

# Assessing the Impact of Antidepressants on Cancer Treatment: A Retrospective Analysis of 14 Antineoplastic Agents

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**Background:** Rates of depression among patients with cancer have increased, illustrating the importance of mental health care during treatment. This study sought to identify antidepressants with boxed warnings for increased suicidal risk and known to have drug-drug interactions.

**Methods:** This retrospective analysis used the US Department of Defense Cancer Registry, Comprehensive Ambulatory/Professional Encounter Record, and Pharmacy Data Transaction Service databases. Patients with cancer were identified, and data collected included patient diagnoses and dispensed medications. Medications were divided into groups based on the pharmacy database therapeutic codes.

**Results:** This analysis identified 2210 patients with 2104 documented diagnoses, 2113 recorded prescriptions treated with 14 antineoplastic agents. Breast, lung, testicular, endometrial, and ovarian were the most common cancers among the 51 types treated. Of the 2113 patients with recorded prescriptions, 1297 patients (61.4%) received 109 cancer medications, including 96 different antineoplastics;

750 (35.5%) patients were prescribed 17 different types of antidepressants. In addition, 1089 unique prescriptions were filled (8 medications prescribed for  $\geq 1000$  patients). Patients who took antidepressants had more diagnosed health issues and received more prescription medications. The mean number of prescriptions dispensed in patients prescribed antidepressants vs those not prescribed antidepressants showed a significant difference ( $P < .05$ ) in all groups, except anticonvulsants ( $P = .12$ ) and other antipsychotics ( $P = .09$ ). Although antidepressant treatment increased, there was no significant change in antidepressants prescribed annually (mean [SD] 23% [5%]).

**Conclusions:** The study provides a comprehensive overview of noncancer medication use in the Military Health System during systemic cancer treatment, specifically the use of antidepressants from 2003 to 2022, and highlights potential drug interactions that may affect treatment outcomes. Future research should prioritize the analysis of drug-drug interactions between cancer and noncancer drugs with antidepressants.

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Cancer patients experience depression at rates  $> 5$  times that of the general population.<sup>1-11</sup> Despite an increase in palliative care use, depression rates continued to rise.<sup>2-4</sup> Between 5% to 16% of outpatients, 4% to 14% of inpatients, and up to 49% of patients receiving palliative care experience depression.<sup>5</sup> This issue also impacts families and caregivers.<sup>1</sup> A 2021 meta-analysis found that 23% of active military personnel and 20% of veterans experience depression.<sup>11</sup>

Antidepressants approved by the US Food and Drug Administration (FDA) target the serotonin, norepinephrine, or dopamine systems and include boxed warnings about an increased risk of suicidal thoughts in adults aged 18 to 24 years.<sup>12,13</sup> These medications are categorized into several classes: monoamine oxidase inhibitors (MAOIs), tricyclic antidepressants (TCAs), tetracyclic antidepressants (TeCAs), norepinephrine-dopamine reuptake inhibitors (NDRIs), selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SRNIs), serotonin receptor modulators (SRMs), serotonin-melatonin receptor antagonists (SMRAs), and *N*-methyl-D-aspartate receptor antagonists (NMDARs).<sup>14,15</sup> The first

FDA-approved antidepressants, iproniazid (an MAOI) and imipramine (a TCA) laid the foundation for the development of newer classes like SSRIs and SRNIs.<sup>15-17</sup>

Older antidepressants such as MAOIs and TCAs are used less due to their adverse effects (AEs) and drug interactions. MAOIs, such as iproniazid, selegiline, moclobemide, tranylcypromine, isocarboxazid, and phenelzine, have numerous AEs and drug interactions, making them unsuitable for first- or second-line treatment of depression.<sup>14,18-21</sup> TCAs such as doxepin, amitriptyline, nortriptyline, imipramine, desipramine, clomipramine, trimipramine, protriptyline, maprotiline, and amoxapine have a narrow therapeutic index requiring careful monitoring for signs of toxicity such as QRS widening, tremors, or confusion. Despite the issues, TCAs are generally classified as second-line agents for major depressive disorder (MDD). TCAs have off-label uses for migraine prophylaxis, treatment of obsessive-compulsive disorder (OCD), insomnia, and chronic pain management first-line.<sup>14,22-29</sup>

Newer antidepressants, including TeCAs and NDRIs, are typically more effective, but also come with safety concerns. TeCAs like mirtazapine interact with several medications,

**TABLE 1.** Antineoplastic Agents Prescribed to Patients in the DoD Cancer Registry JPC<sup>a</sup>

Agent	Patients, No.	Metastasis, No.	FDA approval	Years observed	Year extracted	CYP pathway
Paclitaxel	687	15	1992	1996-2021	2022	2C8 <sup>b</sup> , 3A4
Cisplatin	600	3	1978	1994-2022	2022	NA
Erlotinib	382	5	2004	2001-2020	2021	3A4 <sup>b</sup> , 1A1, 1A2, 2C
Docetaxel	337	2	1995	1988-2022	2022	3A4
Pemetrexed	102	0	2004	2003-2021	2022	NA
Osimertinib	34	0	2015	2015-2021	2023	3A4
Gefitinib	33	0	2003	2002-2017	2021	3A4 <sup>b</sup> , 3A5, 2D6
Trastuzumab E	25	0	2013	2008-2022	2023	NA
Alectinib	10	0	2015	2015-2021	2023	3A4
Crizotinib	8	0	2011	2013-2021	2023	3A4
Lorlatinib	2	0	2021	2021-2022	2023	3A4 <sup>b</sup> , 2C8, 2C19, 3A5
Brigatinib	1	0	2017	2021	2023	2C8, 3A4
Entrectinib	1	0	2019	2021	2023	3A4
Trastuzumab D	1	0	2019	2021	2023	NA

Abbreviations: CYP, cytochrome P450; D, deruxtecán; DoD, US Department of Defense; E, emtansine; FDA, US Food and Drug Administration; JPC, Joint Pathology Center; NA, not applicable.

