Systematic Review of the Kynurenine Pathway and Psychoneurological Symptoms Among Adult Cancer Survivors

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Abstract

The co-occurrence of multiple psychoneurological symptoms, including pain, sleep disturbance, fatigue, depression, anxiety, and cognitive disturbance among adult cancer survivors led us to question which common biological mechanisms are shared among these conditions. Variances in tryptophan (Trp) levels and downstream metabolites of the kynurenine (Kyn) metabolic pathway are known to affect immune response and psychoneurological symptoms. The objective of this systematic review was to help us (a) better understand the role of the Kyn pathway in psychoneurological symptoms among adult cancer survivors and (b) identify common significant biomarkers across psychoneurological symptoms as a guide for future research. Some evidence has shown that decreased Trp levels and increased Kyn, Trp/Kyn ratio, and kynurenic acid/Trp ratio in parallel with immune activation are correlated with some psychoneurological symptoms among people undergoing cancer treatment, although discrepancies exist between studies. Kyn pathway activation could also be associated with psychoneurological symptoms among adult cancer survivors, but further research is needed to confirm its exact etiological role with respect to psychoneurological symptoms.

Keywords

kynurenine, tryptophan, metabolite, psychoneurological, symptom, cancer, survivor

Psychoneurological symptoms including pain, fatigue, depression, anxiety, cognitive disturbance, and sleep disturbance are common and distressing symptoms experienced by adult cancer survivors (Doong et al., 2015; Kim et al., 2008; Langford et al., 2016). People who receive a cancer diagnosis are referred to as cancer survivors from the time of diagnosis until the end of life. It is estimated that there will be 21.7 million cancer survivors in the United States by 2020 (Bluethmann et al., 2016). Up to 68% of cancer survivors report psychoneurological symptoms during cancer treatment (Starkweather et al., 2017). Some psychoneurological symptoms can persist even 5–10 years after completion of cancer treatment (Bower et al., 2006; Mejdahl et al., 2013). These psychoneurological symptoms have a detrimental impact on survivors' functional status and quality of life (Denieffe et al., 2014; Garreau et al., 2006).

The co-occurrence of multiple psychoneurological symptoms with the onset of cancer has led researchers to interrogate the common mechanisms that may underlie such symptom clusters. Historically, authors have considered the model of cytokine-induced sickness behavior to be the biological mechanism that results in psychoneurological symptoms

(Cleeland et al., 2003). Specifically, researchers have gathered a large amount of evidence supporting a link between increased levels of inflammatory cytokines and the onset of fatigue and depression among people living with cancer (Kwekkeboom et al., 2018; Starkweather et al., 2013).

The overarching hypothesis of this research area is that inflammation and dysregulation of the hypothalamic-

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Figure 1. Conceptual diagram of effects of inflammatory and hypothalamic-pituitary-adrenal (HPA)-axis activation on tryptophan and kynurenine pathways. Cancer and cancer treatment can activate inflammation and the HPA axis, which results in increased levels of inflammatory cytokines and cortisol. Stimulated by inflammatory cytokines and cortisol, the rate-limiting enzymes IDO and TDO are induced and catabolize tryptophan to kynurenine. CRP = C-reactive protein; IDO = indoleamine 2,3-dioxygenase 1; IFN- γ = interferon gamma; IL = interleukin; KAT = kynurenine aminotransferase; KMO = kynurenine monooxygenase; TDO = tryptophan 2,3-dioxygenase; TNF = tumor necrosis factor.

pituitary-adrenal (HPA) axis, circadian rhythms, and the serotonin system are putative biological mechanisms underlying psychoneurological symptoms (Kim, Barsevick, Fang, & Miaskowski, 2012). More recently, research has demonstrated that inflammation-induced activation of the kynurenine (Kyn) metabolic pathway of tryptophan (Trp) degradation plays a critical role in depression and fatigue among people living with cancer (Kim et al., 2015; Sforzini et al., 2019). This finding raises the possibility that the Kyn pathway plays an important role in cancer-related psychoneurological symptoms and warrants further investigation.

The activation of the indoleamine 2,3-dioxygenase 1 (IDO) and tryptophan 2,3-dioxygenase (TDO) pathways are relevant to Kyn metabolism (Figure 1). Trp is an essential amino acid that can only be acquired through diet. Humans utilize Trp for multiple vital functions, including structural and functional processes of protein biosynthesis and immunoregulation (Ball et al., 2014). Over 90% of available Trp is metabolized by the liver along the Kyn pathway (Badawy & Dougherty, 2016).

