv. 2023 December ; 17(6): 1688–1697. doi:10.1007/s11764-022-01274-0.

Polypharmacy and medication fill nonadherence in a population-based sample of adolescent and young adult cancer survivors, 2008–2017

Andrea C. Betts, PhD, MPH[1], **Caitlin C. Murphy, PhD, MPH**[2,6], **L. Aubree Shay, PhD, MSSW**[3], **Bijal A. Balasubramanian, PhD, MBBS**[4,5], **Christine Markham, PhD**[2,6], **Michael E. Roth, MD**[7], **Marlyn Allicock, PhD, MPH**[1,5]

[1]Department of Health Promotion and Behavioral Sciences, University of Texas Health Science Center at Houston (UTHealth) School of Public Health, Dallas, TX, USA

[2]Department of Health Promotion and Behavioral Sciences, UTHealth School of Public Health, Houston, TX, USA

[3]Department of Health Promotion and Behavioral Sciences, UTHealth School of Public Health, San Antonio, TX, USA

[4]Department of Epidemiology, Human Genetics, and Environmental Sciences, UTHealth School of Public Health, Dallas, TX, USA

[5]Center for Health Promotion and Prevention Research, UTHealth School of Public Health, Dallas, TX, USA

[6]Center for Health Promotion and Prevention Research, UTHealth School of Public Health, Houston, TX, USA

[7]Division of Pediatrics, University of Texas MD Anderson Cancer Center, Houston, TX, USA.

Abstract

Purpose: We examined the association between polypharmacy—an established risk factor for nonadherence in the elderly—and medication fill nonadherence in a large national sample of adolescent and young adult cancer survivors (AYAs) in the U.S.

Methods: We pooled data (2008–2017) from the Medical Expenditure Panel Survey. We defined polypharmacy as ≥3 unique medications prescribed, based on self-report and pharmacy data, and medication fill nonadherence as self-reported delay or inability to obtain a necessary medication.

Corresponding author: Andrea C. Betts, UTHealth School of Public Health, 2777 N. Stemmons Fwy., Ste. 8400, Dallas, TX 75207; Andrea.C.Betts@uth.tmc.edu; (214) 546-2928.

Authors' contributions:

Conceptualization: A.C.B., C.C.M. Methodology: A.C.B, C.C.M., L.A.S., B.A.B., M.A., C.M. Formal analysis: A.C.B. Writing, original draft: A.C.B Writing, review and editing: A.C.B, C.C.M., L.A.S., B.A.B., C.M., M.R., M.A. Supervision: M.A., C.M.

Financial interests: A.C.B. reports consulting for Substack, Inc. C.C.M. reports consulting for Freenome. L.A.S., B.A.B., M.A., M.R., and C.M. have no disclosures.

Ethics approval: The study received an exemption from the Institutional Review Board at the University of Texas Health Science Center (#HSC-SPH-20-0207), as all data used in the study are publicly available.

Consent to participate/publish: Not applicable.

We estimated prevalence of medication fill nonadherence among AYAs (age 18–39 years with a cancer history). We used logistic regression to estimate the association between 1) polypharmacy and medication fill nonadherence in AYAs, and 2) total number of medications prescribed and medication fill nonadherence, controlling for sex, number of chronic conditions, disability, and survey year.

Results: AYAs (n=598) were predominantly female (76.2%) age 30–39 years (64.9%), and non-Hispanic White (72.1%). Nearly half were poor (19.0%) or near-poor/low income (21.6%). One in ten AYAs reported medication fill nonadherence (9.75%). Of these, more than 70% cited cost-related barriers as the reason. AYAs with polypharmacy had 2.49 times higher odds of medication fill nonadherence (95%CI 1.11–5.59), compared to those without polypharmacy. Odds of medication fill nonadherence increased by 16% with each additional medication prescribed (AOR 1.16, 95% CI 1.07–1.25).

Conclusions: Polypharmacy may be an important risk factor for medication fill nonadherence in AYAs in the U.S.