<sup>a</sup>Data extraction occurred 3 times from 2021 to 2023; data for erlotinib, gefitinib, and paclitaxel were published.<sup>78,79</sup>

<sup>b</sup>Major pathways.

including MAOIs, serotonin-increasing drugs, alcohol, cannabidiol, and marijuana. Mirtazapine is FDA-approved for the treatment of moderate to severe depression in adults. It is also used off-label to treat insomnia, panic disorder, posttraumatic stress disorder (PTSD), generalized anxiety disorder (GAD), social anxiety disorder (SAD), headaches, and migraines. Compared to other antidepressants, mirtazapine is effective for all stages of depression and addresses a broad range of related symptoms.<sup>14,30-34</sup> NDRI, such as bupropion, also interact with various medications, including MAOIs, other antidepressants, stimulants, and alcohol. Bupropion is FDA-approved for smoking cessation and to treat depression and SAD. It is also used off-label for depression-related bipolar disorder or sexual dysfunction, attention-deficit/hyperactivity disorder (ADHD), and obesity.<sup>14,35-42</sup>

SSRIs, SNRIs, and SRMs should be used with caution. SSRIs such as sertraline, citalopram, escitalopram, fluoxetine, paroxetine, and fluvoxamine are first-line treatments for depression and various psychiatric disorders due to their safety and efficacy. Common AEs of SSRIs include sexual dysfunction, sleep disturbances, weight changes, and gastrointestinal (GI) issues. SSRIs can prolong the QT interval, posing a risk of life-threatening arrhythmia, and may interact with other medications, necessitating treatment adjustments. The FDA approved SSRIs for MDD, GAD, bulimia nervosa, bipolar depression, OCD, panic disorder, premenstrual dysphoric disorder, treatment-resistant depression,

PTSD, and SAD. Off-label uses include binge eating disorder, body dysmorphic disorder, fibromyalgia, premature ejaculation, paraphilias, autism, Raynaud phenomenon, and vasomotor symptoms associated with menopause. Among SSRIs, sertraline and escitalopram are noted for their effectiveness and tolerability.<sup>14,43-53</sup>

SNRIs, including duloxetine, venlafaxine, desvenlafaxine, milnacipran, and levomilnacipran, may increase bleeding risk, especially when taken with blood thinners. They can also elevate blood pressure, which may worsen if combined with stimulants. SNRIs may interact with other medications that affect serotonin levels, increasing the risk of serotonin syndrome when taken with triptans, pain medications, or other antidepressants.<sup>14</sup> Desvenlafaxine has been approved by the FDA (but not by the European Medicines Agency).<sup>54-56</sup> Duloxetine is FDA-approved for the treatment of depression, neuropathic pain, anxiety disorders, fibromyalgia, and musculoskeletal disorders. It is used off-label to treat chemotherapy-induced peripheral neuropathy and stress urinary incontinence.<sup>57-61</sup> Venlafaxine is FDA-approved for depression, SAD, and panic disorder, and is prescribed off-label to treat ADHD, neuropathy, fibromyalgia, cataplexy, and PTSD, either alone or in combination with other medications.<sup>62,63</sup> Milnacipran is not approved for MDD; levomilnacipran received approval in 2013.<sup>64</sup>

SRMs such as trazodone, nefazodone, vilazodone, and vortioxetine also function as serotonin reuptake inhibitors.<sup>14,15</sup> Trazodone is FDA-approved for MDD. It has been used