Currently, the literature recognizes two enzymes as catalyzing Trp to Kyn conversion: TDO and IDO. A recently discovered gene referred to as indoleamine 2,3-dioxygenase 2 (*IDO2*) has been implicated in Trp metabolism under nonphysiological conditions in vitro, but has yet to show a profound impact on Trp or Kyn levels in vivo. TDO is highly and constitutively expressed in the liver, but it is also present in the brain and induced or upregulated by endogenous and exogenous glucocorticoid(-like) molecules including cortisol and dexamethasone (Schröcksnadel et al., 2006). Under healthy physiological conditions, a majority of Trp is metabolized by TDO via the hepatic Kyn energy-producing pathway.

However, under conditions of physiological or psychological stress, IDO is induced by pro-inflammatory cytokines arising from systemic inflammation and oxidative stress (Dantzer, 2016; Karu et al., 2016). Pro-inflammatory cytokines (interferon- γ) can stimulate increases in neopterin, an important biomarker of cellular immune system activation and inflammation (Heistermann & Higham, 2015; Kilicarslan et al., 2019). Pro-inflammatory cytokines including interleukin (IL)-6, tumor necrosis factor alpha (TNF- α), and C-reactive protein (CRP) are often used as biomarkers to assess systematic inflammation, which can activate and/or induce/enhance IDO expression levels (Cho et al., 2017). IDO plays an important immunomodulatory role in autoimmunity, cancer, infectious disease, and tolerance during pregnancy (Van der Leek et al., 2017). Stimulated by inflammatory cytokines and cortisol, the rate-limiting enzymes IDO and TDO are induced and catabolize Trp to Kyn.

Trp metabolism affects psychoneurological symptoms in two ways: (a) under conditions of physiologic/psychological stress, IDO and TDO activity increases, which degrades Trp into Kyn, resulting in deprivation of Trp hydroxylase (a precursor of 5-hydroxytryptamine [5-HT] and serotonin); and (b) the neurotoxic metabolites 3-hydroxykynurenine (3-HK) and quinolinic acid (QA) and the neuroprotective metabolite kynurenic acid (KYNA) are synthesized (Karu et al., 2016). Kyn is catabolized through two distinct pathways: (a) synthesis of neurotoxic metabolites including 3-HK and QA by the enzyme kynurenine monooxygenase (KMO); and (b) catabolism into the neuroprotective metabolite KYNA (Ogyu et al., 2018). Kyn pathway metabolites (i.e., KYNA, 3-HK, and QA) have been found to have relationships with Alzheimer's disease (Zwilling et al., 2011), major depressive disorder (Savitz et al.,

Figure 2. Study selection process.

2015), fatigue (Kim et al., 2015), and sleep problems (Cho et al., 2017). Recently, authors have questioned the hypothesis that Trp depletion and metabolism leads to immune response and depression, and research has focused more attention on the activity of Kyn metabolism (Dantzer, 2016).

With the increasing emphasis on symptom cluster research (Miaskowski et al., 2017), it is important to identify common biomarkers that may help to explain the underlying mechanisms common to the components of the psychoneurological symptom cluster among cancer survivors. However, few studies have identified common metabolomics biomarkers in the Kyn pathway that may be associated with psychoneurological symptoms among adult cancer survivors. The purposes of this systematic review were to (a) synthesize existing literature in order to better understand the role of the kynurenine pathway in psychoneurological symptoms among cancer survivors and (b) identify common significant biomarkers across psychoneurological symptoms as a guide for future research.

Methods

We performed a literature search to identify metabolites of the Kyn pathway associated with common psychoneurological symptoms among cancer survivors. We used the terms “kynurenine” and “cancer (or neoplasms or carcinoma)” along with “pain (or musculoskeletal pain),” “fatigue,” “sleep

disturbance,” “depression,” “anxiety,” or “cognitive disturbance” to search for relevant articles in the PubMed, CINAHL, PsycINFO, and Web of Science databases (Figure 2). Two members of the study team (HL and TL) developed the inclusion and exclusion criteria for this review as well as the data abstraction criteria.

We included full-length articles in the present review if the study (a) presented data on the relationship between any of our symptoms of interest (pain, fatigue, sleep disturbance, depression, anxiety, or cognitive disturbance) and the metabolites of interest (Kyn-related metabolites), (b) focused on adult cancer survivors, (c) measured metabolite levels in serum or plasma, and (d) was conducted anywhere in the world but published in English. Because this is the first review of multiple psychoneurological symptoms among cancer survivors, we included any relevant articles published before April 2020 and did not limit the date range. We excluded animal studies, reviews, and editorials. The reasons for excluding animal studies were that it is difficult to assess psychological symptoms in animals, human studies have considered previous findings from animal studies, and there may be differences in the relationships between symptoms and metabolites in humans and other animals.