Implications for Cancer Survivors: Improving AYAs' medication adherence requires eliminating cost-related barriers, particularly for those with polypharmacy.

Keywords

adolescent and young adult cancer; medication adherence; polypharmacy; cancer survivors; prescription drugs

Introduction

Adherence to medications to treat cancer and chronic conditions is critical to achieving optimal health outcomes for cancer survivors.[1–5] The World Health Organization defines adherence as the "extent to which a person's behavior—taking medication, following a diet, and/or executing lifestyle changes—corresponds with agreed medical recommendations" (WHO, 2003, p. 3). Other definitions have emphasized the active and interactive nature of adherence (and conversely, nonadherence), in terms of the degree to which a patient assumes responsibility for and works to maintain health in collaboration with health care providers.[6,7] The National Comprehensive Cancer Network (NCCN) and the National Cancer Institute (NCI) have identified nonadherence as a primary concern in adolescents and young adults diagnosed with cancer between the ages of 15 to 39 (hereafter, AYAs).[6,8,9] Adherence to anticancer treatments is crucial to preventing poor response to therapy, recurrence/relapse, and progression.[3,10–15] Many AYAs face long cancer maintenance phases with oral chemotherapy, immunotherapy, and/or targeted agents which can last months to years beyond intensive treatment.[16–19] In addition, AYAs experience a high burden of early onset-chronic health conditions secondary to their cancer treatment; up to half of AYAs experience one or more comorbidities in addition to cancer.[20–24] These conditions, such as cardiovascular disease, often require one or more medications.[20,25] Yet nonadherence to medications ranges from 21% to 60% in AYAs during and after intensive treatment, compromising health, quality of life, and survival.[1,4,5,26–28]

Achieving treatment goals, including management of chronic conditions other than cancer, requires understanding drivers of nonadherence in this underserved population. Fifteen years ago, the NCI called for research identifying drivers of nonadherence in AYAs,[6,9] yet to date, research specific to this population has predominantly been conducted in small samples[29–38] and/or single-center studies.[3,39] Polypharmacy—taking multiple medications—is a known risk factor for nonadherence in the elderly; for example, in cohort studies, polypharmacy resulted in 33–44% lower odds of medication adherence, and each additional medication reduced adherence by 16%.[40–42] Recent studies demonstrate that AYAs have double the prevalence of polypharmacy compared to age- and sex-matched peers without cancer.[20,25,43] Further, AYAs have a high financial burden of treatment, are frequently uninsured, and have reported cost as a barrier to accessing medications, suggesting that having more prescriptions to fill may impede adherence.[27,44–47] However, to our knowledge, no studies have examined the association between polypharmacy and medication fill nonadherence in AYAs.

Research to determine whether polypharmacy and number of medications prescribed are risk factors for nonadherence can inform interventions and guide patient-provider discussions around AYAs' prescription medications to facilitate adherence. Such knowledge is particularly needed given recent suggestions that prescription medications may be may be a primary strategy for reducing the burden of accelerated aging in AYAs.[48] To address these gaps, we used the Medical Expenditure Panel Survey (MEPS) to examine the association between polypharmacy and medication fill nonadherence in a large, nationally representative sample of AYA cancer survivors in the United States. We focused on delay in obtaining or inability to obtain prescription medications (hereafter, "medication fill nonadherence"), one of the most commonly studied dimensions of nonadherence.[49,50]

Methods

Data source and population.

MEPS is a population-based survey of U.S. households, in which adults (age ≥ 18 years) are invited to participate in five interviews (hereafter, "Rounds") over two years to collect detailed information on healthcare utilization, expenditures, and health status of each member of the household. Details of the survey design are reported elsewhere.[51] Our cross-sectional study pooled data from 2008–2017 (Panels 13–21).[52] To minimize missing data, we included only individuals who participated in both survey years (n=147,082).

AYAs.

