

REVIEW

Psychological and behavioral symptoms in patients with melanoma: A systematic review and meta-analysis

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Abstract

Objective: Improved survival rates have made it increasingly important for clinicians to focus on cancer survivorship issues affecting the quality of life of melanoma patients. To provide a comprehensive overview of the disease and treatment-related issues affecting such patients, we conducted a systematic review and meta-analysis of the literature to estimate the prevalence of symptoms of depression, anxiety, fatigue, sleep disturbance, and cognitive problems among melanoma patients, both uveal and cutaneous, before, during and after treatment.

Methods: The review was preregistered with PROSPERO (#CRD42020189847) and reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. A comprehensive search of the literature published up until June 2022 was undertaken using PubMed, PsycInfo, the Cochrane Library, and CINAHL. Two independent reviewers screened 1418 records and quality-rated included studies. The reported prevalence rates of symptoms were pooled using a random-effects model.

Results: Sixty-six studies including a total of 12,400 melanoma patients published between 1992 and 2022 were included. Pooled prevalence rates ranged from 6% to 16% for depression and 7%–30% for anxiety across diagnoses (uveal and cutaneous melanoma) and assessment time points. One third of the patients (35%) reported clinically significant fatigue, 20%–44% had cognitive complaints, while prevalence of sleep disturbance was not reported. Quality assessment indicated that 80% of the studies were of good quality.

Conclusion: A large body of research shows that depression and anxiety symptoms are prevalent in melanoma patients before, during and after treatment. However, research examining other symptoms known to affect quality of life, such as fatigue, sleep disturbances, and cognitive problems, is still needed.

KEYWORDS

cancer, cancer survivorship, late effects, melanoma, meta-analysis, oncology, prevalence, psycho-oncology, side effects

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1 | INTRODUCTION

Melanoma is an aggressive form of cancer, especially in its later stages, that originates from malignant transformed melanocytes.¹ In 2020, the incidence of melanoma was approximately 325,000 cases worldwide.²⁻⁴ This number is estimated to increase to 510,000 newly diagnosed cases by 2040.⁴ Melanoma affects people of all ages, but occurs most often during middle adulthood between the ages of 40 and 60 years.⁵ The estimated lifetime prevalence rate is one in 34 males and one in 53 women,⁶ with melanoma accounting for six out of seven skin cancer deaths.² Historically melanoma patients have been treated with chemotherapy, radiotherapy, and cytokine-based immune therapies (e.g., interferon- α , interleukin-2).^{2,3,7} The development of modern immunotherapy with checkpoint inhibitors together with targeted therapies with BRAF and MEK inhibitors in patients with BRAF mutated melanoma has led to new treatments with substantially improved survival rates over the past 10 years.^{3,7-10} The treatment of metastatic melanoma has particularly been improved by the introduction of CTLA4 and PD1 inhibitors that have beneficially impacted the prognosis for many patients.¹¹⁻¹⁴ CTLA4 and PD1 antibodies are immune checkpoint inhibitors (ICIs) that enhance activation of the immune system and tumor cell targeting.^{15,16} ICIs differ from classical cytokine-based immunotherapy (e.g., interferon- α , interleukin-2) and are associated with autoimmune like side effects. However, surgery is still the primary treatment for most melanoma patients (stage I-III), and currently adjuvant treatment is indicated for radically resected stage III-IV disease. ICIs and targeted therapy are also used in non-operable stage III-IV disease.^{2,3}

As a consequence of improved survival, there has been an increased focus on short- and longer-term side and late effects experienced by cancer patients and survivors in general.¹⁷ Across different cancers and treatments, a significant proportion of patients experience a wide range of co-occurring symptoms, including depression, anxiety, fatigue, sleep disturbances, and cognitive problems.¹⁸⁻²⁰ While the etiology of these symptoms, that is, whether they are due to the cancer or its treatment, is not always clear, these symptoms are associated with lower quality of life, poor daily functioning, slower recovery, and increased morbidity.²¹⁻²⁶

A systematic review of 44 studies published in 2009 indicated that approximately one third of patients with melanoma report high levels of psychological distress requiring clinical intervention.²⁷ A more recent systematic review of 18 studies showed that patients with uveal melanoma experienced impaired physical functioning and well-being after treatment.²⁸ Several studies included in these reviews have focused on psychological distress and quality of life in melanoma patients,^{27,29-31} but have typically not examined other symptoms that often co-occur in cancer patients. Indeed, in cancer patients, such symptoms may contribute to or even exacerbate each other over time^{19,32} with important treatment implications. For example, successful treatment of one symptom may have a beneficial impact on other symptoms in the cancer symptom cluster.³³ There is thus a need for a comprehensive systematic review with meta-analysis of important symptoms in uveal and cutaneous melanoma

patients beyond psychological symptoms, and which includes studies of other psychological and behavioral symptoms typically present in the cancer symptom cluster.

In view of the recent evolution of treatments for melanoma patients, we aimed to conduct a comprehensive systematic review to investigate the nature and prevalence of psychological and behavioral symptoms in the cancer-related symptom cluster, that is, depression, anxiety, fatigue, sleep disturbances, cognitive problems, before, during, and after treatment in patients and survivors with melanoma. Such information could have important implications for the development of targeted interventions to ameliorate such symptoms in this population.

2 | METHODS

The present study was conducted in accordance with the guidelines for Meta-Analysis Of Observational Studies in Epidemiology (MOOSE).³⁴ The protocol was preregistered in The International Prospective Register of Systematic Reviews (PROSPERO)³⁵ (#CRD42020189847), and the review is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.³⁶

2.1 | Search strategy and selection criteria

A comprehensive literature search with no publication date restrictions was undertaken on September 9, 2021 with an updated search conducted on June 8, 2022 in the PubMed, PsycInfo, Cochrane Library, and CINAHL electronic databases. When possible, relevant MeSH terms or MeSH term equivalents were included in each database. Key words related to the population (melanoma* OR "malignant melanoma*" OR "metastatic melanoma*") were combined with key words related to outcomes (depressi* OR anxiety OR fatigue* OR "cancer-related fatigue*" OR cognition* OR "cognitive function*" OR sleep* OR "sleep disturbances*" OR "cognitive impairment*" OR "cognitive dysfunction*" OR "cognitive deficit*" OR chemobrain OR "chemo-brain*" OR neuropsycholog* OR "cogniti*" OR "sleep disturb*" OR "chemo fog*" OR insomnia*). The first and second author (JTD and LSL) conducted the search independently.