We developed a data abstraction tool to capture detailed data from the included studies, including author, year, study purpose, study design, sample characteristics, metabolites,

symptom measurement, key findings, limitations, and strengths. Two reviewers independently abstracted the above data points from the final articles, and the study team compiled the results. We resolved disagreements through discussion to reach consensus. We then summarized common significant metabolites associated with psychoneurological symptoms. Two reviewers independently assessed the quality of the observational studies using the Newcastle–Ottawa scale (Luchini et al., 2017). They initially assessed three categories using this scale, including selection of the study population, comparability, and description of the outcome and then added sample size as an additional category. We defined high-quality studies as those with an overall score above 10, while intermediate-quality studies scored from 5 to 9 and low-quality studies from 0 to 4.

Results

The initial database search yielded 791 journal articles published through April 2020 that addressed Kyn metabolites and psychoneurological symptoms, with 509 duplicates. After an initial preliminary review, we excluded 272 studies for not meeting the inclusion criteria. Finally, we reviewed 10 studies in detail and included them in this systematic review and quality synthesis (see Figure 2).

Characteristics of Clinical Studies and Quality of Evidence

Table 1 summarizes study characteristics and findings. Across the 10 articles, sample sizes ranged from 17 to 244. Studies addressed a large variety of cancer types: breast cancers, lung cancers, pancreatic adenocarcinomas, metastatic renal cell carcinomas, melanomas, lymphomas, gastrointestinal tumors, hematological malignancies, and gynecological neoplasms. Assessments took place prior to surgery, during interferon- α (IFN- α) therapy, during chemotherapy, and after completing major treatments. Researchers quantified all metabolites from peripheral blood. The majority of the studies included a measure of depression ($n = 7$), but studies also looked at fatigue ($n = 5$), anxiety ($n = 5$), pain ($n = 1$), and cognitive disturbance ($n = 1$). We rated three of the studies (Fosså et al., 2020; Hüfner et al., 2015; Kurz et al., 2012) as high quality and the remaining seven as intermediate quality (Bannink et al., 2007; Botwinick et al., 2014; Capuron et al., 2003; Lyon et al., 2018; Pertl et al., 2013; Schroecksnadel et al., 2007; Van Gool et al., 2008). Details of the quality assessment of the included studies are presented in Table 2.

Association Between Metabolites and Psychoneurological Symptoms

Discrepancies exist between the studies regarding the correlation between psychoneurological symptoms and Kyn pathway metabolites. Evidence from eight studies showed that decreased Trp levels and increased values for Kyn, Trp/Kyn and KYNA/Trp ratios in parallel with immune activation with

increased CRP and neopterin are correlated with certain psychoneurological symptoms among cancer survivors (Botwinick et al., 2014; Capuron et al., 2003; Fosså et al., 2020; Hüfner et al., 2015; Kurz et al., 2012; Lyon et al., 2018; Pertl et al., 2013; Schroecksnadel et al., 2007).

Among the five studies addressing fatigue and cancer, three found a significant correlation between Kyn pathway metabolites and fatigue (Fosså et al., 2020; Kurz et al., 2012; Schroecksnadel et al., 2007). Decreased Trp levels and increased Kyn/Trp ratios, CRP levels, and neopterin levels were correlated with more-severe fatigue. Two other studies did not find a correlation (Lyon et al., 2018; Pertl et al., 2013).

Among the seven studies addressing depression and anxiety, four found a significant correlation between Kyn pathway metabolites and depression or anxiety (Botwinick et al., 2014; Capuron et al., 2003; Hüfner et al., 2015; Pertl et al., 2013). Decreased Trp levels and KYNA/Trp ratios and increased Kyn/Trp ratios and neopterin levels were correlated with more-severe depression or anxiety. The remaining three studies did not find a significant correlation (Bannink et al., 2007; Lyon et al., 2018; Van Gool et al., 2008).

Finally, two studies found significant correlations between Kyn pathway metabolites and cognitive disturbance (Capuron et al., 2003) or pain (Lyon et al., 2018). Decreased Trp levels were associated with more-severe pain and cognitive disturbance.

Discussion

This systematic review is the first to explore Kyn metabolites and multiple psychoneurological symptoms among adult cancer survivors. The Kyn pathway may play a role in the development of psychoneurological symptoms among cancer survivors, but there are inconsistent findings regarding the exact relationships between metabolites and symptoms. Differences in cancer type and stage, cancer treatment, antidepressant drugs, age, gender, and study design might have played a role in these discrepancies. This review includes studies that measured metabolites and symptoms during different cancer treatments. Thus, we discuss the results separately by cancer-treatment status.