We defined AYAs as individuals age 18–39 years in the year of the first survey (n=43,263) and who reported having ever been diagnosed with cancer or malignancy by a doctor or other healthcare professional (n=689). MEPS only collects cancer information for individuals age ≥ 18 years, and since 2012, age at diagnosis is not reported. Based on the subset of respondents for whom age at diagnosis is reported (i.e., surveys conducted before 2012), we estimate that more than 90% of our sample were diagnosed between the ages of 15 to 39 years, with the remainder diagnosed before age 15 years. Similar to other

analyses,[27,43,53] we excluded those who reported a history of non-melanoma skin cancer or skin cancer of an unknown type (n=88).

Sociodemographic characteristics.

Sociodemographics were measured in the year of the first survey and included age, sex, race and ethnicity, marital status, education, poverty status, health insurance, and usual source of care. MEPS includes poverty status categories based on family income as a percentage of the applicable poverty line, including poor (<100%), near poor (100% to less than 125%), low income (125% to less than 200%), middle income (200% to less than 400%), and high income (≥400%). For usual source of care, interviewers asked whether, for each household member, there is a particular doctor's office, clinic, health center, or other place that the household member usually goes to if he/she is sick or needs advice about his/her health.

Clinical factors and health indicators.

We examined cancer types and health indicators including chronic conditions and disability. Cancer types included breast, cervix, melanoma, lymphoma, and uterine. Beginning in 2012, cancer types reported with a frequency of <20 per year among all MEPS participants or those that were considered clinically rare (defined by the National Institutes of Health's list of rare diseases[54]) were categorized as "other" due to privacy concerns. Common cancers in AYAs that MEPS categorized as "other" included brain, leukemia, thyroid, and testicular cancers. Similarly, we categorized the following cancer types with frequency <20 in our sample as "other": bladder, blood, colon, esophageal, kidney, larynx, liver, lung, mouth/tongue/lip, ovarian, pancreatic, prostate, rectal, muscle/soft tissue/fat, and stomach cancers. We derived chronic conditions from among priority conditions asked about in MEPS, a majority of which have demonstrated prevalence in AYAs.[23,55,56] These included arthritis, asthma, diabetes, emphysema, heart disease (including angina, coronary heart disease, myocardial infarction, and other heart disease), hypercholesterolemia, hypertension, and stroke. We summed MEPS priority conditions for each individual to create a count of chronic conditions (0,1,2+). Disability (yes/no) was based on reporting any limitation in the following domains: instrumental activities of daily living; activities of daily living; physical function; work, school, or housework; or seeing and/or hearing.

Polypharmacy.

We used prescription drug information collected in Rounds 1–3 (approximately one calendar year) to estimate polypharmacy in AYAs. MEPS verifies self-reported information on prescription medications collected during interviews by contacting a subset of participants' pharmacies. Non-prescription medications (e.g., over-the-counter, supplements) are not included. We used generic drug names reported for each individual to determine the number of unique prescribed medications per individual, so that drugs differing by dose or manufacturer were not double-counted. Consistent with our prior work on polypharmacy,[43] we summed the number of unique prescribed medications across Rounds 1–3. Consistent with the literature suggesting that optimal cutpoints for polypharmacy vary by outcome,[57] we examined the proportion of AYAs who were nonadherent by the number of medications prescribed and selected a threshold of ≥3 medications to define polypharmacy. This threshold has been used in the literature[58] and increased the precision of estimates. We

also examined the number of prescribed medications as a continuous variable in a separate model.

Medication fill nonadherence.

Adherence to medication is a complex behavior, consisting of deciding to take the medication in consultation with a provider, filling the medication, initiating and taking it as prescribed, and continuing to take it for the recommended course.[59,60] Consistent with other studies of medication adherence/nonadherence,[49,50,59,61] we focused on the behavior of filling the medication. In Round 4, MEPS asks participants if, in the past 12 months, they were 1) delayed in getting prescription medicines they or a doctor believed necessary; and 2) unable to get prescription medicines they or a doctor believed necessary. We measured medication fill nonadherence as a dichotomous variable; participants responding "yes" to either question in Round 4 were categorized as having medication fill nonadherence. Participants were also asked to identify, from among predetermined response options, the main reason for the delay and/or inability to get needed prescriptions. Response options included: could not afford care, insurance would not approve/cover/pay, doctor refused insurance plan, problems getting to doctor's office, different language, couldn't get time off work, didn't know where to go to get care, was refused services, couldn't get childcare, didn't have time or took too long, or other.

