Brain, Behavior, & Immunity - Health 21 (2022) 100449

Contents lists available at ScienceDirect

Brain, Behavior, & Immunity - Health

journal homepage: www.editorialmanager.com/bbih/default.aspx

A systematic review of pharmacologic treatment efficacy for depression in older patients with cancer

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ARTICLE INFO

Keywords:
Aging
Elderly
SSRI
Senescence
Neuroinflammation
Glioblastoma
Breast
Lung
Prostate

ABSTRACT

Background: Older adults ≥65 years of age represent the majority of new cancer diagnoses and are vulnerable to developing depression-like symptoms. Evaluation and management of depression in older cancer patients is underappreciated despite its high prevalence and impact on health-related quality of life. Although antidepressants are the primary pharmacologics used to treat depressive-like symptoms, the efficacy and overall benefit(s) are not well-characterized in older adult patients with cancer. The objective of this investigation was to review what is known about the efficacy of pharmacologic treatment for older adults with depression and cancer.
Methods: PubMed (Medline) and EMBASE (Elsevier) databases were analyzed for relevant literature in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.
Results: 1,919 unique studies were identified for title and abstract screening. Forty-eight publications were retrieved for full review. None of the identified studies evaluated the potential for benefit after pharmacological treatment among older adults with cancer and depression. Twenty-seven publications met all study criteria except for an analysis focused on older patients.
Conclusion: We discovered a universal absence of literature with a relevance to pharmacologic antidepressant treatment effects in older adult patients with cancer. This included a lack of evaluation in patients with brain tumors who have an unusually high predilection for developing depression. Our findings suggest that new research is critically needed for understanding optimal clinical management strategies in older adults with cancer and depression who are treated with antidepressants.

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https://doi.org/10.1016/j.bbih.2022.100449
Received 12 December 2021; Received in revised form 3 March 2022; Accepted 12 March 2022

1. Introduction

An estimated 19.3 million new global cancer diagnoses were made in 2020 and roughly 10 million individuals succumbed to their malignancy in the same year (Sung et al., 2021). Age is a well-known risk factor that contributes to cancer incidence with 60% of new diagnoses representing older adult patients ≥65 years of age in the United States (Cinar and Tas, 2015; Berger et al., 2006). The U.S. Census Bureau estimates that the elderly population will double to nearly 70 million by the year 2030 (Yancik, 2005) and will parallel a rise in the number of older adults who are diagnosed with cancer (Smith et al., 2009). A cancer diagnosis is often associated with a tremendous impact on the quality of life (Nayak et al., 2017; Disease, 2016) with 40% of adults ≥70 years of age who experience a functional decline after a new diagnosis (Presley et al., 2019). In data released from the Substance Abuse and Mental Health Administration in 2020, an estimated 8.4% of US adults had at least one major depressive event (Substance Abuse and Menta, 2021). In patients with cancer, one meta-analysis estimated 24% of cohort patients showed clinical signs of depression (Massie, 2004), though others suggest this figure may be higher as depressive-like symptoms often go underrecognized (McDonald et al., 1999; Fisch, 2004; Otto-Meyer et al., 2019). The most common symptoms of older adult patients with advanced cancer include pain, anorexia, fatigue, insomnia, anxiety, delirium, and depression (Parpa et al., 2015). The burden of disease combined with the side effects of cancer treatments can be severely debilitating. Patients often face a decreased health-related quality of life, relationship challenges, difficulty sleeping, and other burdens (Alexopoulos, 2005). In elderly patients without cancer, depression is managed with pharmacologics and non-pharmacologics (e.g. psychotherapy, transcranial magnetic stimulation (TMS), electroconvulsive therapy (ECT), and alternative treatment). After conservative non-medical management, selective serotonin reuptake inhibitors (SSRIs) are the first line of antidepressant treatment because of their relative tolerability and high safety profiles (Gautam et al., 2017).

Despite the high level of depressive-like symptoms among cancer patients, the efficacy and characterization of antidepressant treatment in older adults with cancer and clinically-diagnosed depression has not been comprehensively investigated (Findley et al., 2012; Rodin et al., 2007). To care for elderly cancer patients optimally, while also attempting to anticipate their medical needs and challenges, it's essential to better understand this age group. Here, we systematically reviewed the efficacy of antidepressant agents in elderly patients ≥65 years of age who are diagnosed with depression and cancer.

2. Methods

2.1. Literature search

In accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines (Page et al., 2021) a systematic review of treatments for elderly patients with depression and cancer was performed. In June 2021, PubMed (MEDLINE) and EMBASE (Elsevier) were searched for relevant articles. The search was conducted involving specific MeSH keywords by combining variants of 'antidepressant agents', 'depression', 'cancer', and, 'aged'. The full search strategy is provided in the **Appendix**.

2.2. Inclusion criteria

To meet the inclusion criteria, an article's study objective must have included a determination of antidepressant efficacy among patients with cancer ≥65 years of age with an associated diagnosis of a clinical depression disorder, or at minimum, a subgroup analysis specifically analyzing this age group. Clinical depression was defined as Major Depressive Disorder, Minor Depressive Disorder, or another depressive disorder (**Appendix**). Antidepressants were recognized for study inclusion if the pharmacologic treatment was tested for its efficacy in modifying depressive-like symptoms in the specified population. Articles were excluded if: (i) subject age was not distinguished as a stratified variable during analysis, (ii) patients received non-pharmacologic therapy to treat depression, (iii) publications were not written in English, and/or (iv) studies were not peer-reviewed full-length controlled trials or cohort studies. Articles were initially screened for title and abstract followed by final inclusion after a full-text review. Randomized and non-randomized controlled trials and cohort studies were intended for inclusion. Manuscripts other than full-length peer-reviewed articles including abstracts, posters, dissertations, and editorials were excluded. Articles were not limited by publication date. Studies that met the inclusion and exclusion criteria were preferred if using standardized depression labels that included Diagnostic and Statistical Manual of mental disorders (DSM) classification or International Classification of Disease (ICD) criteria. For depressive symptoms, studies that included validated scales due to variability of depression diagnosis within populations were preferred. Duplicate records were removed. Two reviewers independently screened all of the articles. Disagreements were reconciled with a discussion.

2.3. Data collection process

Data extraction was conducted on prespecified criteria. The primary outcome was a change in depression symptomology as measured by a validated scale at the time of final follow-up. This was measured through a mean change in depression including the Hamilton Rating Scale for Depression (HAM-D) (Hamilton, 1960), Hospital Anxiety and Depression Scale-Depression (HADS-D) (Zigmond and Snaith, 1983), Montgomery-Åsberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979), the Beck Depression Inventory (BDI) (Beck et al., 1961), Patient Health Questionnaire (PHQ-9) (Kroenke et al., 2001), and was collected as written within publications. Secondary outcomes included emotional distress and quality of life. For quantification of distress, validated measurement tools included the Hospital Anxiety and Depression Scale (HADS-A), Distress Thermometer (DT),(practice guidelines, 1999), and Mini-Mental Adjustment (MINI-MAC) (Johansson et al., 2011) scales. Quality of life scales included the European Organization for Research and Treatment of Cancer (EORTC QLQ-C30)(Aaronson et al., 1993), the Functional Assessment of Cancer Therapy (FACT) (Weitzner et al., 1995), and the 36-item Short-Form Health Survey (SF-36) (McHorney et al., 1993). Response to treatment was defined as a decrease of at least 50% in depression scores to trial endpoint (Nierenberg and DeCecco, 2001).