Study eligibility was determined using the Population, Intervention/Exposure, Comparator, Outcome approach³⁷ referring to *population*, *intervention/exposure*, *comparator*, and *outcome*.³⁷ *Population*: studies of adults in treatment or previously treated for melanoma; *Intervention/exposure*: any melanoma treatment; *Comparator*: N/A; *Outcome*: one or more of the following symptoms: depression, anxiety, fatigue, sleep disturbances, and cognitive problems prior to, during, and/or after treatment assessed independently with a standardized validated measurement/symptom scale.

Only English-language reports published in peer-reviewed journals were considered eligible. We excluded non-human research, reports that were not primary research papers, for example, review

articles, single case studies, and “grey literature,” for example, conference abstracts and dissertations. Intervention studies were also excluded.

The literature search and data extraction were conducted using the Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia, www.covidence.org). In the first round of screening, JTD and LSL independently screened the title and abstract of all identified references and excluded ineligible reports. In the second round of screening, the full-text of the remaining reports were evaluated independently by JTD and LSL and reasons for exclusion were registered. Uncertainties and disagreements were discussed with the last author (RZ). After each screening, the two authors discussed discrepancies, and reached a negotiated decision. Following each screening, interrater agreement was assessed using Cohen's Kappa statistic, κ .³⁸

2.2 | Quality assessment

Methodological quality and risk of bias assessment was undertaken independently by two authors (JTD and SMK) for all included studies, using the National Institutes of Health Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies.³⁹

2.3 | Data extraction and synthesis

Data extraction was performed independently by two authors (JTD and SMK) and included authors, publication year, aim of study, study design, sampling strategy, setting, follow-up (number and assessment time points), number of participants, mean sample age, gender of participants (percent women), mean education level in years, participation rate of eligible persons, loss to follow up (percentage), melanoma diagnoses of participants (cutaneous and/or uveal melanoma), cancer stage (I–IV), treatment type (surgery, radiotherapy, chemotherapy, targeted therapy, ICI and/or cytokine-based immunotherapies), outcomes (cancer symptoms represented; depression, anxiety, fatigue, sleep and cognition), method used for assessing cancer symptoms and results (measurement, mean, standard deviation and prevalence rates of symptoms). A meta-analysis was conducted when a minimum of three studies assessing the same symptom were available. Analyses were conducted separately for each outcome, assessment time point (prior to treatment, during treatment and after treatment) and melanoma subtype (cutaneous or uveal melanoma).

2.4 | Meta-analytic strategy

A pooled inverse-variance weighted event rate (ER) was calculated for each outcome as the summary statistic of prevalence. ER is defined as the proportion of patients reporting high/clinical levels of the symptom in question while taking the individual study sample size into consideration, yielding an ER-range from 0 to 1. When

available, ERs were calculated for the following four time points: (1) before treatment, (2) during treatment, (3) less than 1 year after treatment, and (4) 1 year or longer after treatment. A random effects model was chosen over a fixed effects model as ERs were assumed to vary according to underlying study characteristics, for example, between study populations of different ages, with different gender distributions, with different diagnoses, and receiving different combinations of treatments. The possibility of publication bias, a widespread problem when conducting meta-analysis, was inspected visually with funnel plots⁴⁰ and analyzed with Egger's method.⁴¹ If our analyses indicated possible publication bias, it was planned to use the trim-and-fill procedure⁴² to impute “missing studies” and calculate an adjusted pooled ER.

Study heterogeneity was quantified by calculating the I^2 statistic which describes the percentage of the variability in prevalence estimates that is likely to be due to heterogeneity, that is, systematic differences between studies, rather than sampling error.⁴⁰ The I^2 statistic tends to overestimate heterogeneity when the number of studies in the meta-analysis is small and should be interpreted with caution. As recommended, we therefore supplement the point estimate I^2 with its confidence interval.⁴³

Based on the prevalence estimate from the meta-analysis, we calculated two interval estimates. In addition to the confidence interval (i.e., the precision of the estimate), we identified the 95% prediction interval based on τ as an estimate of the standard deviation of the true effect sizes ($\mu \pm Z^\alpha \sqrt{\tau^2}$). The prediction interval represents the range of values that the results of 95% of future similar studies are expected to fall within.⁴⁴

If three or more studies reported relevant data, we conducted sub-group analyses of ERs for each of the symptoms with respect to assessment time point (before, during, <1 year after, ≥ 1 year after treatment), melanoma diagnosis (uveal and cutaneous melanoma), and disease stage (early (I–II) and late stage (III, IV)). Finally, we conducted exploratory meta-regression analyses to investigate the role of potential continuous moderators (mean age of the sample, percent women in the sample, time since treatment, publication year) as well categorical moderators (diagnosis and treatment types, i.e., surgery, chemotherapy, radiotherapy, classical immunotherapy, ICIs, and targeted therapy).

Finally, if means and standard deviations or standard errors were reported for a sufficiently large number of studies, we calculated the pooled means for the most commonly used instruments, for example, the Hospital Anxiety and Depression Scale (HADS).⁴⁵

All analyses were conducted using Comprehensive Meta-Analysis, version 3⁴⁶ and various formulas in Microsoft Excel.

3 | RESULTS

3.1 | Search results

A total of 1798 articles were identified through database searches and an additional eight from other sources. After removal of

duplicates, a total of 1410 records were eligible for abstract screening. A total of 1108 records were excluded after screening, leaving 302 articles eligible for full text screening. Two hundred and thirty-six articles were then excluded primarily due to reporting a “non-relevant outcome” (52%), leaving 66 papers that were included in the systematic review. Ninety-percent agreement was achieved by reviewers during the abstract review process and 96% agreement during full-text screening. All disagreements were resolved through negotiation. The study selection process is visualized in Figure 1. Authors of 31 studies were contacted and asked to provide additional data. Ten authors replied and provided the requested data.