Statistical analysis.

We described sociodemographic characteristics, clinical factors, and health indicators of AYAs. We estimated prevalence of medication fill nonadherence and reasons among AYAs.

We then used multivariable logistic regression to estimate the associations of polypharmacy (≥3 medications) and medication fill nonadherence (Model 1), as well as the continuous number of medications prescribed and medication fill nonadherence in AYAs (Model 2). We used a theory-based model[62] consistent with Gellad et al.'s conceptual model of medication adherence in adults[63] to guide the selection of potential confounders identified in the AYA literature.[3,26,29,43,64,65,66] These included sex, chronic conditions, and disability. To control for secular trends, we also included year of first survey in the multivariable models.

Because of the complex survey design, we used survey weights, sampling strata, and sampling units in all analyses. We conducted analyses using SAS version 9.4 (SAS Institute, Cary, NC). Our study received Institutional Review Board exemption from the University of Texas Health Science Center at Houston (#HSC-SPH-20-0207).

Results

We excluded participants with missing data on the primary outcome (n=3) from the analysis. We identified 598 AYAs, the majority of whom were age ≥30 years, female, and non-Hispanic White (Table 1). Nearly half were either poor or near-poor/low income. Approximately one in four AYAs used Medicaid or other public insurance, and one in six were uninsured. More than one-fourth of AYAs did not have a usual source of care. The most common cancer type was "other," followed by cervix and melanoma. Roughly half

of AYAs reported having been diagnosed with a chronic condition other than cancer, and one-fourth reported a disability. More than half of AYAs had polypharmacy.

Approximately one in ten AYAs reported medication fill nonadherence (9.75%, 95% CI 6.76%–12.75%). Among those with medication fill nonadherence (n=48), reasons were similar for delaying and not obtaining medications (Figure 1). Specifically, more than a third of AYAs who delayed or did not obtain a needed medication reported that they could not afford it, and a similar proportion reported that insurance would not approve/cover/pay for it.

As shown in Table 2, AYAs with polypharmacy had nearly two and a half times higher odds of medication fill nonadherence compared to those without polypharmacy (Model 1). When modeled as a continuous variable (Model 2), odds of medication fill nonadherence increased by 16% with each additional medication prescribed.

Discussion

In a large, nationally representative sample using one of the most comprehensive and robust sources of national data on healthcare utilization and expenditures,[67–68] we found that AYA cancer survivors who were prescribed three or more medications were more than twice as likely to delay or not obtain needed medications, compared to those prescribed fewer medications. Furthermore, each additional medication conferred a 16% increase in odds of medication fill nonadherence. Thus managing the overall number of medications prescribed, with an eye toward cost, may facilitate adherence to critical medications in AYAs. While other studies have examined medication nonadherence due to cost,[27,53] to our knowledge, our study is the first to identify polypharmacy as a driver of medication fill nonadherence in AYAs and to demonstrate negative consequences of being prescribed multiple medications. These findings fill a critical gap in the sparse literature on nonadherence in AYAs, identifying polypharmacy as a key risk factor that can be screened for in a clinical encounter.