2.4. Quality assessment

Risk of bias was evaluated by using the revised cochrane risk-of-bias tool for randomized trials (RoB 2) and the risk of bias in non-randomized Studies of Interventions (ROBINS-I)(Sterne et al., 2016), by EER and A.M (Sterne et al., 2019). Bias was evaluated in confounding, selection, classification of interventions, randomization, deviation from intended, missing outcome data, selection of outcome, reported result, and overall risk of bias. Any disagreement between the authors was reconciled by a discussion and a consultation with an additional reviewer.

2.5. Statistical analysis

In the event that two or more Randomized Controlled Trials (RCTs) demonstrated a high similarity in population, intervention, and outcome measures, a meta-analysis was performed. This analysis was intended to be performed using the Hartung-Knapp-Sidik-Jonkman method for random-effects models. All statistical analysis was performed using R version 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria) using the meta and metafor packages. Calculated odds ratios (ORs) from event rates were used to pool dichotomous variables and mean differences to pool continuous variables. I^2 values were used to assess study

heterogeneity. The summary of representative population demographics, primary, and secondary outcomes was recorded and is presented in Tables 1–4.

3. Results

3.1. Identification of potentially relevant studies

1,919 publications underwent title and abstract screening and were selected by searching for specific MeSH keywords and combing variants of, 'antidepressant agents', 'depression', 'cancer', and, 'aged.' Forty-eight of those manuscripts were identified to be relevant and were fully reviewed. No eligible studies met both the inclusion and exclusion criteria as summarized in Fig. 1. Of the 48 studies, 27 publications met all criteria except for directly analyzing the efficacy of pharmacologic treatment in cancer patients ≥65 years of age or subgroup analysis of this age group. There is a complete lack of studies that have exclusively analyzed antidepressant treatment effects in elderly cancer patients with depression. Composition of the 27 publications included 10 Randomized Controlled Trials (RCTs), 15 Prospective Non-Randomized Trials (PNRTs), and 2 Parallel-Group Randomized Trials (PGRTs). All studies included a clinical diagnosis of depression or clinical 'depressive-like' symptoms. Mean age and follow-up times for those studies are included in Table 1.

The number of cancers analyzed across the 27 included studies are listed in Table 2. Pooled numbers of cancers by type, as well as the number of publications including cancer type, are shown in Fig. 2. 81.5% of the manuscripts involved breast cancer, 63.0% involved gastrointestinal cancer, and 48.1% included lung cancer, representing 45.7%, 15.1%, and 9.9% of evaluable patients, respectively. Head and neck, gynecologic, hematologic, prostate, bone, dermatologic, brain, and renal cancers made up 13.6% of patients and cancer type was represented in 7.4%–40.7% of the 27 publications (Fig. 2, Table 2).

Eighteen of the 27 publications included the analysis of SSRIs, 2 publications included serotonin and norepinephrine reuptake inhibitors (SNRIs), 5 publications included tricyclic antidepressants (TCAs), and 7 publications included other atypical antidepressant medications. Tables 1, 3 and 4 provide the details regarding initial and follow-up measures of depression and anxiety in cancer patients treated with antidepressants across study groups and measures of significance as reported in publications. Follow-up times varied that ranged between 1 and 24 weeks. The numbers of treated patients ranged from 10 to 175. Antidepressant treatments included SSRIs, SNRIs, TCAs, and atypical antidepressants (Table 5). Strengths and weaknesses of depression scales are listed in the **Appendix**. Major article findings from the articles are addressed below.

3.2. Selective serotonin reuptake inhibitors (SSRIs)

SSRIs exert actions through the inhibition of presynaptic serotonin reuptake that increases the availability and activity of serotonin at the synapse (Edinoff et al., 2021). We identified several studies that evaluated SSRI treatment in oncologic patients with a positive depression screening. In one study, a 12-week trial of escitalopram showed a significant improvement in HAM-D and Distress Thermometer (DT) scores among breast cancer patients (n = 79) (Park et al., 2012). Another study evaluated escitalopram within malignant melanoma patients but did not find significant differences in HAM-D scores as compared to the placebo group (n = 24) (Musselman et al., 2013). Treatment with Sertraline demonstrated an improvement of depression and anxiety scales such as HADS-D (n = 35) (Torta et al., 2008), HAM-A, HAM-D, as well as quality of life measures on the 36-Item Short Form Survey (SF-36) including general health, mental health, role limitation of physical, emotional, and social function dimensions (n = 86) (Li et al., 2014). In a study that explored citalopram, severely depressed cancer patients showed a significant improvement in the Zung Self Rating Depression Scale (ZSRDS) score, as well as a significant improvement in boredom levels over eight weeks (n = 21) (Theobald et al., 2003). In a smaller trial, the treatment with citalopram demonstrated an 8.4 point improvement in Patient Health Questionnaire-9 (PHQ-9) scores (n = 10) indicating a decrease in depressive symptoms with pharmacologic treatment in patients with cancer and MDD (Raddin et al., 2014). Women with advanced cancer and depressive symptoms treated with fluoxetine was associated with a significant improvement in HAM-D, HAM-A, and Clinical Global Impression (CGI) severity and items on the SF-36 including Role Functioning (RF), Social Functioning (SF), Mental Health (MH), and Vitality (V) (Holland et al., 1998a). Similarly, in patients treated with desipramine, a reduction in HAM-D, HAMA-A, CGI, and SF-36 was found, but unlike Fluoxetine, failed to show a reduction in mood and pain intensity as well as improvements in RF after adjusted analysis. Despite fluoxetine showing an improvement in overall global symptoms in patients with major depression or adjustment disorders, it did not demonstrate significant differences in HADS response rates (n = 30) (Razavi et al., 1996). After treatment with fluvoxamine in patients with depression or adjustment disorder, HADs scores were significantly reduced at 6 weeks post-treatment. In the depression group, vitality and emotional health was also improved in this cohort as evaluated by the SF-36 scale (n = 10) (Suzuki et al., 2011).

3.3. Serotonin and norepinephrine reuptake inhibitors (SNRIs)

SNRIs inhibit the reuptake of serotonin and variable amounts of norepinephrine (Stahl et al., 2005). Patients with the diagnosis of major depression were found to have significant improvements over the course of a 12 week-long trial of duloxetine according to MADR, HADS-D, and HADs-A measures (n = 27) (Torta et al., 2011). After 8 weeks of treatment with the norepinephrine receptor inhibitor, reboxetine, breast cancer patients with major depressive disorder showed a significant reduction in HAM-D, Brief Symptom Inventory (BSI), and Mini-MAC hopelessness and anxious preoccupation scores, as well as an improvement in the quality-of-life measure, EORTC-QLQ-C30 (n = 22) (Grassi et al., 2004).

3.4. Tricyclic antidepressants (TCAs)

TCAs block the reuptake of serotonin and norepinephrine (NE) at the presynaptic cleft and also act as a competitive agonist at the post-synaptic terminus against alpha cholinergic, muscarinic, and histaminergic receptors (Moraczewski and Aedma, 2021). In breast cancer patients with depression, use of the TCA, amitriptyline, showed improvements in MADRS at the end of 8 weeks (n = 175) (Pezzella et al., 2001). In women with advanced cancer, the use of desipramine improved depression and anxiety symptoms at 6 weeks as well as improvements in quality of life measures (n = 38) (Holland et al., 1998b). In contrast, a 6 week-long trial aimed at treating major depression or adjustment disorder with paroxetine or desipramine showed no significant difference in HAM-D, HAM-A, or CGI scores within and between groups as compared to placebo-treated patients (n = 35) (Musselman et al., 2006).