Prior to Tumor Surgery

Only one study found a negative correlation between the KYNA/Trp ratio and severity of depression and anxiety (Botwinick et al., 2014). In the study, which evaluated 17 cancer survivors with pancreatic adenocarcinoma prior to surgery, Researchers reported that tumor burden was positively correlated to Kyn level. These results indicate that pancreatic cancer may influence depression and anxiety through the Kyn pathway and that tumor burden can influence Kyn activity. Prior to surgery and cancer treatment, IDO activity and Trp catabolism play a critical role in tumor progression and immunobiology. Emerging evidence shows that IDO activity and Trp metabolism may suppress tumor immune surveillance and support tumor escape from the immune system (Hornyák et al.,

Table 1. Summary of Included Studies of Kynurenine Metabolites and Psychoneurological Symptoms.

Author, Location	Year	Study Purpose	Study Design	Sample Characteristics	Metabolites	Symptoms (Instruments)	Limitations	Strengths	Key Findings
Fosså et al. (2020), Norway		Evaluate possible changes in metabolites in cancer survivors with chronic fatigue; focused on amino acids, pathways related to inflammation, immune activation, and vitamin B6	Cross-sectional	<ul style="list-style-type: none"> N = 244 people with malignant lymphoma (167 had no chronic fatigue, 77 had chronic fatigue) Age: mean 55.5 years Sex: 62.7% male Treatment: prior treatment with high-dose therapy and autologous stem-cell transplantation 	<ul style="list-style-type: none"> Trp Kyn KYNA 3-HK XA 3-HAA QA Biomarkers related to vitamin B6 status Pic NA NAM Neopterin CRP 	<ul style="list-style-type: none"> Fatigue (fatigue questionnaire) Neuroticism (Eysenck Personality Questionnaire) Mental distress (HADS) 	<ul style="list-style-type: none"> Cohort heterogeneous in terms of lymphoma entities and medical complications after treatment Most survivors in remission at time of analysis; some biomarkers in normal range Did not control for influence of pharmacologic agents 	<ul style="list-style-type: none"> Large sample size Fasting blood draws All analyses done in males and females separately 	<ul style="list-style-type: none"> Decreased Trp, increased PAR index found in fatigued survivors Kyn/Trp ratio, neopterin higher in fatigued than nonfatigued survivors with borderline significance; the difference more prominent in males than females
Lyon et al. (2018), Mid-Atlantic region, US		Identify metabolites associated with changes in levels of psychoneurological symptoms after chemotherapy	Longitudinal (pre chemotherapy, 1–2 weeks post chemotherapy)	<ul style="list-style-type: none"> N = 19 women with early-stage breast cancer Age: mean 58.7 (SD 5.2) years Race: 68.4% White Treatment: chemotherapy 	<ul style="list-style-type: none"> Trp Kyn Serotonin 	<ul style="list-style-type: none"> Pain (BPI) Fatigue (BFI) Depression (HADS) 	<ul style="list-style-type: none"> Small sample size Unknown fasting status Did not control for confounders or influence of pharmacologic agents 	<ul style="list-style-type: none"> Longitudinal study 	<ul style="list-style-type: none"> Decreased Trp correlated with increased pain No correlations observed between targeted metabolites and fatigue or depression Higher Kyn and Kyn/Trp ratio post chemotherapy
Hüfner et al. (2015), Innsbruck, Austria		Investigate the complex pathophysiology behind the interaction of breast cancer and psychological distress	Cross-sectional	<ul style="list-style-type: none"> N = 154 (51 BCA⁺DPR⁻, 29 BCA⁺DPR⁺, 28 BCA⁻DPR⁻, 46 BCA⁻DPR⁺) Age: mean 45.7 (SD 0.8) years, mean 53.9 (SD 1.6) years, mean 42.9 (SD 2.1) years, mean 43.9 (SD 1.6) years, respectively Treatment: prior completion of primary cancer treatment 	<ul style="list-style-type: none"> Trp Kyn Neopterin Phenylalanine Tyrosine 	<ul style="list-style-type: none"> Depression (HADS for BCA⁺, HAM-D or BDI for BCA⁻) Anxiety (HADS for BCA⁺, STAI for BCA⁻) 	<ul style="list-style-type: none"> Nonfasting blood Used different psychometric assessment instruments to assess patients with BCA⁺ versus BCA⁻ 	<ul style="list-style-type: none"> Health control group Analysis controlled for age, BMI, smoking status, antidepressant 	<ul style="list-style-type: none"> In BCA⁺ patients Kyn/Trp ratio correlated with state anxiety and phenylalanine/tyrosine ratio correlated with depressive symptoms

(continued)

Table 1. (continued)