TABLE 2. JPC DoD Cancer Registry Overview<sup>a</sup>

Demographics	Patients, No. (%) (n = 2242)	ADs, No. (%) (n = 750)
Age		
≤ 50 y	701 (31)	269 (36)
> 50 y	1541 (69)	481 (64)
Cancer stage		
I, II, unknown	1267 (57)	436 (58)
III, IV	975 (43)	314 (42)
Common cancers (≥ 1%)		
Breast	800 (36)	299 (40)
Lung	394 (18)	130 (17)
Testicular	110 (5)	27 (4)
Endometrial	102 (5)	34 (5)
Ovarian	100 (4)	36 (5)
Tongue	90 (4)	21 (3)
Tonsil	84 (4)	22 (3)
Cervical	64 (3)	21 (3)
Prostate	51 (2)	14 (2)
Bladder	47 (2)	16 (2)
Esophagus	28 (1)	8 (1)
Oropharynx	28 (1)	11 (1)
Stomach	27 (1)	4 (1)
Fallopian tube	25 (1)	10 (1)
Nasopharynx	24 (1)	8 (1)
Pancreatic	22 (1)	9 (1)
Larynx	21 (1)	7 (1)
Liver	21 (1)	8 (1)
Unknown primary	20 (1)	6 (1)
Bone, joint, cartilage	17 (1)	6 (1)
Kidney/renal	16 (1)	3 (< 1)
Mouth	13 (1)	4 (1)
Peritoneal	13 (1)	5 (1)
Rare cancers (< 1%)		
Mediastinum and pleura	11 (< 1)	4 (1)
Biliary tract	9 (< 1)	4 (1)
Nasal and sinus	8 (< 1)	3 (< 1)
Sarcoma	8 (< 1)	6 (1)
Vaginal	8 (< 1)	1 (< 1)
Vulvar	8 (< 1)	3 (< 1)
Urethral	7 (< 1)	2 (< 1)
Gallbladder	6 (< 1)	3 (< 1)
Other/ill-defined	6 (< 1)	1 (< 1)
Salivary gland	6 (< 1)	2 (< 1)
Anal	5 (< 1)	2 (< 1)
Colon	5 (< 1)	0 (0)
Colorectal	5 (< 1)	1 (< 1)
Lymphoma	5 (< 1)	1 (< 1)
Gum	4 (< 1)	0 (0)
Thymus	4 (< 1)	2 (< 1)
Hypopharyngeal	3 (< 1)	1 (< 1)
Pharyngeal	3 (< 1)	2 (< 1)
Trachea	3 (< 1)	1 (< 1)
Pyriform sinus	2 (< 1)	1 (< 1)
Thyroid gland	2 (< 1)	0 (0)
Duodenal	1 (< 1)	1 (< 1)
Endocrine	1 (< 1)	0 (0)
Gastrointestinal	1 (< 1)	0 (0)
Medulloblastoma	1 (< 1)	0 (0)
Penile	1 (< 1)	0 (0)
Retinoblastoma	1 (< 1)	0 (0)
Squamous cell skin	1 (< 1)	0 (0)

Abbreviations: ADs, antidepressants prescribed; DoD, US Department of Defense; JPC, Joint Pathology Center.

<sup>a</sup>Of 2242 entries for 2210 patients, 51 types of cancer were recorded, with 42 types documented among the 750 patients prescribed antidepressants.

off-label to treat anxiety, Alzheimer disease, substance misuse, bulimia nervosa, insomnia, fibromyalgia, and PTSD when first-line SSRIs are ineffective. A notable AE of trazodone is orthostatic hypotension, which can lead to dizziness and increase the risk of falls, especially in geriatric patients.<sup>65-70</sup> Nefazodone was discontinued in Europe in 2003 due to rare cases of liver toxicity but remains available in the US.<sup>71-74</sup> Vilazodone and vortioxetine are FDA-approved.

The latest classes of antidepressants include SMRAs and NMDARAs.<sup>14</sup> Agomelatine, an SMRA, was approved in Europe in 2009 but rejected by the FDA in 2011 due to liver toxicity.<sup>75</sup> NMDARAs like esketamine and a combination of dextromethorphan and bupropion received FDA approval in 2019 and 2022, respectively.<sup>76,77</sup>

This retrospective study analyzes noncancer drugs used during systemic chemotherapy based on a dataset of 14 antineoplastic agents. It sought to identify the most dispensed noncancer drug groups, discuss findings, compare patients with and without antidepressant prescriptions, and examine trends in antidepressant use from 2002 to 2023. This analysis expands on prior research.<sup>78-81</sup>

METHODS

The Walter Reed National Military Medical Center Institutional Review Board approved the study protocol and ensured compliance with the Health Insurance Portability and Accountability Act as an exempt protocol. The Joint Pathology Center (JPC) of the US Department of Defense (DoD) Cancer Registry Program and Military Health System (MHS) data experts from the Comprehensive Ambulatory/Professional Encounter Record (CAPER) and Pharmacy Data Transaction Service (PDTs) provided data for the analysis.

Data Sources

The JPC DoD Cancer Registry Program contains data from 1998 to 2024. CAPER and PDTs are part of the MHS Data Repository/Management Analysis and Reporting Tool database. Each observation in CAPER represents an ambulatory encounter at a military treatment facility (MTF). CAPER records are available from 2003 to 2024. PDTs records are available from 2002 to 2004. Each observation in PDTs represents a prescription filled for an MHS beneficiary, excluding those filled at international civilian pharmacies and inpatient pharmacy prescriptions.

This cross-sectional analysis requested data extraction for specific cancer drugs from the DoD Cancer Registry, focusing on treatment details, diagnosis dates, patient demographics,