3.5. Atypical antidepressants

Atypical antidepressants are newer approaches that affect 5-hydroxytryptamine (5-HT) and NE through different mechanisms of action (Horst and Preskorn, 1998). In a 6 week-long treatment, cancer patients with depression were treated with the tetracyclic antidepressant with properties similar to TCAs (TeCA), mianserin. Treatment significantly improved depressive symptoms as compared to the placebo-treated group (n = 55) (van Heeringen and Zivkov, 1996). Similar results were found in a 4 week-long study that also demonstrated improvements in sleep disturbance and anxiety as recorded on the HDRS scale (n = 36) (Costa et al., 1985). In terminally ill patients with depression, treatment with mirtazapine improved the MADRS score from 32.25 to 26.73 by day

Table 1

Articles removed in the full text review that reported efficacy of pharmacological treatment of depression or depressive disorders in patients with cancer. Mood Depression (MD), Major Depression Disorder (MDD), Persistent Depressive Disorder (PDD) previously called Dysthymic Disorder (DD) (Diagnostic and statistica, 2013), Adjustment Disorder with Depressed Mood (ADDM) (O'Donnell et al., 2019), Prospective Non-Randomized Trial (PNRT), Parallel-Group randomized trial (PGRT), MTZ: Mirtazapine, MPH: Methylphenidate, PLB: Placebo. E: Escitalopram, I: Imipramine, M: Mirtazapine, C: Citalopram, M: Mirtazapine, P: Paroxetine, D: Desipramine, F: Fluoxetine, A: Amitriptyline.

Article	Year	Type of study	Drug	Drug Class	Diagnosed depression	Patients with Cancer and Depression Treated pharmacologically	Mean Age: range/ standard deviation	Follow-up time (weeks)
Dai et al. (Dai et al., 2017)	2017	RCT	Fluoxetine	SSRI	Y	108	N/A	6
Fan et al. (Fan et al., 2017)	2017	RCT	Ketamine	Analgesic	Y	20	46.75 ± 14.04	1
Li et al. (Li et al., 2014)	2014	PNRT	Sertraline	SSRI	Y	86	59.6 ± 12.2	12
Raddin et al. (Raddin et al., 2014)	2014	PNRT	Citalopram Mirtazapine	SSRI, Tetracyclic Antidepressant	Y	21	C: 48.7 ± 16.6 M: 54.2 ± 16.9	9
Guan et al. (Ng et al., 2014)	2014	RCT	Mirtazapine, Methylphenidate	Tetracyclic Antidepressant, CNS stimulant	Y	88	MTZ/MPH:59.52 ± 11.3 MTZ/PLB: 55.89 ± 11.5	4
De fazio et al. (De Fazio et al., 2013)	2013	PNRT	Escitalopram	SSRI	MDD, ADDM, DD	15	53.9 ± 8.8	12
Park et al. (Park et al., 2012)	2012	PNRT	Escitalopram	SSRI	Y	79	49.1 ± 7.6	12
Amodeo et al. (Amodeo et al., 2012)	2012	RCT	Paroxetine	SSRI	MDD, DD, ADDM	30	60.9 ± 10.9	8
Torta et al. (Torta et al., 2011)	2011	PNRT	Duloxetine	SNRI	MDD, ADDM	27	63.6 ± 10.9	12
Schillani et al. (Schillani et al., 2011)	2011	PNRT	Escitalopram	SSRI	Y	18	N/A	2
Vega et al. (Rodriguez Vega et al., 2011)	2011	RCT	Escitalopram	SSRI	Y	33 (E only)	56 ± 10.8 (E only)	24
Suzuki et al. (Suzuki et al., 2011)	2011	PNRT	Fluvoxamine	SSRI	MDD, ADDM	10	53 (33–66)	8
Capozzo et al. (Capozzo et al., 2009)	2009	PNRT	Citalopram	SSRI	Y	21	71.1 ± 12.1	2
Schillani et al. (Schillani et al., 2008)	2008	PNRT	Sertraline	SSRI	Y	11	N/A	2
Torta et al. (Torta et al., 2008)	2008	PNRT	Sertraline	SSRI	MD	35	51.97 ± 13.26	12
Cankurtaran et al. (Cankurtaran et al., 2008)	2008	RCT	Imipramine Mirtazapine	TCAS, Tetracyclic Antidepressant	MDD, DD, ADDM	33	I: 43 (26–49) M: 46 (34–60)	6
Ersoy et al. (Ersoy et al., 2008)	2008	PNRT	Mirtazapine	Tetracyclic Antidepressant	Y	19	55.47 ± 11.04	24
Navari et al. (Navari et al., 2008)	2008	RCT	Fluoxetine	SSRI	Clinical Depressive symptoms	193	55.9 (37–85)	24
Torta et al. (Torta et al., 2007)	2007	PNRT	Amisulpride	Atypical Antipsychotic	Depressed mood, MDD, DD, ADDM	106	62 (32–82)	4
Musselman et al. (Musselman et al., 2006)	2006	PGRT	Paroxetine, Desipramine	SSRI, TCAS	MDD, ADDM	24	P: 54.6 ± 12.7 D: 47.7 ± 9.0	6
Grassi et al. (Grassi et al., 2004)	2004	PNRT	Reboxetine	SNRI	Y	20	58 ± 7	8
Theobald et al. (Theobald et al., 2003)	2003	PNRT	Citalopram	SSRI	Y	21	57.32 ± 12.6	8
Homsi et al. (Homsi et al., 2001)	2001	PNRT	Methylphenidate	CNS stimulant	Y	30	30–90	1
Pezzela et al. (Pezzella et al., 2001)	2001	PGRT	Paroxetine, Amitriptyline	SSRI, TCAS	Y	175	P 52.2 (36–72) A: 50.8 (34–69)	8
Holland et al. (Holland et al., 1998a)	1998	RCT	Fluoxetine, Desipramine	SSRI, TCAS	Y	38	F: 48.8 ± 10.9 D: 52.1 ± 7.9	6
Razavi et al. (Razavi et al., 1996)	1996	RCT	Fluoxetine	SSRI	MDD, AD	30	53.2 ± 11.4	5
Costa et al. (Costa et al., 1985)	1985	RCT	Mianserin	Tetracyclic Antidepressant	Y	36	48.8 ± 10.7	4

Table 2
Cancer type, count, and patients by publication. Data extracted as written in the methods. Does not include loss to follow-up during the course of disease.