Author, Location	Year	Study Purpose	Study Design	Sample Characteristics	Metabolites	Symptoms (Instruments)	Limitations	Strengths	Key Findings
Botwinick et al. (2014), New York, US		Test the role of the kynurenine pathway in depression and tumor-induced immunosuppression	Cross-sectional	<ul style="list-style-type: none"> N = 17 people with pancreatic adenocarcinoma Age: mean 65 years Sex: 52.9% male Race: 100% White Treatment: prior to surgery 	<ul style="list-style-type: none"> Trp Kyn KYNA QA 	<ul style="list-style-type: none"> Depression (BDI) Anxiety (BAI) 	<ul style="list-style-type: none"> Small sample size Unknown fasting status Did not control for common confounders, age, sex 	<ul style="list-style-type: none"> Excluded patients with antidepressants Controlled for positive lymph nodes and maximal primary tumor diameter 	<ul style="list-style-type: none"> Negative correlations between KYNA/Trp ratio and depression and anxiety Positive correlation between tumor burden and Kyn level
Perli et al. (2013), Dublin, Ireland		Investigate the associations between fatigue and inflammatory cytokines and Trp metabolism in breast cancer patients	Longitudinal (pre chemotherapy, post cancer treatment, several months post treatment)	<ul style="list-style-type: none"> N = 61 women with breast cancer Age: mean 50.15 (SD 9.87) years Treatment: adjuvant or neoadjuvant chemotherapy 	<ul style="list-style-type: none"> Trp Kyn IL-6 IFN-γ TNF-α CRP 	<ul style="list-style-type: none"> Fatigue, (FACT-F) Depression (HADS) 	<ul style="list-style-type: none"> Small sample size Variation in time of day of blood collection Unknown fasting status Did not control for influence of pharmacologic agents 	<ul style="list-style-type: none"> Controlled for age and BMI 	<ul style="list-style-type: none"> No relationship between fatigue or depression and Trp, Kyn, or Kyn/Trp Higher CRP correlated with fatigue and depression pre chemotherapy Trp increased during cancer treatment Kyn levels significantly predicted changes in depression
Kurz et al. (2012), Innsbruck, Austria		Characterize the relationships between concentrations of immune-activation markers and QoL and fatigue	Cross-sectional	<ul style="list-style-type: none"> N = 50 people with lung cancer Age: median 65 years Sex: 74% male Treatment: chemotherapy (72%) 	<ul style="list-style-type: none"> Trp Kyn Neopterin CRP 	<ul style="list-style-type: none"> Fatigue (FACT-F) QoL (scale of 1–5) Anemia (FACT-Anemia) Coping strategy (Mental Adjustment to Cancer Scale) 	<ul style="list-style-type: none"> Unknown fasting status Population heterogeneous for type of lung cancer, stage of treatment, and treatment regimen No direct measure of enzymes, IDO, TDO 	<ul style="list-style-type: none"> Separate analysis for patients taking antidepressants Controlled for sex, age, tumor stage 	<ul style="list-style-type: none"> Higher CRP, neopterin, and Kyn/Trp ratio and lower hemoglobin levels associated with severe fatigue and impaired QoL Immune activation and Trp breakdown not related to coping strategies

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Table 1. (continued)