**TABLE 3.** Analysis of 30 Groups With and Without Antidepressants<sup>a</sup> (N = 2113)

Group	Patients, No. (%) [Mean]	With ADs, No. [Mean]	Without ADs, No. [Mean]	P value	Therapeutic codes, No.	Top medicine (No. of patients)
Total	2113 (100) [29]	750 [33]	1363 [26]	< .001	273	Dexamethasone (1668)
Antiemetics	2003 (95) [30]	724 [34]	1279 [27]	.001	5	Prochlorperazine (1609)
Opioids	1938 (92) [30]	715 [34]	1223 [27]	.002	3	Oxycodone (1154)
Nonopioids	1885 (89) [30]	687 [34]	1198 [28]	.002	13	Acetaminophen (1299)
Adrenals steroids	1771 (84) [30]	654 [35]	1117 [28]	.01	1	Dexamethasone (1668)
Anticonstipation	1766 (84) [31]	650 [35]	1116 [28]	.002	2	Docusate (1317)
Antibiotics	1732 (82) [31]	653 [35]	1079 [28]	.003	13	Amoxicillin clavulanate (492)
Reflux	1513 (72) [32]	587 [36]	926 [30]	.007	6	Omeprazole (672)
Anesthetics	1459 (69) [31]	606 [35]	853 [29]	.03	6	Lidocaine (557)
Antihistamine	1358 (64) [32]	533 [36]	825 [30]	.009	9	Diphenhydramine (509)
Cancer drugs	1306 (62) [33]	490 [36]	816 [30]	.003	4	Paclitaxel (371)
Hypertension	1200 (57) [32]	439 [36]	761 [30]	.004	28	Lisinopril (405)
Anticonvulsants	1014 (48) [34]	459 [37]	555 [31]	.12	4	Gabapentin (797)
Corticosteroids	1014 (48) [33]	393 [36]	621 [31]	.009	3	Fluticasone (579)
Cholesterol	816 (39) [33]	294 [36]	522 [31]	.002	8	Atorvastatin (450)
Vitamins	768 (36) [33]	304 [36]	464 [31]	.01	7	Vitamin D3 (250)
Antidepressants	750 (35) [33]	750 [33]	0 [0]	NA	1	Duloxetine (183)
Asthma	742 (35) [34]	309 [38]	433 [32]	.02	12	Albuterol (425)
Hematopoietic	691 (33) [33]	271 [37]	420 [31]	.007	1	Pegfilgrastim (605)
Antifungals	688 (33) [34]	266 [38]	422 [32]	.005	5	Fluconazole (343)
Cold-cough	666 (32) [35]	257 [38]	409 [33]	.006	4	Benzonatate (326)
Antidiarrheals	632 (30) [34]	245 [38]	387 [32]	.005	1	Loperamide (585)
Antipsychotics-CNS	619 (29) [33]	281 [37]	338 [30]	.09	12	Olanzapine (395)
Anticoagulants	554 (26) [32]	201 [36]	353 [30]	.001	1	Enoxaparin (317)
Microbacteria	489 (23) [34]	198 [38]	291 [32]	.01	15	Metronidazole (193)
Diabetics	406 (19) [35]	139 [39]	267 [33]	< .001	13	Metformin (291)
Hormone	448 (21) [31]	192 [35]	256 [29]	.04	8	Tamoxifen (123)
Thyroid	360 (17) [32]	140 [36]	220 [30]	.004	5	Levothyroxine (340)
Heart medicines	321 (15) [33]	123 [36]	198 [32]	.005	6	Oxybutynin (88)
Erectile dysfunction	148 (7) [32]	42 [38]	106 [30]	< .001	1	Sildenafil (122)
Others	1920 (91) [30]	706 [34]	1217 [28]	.003	76	Sodium chloride (511)

Abbreviations: AD, antidepressant; CNS, central nervous system; NA, not applicable; PDTS, Pharmacy Data Transaction Service.

<sup>a</sup>Groups analyzed from 273 therapeutic PDTS codes; the mean number of dispensed antidepressants was compared with those not receiving them. Of 2113 patients, PDTS noted 1089 unique prescriptions with 1049 having ≥ 100 patients prescribed.

and physicians' comments on AEs. After identifying patients, CAPER was used to identify additional health conditions. PDTS was used to compile a list of prescription medications filled during systemic cancer treatment or < 2 years postdiagnosis.

The 2016 Surveillance, Epidemiology, and End Results Program Coding and Staging Manual and *International Classification of Diseases for Oncology*, 3rd edition, 1st revision, were used to decode disease and cancer types.<sup>82,83</sup> Data sorting and analysis were performed using Microsoft Excel. The percentage for the total was calculated by using the number of patients or data available within the subgroup divided by the total number of patients or data variables. To compare the mean number of dispensed antidepressants to those without antidepressants, a 2-tailed, 2-sample z test was used to calculate the *P* value and de-

termine statistical significance (*P* < .05) using socscistatistics.com.

Data were extracted 3 times between 2021 and 2023. The initial 2021 protocol focused on erlotinib and gefitinib. A modified protocol in 2022 added paclitaxel, cisplatin, docetaxel, pemetrexed, and crizotinib; further modification in 2023 included 8 new antineoplastic agents and 2 anticoagulants. Sotorasib has not been prescribed in the MHS, and JPC lacks records for noncancer drugs. The 2023 dataset comprised 2210 patients with cancer treated with 14 antineoplastic agents; 2104 had documented diagnoses and 2113 had recorded prescriptions. Data for erlotinib, gefitinib, and paclitaxel have been published previously.<sup>78,79</sup>

## RESULTS

Of 2113 patients with recorded prescriptions, 1297 patients (61.4%) received 109 cancer