Article	Number of Tumors Types	Cancer Type (Number)	Total Patients with Cancer
Dai et al. (Dai et al., 2017)	4	Digestive System (48), Respiratory System (72), Breast (23), Ovarian (23), Other locations (20)	186
Fan et al. (Fan et al., 2017)	4	Lung (7), Gastric (12), Bone (7), Pancreatic (11)	37
Li et al. (Li et al., 2014)	NA	GI (55), Respiratory (31), Hematologic (21), unspecified (15)	122
Raddin (Raddin et al., 2014)	NA	Solid Tumor non-metastatic (12), Solid Tumor, metastatic (4), Hematologic (5)	21
Guan et al. (Ng et al., 2014)	8	Breast (34), Upper GI (7), Colorectal (9), Renal (4), Pancreas (6), Bone (5), Urinary Tract and Prostate (6), Uterine/cervical/ovarian (5), Unspecified (12)	88
De fazio et al. (De Fazio et al., 2013)	2	Non-specific: "most common digestive and breast cancer"	44
Park et al. (Park et al., 2012)	1	Breast Cancer (79)	79
Amodeo et al. (Amodeo et al., 2012)	7	Colorectal (6), Dermatologic (1), Hematologic (3), Gastric (1), Breast (9), Lung (6), Head and Neck (2), Unspecified (2)	30
Torta et al. (Torta et al., 2011)	8	Breast (7), Colorectal (5), Hematologic (4), Gastric (3), Lung (3), Ovarian (2), Prostate (2), Hepatopancreas (1)	27
Schillani et al. (Schillani et al., 2011)	12	Lung (9), Breast (6), Prostate (5), Colon (5), Ovarian (4), Pancreas (3), Brain (2), Kidney (2), Stomach (2), Biliary Tract (1), Tongue (1), Leukemia (4), Unspecified (1)	45
Vega et al. (Rodriguez Vega et al., 2011)	3	Breast (48), Colorectal (15), Lung (9)	72
Suzuki et al. (Suzuki et al., 2011)	3	Cervical (2), Ovarian (3), Endometrial (5)	10
Capozzo et al. (Capozzo et al., 2009)	11	Colon/Rectum (4), Pancreas (3), Lung (2), Prostate (2), Breast (2), Liver (2), Esophagus (2), Brain (1), Stomach (1), Ethmoid bone (1), Hematologic (1)	21
Schillani et al. (Schillani et al., 2008)	11	Lung (5), Bowel (3), Stomach (3), Kidney (2), Prostate (1), Duodenum (1), Breast (1), Submandibular Gland (1), Biliary Duct (1), Bronchus (1), Plasmacytoma (1), Unspecified (3)	23
Torta et al. (Torta et al., 2008)	4	Breast (19), Colorectal (7), Hematologic (6), Lung (3)	35
Cankurtaran et al. (Cankurtaran et al., 2008)	NA	NA	53
Ersoy et al. (Ersoy et al., 2008)	6	Breast (6), Hematologic (4), Brain (3), Gynecologic (3), Larynx/Nasopharynx (2), Hepatocellular (1)	19
Navari et al. (Navari et al., 2008)	1	Breast (193)	193
Torta et al. (Torta et al., 2007)	10	Head and Neck (20), Colon (12), Gastric (12), Breast (12), Ovarian (12), Prostate (12), Hematologic (10), Lung (10), Skin (4), Pancreatic (2)	106
Musselman et al. (Musselman et al., 2006)	1	Breast (35)	35
Grassi et al. (Grassi et al., 2004)	1	Breast (22)	22
Theobald et al. (Theobald et al., 2003)	3	Colon (7), Lung (4), Hematologic (4), unspecified (6)	21
Homsi et al. (Homsi et al., 2001)	6	Breast (5), Esophagus (4), Head and Neck (4), Lung (4), Pancreas (4), Colorectal (2), Unspecified (7)	30
Pezzela et al. (Pezzella et al., 2001)	1	Breast (175)	175
Holland et al. (Holland et al., 1998a)	3	Breast (30), Colorectal (4), Gynecological (4)	38
Razavi et al. (Razavi et al., 1996)	NA	Gynecologic or breast, Hematologic	69
Costa et al. (Costa et al., 1985)	8	Breast (47), Ovary (4), Uterine (7), Other (15)	73

28 (n = 88) (Ng et al., 2014). In a cohort of 19 cancer patients diagnosed with depression, treatment with mirtazapine showed a significant HAM-D reduction with all patients in the observational study achieving a 50% response (n = 19) (Ersoy et al., 2008). Another study examined the efficacy of mirtazapine for depression treatment in the adult oncology population and showed a 4.5 point improvement in PHQ-9 score from initial and final visits with a minimum of nine weeks (n = 79) (Raddin et al., 2014). These findings were further demonstrated in cancer patients diagnosed with depression, adjustment disorder, and/or anxiety disorders where there was a significant reduction in HADS scores between the first and third visits for patients treated with mirtazapine (n = 53) (Cankurtaran et al., 2008).

4. Discussion

A diagnosis of major depressive disorder (MDD) by the DSM-V requires five or more criteria that includes a depressed mood or loss of interest that is not due to bereavement with persistence that lasts longer than 2 months and is associated with marked functional impairment (Diagnostic and statistica, 2013). Over time, several depression indices have become widely utilized including the HAM-D, MADRS, BDI, and the HADS-D. Each has its strengths (Schaaber et al., 1990; Kearns et al., 1982; Gibbons et al., 1993; Bagby et al., 2004; Bech, 2006; Garcia-Batista et al., 2018), shortcomings (Kearns et al., 1982; Carrozzino et al., 2020; Svanborg and Asberg, 2001), and geographical uses (Bech, 2006; Carmody et al., 2006). To-date and to our knowledge, there have been no randomized controlled, non-randomized controlled, or cohort studies that have analyzed the utility of pharmacologic antidepressant therapy among older adult patients ≥65 years of age with depression and cancer. This has also been noted by others (Fisch, 2004; Williams and Dale, 2006; Walker et al., 2014). Previous work identified 8 publications that studied depression and cancer in elderly patients (Spoletini et al., 2008). Studies investigating this group included topics such as heightened pain (Bernabei et al., 1998), comorbidities (Charlson and Peterson, 2002), risks of developing depression (de Jonge et al., 2006), suicide risk, (Labisi, 2006a, 2006b; Llorente et al., 2005), and symptom management (Rao and Cohen, 2004; Roth and Modi, 2003). Despite this, there is still an absence of investigation on pharmacologic efficacy in elderly cancer patients even though this cohort possesses well-described associations with depression, pain management, and complex social needs. Recently, the Francophone Society of Geriatric Oncology (SOFOG) released a systematic review on treating depression in older cancer patients (Lloyd-Williams et al., 2009). However, these studies explored non-pharmacologic interventions and/or did not perform discrete elderly

Table 3
MADRS, HADS-D, and HADS-A initial and last follow-up scores in the treatment of depression or depressive symptomology in patients with cancer. SE: Standard Error, + slow and standard titrations for paroxetine. I: Imipramine, M: Mirtazapine, MTZ: Mirtazapine, MPH: Methylphenidate.

Paper	Initial MADRs	MADRs at last follow-up	p	Initial HADs-D	HADs-D at last follow-up	p	Initial HADs-A	HADs-A at last follow-up	p	Follow up (weeks)
Razavi et al. (Razavi et al., 1996)	26.1 ± 7.1	13.6 ± 7.2	<0.05	Total HADS 22.7 ± 6	Total HADS 15.0 ± 6.1	<0.05	–	–	–	5
Amodeo et al. (Amodeo et al., 2012)	+Slow 27.9 ± 7.0, +Standard 30.7 ± 9.1	+Slow 10.2 ± 7.0 +Standard 16.1 ± 7.9	No paired analysis	+Slow: 12.5 ± 2.7 +Standard 14.2 ± 3.8	+Slow: 5.3 ± 3.2 +Standard 10.0 ± 5.1	No paired analysis	+Slow: 14.0 ± 1.8 +Standard 14.3 ± 4.5	+Slow: 6.6 ± 2.8 +Standard 9.8 ± 3.0	No paired analysis	8
Cankurtaran et al. (Cankurtaran et al., 2008)	–	–	–	M 12.5 ± 5.1 I: 10.7 ± 3.8	M: 7.8 ± 3.7 I: 10.1 ± 1.9	M:0.025 I: 0.008	M: 10.3 ± 4.7 I: 10.6 ± 3.9	M 6.6 ± 3.2 I: 9.1 ± 4.5	M:0.003 I: 0.04	6
Capozzo et al. (Capozzo et al., 2009)	–	–	–	9.8 ± 1.3	7.8 ± 1.1	0.047	5.5 ± 1.2	4.3 ± 1.1	0.047	2
De fazio et al. (De Fazio et al., 2013)	–	–	–	18.1 ± 3.4	14.4 ± 3.5	No paired analysis	19.4 ± 4.0	14.3 ± 4.1	No paired analysis	12
Fan et al. (Fan et al., 2017)	Ket: 34.89 ± 8.04	25.09 ± 7.07 (day 3)	No paired analysis	–	–	–	–	–	–	1
Guan (Ng et al., 2014)	MTZ/MPH 31.89 ± 6.24 MTZ/PLB 32.25 ± 6.14	MTZ/MPH 15.86 ± 6.65 MTZ/PLB 26.73 ± 8.45	No paired analysis	–	–	–	–	–	–	4
Schillani et al. (Schillani et al., 2011)	–	–	–	–	–		8.2 ± 3.8	5.9 ± 3.9	0.006	2
Schillani et al. (Schillani et al., 2008)	–	–	–	11.3 ± 0.9	6.7 ± 1.0	0.003	6.7 ± 1.3	3.5 ± 0.9		2
Suzuki et al. (Suzuki et al., 2011)	–	–	–	Total HADs MDD: 25 (21–28) ADDM: 15 (13–17)	Reduced	<0.05	Not specified	Reduced	<0.01	8
Torta et al. (Torta et al., 2011)	32.3 ± 8.9	14.5 ± 10.8	<0.05	14.4 ± 3.8	7.2 ± 4.6	<0.05	13.2 ± 4.5	6.6 ± 4.5	<0.05	12
Torta et al. (Torta et al., 2007)	37.6 ± 6.9	18.7 ± 10.6	<0.002	–	–	–	–	–		4
Torta et al. (Torta et al., 2008)	28.4 ± 9.90	13.26 ± 10.58	<0.05	11.46 ± 4.286	7.04 ± 4.155	0.000	12.94 ± 3.548	7.7 ± 4.631	0.000	12
Vega et al. (Rodriguez Vega et al., 2011)	–	–		12.48 ± 0.51 (SE)	6.72 ± 0.51 (SE)	No paired analysis	–	–	–	24