3.2 | Study characteristics

The participants, treatments, symptoms examined, and other characteristics of the included studies are summarized in Table 1. The eligible papers reported on 72 independent samples including a total of 12,400 melanoma patients and survivors, with sample sizes ranging from 7⁴⁷ to 1109.⁴⁸ The included articles were published between 1992 and 2022 and reported on 54 samples of cutaneous melanoma patients and 18 samples of uveal melanoma patients. The

studies were broadly geographically distributed with 49 studies conducted in Europe, 13 in North America, 3 in Oceania, and 1 in South America. Mean sample ages ranged from 42.4⁴⁷ to 69.48⁴⁹ years with an overall weighted mean sample age of 61.2 years. Approximately one-third of the studies ($K = 24$ (36%)) had used a longitudinal design, that is, presented prevalence data for more than one time-point.

3.3 | Quality rating and risk of bias

See online Table S1 for an overview of the quality ratings of each study. Fifty-three studies were assessed to be of good quality (>9 criteria met) and 13 studies to be of fair quality (5–9 criteria meet). Overall, studies received high ratings in terms of presenting clear definitions of the research question, study population, exposure and outcome measures as well as having a sufficient timeframe between measurement of outcome and exposure. Only 24 studies reported follow-up data on psychological outcomes and over half of these studies either did not report follow-up rates or had dropout rates greater than 20%. Statistical power justification was only reported in five studies, and 23 studies reported effect estimates.

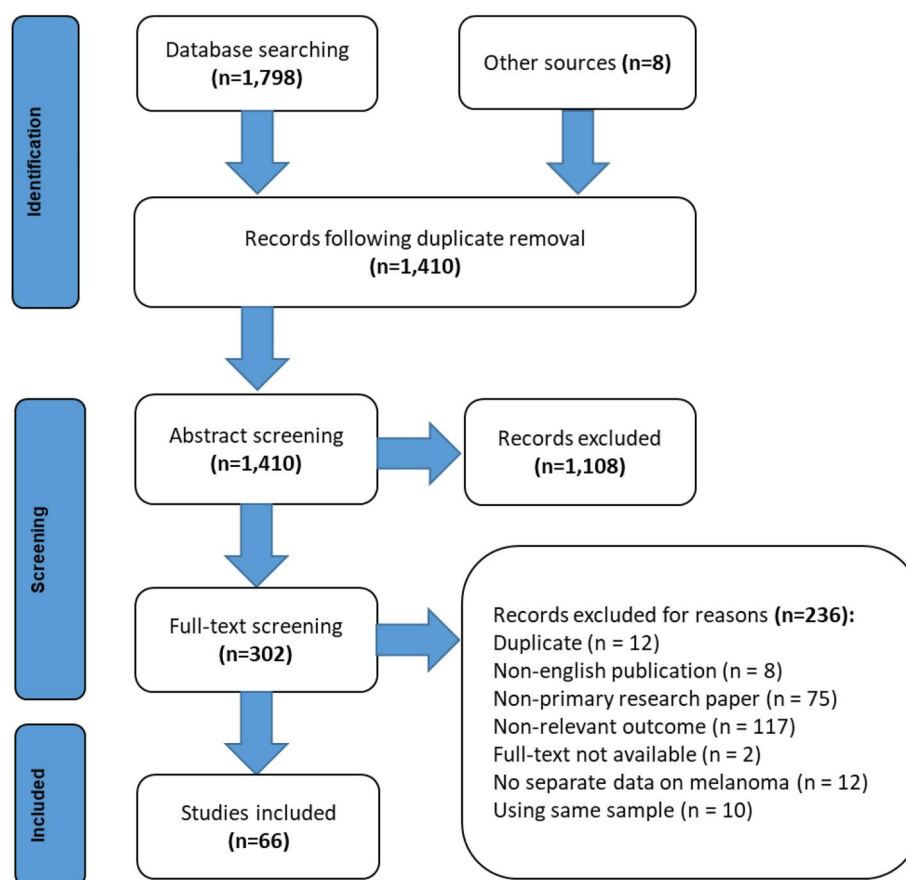


FIGURE 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses diagram.

TABLE 1 Characteristics of included studies.

Author year	Outcome	Instrument	Sample size	Mean age	Percent women	Melanoma type	Study design	Surgery	CT	RT	ICI	Treatment Targeted	Classical IT
Albrecht 2013	Depression	HADS	175	58.5	0.47	Cutaneous	Cross-sectional	+					+
Al-Shakhli 2006	Anxiety	STAI-SSF	10			Cutaneous	Longitudinal						
Amaro 2010	Depression	BDI	20	52	0.35	Uveal	Longitudinal	+					
Bartels 2019	Cognition		84	59.3	0.51	Cutaneous	Cross-sectional	+	+	+			
Beesley 2020	Depression, anxiety	HADS	674	62	0.42	Cutaneous	Longitudinal	+					
Bergenmar 2004	Depression, anxiety	HADS	435		0.47	Cutaneous	Cross-sectional	+					
Boekhout 2021	Depression, anxiety, fatigue	HADS, MFI	89	64	0.43	Cutaneous	Cross-sectional	+		+	+		
Bøhn 2019	Depression, anxiety, fatigue	HADS, PHQ-9, CFQ	246	50.1	0.7	Cutaneous	Cross-sectional	+					
Bourdon 2019	Depression, anxiety	HADS	74	51.3	0.42	Cutaneous	Longitudinal	+	+	+			
Brandberg 2000a	Depression, anxiety	HADS	46	63.5	0.53	Uveal	Longitudinal	+					
Brandberg 2000b	Depression, anxiety	HADS	50	63.5	0.47	Uveal	Longitudinal				+		
Brandberg 1995	Depression, anxiety	HADS	141	51	0.5	Cutaneous	Longitudinal	+					
Brandberg 1992a	Depression, anxiety	HADS	123	50	0.54	Cutaneous	Cross-sectional	+					
Brandberg 1992b	Depression, anxiety	HADS	57	56	0.37	Cutaneous	Cross-sectional	+	+				
Brown 2020	Depression, anxiety	HADS	435	69.48	0.47	Uveal	Longitudinal	+	+	+			
Brown 2018	Depression, anxiety	HADS	261		0.49	Uveal	Longitudinal	+	+	+			
Brown 2022	Depression, anxiety	HADS	824	68.94	0.47	Uveal	Longitudinal	+	+	+			
Capuron 2003	Depression	HAM-D	14		0.36	Cutaneous	Longitudinal				+		
Caraceni 1993	Cognition		7	42.4	0.14	Cutaneous	Longitudinal	+					+
Chabert 2004	Depression, anxiety	HADS	98	63	0.48	Uveal	Cross-sectional		+				
Damato 2018a	Depression, anxiety	HADS	415		0.48	Uveal	Cross-sectional	+					
Damato 2018b	Depression, anxiety	HADS	1109		0.48	Uveal	Cross-sectional						
Erim 2013	Anxiety	HADS	70	58.1	0.37	Cutaneous	Cross-sectional	+					
Friebe 2010a	Depression	SDS	17	55.9	0.47	Cutaneous	Longitudinal	+					+
Friebe 2010b	Depression	SDS	29	56.3	0.62	Cutaneous	Longitudinal	+					+
Friebe 2007	Depression	SDS	33	57.97		Cutaneous	Longitudinal	+					+
Fu 2002	Fatigue	PFS	12	52	0.58	Cutaneous	Cross-sectional	+				+	
Gibertini 1992	Depression	IDD	57	52.5	0.33	Cutaneous	Cross-sectional						