**TABLE 4.** Analysis of Antidepressants from CAPER and PDTS<sup>a</sup>

CAPER diagnosis (n = 2104)					PDTS prescriptions dispensed (n = 2113)						
		With patients, No. (mean)	Without patients, No. (mean)	P value		With patients, No. (mean)	Without patients, No. (mean)	P value	Years dispensed	Year FDA approved	AD type
Medication	%				%						
ADs	36	745 (55)	1359 (46)	< .001	35	750 (33)	1363 (26)	< .001	2003-2023	NA	NA
Duloxetine	9	183 (60)	1921 (49)	< .001	9	183 (37)	1930 (28)	< .001	2005-2023	2004	SNRI
Venlafaxine	8	158 (52)	1946 (49)	< .001	7	158 (34)	1955 (29)	< .001	2012-2023	1993	SNRI
Trazodone	6	118 (56)	1986 (49)	< .001	6	118 (35)	1995 (29)	< .001	2007-2023	1981	SRM
Sertraline	5	106 (56)	1998 (49)	< .001	5	107 (33)	2006 (29)	< .001	2004-2023	1991	SSRI
Mirtazapine	4	82 (65)	2022 (49)	< .001	4	83 (36)	2030 (29)	< .001	2004-2023	1997	TeCA
Citalopram	4	79 (64)	2025 (49)	< .001	4	82 (36)	2031 (29)	< .001	2003-2022	1998	SSRI
Bupropion	4	78 (54)	2026 (49)	< .001	4	79 (34)	2034 (29)	< .001	2004-2023	1985	NDRI
Amitriptyline	3	66 (62)	2038 (50)	< .001	3	68 (37)	2045 (29)	< .001	2003-2023	1961	TCA
Escitalopram	3	64 (46)	2040 (50)	< .001	3	64 (34)	2049 (29)	< .001	2004-2023	2002	SSRI
Fluoxetine	3	60 (57)	2044 (49)	< .001	3	60 (35)	2053 (29)	< .001	2004-2023	1987	SSRI
Paroxetine	2	36 (61)	2068 (49)	NA	2	36 (37)	2077 (29)	NA	2004-2023	2001	SSRI
Nortriptyline	1	24 (58)	2080 (49)	NA	1	24 (37)	2089 (29)	NA	2005-2023	1964	TCA
Doxepin	1	12 (59)	2092 (49)	NA	1	12 (38)	2101 (29)	NA	2014-2022	1969	TCA
Imipramine	< 1	3 (41)	2101 (50)	NA	< 1	3 (30)	2110 (29)	NA	2010-2022	1959	TCA
Desipramine	< 1	2 (46)	2102 (50)	NA	< 1	2 (33)	2111 (29)	NA	2008-2022	1964	TCA
Desvenlafaxine	< 1	2 (42)	2102 (50)	NA	< 1	2 (35)	2111 (29)	NA	2010-2020	2008	SNRI
Nefazodone	< 1	1 (17)	2103 (50)	NA	< 1	1 (20)	2112 (29)	NA	2017-2018	1994	SRM

Abbreviations: AD, antidepressant; CAPER, Comprehensive Ambulatory/Professional Encounter Record; FDA, US Food and Drug Administration; NA, not applicable; NDRI, norepinephrine-dopamine reuptake inhibitor; PDTS, Pharmacy Data Transaction Service; SNRI, serotonin-norepinephrine reuptake inhibitor; SRM, serotonin receptor modulator; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant; TeCA, tetracyclic antidepressant.

<sup>a</sup>Of 2104 patients, 745 prescribed antidepressants had CAPER data for diagnoses. Among 2113 patients, 750 were prescribed antidepressants.

drugs, including 96 antineoplastics, 7 disease-modifying antirheumatic agents, 4 biologic response modifiers, and 2 calcitonin gene-related peptides. Fourteen antineoplastic agents had complete data from JPC, while others were noted for combination therapies or treatment switches from the PDTS (Table 1). Seventy-six cancer drugs were prescribed with antidepressants in 489 patients (eAppendix, available at doi:10.12788/fp.0586).

The JPC provided 2242 entries for 2210 patients, ranging in age from 2 months to 88 years (mean, 56 years), documenting treatment from September 1988 to January 2023. Thirty-two patients had duplicate entries due to multiple cancer locations or occurrences. Of the 2242 patients, 1541 (68.7%) were aged > 50 years, 975 patients (43.5%) had cancers that were stage III or IV, and 1267 (56.5%) had cancers that were stage 0, I, II, or not applicable/unknown. There were 51 different types of cancer: breast, lung, testicular, endometrial, and ovarian were most common (n ≥ 100 patients). Forty-two cancer types were documented among 750 patients prescribed antidepressants (Table 2).

The CAPER database recorded 8882 unique diagnoses for 2104 patients, while PDTS noted 1089 unique prescriptions within 273 therapeutic codes for 2113 patients. Nine therapeutic codes

(opiate agonists, adrenals, cathartics-laxatives, nonsteroidal anti-inflammatory agents, antihistamines for GI conditions, 5-HT<sub>3</sub> receptor antagonists, analgesics and antipyretic miscellaneous, antineoplastic agents, and proton-pump inhibitors) and 8 drugs (dexamethasone, prochlorperazine, ondansetron, docusate, acetaminophen, ibuprofen, oxycodone, and polyethylene glycol 3350) were associated with > 1000 patients (≥ 50%). Patients had between 1 and 275 unique health conditions and filled 1 to 108 prescriptions. The mean (SD) number of diagnoses and prescriptions was 50 (28) and 29 (12), respectively. Of the 273 therapeutic codes, 30 groups were analyzed, with others categorized into miscellaneous groups such as lotions, vaccines, and devices. Significant differences in mean number of prescriptions were found for patients taking antidepressants compared to those not ( $P < .05$ ), except for anticonvulsants and antipsychotics ( $P = .12$  and  $.09$ , respectively) (Table 3).