patient subgroup analysis (Ostuzzi et al., 2018a; Dai et al., 2017). Primary care providers can have a difficult time detecting depression in elderly cancer patients even though it is known to be a risk factor for poor quality of life and overall morbidity (Gouveia et al., 2015; Passik et al., 1998; Werner et al., 2012). As happens often for this patient population, symptoms of depression may be overlooked as a normal response to aging (Raj, 2004). One study determined that oncologists were able to identify 80% of patients without depression (Passik et al., 1998).

Antidepressant efficacy in patients with cancer remains a widely debated area of research. One meta-analysis concluded that there is no difference in alleviating symptoms of depression when antidepressants are compared to placebo. They also found no statistical difference between medication classes evaluated at 1–4 and 6–12 weeks of treatment (Ostuzzi et al., 2015, 2018b). A conflicting report estimated a 1.56 effect size reduction in depression/depressive-like symptoms in cancer patients with the use of antidepressants (Laoutidis and Mathiak, 2013). In 2006, Williams & Dale commented on the reported effectiveness of antidepressants in reducing symptoms and posed the argument that few studies reported antidepressant treatment efficacy in terms of clinical depression changes as compared to a change in depressive-like symptoms (Williams and Dale, 2006). A 2014 systematic review (Walker et al., 2014) examining the treatment of depression in cancer patients only identified 7 publications that met the inclusion criteria. Two of the studies examined the effect of pharmacologic therapies (Pezzella et al., 2001; Costa et al., 1985) and 1 explored pharmacologic versus psychologic treatment effects (Veitenhansl et al., 2004). Recently, the relationship between depression and inflammation was explored in cancer patients treated for depression. However, this study did not remove investigations that evaluated non-pharmacologic therapies and included literature examining patients with sub- and below-threshold depression scores (Panjwani and Li, 2021). Despite the related reviews in existence, no study to-date has focused on conducting an age-specific analysis.

In a retrospective analysis of older adults enrolled in clinical cancer trials, only 25% of participants were identified as being >65 years of age despite ≥60% of new malignancy diagnoses occurring among this age group (Berger et al., 2006; Lewis et al., 2003). Similar findings were obtained from the Southwest Oncology Group (SWOG) (Hutchins et al., 1999). Of the reviewed publications, age classifications were rare and those that included stratifications presented few patients within the ≥65 years of age group. Despite the American Society of Clinical Oncology (ASCO) acknowledging the underrepresentation of older adults (Hurria et al., 2015; Sedrak et al., 2021), the integration of geriatric populations

Table 4
HAM-D and HAM-A initial and last follow-up scores in the treatment of depression or depressive symptomology in patients with cancer. p-values are reported from a change in treatment baseline score and does not include significant values across a comparison treatment or placebo groups. F: Fluoxetine, D: Desipramine, P: Paroxetine.

Paper	Initial HAM-D	HAM-D at last follow-up	p	Initial HAM-A	HAM-A at last follow-up	p	Follow up (weeks)
Costa et al. (Costa et al., 1985)	20.6 ± 3.62	8.19 ± 6.38	No paired analysis	–	–	–	4
Dai et al. (Dai et al., 2017)	–	Reduction	<0.05	–	–	–	6
De Fazio et al. (De Fazio et al., 2013)	18.1 ± 3.5	10.8 ± 6.0	No paired analysis	22.0 ± 6.7	14.3 ± 7.9	–	12
Ersoy et al. (Ersoy et al., 2008)	21.4 ± 4.9	6.5 ± 3.2	<0.001	–	–	–	24
Grassi et al. (Grassi et al., 2004)	21.76 ± 3.89	11.61 ± 9.87	<0.01	–	–	–	8
Holland et al. (Holland et al., 1998a)	F: 23.58 D: 22.79	Significant reduction at 6 weeks with no difference between fluoxetine and desipramine total HAM	F: <0.05 D: <0.05	F: 20.00 D: 19.79	Significant reduction at 6 weeks. No difference between fluoxetine and desipramine total HAM	F: <0.002 D:<0.001	6
Li et al. (Li et al., 2014)	27.4 ± 5.4	14.6 ± 5.3		25.6 ± 6.5	12.5 ± 4.0	–	12
Musselman et al. (Musselman et al., 2006)	D: 23.00 ± 6.16 P: 21.00 ± 5.66	ΔD: 10.09 ± 9.42 ΔP: 7.62 ± 5.80	NS	D: 18.45 ± 6.67 P: 19.62 ± 7.19	ΔD: 5.09 ± 9.70 ΔP: 4.38 ± 5.85	NS	6
Park et al. (Park et al., 2012)	–	Reduction	<0.001	–	–	–	12