TABLE 1 (Continued)

Author year	Outcome	Instrument	Sample size	Mean age	Percent women	Melanoma type	Study design	Surgery	CT	RT	Treatment ICI	Classical Targeted IT
Gjorup 2017	Depression, anxiety	HADS	431	58	0.52	Cutaneous	Cross-sectional	+				
Gollrad 2022	Depression, anxiety	GAD-7, PHQ-9	121	58.8	0.59	Uveal	Cross-sectional		+			
Hartung 2017	Depression	PHQ-9	66	54.7	0.39	Cutaneous	Cross-sectional	+	+	+		
Heinze 2010	Depression	BDI	282	52	0.48	Cutaneous	Longitudinal	+				+
Hope-Stone 2015	Depression, anxiety	HADS	141	66.7	0.44	Uveal	Cross-sectional	+				
Hope-Stone 2016	Depression, anxiety	HADS	411	64.2	0.47	Uveal	Longitudinal	+		+		
Hyatt 2019	Fatigue	PROMIS fatigue	55	54	0.62	Cutaneous	Cross-sectional	+		+		
Jansen 2020	Depression, anxiety	HADS, STAI-S	62	54.4	0.56	Cutaneous	Longitudinal	+				
Kovács 2015	Depression, anxiety	STAI-S, BDI	127	54.67	0.49	Cutaneous	Longitudinal	+				+
Kovács 2014a	Depression, anxiety	STAI, SDS	10	60.4	0.8	Cutaneous	Longitudinal	+	+	+		
Kovács 2014b	Depression, anxiety	STAI, SDS	18	50.11	0.72	Cutaneous	Longitudinal	+				+
Krajewski 2018	Depression, anxiety	HADS	411	62.1	0.48	Cutaneous	Cross-sectional					
Lehto 2008	Depression	DEPS	70	55	0.5	Cutaneous	Longitudinal	+				+
MacDonald 2021	Depression	CES-D	107	58.96	0.46	Uveal	Longitudinal	+		+		
Mayer 2017	Depression, anxiety	HADS	239	56.32	0.48	Cutaneous	Cross-sectional	+	+	+		+
Melia 2006a	Depression, anxiety	HADS	106		0.46	Uveal	Cross-sectional	+				
Melia 2006b	Depression, anxiety	HADS	103		0.46	Uveal	Cross-sectional		+			
Minioti 2019	Depression, anxiety	HADS	208		0.53	Cutaneous	Cross-sectional	+				
Molassiotis 2014	Depression, anxiety	HADS	455	60	0.54	Cutaneous	Cross-sectional	+				
Moncrieff 2020	Anxiety	STAI-S	207	62	0.49	Cutaneous	Longitudinal	+				
Moschos 2018	Depression	PHQ-9	50	49.88	0.5	Uveal	Cross-sectional		+			
Naeser 2022	Depression, anxiety	HADS	204	64.09	0.39	Cutaneous	Longitudinal	+	+	+		
Newton-Bishop 2004	Depression, anxiety	HADS	133	62.2	0.43	Cutaneous	Longitudinal	+				
Paterson 2005	Depression, fatigue	BDI, RPFS	21	43.67	0.43	Cutaneous	Longitudinal	+				+
Pereira 2017	Depression, anxiety	HADS	35	58.8	0.8	Cutaneous	Cross-sectional	+				
Pompili 2017	Depression, anxiety	HARS, HDRS	77	54.14	0.58	Cutaneous	Cross-sectional					
Porock 2005	Depression, anxiety	HADS	19	47.5	0.32	Cutaneous	Cross-sectional	+				+
Reuter 2014a	Depression	HADS	48	52	0.37	Cutaneous	Longitudinal	+				+

(Continues)

TABLE 1 (Continued)

Author year	Outcome	Instrument	Sample size	Mean age	Percent women	Melanoma type	Study design	Surgery	CT	RT	ICI	Treatment Targeted	Classical IT
Reuter 2014b	Depression	HADS	48	54.2	0.48	Cutaneous	Longitudinal	+					
Rogiers 2020 1a	Depression, anxiety, fatigue, cognition	HADS, FSS	25	58	0.72	Cutaneous	Longitudinal	+	+	+	+	+	+
Rogiers 2020 2a	Depression, anxiety, fatigue, cognition	HADS, FSS	15	63.4	0.71	Cutaneous	Longitudinal	+	+	+	+	+	+
Schaefer 2004	Depression	SDS	41	57	0.48	Cutaneous	Longitudinal	+					+
Schuermeier 2016	Depression, anxiety	HADS	96	60.7	0.44	Uveal	Longitudinal	+	+				
Sigurdardóttir 1996	Depression, anxiety	HADS	95	53	0.35	Cutaneous	Longitudinal	+					
Tesio 2017	Depression, anxiety	HADS	204	53.1	0.53	Cutaneous	Cross-sectional	+					
Tibubos 2019	Depression, anxiety, fatigue	GAD-7, PHQ-9, MFI	684	61.71	0.51	Cutaneous	Cross-sectional						
Trask 2001	Anxiety	STAI	178	52.2	0.53	Cutaneous	Cross-sectional	+					
Trivedi 2021	Sleep	PSQI, ISI, ESS	29	59.5	0.31	Cutaneous	Cross-sectional	+					
vanBeek 2018	Anxiety	STAI	113	65	0.47	Cutaneous	Longitudinal	+	+				
Vogel 2017	Depression, anxiety	HADS	724		0.6	Cutaneous	Cross-sectional	+					
Vurnek 2007	Depression	BDI	31	50	0.55	Cutaneous	Cross-sectional	+					
Vurnek 2008	Depression	BDI	60	52	0.57	Cutaneous	Cross-sectional	+					
Wagner 2018	Depression, anxiety	HADS	136	54.3	0.46	Cutaneous	Cross-sectional	+					
Wiley 2013	Depression	CES-D	99	63.71	0.48	Uveal	Cross-sectional	+	+				