Approximately one in ten AYAs in our study reported that they delayed or were unable to obtain medications they perceived to be necessary. Our study focused on medication fill nonadherence, and nonadherence is likely higher when other dimensions of use (e.g., deciding not to take the medication, skipping doses, taking fewer doses than prescribed) are considered. The association between polypharmacy and nonadherence may persist or be even stronger in AYAs when these dimensions are assessed because individuals with polypharmacy may have more opportunities to miss doses and more complex medications regimens.[60] Importantly, nonadherence may also vary depending on the conditions being treated and the types of medications studied.[60,64] For example, in a retrospective cohort study of breast cancer survivors' adherence to adjuvant endocrine therapy (AET),[58] survivors with polypharmacy who were frequently taking antihypertensives or lipid-lowering drugs were more likely to adhere to AET, while those frequently taking anxiolytics/antipsychotics, antidepressants, insulin, or opioids were less likely to adhere to AET. Notably, AYAs experience a high burden of mental health conditions, which have been linked to nonadherence.[29,69] Future research should examine the association of polypharmacy and nonadherence in terms of medication use (versus fill) and specific

medications of interest in AYAs, such as oral anticancer medications and cardiovascular agents. In addition, variation by factors such as mental health conditions should be explored.

More than 70% of AYAs who delayed or did not obtain a medication in our study attributed this to cost-related barriers—most commonly an inability to afford the medication and, secondarily, problems with insurance coverage. These findings reinforce those of two other national studies demonstrating cost-related medication nonadherence in up to one-fourth of AYAs.[27,53] Notably, those studies used a measure of adherence that included skipping medication doses to save money, taking less medicine to save money, and delaying filling a prescription to save money. Affordability is influenced by financial resources, and about 40% of AYAs in our sample were poor, near poor, or low income, and one in six were uninsured. This is consistent with other studies showing high poverty and lack of insurance in AYAs.[70–77] A large literature documents the financial burden of cancer treatment in AYAs, whose education, early career development, earnings, and eligibility for employer-based insurance may be disrupted by cancer at the same time that they incur considerable out of pocket medical costs,[44,45,47,55,78–82] including rising prescription costs.[83] Although the Patient Protection and Affordable Care Act introduced key provisions to reduce uninsurance in AYAs,[44,84] many remain underinsured or have high out-of-pocket expenses.[44,47]

Our study's findings underscore recent NCCN Guidelines for AYAs[85] and a growing literature recommending clinical assessment of medication adherence and reasons for nonadherence and provision of resources to address financial barriers.[26,27,47,86] Evidence supports the routine clinical use of valid patient-reported measures of adherence,[87] such as the brief Morisky Adherence Questionnaire[88,89] or the interview-based Medication Adherence Measure.[90] While important to determining polypharmacy, medication reviews in which patients are asked if they take a medication (yes/no) do not adequately capture adherence. Consideration should also be given to the clinical workflow and visibility of polypharmacy and adherence assessments to the medical provider, as nurses or medical assistants often assess medication use at the beginning of an appointment when the provider is not present. In addition, technology may be leveraged to assess polypharmacy and medication fill nonadherence. For example, regionally integrated electronic health record platforms may facilitate accurate medication review, given that AYAs' care is often fragmented,[91–93] and integration with pharmacy systems could enable providers to be notified when a medication has not been filled. When cost is identified as a barrier, AYAs should be connected to resources such as medication assistance programs and financial counseling;[47,85] NCCN offers tools for locating these resources including a searchable app (available at https://www.nccn.org/business-policy/business/virtual-reimbursement-resource-room-and-appresources). Finally, reform at the payor-level is urgently needed to prevent financial toxicity of cancer treatment and ensure affordability of medications for AYAs in the United States, who may live with the physical, psychosocial, and financial costs of cancer for many years.

Our findings using a national sample of AYAs in the U.S. cannot be generalized to AYAs in other countries, where health care systems differ. Further, our findings should be considered in light of limitations. Notably, MEPS does not collect information on

cancer stage, treatment status, or time since diagnosis, and further research is needed to identify differences in polypharmacy and its association with medication fill nonadherence by key clinical factors, such as whether patients are on or off active cancer treatment. In addition, our measure of medication fill nonadherence was based on self-report and may underestimate prevalence of medication fill nonadherence in AYAs. Finally, while our models controlled for chronic conditions and disability, it is important to note that these factors frequently co-occur with polypharmacy. Qualitative studies should explore how AYAs, including those with chronic conditions and disabilities, experience polypharmacy and nonadherence.