into clinical trials has yet to improve (Kimmick et al., 2005). Inclusion of elderly patients into clinical trials is limited due to stringent eligibility criteria, the unwillingness of elderly patients to enroll, comorbidities, toxicities associated with the experimental treatment, as well as emotional and financial burdens. These considerations are exacerbated by older adult patient dependency on family members, primary caregivers, or facilities in which they reside (Sedrak et al., 2021). Enrollment in US Food and Drug Administration (FDA) approved drug trials from 1995 to 2002 showed that elderly patients were significantly underrepresented in all registered studies except hormonal therapy for breast cancer, with the lowest representation of patients in the ≥70 years of age group (Talarico et al., 2004). Geriatric patients are treated with nearly one third of medications in the United States and have high rates of polypharmacy (Avorn, 1995), but have inadequate representation in experimental drug treatment-involved clinical trials (Sedrak et al., 2021; Talarico et al., 2004; Parikh, 2000; Salzman et al., 1993). Age-related physiological changes influence how older patients react to medications, and increase their risk for adverse side effects due to comorbidities and polypharmacy (Shenoy and Harugeri, 2015). Polypharmacy also adds to the therapeutic burden which can be a major source of morbidity. 10–30% of geriatric hospitalizations are related to adverse medication events (Repetto et al., 2003; Parameswaran Nair et al., 2016; Dubrall et al., 2020) that include substance-induced depression (Alexopoulos, 2005). Between 2011 and 2014 in the general population, 19.1% of individuals ≥60 years of age reported being treated with an antidepressant in the past month (Pratt et al., 2017). Furthermore, it is estimated that 47.5% of patients within nursing homes were prescribed an antidepressant in 2006 (Giovannini et al., 2020). For these older adults, SSRIs are considered first-line treatments (Alexopoulos, 2005) followed by the use of SNRIs and atypical antidepressants including bupropion and mirtazapine. TCAs and MAOIs are typically avoided in the cancer patient and general population due to their side effect profiles (Casey, 2017; Grassi et al., 2018). Despite the wide use of these medications (Fuentes et al., 2018), drug interactions may be overlooked in elderly patients such as CYP450 enzyme inhibition (Nemeroff et al., 1996; Crewe et al., 1992; van der Weide and Hinrichs, 2006). Metabolically, antidepressants have the potential to interact with chemotherapies among other cancer treatments (Caraci et al., 2011). For example, paroxetine, fluoxetine, venlafaxine, and bupropion have been implicated to decrease the active metabolite of tamoxifen, but the long-term impact of this treatment remains controversial and more research is needed (Grassi et al., 2018; Bradbury et al., 2021; Nevels et al., 2016; Del Re et al., 2016).

Older adults are also more likely to have poorer hepatic and renal function that can inhibit metabolism and drug excretion, thereby contributing to increased adverse effects and toxicity (Mangoni and Jackson, 2004). For these reasons, antidepressant treatment that minimizes CYP inhibition has been recommended (Miguel and Albuquerque, 2011; Binkhorst et al., 2016). Medication side effects may include GI disturbances, weight gain, headaches, insomnia, anxiety, and serotonin syndrome, with adverse effects varying by intra- and inter-drug class (Table 5). TCAs may also cause anticholinergic effects in older adults with cancer (Grassi et al., 2018). For example, bupropion is typically avoided in neurologic disease for elevated seizure risk (Ramasubbu et al., 2012). Various guidelines exist for the prescription of antidepressants in cancer patients that often suggest a patient-centered consideration of antidepressant side effect profiles, drug interactions, response to previous treatments, comorbidities, the potential for benefit, and cancer prognosis (Ramasubbu et al., 2012; Andersen et al., 2014; Butow et al., 2015). Guidelines from the European Palliative Care Research Collaborative (EPCRC) proposed that clinicians should consider recommending antidepressants for the treatment of depression during palliative care (Rayner et al., 2011). In older adults without cancer, the treatment of depression involves pharmacologic and non-pharmacologic therapies. It has been suggested that while antidepressant effects in older adults are similarly effective as in younger patients, they exhibit more side effects (Anstey and Brodaty, 1995) with a longer time for responding to therapy among individuals with advanced age (Parikh, 2000). Meta-analyses have found evidence of effective treatments across the antidepressant classes (Thorlund et al., 2015; Kok et al., 2012; Nelson et al., 2008). However, research regarding the efficacy of treatment for depression specifically in elderly adult patients is limited to more advanced age groups such as ≥75 years of age (Fisch, 2004; Taylor and Doraiswamy, 2004; Wilkinson et al., 2018). Despite the need for more research in the oldest age group of patients, there is some evidence of pharmacologic benefit for the treatment of elderly adults with depression that cannot be generalized to patients with cancer of the same age. These individuals are not characteristically similar and differ in polypharmacy,

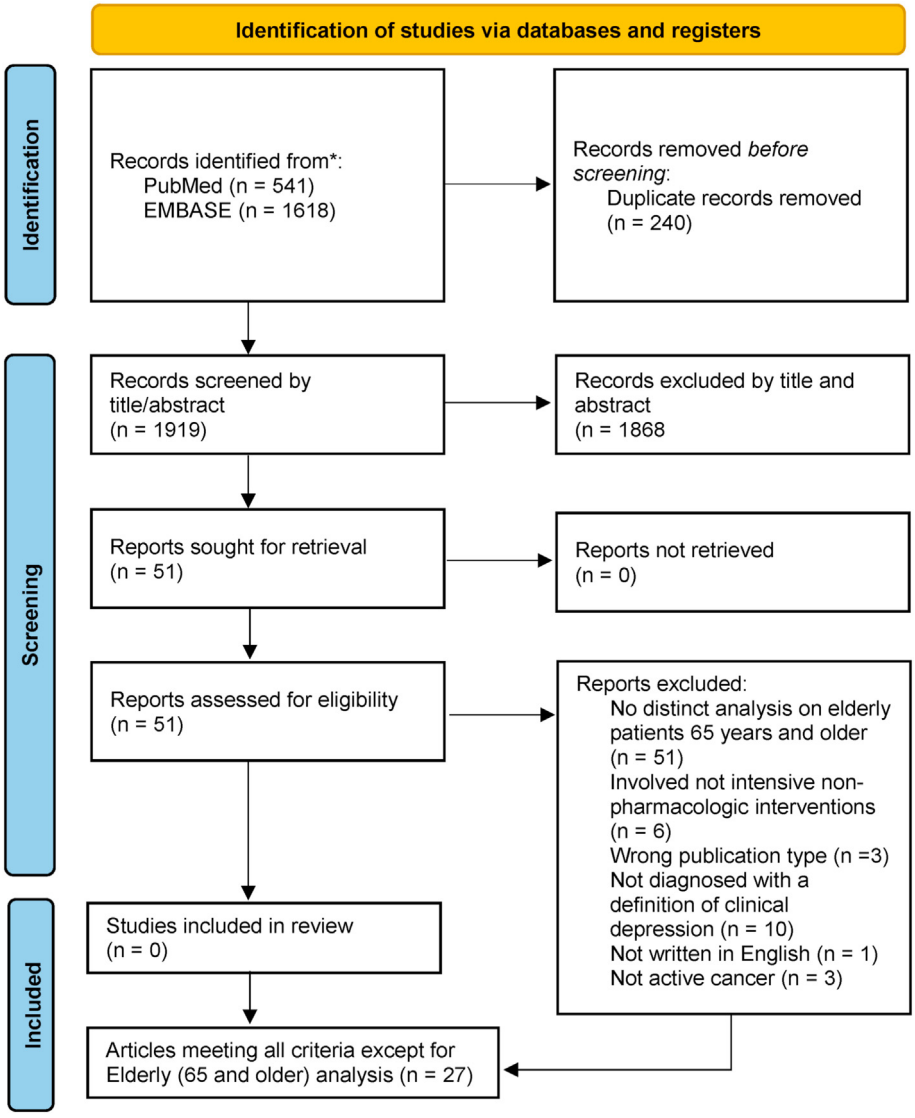

Fig. 1. PRISMA flow chart for literature search and study selection (Page et al., 2021).