Abbreviations: BDI, Beck Depression Inventory; CES-D, Center for Epidemiologic Studies Depression Scale; CFQ, Chalder Fatigue Scale; CT, chemotherapy; ESS, Epworth Sleepiness Scale; FSS, The Fatigue Severity Scale; GAD-7, The General Anxiety Disorder-7; HADS, Hospital Anxiety and Depression Scale; HAM-D, Hamilton Depression Rating Scale; HAM-A, Hamilton Anxiety Rating Scale; HDRS, Hamilton Depression Rating Scale; ICI, immune checkpoint inhibitors; IDD, The Inventory to Diagnose Depression; IES, Impact of Event Scale; ISI, Insomnia Severity Index; IT, immunotherapy; MFI, Multidimensional Fatigue Inventory; PHQ-9, Patient Health Questionnaire; PROMIS fatigue, The Patient Reported Outcome Measurement Information System Fatigue; PSQI, Pittsburgh Sleep Quality Index; RPPS, The Revised Piper Fatigue Scale; RT, radiotherapy; SDS, Sheehan Disability Scale; STAI, State-Trait Anxiety Inventory; STAI-S, State-Trait Anxiety Inventory Short; STAI_SSF, Spielberger State-Trait Anxiety Inventory.

3.4 | Anxiety

The most commonly used scale to assess anxiety was the HADS ($K = 33$), followed by the State-Trait Anxiety Inventory ($K = 6$). As seen in Table 2, the highest prevalence of anxiety was found before (19%) and during treatment (19%). Before treatment, more than four times as many uveal melanoma patients (30%) had clinical levels of anxiety than cutaneous melanoma patients (7%). The same pattern, although much less pronounced, was observed after treatment, but, as seen in Table 3, the difference between uveal and cutaneous melanoma only reached statistical significance for anxiety assessed before treatment. After treatment, more patients with late stage melanoma, that is, stage III and IV, had clinically significant levels of

anxiety (20%) than those with early stage melanoma, that is, stage I and II (13% respectively), but, as seen in Table 3, the difference did not reach statistical significance (See online supplementary material, Figure S2 for a forest plot of anxiety after treatment). When examining the remaining potential categorical and continuous moderators, only two results reached statistical significance. A higher percentage of women in the sample was statistically significantly associated with higher numbers of survivors with clinical levels of anxiety. Likewise, in studies where participants had received chemotherapy, there were statistically significantly more melanoma survivors with clinical levels of anxiety than in the studies where participants had not received chemotherapy. When adjusting for disease stage in the 11 studies which had provided data on both

TABLE 2 Pooled event rates of anxiety, depression, and fatigue grouped by time of assessment, melanoma sub-diagnosis, and stage.

Symptom	Subsample	Time-point	K^a	N	Event rate ^b	95% CI	Heterogeneity (%)		
							I^2 (95% CI) ^c	τ^2	95% PI ^d
Depression	All	Before treatment	16	1699	0.08	0.05–0.13	82.8 (53.1–100)	0.92	0.01–0.43
		During treatment	10	715	0.12	0.06–0.22	85.4 (34.2–100)	1.27	0.01–0.68
		After treatment	31	7051	0.10	0.08–0.12	80.4 (64.6–96.2)	0.26	0.03–0.24
		<1 year after	14	3050	0.08	0.05–0.11	84.3 (51.2–100)	0.41	0.02–0.25
		>1 year after	20	5625	0.09	0.07–0.12	83.0 (60.1–100)	0.26	0.03–0.23
Anxiety	All	Before treatment	9	1308	0.19	0.11–0.30	91.7 (55.0–100)	0.69	0.03–0.66
		During treatment	4	219	0.19	0.09–0.34	78.6 (09.0–100)	0.50	0.01–0.89
		After treatment	26	6830	0.16	0.13–0.19	90.3 (75.2–100)	0.30	0.06–0.38
		<1 year after	11	2891	0.17	0.12–0.23	92.6 (65.1–100)	0.38	0.04–0.46
		>1 year after	18	5559	0.15	0.12–0.19	90.9 (71.4–100)	0.29	0.05–0.36
Fatigue	All	During + after treatment	4	298	0.35	0.16–0.61	86.2 (24.5–100)	0.96	0.00–0.98
Depression	Uveal	Before treatment	5	319	0.16	0.07–0.30	81.9 (0.20–100)	0.69	0.01–0.79
	Cutan. melanoma	Before treatment	11	1380	0.06	0.03–0.10	63.8 (22.0–100)	0.48	0.01–0.26
	Cutan. melanoma	During treatment	9	647	0.13	0.06–0.25	86.3 (27.8–100)	1.30	0.01–0.72
	Uveal	After treatment	12	3139	0.11	0.08–0.14	79.1 (22.1–100)	0.20	0.04–0.26
	Cutan. melanoma	After treatment	19	3912	0.09	0.07–0.12	80.3 (53.9–100)	0.33	0.03–0.26
Anxiety	Uveal	Before treatment	5	401	0.30	0.21–0.41	78.5 (16.3–100)	0.23	0.07–0.70
	Cutan. melanoma	Before treatment	4	907	0.07	0.03–0.18	80.7 (11.2–100)	0.72	0.00–0.85
	Cutan. melanoma	During treatment	3	151	0.13	0.05–0.30	72.5 (08.5–100)	0.60	0.00–1.00
	Uveal	After treatment	9	3004	0.18	0.13–0.25	93.2 (61.0–100)	0.34	0.05–0.49
	Cutan. melanoma	After treatment	17	3826	0.14	0.11–0.18	87.4 (63.8–100)	0.29	0.05–0.40
Depression	Early stage (I–II)	After treatment	8	1905	0.08	0.06–0.10	47.2 (2.0–96.0)	0.06	0.04–0.15
	Late stage (III, IV)	After treatment	3	146	0.14	0.09–0.22	10.9 (2.0–92.0)	0.03	0.00–0.91
Anxiety	Early stage (I–II)	After treatment	8	1959	0.13	0.09–0.18	83.6 (31.0–100)	0.20	0.04–0.33
	Late stage (III, IV)	After treatment	3	146	0.20	0.09–0.37	68.3 (12.5–100)	0.40	0.00–1.00

^a K = number of independent samples (some studies report data on several independent subsamples, e.g., receiving different treatments).