Author, Location	Year	Study Purpose	Study Design	Sample Characteristics	Metabolites	Symptoms (Instruments)	Limitations	Strengths	Key Findings
Van Gool et al. (2008), Rotterdam, Netherlands		Investigate the balance between neurotoxic and neuroprotective metabolites of Kyn in a subgroup of patients with metastatic renal cell carcinoma	Longitudinal (pre standard IFN- α , and at 4 weeks, 8 weeks, and 6 months on standard IFN- α)	<ul style="list-style-type: none"> N = 24 people with metastatic renal cell carcinoma Age: mean 60.5 years Sex: 67% male Treatment: IFN-α 	<ul style="list-style-type: none"> Kyn Kyn QA 3-HAA 	<ul style="list-style-type: none"> Anxiety (SCL-90) Depression (SCL-90) Hostility (SCL-90) 	<ul style="list-style-type: none"> Small sample size Considerable attrition Variation in time of day of blood collection Peripheral measures of metabolites Did not control for other confounders 	<ul style="list-style-type: none"> Excluded patients currently on antidepressants Longitudinal study with repeated measurements 	<ul style="list-style-type: none"> No relationships observed between changes in depression and anxiety and metabolites of Kyn, with some exceptions Increased Kyn, decreased KYNA/Kyn and KYNA/3-HAA ratios during IFN-α
Bannink et al. (2007), Rotterdam, Netherlands		Investigate whether alterations in Trp metabolism occur during IFN- α treatment in oncology patients and whether these changes are associated with emerging psychiatric symptoms	Longitudinal (pre standard IFN- α , and at 4 weeks, 8 weeks, and 6 months on standard IFN- α)	<ul style="list-style-type: none"> N = 43 people with metastatic renal cell carcinoma or melanoma Age: median 58 years Sex: 58.1% male Treatment: IFN-α 	<ul style="list-style-type: none"> Trp Kyn Neopterin 5-HIAA Biopterin LNAA Phenylalanine 	<ul style="list-style-type: none"> Depression (MADRS) Anxiety (BAS) Hostility (SCL-90) 	<ul style="list-style-type: none"> Unknown fasting status Variation in time of day of blood collection KYNA and QA not measured; can't know impact of neurodegenerative component of the Kyn pathway Heterogeneous study population Did not control for main confounders 	<ul style="list-style-type: none"> Excluded patients on antidepressants and with depression at baseline Longitudinal study with repeated measurements 	<ul style="list-style-type: none"> Decreased Trp and increased neopterin, Phe/Tyr ratio, Kyn, Kyn/Trp ratio, and Kyn/LNAA ratio during IFN-α No correlations found between metabolites and depression and anxiety
Schroeksnadel et al. (2007), Innsbruck, Austria		Explore the relationships of QoL and fatigue with Trp metabolic changes and immune activation status among patients with various types of malignancy	Cross-sectional	<ul style="list-style-type: none"> N = 146 people with gastrointestinal tumor, hematological malignancy, gynecological neoplasm, lung cancer Age: mean 66.7 (SD 1.2) years Sex: 36.3% male Treatment: prior chemotherapy (30.1%) 	<ul style="list-style-type: none"> Trp Kyn Neopterin CRP Hemoglobin 	<ul style="list-style-type: none"> Fatigue (scale of 1–5) QoL (scale of 1–5) 	<ul style="list-style-type: none"> Unknown fasting status Did not control for influence of pharmacologic agents 	<ul style="list-style-type: none"> Controlled for tumor stage Blood collected in the morning 	<ul style="list-style-type: none"> Trp concentrations lower in people with progressive disease Decreased Trp concentrations related to decreased QoL and increased fatigue Increased Kyn/Trp ratio, neopterin, CRP, ESR-1, and ESR-2 related to increased fatigue

(continued)

Table 1. (continued)

Author, Location	Year	Study Purpose	Study Design	Sample Characteristics	Metabolites	Symptoms (Instruments)	Limitations	Strengths	Key Findings
Capuron et al. (2003), Atlanta, GA, US		Examine the relationships among TRP metabolism, immune cell activation, and development and treatment of depressive symptoms during IFN- α therapy	RCT (placebo or paroxetine)	<ul style="list-style-type: none"> N = 26 people with malignant melanoma (15 placebo, 11 paroxetine) Age: mean 53 (SD 10) years Sex: 53.8% male Treatment: IFN-α 	<ul style="list-style-type: none"> Trp Kyn Neopterin 	<ul style="list-style-type: none"> Depression (HAM-D) Anxiety (HAS) Cognitive (NRS) Neurovegetative and somatic symptoms (NRS) 	<ul style="list-style-type: none"> Small sample size Unknown fasting status 	<ul style="list-style-type: none"> Considered antidepressant influence Analysis in antidepressant-free patients increased depressive, anxious, and cognitive symptoms Controlled for age and sex 	<ul style="list-style-type: none"> In antidepressant-free patients, decreases in Trp correlated with increased depressive, anxious, and cognitive symptoms Patients who developed major depression had significantly greater increases in Kyn and neopterin and more prolonged decreases in Trp than nondepressed patients Higher Kyn, neopterin, and Kyn/Trp ratio during IFN-α therapy

Notes. 3-HAA = 3-hydroxyanthranilic acid; 3-HK = 3-hydroxykynurenine; 5-HIAA = 5-hydroxyindoleacetic acid; ANX +/- = patients with/without anxiety; BAI = Beck Anxiety Inventory; BAS = Brief Anxiety Scale; BCA +/- = patients with/without breast cancer; BDI = Beck Depression Inventory; BFI = Brief Fatigue Inventory; BMI = body mass index; BPI = Brief Pain Inventory; CRP = C-reactive protein; DPR +/- = patients with/without a diagnosis of depression; ESR = erythrocyte sedimentation rate; FACT-F = Functional Assessment of Cancer Therapy–Fatigue scale; HADS = Hospital Anxiety and Depression Scale; HAM-D = Hamilton Depression Rating Scale; HAS = Hamilton Anxiety Scale; IDO = indoleamine 2,3-dioxygenase 1; IFN = interferon; IL = interleukin; Kyn = kynurenine; KYNA = kynurenic acid; LNAA = large neutral amino acids; MADRS = Montgomery–Asberg Depression Rating Scale; NA = nicotinic acid; NAM = nicotinamide; NRS = Neurotoxicity Rating Scale; PAR index = pyridoxal + pyridoxal 5'-phosphate; Pic = picolinic acid; QA = quinolinic acid; QoL = quality of life; RCT = randomized controlled trial; SCL-90 = Symptom Check List–90; STAI = Spielberger et al. State–Trait Anxiety Inventory; TDO = tryptophan 2,3-dioxygenase; TNF = tumor necrosis factor; Trp = tryptophan; XA = xanthurenic acid.