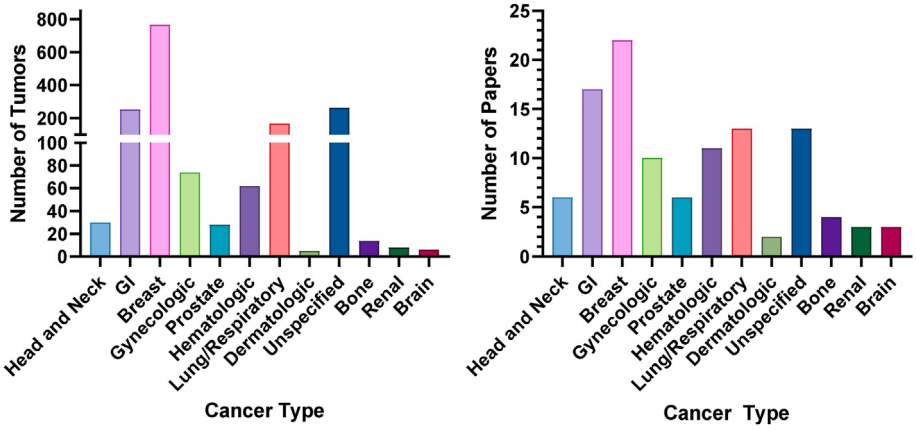

Fig. 2. Characteristics of Reviewed Studies. Distribution of tumors within the reviewed studies (left). Of the studies that were reviewed, the number of publications that included at least one cancer by type is shown (right).

co-morbidities, and other known and unknown variations (Jørgensen et al., 2012; Shrestha et al., 2019).

As the global incidence of cancer has increased, the most frequently incident cancers have also increased including those arising from the

Table 5
Selected list of antidepressants and their adverse reactions for medications included or observed during review screening.

Drug Classification	Generic Name (Brand Name)	Major Adverse Effects
Selective Serotonin Reuptake Inhibitors (SSRI)	Citalopram (Cipramil), Escitalopram (Cipralex), Fluoxetine (Prozac, Oxactin), Fluvoxamine (Faverin), Paroxetine (Seroxat), Sertraline (Lustral), Vortioxetine (Brintellix)	Sexual dysfunction, nausea, diarrhea, agitation, fatigue, insomnia, headache, weight gain. (Ferguson, 2001; Santarsieri and Schwartz, 2015)
Selective Norepinephrine Reuptake Inhibitors (SNRI)	Desvenlafaxine (Pristiq), Duloxetine (Cymbalta), Venlafaxine(Effexor), Milnacipran (Savella), Levomilnacipran, (Fetzima)	Nausea, insomnia, dry mouth, headache, increased blood pressure, sexual dysfunction, diarrhea, weight gain, serotonin syndrome (Gillman, 2007)
Tricyclic Antidepressants (TCA)	Amitriptyline (Elavil), Desipramine (Norpramin), Doxepin (Sinequan), Imipramine (Tofranil), Nortriptyline (Pamelor), Amoxapine (Asendin), Clomipramine (Anafranil), Maprotiline (Ludiomil), Trimipramine (Surmontil), Protriptyline (Vivactil)	Weight gain, sedation, dry mouth, nausea, blurred vision, constipation, tachycardia, orthostatic hypotension, tremor, respiratory depression, hyperpyrexia, serotonin syndrome. (Gillman, 2007; Pezzella et al., 2001; Santarsieri and Schwartz, 2015)
Monoamine Oxidase Inhibitors (MAOI)	Isocarboxazid (Marplan) Phenelzin (Nardil) Selegiline (Emsam) Tranylcypromine (Parnate)	Hypertensive crisis with tyramine ingestion, sexual dysfunction, orthostatic hypotension, fatigue, insomnia, nausea, and weight gain, myoclonus, serotonin syndrome (Fiedorowicz and Swartz, 2004; Santarsieri and Schwartz, 2015; Wimbiscus et al., 2010)
Atypical Antidepressants	Bupropion (Wellbutrin)	Headache, dry mouth, nausea, insomnia, constipation, dizziness of appetite, weight loss, reduction of seizure threshold. (Davis et al., 1997; Santarsieri and Schwartz, 2015; Wang et al., 2018)
	Mirtazapine (Remeron)	Sedation, increased appetite, weight gain (Santarsieri and Schwartz, 2015)
	Mianserin (Tolvon)	Drowsiness, mild anticholinergic effects, headache, dizziness. (De Ridder and Mianserin, 1982)
	Nefazodone (Serzone)	Nausea, somnolence, dry mouth, dizziness, constipation. (Davis et al., 1997)
	Trazodone (Desyrel Oleptro)	Sedation, nausea, priapism (Santarsieri and Schwartz, 2015)
	Vilazodone(Viibryd)	Headaches, nausea, vomiting, diarrhea, dry mouth, insomnia, risk of serotonin syndrome. (Cruz, 2012; Santarsieri and Schwartz, 2015)
	Vortioxetine (Brintellix)	Nausea, diarrhea, dizziness. (D'Agostino et al., 2015; Santarsieri and Schwartz, 2015)
Other Medications Observed in Screening	Ketamine	Hallucinations, delirium, increased salivary secretions, arrhythmias, respiratory depression (Pribish et al., 2020)
	Methylphenidate (Daytana XR)	Hypertension, tachycardia, insomnia, headache, dizziness, nervousness, anorexia, weight loss, urticaria. (Challman and Lipsky, 2000)
	Amisulpride (Barhemsys)	Insomnia, weight gain, agitation, anxiety, extrapyramidal disorders. (Challman and Lipsky, 2000)
	Reboxetine (Edronax)	Insomnia, sweating, constipation, dry mouth, hypotension. (Scates and Doraiswamy, 2000)
	Psilocybin	Hallucinations (Johnson and Griffiths, 2017)

breast, GI tract, and lungs (DeSantis et al., 2019). Of 27 articles assessed, breast, GI tract, and lung cancer represented 70.7% of malignancies recorded. Despite this, high-quality clinical trials for pharmacologic or non-pharmacologic depression treatment in patients with lung cancer (Walker et al., 2013) or breast cancer (Carvalho et al., 2014) have yet to be performed. Similarly, a Cochrane Review investigating pharmacologic treatment of patients with primary brain cancer reported that no studies met the inclusion criteria (Rooney and Grant, 2010). This was repeated by the same group in 2013 (Rooney and Grant, 2013) and 2020 (Beevers et al., 2020) without evidence of high-quality studies that included updated queries. Within this review, brain cancer patients made up 0.4% of evaluated patients (Fig. 2) with only 3 studies meeting the majority of our selection criteria that had brain tumor patient involvement (Table 2). (Ersoy et al., 2008; Schillani et al., 2011; Capozzo et al., 2009) This highlights the paucity of data regarding the use of antidepressants in patients with primary brain cancer; a population whereby ~1 of every 3 patients show signs of depression (Otto-Meyer et al., 2019).

From 1990 to 2006, the global incidence of brain tumors rose from 4.6/100,000 to 17.3/100,000 (Brain and Other, 2019). Patients with intracranial neoplasms often present with physical deficits of generalized weakness, visual changes, motor and communication function, and post-operatively, are at a risk for developing new neurologic deficits secondary to tumor resection (Kushner and Amidei, 2015; De La Garza-Ramos et al., 2016). Meningioma patients who pre-operatively demonstrate depressive symptoms have a 7 times increased hazard ratio at the 5-year survival threshold (Bunevicius et al., 2017). In patients with glioblastoma, a high PHQ-9 score is indicative of a more necrotic tumor and correlates with a worse prognosis (Fu et al., 2020); a cancer patient population whereby older age is strongly associated with accelerated mortality (Kim et al., 2021; Ladomersky et al., 2020). Coincidently, a diagnosis of depression in glioma patients is associated with worse survival outcomes (Shi et al., 2018). Patients with WHO grade 3 or 4 malignant astrocytoma and active depression at the time of surgery are associated with decreased survival regardless of tumor grade, treatment, or disability (Gathinji et al., 2009). Similarly, high-grade glioma patients with pre-operative depression and treated with psychological interventions show an improved survival (Wang et al., 2014). In a nationwide South Korean cohort study, 17.0% of brain tumor patients who underwent surgical tumor resection were also newly diagnosed with depression. Both elderly patients $\geq$60 years of age [1.54 (CI 1.27:1.86)] and non-elderly patients <60 years of age [1.68 (CI 1.39:2.04)] showed increased odds of mortality at two years post-diagnosis (Oh et al., 2021). After surgery, antidepressant use increased in patients with low-grade glioma and depression rates in these patients were reported to be relevant to 36% of the population under study (Ryden et al., 1186; Hartung et al., 2017). While these patients are often treated with antidepressants, side effects of antidepressants may include lower seizure threshold, impaired memory formation/recall, and fatigue (Table 5). (Rooney and Grant, 2013; Hill et al., 2015) Some *in vitro* data suggests that SSRIs may have anti-brain tumor effects (Liu et al., 2015; Jeon et al., 2011; Ma et al., 2016; Chen et al., 2018). However, retrospective analyses have yet to report any significance (Gramatzki et al., 2020; Otto-Meyer et al., 2020; Caudill et al., 2011). The use of antidepressant therapy among brain tumor patients may improve mood and function within a population that undergoes treatment with radiation, chemotherapy, and progressive neurosurgical insults to the brain. SSRI and SNRI use have become common in the post-stroke and traumatic brain injury patient populations. Patients treated with these medications have demonstrated