^bRandom effects model, weighted by inverse variance, calculated for $K \geq 3$.

^cHeterogeneity: I^2 (%) and 95% CI (note: I^2 is likely to be biased when K is small).

^d95% prediction interval calculated when $I^2 > 0$.

TABLE 3 Exploring sample-, disease-, and treatment-related predictors of the prevalence of clinically significant anxiety and depression in melanoma patients before, during, and after treatment—results of meta-regression analyses.

Symptom	Time-point	Predictor	K ^a	Slope ^b	95% CI	p ^c	R ²
Depression	Before treatment	Sample age	15	−0.05	−0.18 to 0.08	0.473	0.08
		Percent women	14	−1.87	−7.80 to 4.07	0.538	0.02
		Uveal (ref. cutaneous)	16	1.14	0.12 to 2.16	=0.029	0.33
		Publication year	16	−0.01	−0.08 to 0.05	0.668	0.01
	During treatment	Sample age	9	0.06	−0.15 to 0.27	0.572	0.07
		Percent women	10	−1.94	−8.42 to 4.54	0.558	0.04
		Publication year	10	−0.07	−0.15 to 0.02	0.108	0.25
		Surgery (ref. no surgery)	10	−1.21	−2.74 to 0.32	0.121	0.21
		Chemotherapy (ref. no chemotherapy)	10	−0.43	−1.80 to 0.93	0.533	0.04
		Radiotherapy (ref. no radiotherapy)	10	0.04	−2.31 to 2.39	0.973	0.00
		Classical immunotherapy (ref. none)	10	0.43	−0.02 to 1.80	0.533	0.04
		Immune checkpoint inhibitors (ref. none)	Insufficient number of studies with ICIs (K = 2)				
		Targeted therapy (ref. none)	Insufficient number of studies with targeted therapy (K = 1)				
	After treatment	Sample age	25	−0.01	−0.07 to 0.04	0.591	0.02
		Percent women	31	2.36	−0.49 to 5.21	0.105	0.07
		Publication year	31	0.01	−0.03 to 0.04	0.654	0.00
		Average time since treatment (weeks)	10	0.00	−0.00 to 0.01	0.213	0.02
		Uveal (ref. cutaneous)	31	0.22	−0.25 to 0.69	0.375	0.05
		Late stage (III, IV) (ref. early (stage I, II))	11	0.63	0.12 to 1.13	=0.015	1.00
		Surgery (ref. no surgery)	31	−0.19	−0.71 to 0.34	0.483	0.02
		Chemotherapy (ref. no chemotherapy)	31	0.47	−0.13 to 1.07	0.119	0.10
		Radiotherapy (ref. no radiotherapy)	31	0.42	−0.05 to 0.89	0.079	0.13
		Immune checkpoint inhibitors (ref. none)	Insufficient number of studies with ICIs (K = 2)				
		Targeted therapy (ref. none)	Insufficient number of studies with targeted therapy (K = 1)				
Anxiety	Before treatment	Percent women	9	−3.27	−10.41 to 3.88	0.370	0.00
		Uveal (ref. cutaneous)	9	1.58	0.74 to 2.43	<0.001	0.69
		Publication year	9	−0.05	−0.12 to 0.02	0.181	0.18
	After treatment	Sample age	20	0.02	−0.04 to 0.09	0.511	0.02
		Percent women	26	4.49	1.86 to 7.12	<0.001	0.30
		Publication year	26	0.00	−0.03 to 0.03	0.961	0.00
		Uveal (ref. cutaneous)	26	0.29	−0.20 to 0.79	0.247	0.07
		Late stage (III, IV) (ref. early (stage I, II))	11	0.49	−0.30 to 1.27	0.224	0.10
		Surgery (ref. no surgery)	26	0.46	−0.07 to 0.99	0.091	0.13
		Chemotherapy (ref. no chemotherapy)	26	0.77	0.16 to 1.38	=0.014	0.22
		Radiotherapy (ref. no radiotherapy)	26	0.29	−0.26 to 0.83	0.300	0.04
		Immune checkpoint inhibitors (ref. none)	Insufficient number of studies with ICIs (K = 2)				
		Targeted therapy (ref. none)	Insufficient number of studies with targeted therapy (K = 1)				

Note: Bold values = significant results (=under $p < 0.05$).

^aK = number of independent samples in the analysis (Note: one published study may report on several independent samples).

^bMeta-regression (maximum likelihood method), conducted when $K \geq 8$.

^cTwo-tailed p -value.

chemotherapy and stage, the association did no longer reach statistical significance (Slope = 1.5 [95% CI: -0.1. to 2.9], $p = 0.074$) (No further data shown).

To aid the interpretation of the results, we calculated the pooled mean scores of HADS anxiety across assessment time-points (before, during, after treatment), diagnosis (uveal, cutaneous melanoma), and stage (early, I-II; late, III-IV) (see online supplementary material, Table S2). Mean HADS anxiety scores were approximately twice as high before and during treatment (9.4 and 10.2) compared with after treatment (5.1). After treatment, mean anxiety scores (6.6) were statistically significantly higher ($p = 0.021$) in samples of patients with late stage melanoma than in samples of early stage melanoma (3.4). HADS anxiety scores range between 0 and 21 with scores ≥ 8 denoting possible clinical cases of anxiety.⁴⁵

3.5 | Depression

As seen in Table 1, the HADS was also the most commonly used scale to assess depression ($K = 33$), followed by the Beck Depression Inventory ($K = 6$). (See online supplementary material, Figure S1 for a forest plot of depression after treatment). The highest rate of depressed patients was observed during treatment (12%). Before treatment, almost three times as many uveal melanoma patients had clinically significant levels of depression (16%) than patients with cutaneous melanoma (6%). The same pattern, although much less pronounced, was observed after treatment. When comparing the prevalence with meta-regression (see Table 3), the differences only reached statistical significance for depression assessed before treatment. After treatment, more patients with late stage melanoma, that is, stage III and IV, had clinically significant levels of depression (14%) than those with early stage melanoma, that is, stage I and II (8% respectively) (see Table 2). When comparing the prevalence with meta-regression, the difference reached statistical significance (see Table 3).