### Antidepressants

Of the 2113 patients with recorded prescriptions, 750 (35.5%) were dispensed 17 different antidepressants. Among these 17 antidepressants, 183 (8.7%) patients received duloxetine, 158 (7.5%) received venlafaxine, 118 (5.6%) received trazodone, and 107 (5.1%)



**TABLE 5.** Antidepressants Inhibition and Inducement Effects on CYP Isoenzymes and Metabolism Pathways

Drug	CYP inhibition/inducement	CYP metabolism
Duloxetine	Inhibit: 2D6 (moderate), 1A2 (weak) Uninhibited: 2C9, 2C19, 3A4; uninduced: 1A2, 3A4	2D6, 1A2
Venlafaxine	Inhibit: 2D6 (weak); uninhibited: 1A2, 2C9, 2C19, 3A4	2D6 <sup>a</sup> , 3A4
Trazodone	Unknown/not reported	3A4
Sertraline	Inhibit: 2D6 (moderate), 1A2, 2C9, 2C19, 3A4 (weak)	(3A4, 2B6) <sup>a</sup> , 2C19, 2D6
Mirtazapine	Inhibit: 2D6, 3A4, 1A2 (weak)	2D6, 3A4, 1A2
Citalopram	Inhibit: 2D6 (weak)	(2C19, 3A4) <sup>a</sup> , 2D6
Bupropion	Inhibit: 2D6 (strong)	2B6
Amitriptyline	Unknown/not reported	1A2, 2C, 2D6, 3A4
Escitalopram	Inhibit: 2D6 (weak)	2D6, 2C19, 3A4
Fluoxetine	Inhibit: 2D6 (strong), 2C9 (moderate), 2C19, 3A4, 1A2 (weak)	(2D6) <sup>a</sup> , 3A4, 2C9, 2C19
Paroxetine	Inhibit: 2D6 (strong), 1A2, 2C9, 2C19, 3A4 (weak)	(2D6) <sup>a</sup> , 3A4
Nortriptyline	Unknown/not reported	(2D6) <sup>a</sup> , 1A2, 3A4, 2C19
Doxepin	Unknown/not reported	(2D6) <sup>a</sup> , 1A2, 3A4, 2C9, 2C19
Imipramine	Unknown/not reported	(2D6) <sup>a</sup> , 1A2, 3A4, 2C19
Desipramine	Unknown/not reported	(2D6) <sup>a</sup> , 1A2, 3A4, 2C19
Desvenlafaxine	3A4 (weak)	3A4
Nefazodone	Unknown/not reported	3A4

Abbreviation: CYP, cytochrome P450.

<sup>a</sup>Major pathways.

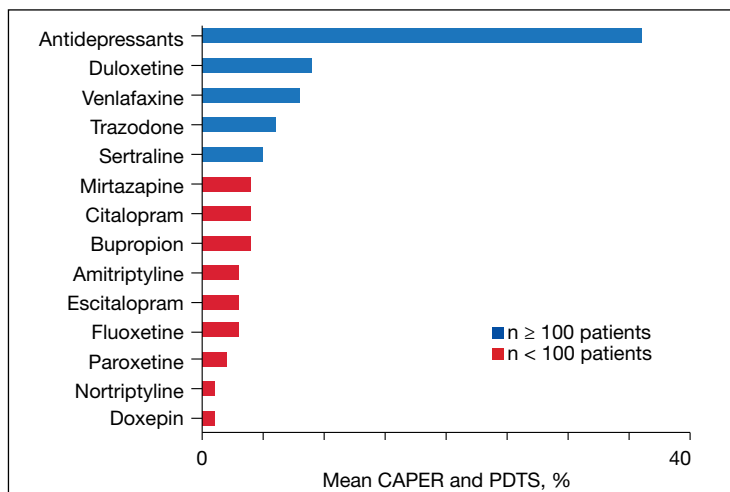
received sertraline (Figure 1, Table 4). Of the 750 patients, 509 (67.9%) received 1 antidepressant, 168 (22.4%) received 2, 60 (8.0%) received 3, and 13 (1.7%) received > 3. Combinations varied, but only duloxetine and trazodone were prescribed to > 10 patients.

Antidepressants were prescribed annually at an overall mean (SD) rate of 23% (5%) from 2003 to 2022 (Figure 2). Patients on antidepressants during systemic therapy had a greater number of diagnosed medical conditions and received more prescription medications compared to those not taking antidepressants ( $P < .001$ ) (Figure 3). The 745 patients taking antidepressants in CAPER data had between 1 and 275 diagnosed medical issues, with a mean (SD) of 55 (31) vs a range of 1 to 209 and a mean (SD) of 46 (26) for the 1359 patients not taking antidepressants. The 750 patients on antidepressants in PDTS data had between 8 and 108 prescriptions dispensed, with a mean (SD) of 32 (12), vs a range of 1 to 65 prescriptions and a mean (SD) of 29 (12) for 1363 patients not taking antidepressants.

## DISCUSSION

The JPC DoD Cancer Registry includes information on cancer types, stages, treatment regimens, and physicians' notes, while noncancer drugs are sourced from the PDTS database. The pharmacy uses a different documentation system, leading to varied classifications.