Table 2. Quality Assessment of Reviews Studies.

Authors, Year	Selection of Study Population	Comparability of Results	Exposure or Outcome	Sample Size	Overall Score
Fosså et al. (2020)	4	1	3	2	10
Lyon et al. (2018)	3	0	3	1	7
Hüfner et al. (2015)	3	2	3	2	10
Botwinick et al. (2014)	4	1	3	1	9
Pertl et al. (2013)	4	1	2	2	9
Kurz et al. (2012)	4	2	3	1	10
Van Gool et al. (2008)	4	1	2	1	8
Bannink et al. (2007)	4	1	3	1	9
Schroeksnael et al. (2007)	4	1	2	2	9
Capuron et al. (2003)	3	2	3	1	9

Note. Scores for each quality-assessment category were defined as follows. Selection of study population: assessed based on representativeness of the sample, selection of non-exposed cohort, ascertainment of exposure, and demonstration that outcome was not present at start of study. Comparability of results: 0 = no adjustment for confounding factors or the use of psychotropic medications, 1 = adjustment for either the main confounding factors or the use of psychotropic medications, 2 = adjustment for both the main confounding factors and use of psychotropic medications. Exposure or outcome: For prospective cohort studies, outcome was assessed based on assessment of outcome, follow-up period adequate to capture outcomes, adequacy of follow-up of cohorts; for cross-sectional studies, exposure was assessed based on inclusion of a precise definition of outcome, assessment of outcome, and use of appropriate statistical tests. Sample size: 1 = 25–50, 2 = more than 50. Overall score: 0–4 = low quality, 5–9 = intermediate quality, 10–11 = high quality.

2018). Moreover, Kyn can bind the aryl hydrocarbon receptor and suppress CD8⁺ T cells and natural killer cells, which creates an immune-suppressive environment and enhances tumor immune escape (Heng et al., 2016). Given the critical role of IDO and Kyn catabolism in the proliferation of tumors, more studies are needed to investigate the relationship between Kyn metabolites and psychoneurological symptoms prior to surgery, especially studies that can control for the stage of cancer.

During Chemotherapy

Established evidence shows that a pro-inflammatory cytokine network can be activated in response to tissue damage during chemotherapy and lead to cancer-related psychoneurological symptoms (Bower & Lamkin, 2013; Kwekkeboom et al., 2018). Few studies have investigated the effect of chemotherapy on the Kyn pathway, and the results are inconclusive. Lyon et al. (2018) found increased Kyn levels and Kyn/Trp ratios after chemotherapy among 19 individuals with breast cancer. Decreased Trp levels were associated only with pain but not with other psychoneurological symptoms. However, Pertl et al. (2013) reported increased Trp levels and no significant changes in Kyn levels during chemotherapy among individuals with breast cancer. Kyn levels predicted significant changes in depression but not fatigue during chemotherapy. Additionally, Kurz et al. (2012) found significant correlations between the Kyn/Trp ratio with immune activation and fatigue among individuals with lung cancer. These differences in findings among studies may be due to different cancer types and chemotherapeutic agents. Nonetheless, some evidence does suggest that chemotherapy may influence depression, pain, and fatigue directly or indirectly through a Kyn pathway. More longitudinal studies are needed to follow individuals with different cancer tumor sites through chemotherapy to confirm the effect of

chemotherapy on Kyn pathways and the association with psychoneurological symptoms.

During IFN- α Therapy

IFN- α therapy has been widely used for people with hepatitis C (HCV) infection, metastatic renal cell carcinoma, and melanoma, with reported neuropsychiatric side effects (Franscina Pinto & Andrade, 2016; Van Gool et al., 2008). All the relevant studies in the present review showed significant changes in Trp and Kyn pathway metabolites during IFN- α therapy, such as decreased Trp levels, increased Kyn levels, increased neopterin levels, and increased Kyn/Trp ratios (Bannink et al., 2007; Capuron et al., 2003; Van Gool et al., 2008).

The influence of IFN- α therapy on the Kyn pathway is clear; nevertheless, findings are still inconclusive regarding whether changes in neuropsychiatric symptoms are related to Kyn pathway activation induced by IFN- α . Capuron et al. (2003) examined the relationships between Trp metabolism and depressive symptoms in a randomized controlled trial of 26 people with malignant melanoma during IFN- α therapy (15 participants received the placebo, and 11 participants received paroxetine). They found decreased Trp levels among participants who were antidepressant-free and had worse depressive, anxious, and cognitive symptoms, but Trp levels were not correlated with neurovegetative symptoms (e.g., fatigue, anorexia) or somatic symptoms (e.g., pain, gastrointestinal distress). Compared with the nondepressed participants, the participants who developed major depression had significantly greater increases in Kyn levels and neopterin levels and decreases in Trp levels.