We also calculated the pooled mean scores of HADS depression across assessment time-points, diagnostic subtype, and stage (see online supplementary material, Table S2). Mean depression scores were approximately twice as high before and during treatment (HADS depression: 7.9 and 7.6) compared with after treatment (HADS depression: 3.3). After treatment, mean depression scores (5.3) were statistically significantly higher ($p = 0.049$) in samples of patients with late stage melanoma than in samples of early stage melanoma (4.8). HADS depression scores range between 0 and 21 with scores ≥ 8 denoting possible clinical cases of depression.⁴⁵

3.6 | Fatigue

Only four studies reported prevalence of fatigue.⁵⁰⁻⁵³ The prevalence of fatigue varied from 15% to 58% in patients with cutaneous melanoma during and after treatment. A total of eight studies reported data on fatigue assessed with eight different instruments

(PROMIS Fatigue, Multidimensional Fatigue Inventory [MFI], Chalder Fatigue Scale [CFQ], The Piper Fatigue Scale [PFS], Fatigue Severity Scale [FSS], The revised Piper Fatigue Scale [RPFS], Patient Health Questionnaire-9 [PHQ-9]). Three studies reported data during treatment, two reported data less than 1 year after treatment, and four reported data more than 1 year after treatment. Boekhout and colleagues⁵⁴ found survivors of cutaneous melanoma to have higher symptom burden of fatigue as compared to matched controls. Similar findings were reported by Paterson and colleagues⁵⁵ who also reported increased levels of fatigue in survivors of cutaneous melanoma. However, Tibubos and colleagues⁵⁶ only found increased levels of fatigue in younger survivors of cutaneous melanoma under 40 years. Hyatt and colleagues⁵⁷ reported levels of fatigue to be only slightly higher ($M = 54.8$) than the standardized mean ($M = 50$) of patient-reported outcome measures of fatigue. The pooled prevalence of fatigue was 35%.

3.7 | Cognitive problems

Three studies reported prevalence rates of cognitive complaints^{52,53,58} varying from 20% to 44% among patients with cutaneous melanoma during and/or after treatment. A total of four studies reported data on cognitive complaints measured by a self-reported scale and a range of neuropsychological tests. Of these, one study reported data before treatment, two reported data during treatment and two reported data more than 1 year after treatment. Bartels and colleagues⁵⁸ found an association between higher degrees of cognitive impairments measured by neuropsychological tests and specific autoantibodies in cutaneous melanoma patients measured either during or after treatment. Caraceni and colleagues⁵⁹ reported cognitive failure in patients with metastatic melanoma after the end of each course of treatment with interleukin-2 which was especially pronounced during tasks requiring higher level of attention. Rogiers and colleagues found, at the $z \leq -1.00$ cutoff, 62%⁵² and 40%⁵³ of the patients to be impaired on two or more neuropsychological tests during⁵³ or more than 1 year after treatment.⁵² No studies reporting data on cognitive complaints or impairments were eligible to be included in the meta-analysis.

3.8 | Sleep

One study reported data on sleep in melanoma survivors assessed approximately 14 months after diagnosis with the Pittsburgh Sleep Quality Index (PSQI), the Insomnia Severity Index, and actigraphy.⁶⁰ The study reported poor subjective sleep quality among melanoma survivors assessed with the PSQI (Mean = 6.6) and slightly lowered actigraphy-assessed sleep efficiency (SE) (Mean = 82.2). However, for self-reported insomnia severity, the mean ISI-score was below cut-offs for subthreshold and clinical insomnia among survivors of melanoma.

3.9 | Heterogeneity

As seen in Table 2, the results were characterized by considerable heterogeneity, with I^2 values ranging from 10.9% (depression, late stage, after treatment) to 93.2% (anxiety, uveal melanoma, after treatment). The 95% CIs for the I^2 estimates tended to be broad for calculations based on smaller numbers of studies, indicating less precise heterogeneity estimates. The heterogeneity estimates remained high for the melanoma subtype and stage-based subgroup analyses. Based on the variation of true values, the prediction intervals, that is, the range of values that the results of 95% of future similar studies are expected to fall within, were wide for several prevalence estimates.

4 | DISCUSSION

In this systematic review and meta-analysis of psychological and behavioral symptoms in patients with melanoma. One strength of our systematic review and meta-analysis is that previously published reviews have primarily focused on depression, anxiety, and quality of life in patients with uveal melanoma.^{29–31} The present review provides an overview of a broader range of psychological and behavioral symptoms that are part of a cancer symptom cluster, and provide a more nuanced picture of, primarily anxiety and depression, in both cutaneous and uveal melanoma patients before, during, and after completion of treatment. The majority of studies investigated depression and anxiety, with pooled prevalence rates of depressive symptoms and anxiety ranging from 8% to 12% and 15%–19% respectively across time points (before, during, and after treatment). Across melanoma diagnoses and treatments, the pooled rate of depression was highest when assessed during treatment (12%) and fell to the before-treatment level (8%) in samples assessed at <1 year follow-ups. This rate still exceeds the estimated 5% prevalence in the general adult population.⁶¹ Similarly, the rates of anxiety were highest before and during treatment (19%), falling to 15% when assessed >1 year after completed treatment. Again, the prevalence in melanoma patients and survivors at both time points exceeds both the global 7.3% prevalence and the 10.4% of anxiety disorders in European and Anglo cultures.⁶² The pooled prevalence of fatigue was 35%. The prevalence of cognitive impairment ranged from 20% to 44% among patients with cutaneous melanoma either during or after treatment. The one study that included sleep reported no prevalence rates but showed that greater sleep regularity was associated with increased global quality of life, better physical functioning and fewer cancer-related symptoms.⁶⁰