Conclusions

Polypharmacy may be an important risk factor for medication fill nonadherence in AYAs. Financial support and cost-reducing measures are needed for AYAs taking multiple medications to increase adherence, improve health outcomes, and enhance quality of life for this population experiencing late effects of cancer and its treatment. Future studies should develop and test interventions to improve adherence to medications among AYAs, with specific attention to affordability and other medications co-prescribed.

Funding:

A.C.B. was supported by the American Cancer Society (ACS; RSG-21-0460) and the Cancer Control Research Training Program, UTHealth School of Public Health (National Cancer Institute/National Institutes of Health Grant T32 CA057712). The content is solely the responsibility of the authors and does not necessarily represent the official views of the NCI, NIH, or ACS.

Data availability:

The data underlying this article were derived from sources in the public domain: IPUMS Health Surveys, Medical Expenditure Panel Survey, Version 1.1 https://doi.org/10.18128/D071.V1.1, and Agency for Healthcare Research and Quality, Medical Expenditure Panel Survey, https://meps.ahrq.gov/mepsweb/.

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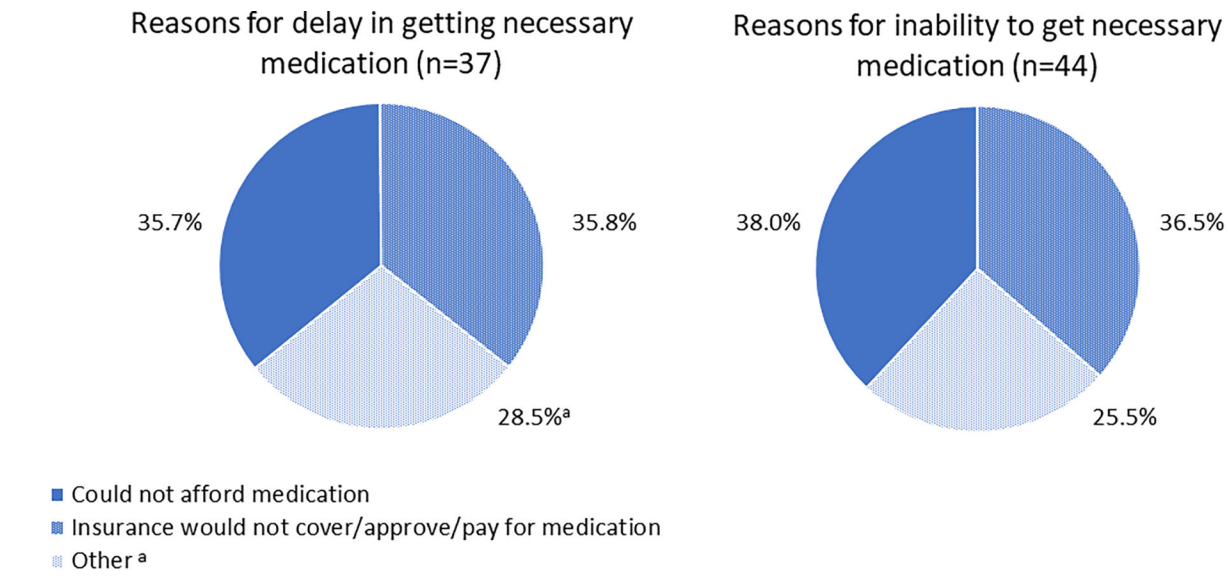

[a] Other reasons for delay getting medications included problems getting to doctor's office (n=1), didn't have time / took too long (n=1), and other unspecified (n=7); other reasons for inability to get medications included problems getting to doctor's office (n=1) and other unspecified (n=4)

Figure 1.

Reasons for delay in getting necessary medication (n=37) and inability to obtain necessary medication (n=44), among AYAs with a history of cancer (n=598)

Table 1.