improvement of motor and cognitive function (Chollet et al., 2011; Plantier et al., 2016) and similar effects should be investigated in brain tumor patients to potentially improve health-related quality of life, improvements in patient lassitude, sleep, and the promotion of participation in therapy services.

Study limitations

Each article measured the efficacy of pharmacologic therapy in patients with cancer and depression, but inclusion and exclusion criteria, medication type and dosage, follow-up, and utilized depression scales were highly variable between studies. Included publications ranged from 1985 to 2017 and included widely changing definitions for clinical forms of depression, with a notable difference in the DSM. Although it is routine to define elderly patients as ≥65 years of age, not all studies define this age group similarly. Publications that did not distinctly analyze older adults, or, older adults versus younger individuals were not investigated. The numbers of treated patients with depression within this review were highly variable with a median number of 30.

Though our search was conducted using PRISMA guidelines, it is possible that our eligibility criteria did not capture all relevant publications despite including studies that represent a mixture of prospective and retrospective investigations. The definition of a depression diagnosis and the use of screening tools within and between scales varied broadly. While conversions between those scales exist, their high level of heterogeneity makes them difficult to compare directly (Furukawa et al., 2019; Leucht et al., 2018; Schneibel et al., 2012) and patients with medical conditions such as physical symptoms may further confound the inter-relatability between indices. Depression scales vary on the ability to identify depressive symptoms among individuals and vary with the emphasis on psychiatric versus somatic origin (Table 6, **Appendix**). Furthermore, a diagnosis of clinical depression cannot be made without clinical interviews, and consideration of scores out of context may add further variance in study outcomes. In practice, antidepressants are frequently used for simultaneous treatment of chronic pain and mood complaints in patients with cancer (Zis et al., 2017). The design of this review excludes studies examining the relationship between pain and mood with the recommendation that future studies focus specifically on this complex clinical connection. Limited studies on specific medications were conducted and were too few for subgroup analysis. Medication dosing and follow-up times varied between studies. Explanations for loss to follow-up varied. Records for adverse reactions were not standardized.

Summary

Despite the need to study pharmacologic antidepressant treatment among older adult patients with cancer, with or without depression, no high-quality studies have been conducted to-date. Research on antidepressant treatment in the general cancer population is not optimal. Meta-analyses often show conflicting observations and the types of cancers under study are highly limited. Clinicians have little to guide intervention-based practice. Older adults face unique multifaceted barriers to enrolling and adhering to treatment and are at a risk for increased incidence of adverse reactions under a therapeutic burden. Systemic therapy adds to the burden of disease and can cause more offending symptomatology in the older adult population (Repetto, 2003). Associated with the side effects of chemotherapies, patients may exhibit a lack of energy, sleep disturbance, weight loss, or other various side effects which may render standard depression screens unreliable for this population (Saracino et al., 2017). Pharmacologic therapy continues to be prescribed within the United States and while more studies are needed to explore treatment efficacy in the elderly cancer patient population with depression, health care workers should consider having individualized discussions and routine assessments of depression with their patients regarding pharmacologic therapeutic options. Future studies are critical to explore this topic and provide strong guidelines for treatment.

Funding

This work was supported in part by National Institutes of Health (NIH) grants P50CA221747 (R.V.L., D.A.W.), R01NS097851 (D.A.W.), K02AG068617 (D.A.W.), Lou Malnati Brain Tumor Institute (R.V.L, D.A.W.), BrainUp grant 2136 (R.V.L. and D.A.W.), the Gail Boyter Magness (GBM) Foundation (D.A.W.), the GBM Foundation (D.A.W.), Grace Giving Foundation (D.A.W.), Stephen Coffman Charitable Trust (D.A.W.), 5 for the Fight Foundation (D.A.W.), and American Cancer Scholar Research Scholar Award RSG-21-058-01 - CCE (D.A.W.).

Declaration

All authors have read and approved of the manuscript submitted for peer review.

Declaration of competing interest

The authors declare no conflicts of interest.

APPENDIX

Full Search Strategy:

PubMed and EMBASE

("depressive disorder" OR "depression") AND ("antidepress" OR "antidepressive agents") AND ("brain cancer" OR "brain neoplasm*" OR "brain tumor" OR "brain tumor malignan*" OR "malignant brain tumor*" OR "intracranial neoplasm" OR "intracranial tumor" OR "primary brain tumor*" OR "primary brain neoplasm*" OR "primary brain malignan*" OR "malignant primary brain neoplasm*" OR "malignant primary brain tumor*" OR "glioma*" OR "astrocytoma" OR "glioblastoma" OR "oligodendroglioma" OR "ependymoma*" OR "meningioma*" OR "medulloblastoma*" OR "craniopharyngioma*" OR "cancer*" OR "malignan*" OR "Tumor*" OR "malignant neoplasm*") AND ("elderly" OR "aged" OR "geriatric" OR "Aged, 80 and over" OR "Centenarians" OR "Nonagenarians" OR "Octogenarians")

Clinical Depression Defined in Review

Clinical depression was defined as having the diagnosis of Major Depressive Disorder, Major Depressive Disorder with atypical features, Major Depressive Disorder with psychotic features, Minor Depressive Disorder, Persistent Depressive Disorder, Adjustment Disorder with Depressed Mood, or another definition of “clinical depression” or “clinical depressive symptoms” as specified within the reviewed articles.

Table 6
Measures by tool. MADRS assesses a low level of somatic symptoms as compared to the other measures. (Kearns et al., 1982)

	HAM-D (1960) (Hamilton, 1960)	HADS-D (1983) (Zigmond and Snaith, 1983)	MADRS (1979) (Montgomery and Asberg, 1979)	BDI-II (1996) (Johnson and Griffiths, 2017)
Overall Depressed Mood	X	X	X	X
Feelings of Guilt	X		X	X
Suicide Ideations	X		X	X
Indecisiveness	X			X
Insomnia/sleep disturbances	X		X	X
Fatigue	X			X
Activity	X	X		X
Lassitude/Stupor	X	X	X	X
Agitation	X	X	X	X
Anxiety	X	X	X	
Somatic Symptoms	X	X	X	X
Sexual dysfunction	X			X
Somatic preoccupation	X			X
Weight Loss	X			X
Loss of Interest/Enjoyment/emotion	X	X	X	X
Body image		X		X
Hopelessness	X		X	X
Reduced Appetite	X		X	X
Attention	X		X	
Pessimistic Thoughts including failure, punishment, self-hate, and self-blame	X		X	X
Social Avoidance				X

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