When exploring the association of symptom rates with various study sample characteristics, few clear findings emerged. At the time of diagnosis but prior to treatment, higher rates of both depression and anxiety were found in patients with uveal melanoma compared with patients with cutaneous melanoma, with symptoms being approximately three times more prevalent in patients with uveal

melanoma. Uveal melanoma is a rare disease with approximately half of the patients developing metastases.^{63,64} The prognostic differences could be one possible explanation for the higher rates of anxiety and depressive symptoms before treatment in patients with uveal melanoma compared with cutaneous melanoma. In addition, uveal melanoma patients will lose an eye or part of their visual capacity from the primary treatment. The difference between diagnoses did not reach statistical significance after completed treatment. One possible explanation could be a higher proportion of patients diagnosed with early stage disease (I and II) in the samples where depression and anxiety had been investigated after completed treatment. While the number of studies with separate data on both diagnosis and stage were too few to explore this hypothesis, the statistically significantly higher rates of depression found in patients with later stages of melanoma (Stage III and IV) compared with those diagnosed with earlier stages, could be taken to support this hypothesis. The finding of higher rates of depression in patients diagnosed with later stage disease is unsurprising, and consistent with results found in other cancer populations.^{65,66} Late stage melanoma patients receive more intensive treatment and often receive combinations of treatments with associated biological side effects and psychological stress potentially leading to higher levels of anxiety and depression.⁶⁷ The only association found between symptom rates and treatments received was the significantly higher rates of anxiety found in those study samples where patients had received chemotherapy. However, when adjusting for cancer stage (early vs. late) in the sub-sample of studies that had provided this information, this result ceased to be statistically significant. Finally, statistically significantly higher rates of anxiety after treatment completion were found in studies with higher percentages of women. This result is consistent with findings in the general population showing that women are significantly more likely to develop an anxiety disorder throughout their lifespan.^{68,69} However, we did not find a sex difference in rates of depression, even though rates of depression are generally higher among women than men in the general population.^{70,71} With the exception of chemotherapy, no other treatment modality was associated with rates of depression or anxiety. With new and more efficacious treatments such as ICIs and targeted therapies, one could expect that fewer patients experience such symptoms. Unfortunately, there were too few available studies that had included data on such treatments, and thus, it was not possible for us to explore this hypothesis. A proxy for more recent treatments could be publication year, but no associations were found between publication year and prevalence rates. The very few studies reporting on fatigue did not allow for an exploration of associations with sample characteristics.

4.1 | Clinical implications

The present systematic review and meta-analysis has a number of practical and clinical implications. The available data show that a

proportion of melanoma patients report clinically elevated levels of depression and anxiety, not only before and during treatment, but also after treatment completion. Our findings highlight vulnerable periods for these patients and the need to screen for distress, that is, anxiety and/or depression, as the “6th vital sign”⁷² before, during, and after treatment and for providing relevant interventions for patients in need. Timely identification of clinically significant symptoms of anxiety and depression has the potential to improve overall quality of life, prognosis, and other treatment outcomes.^{23,24,26,73} While there currently is no agreed-upon universal screening tool, one of the most used screening tools for depression and anxiety, the HADS,⁴⁵ was included in several studies, and our review provides pooled mean HADS depression and anxiety scores at different time points for comparison. Unfortunately, few studies had examined fatigue, cognitive problems, and sleep, preventing us from evaluating the possible factors associated with higher rates of these symptoms.

4.2 | Recommendations for future research

Treatment of melanoma has evolved considerably over the past decade, resulting in increases in overall survival, progression-free survival, and objective response rates.^{3,7,67,74} This underscores the urgent need for longitudinal research examining the side and late effects of current treatment strategies such as ICIs and other targeted treatments. This includes a need for further investigation of the understudied symptoms of fatigue, cognitive problems, and sleep disturbances, their risk factors and mechanisms, and the efficacy of interventions for treating these symptoms.

4.3 | Study limitations

Some limitations should be noted. First, the high I^2 -values indicate substantial heterogeneity of results, suggesting considerable underlying systematic differences between the available studies, which are further reflected in the relatively wide prediction intervals. While we attempted to identify possible sources of the heterogeneous results, the moderating factors explored only explained limited proportions of the variance. Second, the majority of the included studies only reported data on one or two symptoms, with depression and anxiety overwhelmingly being the most widely researched symptoms. This limits our understanding of the broader range of side and late effects experienced by melanoma patients and survivors and underscores the need for more research, for example, on sleep disturbances, fatigue, and cognitive problems. Third, we did not review specific subtypes of anxiety, for example, fear of cancer recurrence (FCR). This has been explored in a recently published individual participant data meta-analysis of 46 studies with 9,311 cancer patients and survivors. Only 302 (3.2%) were melanoma survivors. More than two-thirds (69%) had FCR scores above the suggested cut-off.^{74,75} Finally, symptoms of depression and anxiety were assessed using a range of different

scales, threatening across-study comparability and increasing between-study variability.

5 | CONCLUSION

This, to our knowledge, first comprehensive systematic review and meta-analysis of its kind in the melanoma patient and survivor population demonstrates that symptoms of depression and anxiety are prevalent in patients with melanoma, not only before and during treatment, but also after completed treatment. Furthermore, our results show that, prior to treatment, depression and anxiety are more prevalent in uveal melanoma than in cutaneous melanoma. More research is clearly needed in the area of fatigue, cognitive problems, and sleep, not least in light of the considerable improvements in melanoma treatment in recent years.

AUTHOR CONTRIBUTIONS

All authors contributed to the protocol of this systematic review. The literature search and data export were performed by Josefine T. Danielsen, assisted by a skilled librarian, Gina Bay. Titles and abstracts were screened by Josefine T. Danielsen and Louise Strøm. Josefine T. Danielsen and Louise Strøm performed full text review, validated by Robert Zachariae, Lisa M. Wu and Ali Amidi. Data extraction and quality ratings were performed by Josefine T. Danielsen and Sofie M. Knutzen, and validated by Robert Zachariae. Robert Zachariae and Josefine T. Danielsen were responsible for the analyses. Josefine T. Danielsen and Robert Zachariae wrote the first draft manuscript, and all authors critically revised the manuscript and approved the final version.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

All data used in this article are available in the article and in its online supplementary material.

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