Characteristics of AYAs with a history of cancer, Medical Expenditures Panel Survey, 2008–2017 (n=598)

	n	weighted %
Sociodemographics		
Age in first survey year		
18–24	79	14.3
25–29	130	20.8
30–34	171	26.8
35–39	218	38.1
Sex		
Female	479	76.2
Male	119	23.8
Race/ethnicity		
Hispanic	165	15.5
Non-Hispanic Black	77	7.1
Non-Hispanic White	321	72.1
Other Non-Hispanic	35	5.3
Marital status		
Married	246	45.8
Not married	352	54.2
Education		
Less than high school	108	13.5
High school degree	170	24.7
Some college	165	26.9
College degree or higher	155	34.9
Poverty status		
Poor (<100% FPL)	167	19.0
Near poor and low income (100–199% FPL)	153	21.6
Middle income (200%-399% FPL)	168	32.2
High income (≥400% FPL)	110	27.2
Insurance		
Private	297	61.1
Medicaid/other public	188	23.7
Uninsured (only)	113	15.2
Usual source of care		
No	177	27.1
Yes	416	71.8
Unknown	5	1.1
Clinical factors		
Cancer type		
Breast	42	6.6
Cervix	207	34.7

	n	weighted %
Melanoma	47	10.6
Lymphoma	28	4.4
Uterine[a]	45	5.3
Other[b]	239	39.9
Health indicators		
Arthritis[c]	111	18.0
Asthma	110	18.5
Diabetes	31	3.9
Emphysema	8	1.2
Heart disease[d]	67	13.2
Hypercholesterolemia	91	15.3
Hypertension	118	18.2
Stroke	23	2.8
Number of chronic conditions		
0	293	49.0
1	161	27.1
2+	144	23.9
Disability[e]		
No	411	72.6
Yes	180	26.5
Unknown	7	0.9
Polypharmacy[f]		
No	296	47.7
Yes	302	52.3

NOTE: To account for the complex survey design, we used survey weights, sampling strata, and primary sampling units when calculating standard errors for weighted survey estimates

[a] Uterine cancers reported in the year 2012 were grouped as "Other" because they appeared on National Institutes of Health's list of rare diseases. Weighted percent based on n=530 for whom uterine cancer data are available.

[b] "Other" cancers include bladder, blood, brain, colon, esophageal, kidney, larynx, leukemia, liver, lung, mouth/tongue/lip, ovarian, pancreatic, prostate, rectal, soft tissue, stomach, testicular, thyroid

[c] Includes arthritis, gout, lupus, and fibromyalgia

[d] Includes angina pectoris, myocardial infarction, coronary heart disease, or other heart disease

[e] Includes any reported limitation in activities of daily living, instrumental activities of daily living, work, seeing and/or hearing

[f] ≥3 unique prescription medications

Table 2.

Association between polypharmacy and medication fill nonadherence (Model 1) and number of medications prescribed and medication fill nonadherence (Model 2) in AYAs with a history of cancer (n=598)

	Unadjusted			Model 1[a]			Model 2[a]		
Characteristic	**OR**	**95% CI**	**P**	**AOR**	**95% CI**	**P**	**AOR**	**95% CI**	**P**
Female sex	3.91	1.30–11.73	0.02	3.89	1.21–12.53	0.02	3.70	1.13–12.09	0.03
Chronic conditions			0.03			0.10			0.20
0	REF	REF		REF	REF		REF	REF	
1+	2.57	1.09–6.07		2.07	0.88–4.86		1.82	0.73–4.49	
Disability			0.08			0.95			0.46
No/Unknown	REF	REF		REF	REF		REF	REF	
Yes	1.84	0.91–3.69		1.03	0.46–2.31		0.71	0.29–1.76	
Polypharmacy			<0.01			0.03			
No	REF	REF		REF	REF				
Yes	3.35	1.51–7.40		2.49	1.11–5.59				
Number of prescribed medications	1.17	1.09–1.25	<0.01				1.16	1.07–1.25	<0.01

[a]Adjusted for year of first survey, sex, number of chronic conditions, disability.