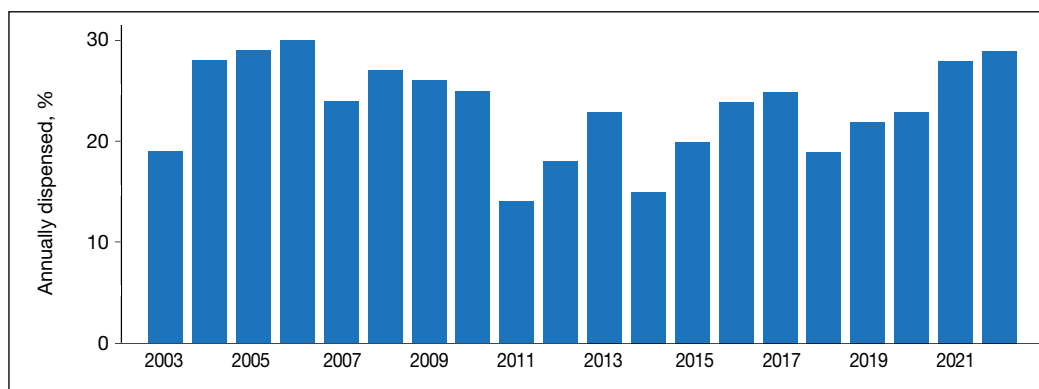
Database reliance has its drawbacks. For example, megestrol is coded as a cancer drug,



**FIGURE 1.** Analysis of antidepressants from CAPER and PDTS. Mean percentages were calculated from both studies, with CAPER based on 2014 patients and PDTS on 2113 patients, as shown in Table 4. Imipramine, desipramine, desvenlafaxine, and nefazodone were excluded as their mean percentages were < 1%.

Abbreviations: CAPER, Comprehensive Ambulatory/Professional Encounter Record; PDTS, Pharmacy Data Transaction Service.

although it's primarily used for endometrial or gynecologic cancers. Many drugs have multiple therapeutic codes assigned to them, including 10 antineoplastic agents: diclofenac, Bacillus Calmette-Guérin (BCG), megestrol acetate, tamoxifen, anastrozole, letrozole, leuprolide, goserelin, degarelix, and fluorouracil. Diclofenac, BCG, and mitomycin have been repurposed for cancer treatment.<sup>84-87</sup> From 2003 to 2023, diclofenac was prescribed to 350 patients for mild-



**FIGURE 2.** Antidepressants annually dispensed from 2003 to 2022. Mean (SD) antidepressants dispensed was 23% (5%).

to-moderate pain, with only 2 patients receiving it for cancer in 2018. FDA-approved for bladder cancer in 1990, BCG was prescribed for cancer treatment for 1 patient in 2021 after being used for vaccines between 2003 and 2018. Tamoxifen, used for hormone receptor-positive breast cancer from 2004 to 2017 with 53 patients, switched to estrogen agonist-antagonists from 2017 to 2023 with 123 patients. Only a few of the 168 patients were prescribed tamoxifen using both codes.<sup>88-91</sup> Anastrozole and letrozole were coded as antiestrogens for 7 and 18 patients, respectively, while leuprolide and goserelin were coded as gonadotropins for 59 and 18 patients. Degarelix was coded as antigonadotropins, fluorouracil as skin and mucous membrane agents miscellaneous, and megestrol acetate as progestins for 7, 6, and 3 patients, respectively. Duloxetine was given to 186 patients, primarily for depression from 2005 to 2023, with 7 patients treated for fibromyalgia from 2022 to 2023.

### Antidepressants Observed

Tables 1 and 5 provide insight into the FDA approval of 14 antineoplastics and antidepressants and their CYP metabolic pathways.<sup>92-122</sup> In Table 4, the most prescribed antidepressant classes are SNRIs, SRMs, SSRIs, TeCAs, NDRIs, and TCAs. This trend highlights a preference for newer medications with weak CYP inhibition. A total of 349 patients were prescribed SSRIs, 343 SNRIs, 119 SRMs, 109 TCAs, 83 TeCAs, and 79 NDRIs. MAOIs, SMRAs, and NMDARAs were not observed in this dataset. While there are instances of dextromethorphan-bupropion and sertraline-escitalopram being dispensed together, it remains unclear whether these were NMDARA combinations.

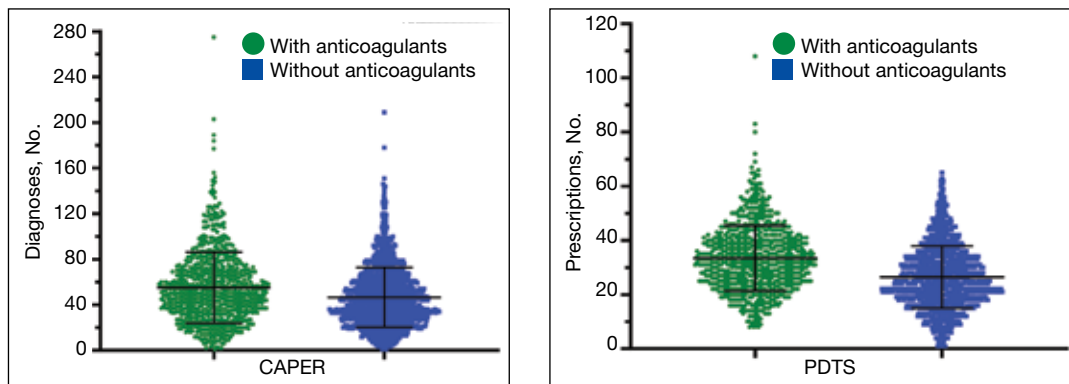
Among the 14 specific antineoplastic agents,

10 are metabolized by CYP isoenzymes, primarily CYP3A4. Duloxetine neither inhibits nor is metabolized by CYP3A4, a reason it is often recommended, following venlafaxine.

Both duloxetine and venlafaxine are used off-label for chemotherapy-induced peripheral neuropathy related to paclitaxel and docetaxel. According to the CYP metabolized pathway, duloxetine tends to have more favorable DDIs than venlafaxine. In PDS data, 371 patients were treated with paclitaxel and 180 with docetaxel, with respective antidepressant prescriptions of 156 and 70. Of the 156 patients dispensed paclitaxel, 62 (40%) were dispensed with duloxetine compared to 43 (28%) with venlafaxine. Of the 70 patients dispensed docetaxel, 23 (33%) received duloxetine vs 24 (34%) with venlafaxine.

Of 85 patients prescribed duloxetine, 75 received it with either paclitaxel or docetaxel (5 received both). Five patients had documented AEs (1 neuropathy related). Of 67 patients prescribed venlafaxine, 66 received it with either paclitaxel or docetaxel. Two patients had documented AEs (1 was neuropathy related, the same patient who received duloxetine). Of the 687 patients treated with paclitaxel and 337 with docetaxel in all databases, 4 experienced neuropathic AEs from both medications.<sup>79</sup>

Antidepressants can increase the risk of bleeding, especially when combined with blood thinners, and may elevate blood pressure, particularly alongside stimulants. Of the 554 patients prescribed 9 different anticoagulants, enoxaparin, apixaban, and rivaroxaban were the most common (each > 100 patients). Among these, 201 patients (36%) received both anticoagulants and antidepressants: duloxetine for 64 patients, venlafaxine for 30, trazodone for 35, and sertraline for 26. There were no data available to assess bleeding rates related to the evaluation of DDIs between these medication classes.



**FIGURE 3.** Diagnoses and prescriptions for patients receiving antidepressants with and without anticoagulants. Mean (center line) and SD (tick marks) shown for each distribution; patients undergoing systemic cancer treatment and taking antidepressants had more diagnosed medical issues and filled more prescriptions compared to patients not taking antidepressants.

Antidepressants can be prescribed for erectile dysfunction. Of the 148 patients prescribed an antidepressant for erectile dysfunction, duloxetine, trazodone, and mirtazapine were the most common.

Antidepressants may have both positive and negative effects on different types of cancer.<sup>123,124</sup> Antidepressant preferences varied by cancer type. Duloxetine was the only antidepressant used for all types of cancer. Venlafaxine, duloxetine, trazodone, sertraline, and escitalopram were the most prescribed antidepressants for breast cancer, while duloxetine, mirtazapine, citalopram, sertraline, and trazodone were the most prescribed for lung cancer. Sertraline, duloxetine, trazodone, amitriptyline, and escitalopram were most common for testicular cancer. Duloxetine, venlafaxine, trazodone, amitriptyline, and sertraline were the most prescribed for endometrial cancer, while duloxetine, venlafaxine, amitriptyline, citalopram, and sertraline were most prescribed for ovarian cancer.

The broadness of *International Statistical Classification of Diseases, Tenth Revision* codes made it challenging to identify nondepression diagnoses in the analyzed population. However, if all antidepressants were prescribed to treat depression, service members with cancer exhibited a higher depression rate (35%) than the general population (25%). Of 2104 patients, 191 (9.1%) had mood disorders, and 706 (33.6%) had mental disorders: 346 (49.0%) had 1 diagnosis, and 360 (51.0%) had multiple diagnoses. The percentage of diagnoses varied yearly, with notable drops in 2003, 2007, 2011, 2014, and 2018, and peaks in 2006, 2008, 2013, 2017, and 2022. This fluctuation was influenced by events like the establishment of PDTS in 2002, the 2008 economic recession, a

hospital relocation in 2011, the 2014 Ebola outbreak, and the COVID-19 pandemic. Although the number of patients receiving antidepressants increased from 2019 to 2022, the overall percentage of patients receiving them did not significantly change from 2003 to 2022, aligning with previous research.<sup>5,125</sup>

Many medications have potential uses beyond what is detailed in the prescribing information. Antidepressants can relieve pain, while pain medications may help with depression. Opioids were once thought to effectively treat depression, but this perspective has changed with a greater understanding of their risks, including misuse.<sup>126-131</sup> Pain is a severe and often unbearable AE of cancer. Of 2113 patients, 92% received opioids; 34% received both opioids and antidepressants; 2% received only antidepressants; and 7% received neither. This study didn't clarify whether those on opioids alone recognized their depression or if those on both were aware of their dependence. While SSRIs are generally not addictive, they can lead to physical dependence, and any medication can be abused if not managed properly.<sup>132-134</sup>

## CONCLUSIONS

This retrospective study analyzes data from antineoplastic agents used in systemic cancer treatment between 1988 and 2023, with a particular focus on the use of antidepressants. Data on antidepressant prescriptions are incomplete and specific to these agents, which means the findings cannot be generalized to all antidepressants. Hence, the results indicate that patients taking antidepressants had more diagnosed health issues and received more medications compared to patients who were not on these drugs.



This study underscores the need for further research into the effects of antidepressants on cancer treatment, utilizing all data from the DoD Cancer Registry. Future research should explore DDIs between antidepressants and other cancer and noncancer medications, as this study did not assess AE documentation, unlike in studies involving erlotinib, gefitinib, and paclitaxel.<sup>78,79</sup> Further investigation is needed to evaluate the impact of discontinuing antidepressant use during cancer treatment. This comprehensive overview provides insights for clinicians to help them make informed decisions regarding the prescription of antidepressants in the context of cancer treatment.

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### Ethics and consent

The study protocol was approved by the Walter Reed National Military Medical Center Institutional Review Board and complied with the Health Insurance Portability and Accountability Act as an exempt protocol.

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