In contrast, Bannink et al. (2007) conducted a longitudinal study of 43 cancer survivors with metastatic renal cell carcinoma or melanoma during IFN- α therapy and found no correlations between Kyn pathway metabolites and depression or anxiety. Similarly, Van Gool et al. (2008) found no evidence to support the idea that the balance of metabolites of the Kyn

pathway underlies the neuropsychiatric side effects of IFN- α in their study among 24 survivors with metastatic renal cell carcinoma. Even though established evidence shows that the activation of the Kyn pathway plays a critical role in depressive symptoms among people with HCV receiving IFN- α therapy (Murakami et al., 2016), its exact role in adult cancer survivors is uncertain. Large studies are needed in study populations of cancer survivors undergoing IFN- α therapy that are homogeneous by tumor type and large enough to allow subgroup analysis of those concurrently taking antidepressants.

Following Major Treatment

Among cancer survivors who finish major treatment, researchers have consistently observed that immune-mediated Trp degradation and Kyn metabolism are related to cancer-related fatigue, depression, and anxiety. Among a group of 154 breast cancer survivors, Hüfner et al. (2015) found increased neopterin levels and phenylalanine/tyrosine ratios in survivors with depression as well as increased Kyn/Trp ratios and neopterin levels in those with state anxiety. Their findings were consistent with those of Schroecksnadel et al. (2007), who found increased Kyn/Trp ratios and immune activation to be associated with increased fatigue among 146 cancer survivors and also found lower Trp levels among those with progressive disease. Recently, Fosså et al. (2020) evaluated changes in metabolites and fatigue among 244 cancer survivors. They found significantly decreased Trp levels in fatigued survivors. Kyn/Trp ratios and neopterin levels were higher in fatigued than in nonfatigued survivors with borderline significance, and the difference was more prominent in men survivors than in women survivors, a finding consistent with other studies showing that the Trp breakdown differs between men and women (Reinighaus et al., 2019). Future studies are needed to control for the effects of gender and cancer stage and to track the changes in Kyn pathway metabolites and symptoms among cancer survivors who have completed major cancer treatment.

Common Biomarkers of Psychoneurological Symptoms

Relationships between Kyn pathway metabolites and psychoneurological symptoms among cancer survivors were insufficiently clear and inconsistent across studies, especially for pain, sleep, and cognitive disturbance. Although the exact relationships between Kyn pathway metabolites and psychoneurological symptoms are uncertain at this point, researchers can use the list of biomarkers (Table 3) that were significant across studies as a base to guide future studies.

Some studies indicated that lower Trp levels were correlated with worse pain, fatigue, depression, anxiety, or cognitive function (Capuron et al., 2003; Fosså et al., 2020; Lyon et al., 2018; Schroecksnadel et al., 2007), while other studies did not find a significant correlation between Trp levels and symptoms. Likewise, while authors have tended to hypothesize that Trp depletion leads to immune response and depression, others have recently challenged this hypothesis (Dantzer, 2016)

Table 3. Kynurenine and Related Metabolites (Biomarkers) Associated With Psychoneurological Symptoms.

Metabolite	Pain	Fatigue	Depression	Anxiety	Cognitive Function
Trp	X ^a	X ^{b,c}	X ^d	X ^d	X ^d
Kyn			X ^{d,h}		
Kyn/Trp		X ^{b,c,g}		X ^f	
KYNA/Trp			X ^e	X ^e	
CRP		X ^{c,g,h}	X ^h		
IL-6		X ^h			
Neopterin		X ^{c,g}	X ^d		

Note. Metabolites in this table were associated with at least two psychoneurological symptoms in adult cancer survivors. CRP = C-reactive protein; IL = interleukin; Kyn = kynurenine; KYNA = kynurenic acid; Trp = tryptophan.

^aLower levels of Trp were related to higher levels of pain (Lyon et al., 2018);

^bLower Trp levels with higher Kyn/Trp ratio and neopterin levels were correlated with higher levels of fatigue (Fosså et al., 2020); ^cLower levels of Trp with higher Kyn/Trp ratio and levels of neopterin and CRP were correlated with higher levels of fatigue (Schroecksnadel et al., 2007); ^dDecreases in Trp level correlated with increased depressive, anxious, and cognitive symptoms, while higher levels of Kyn and neopterin and lower levels of Trp were correlated with the presence of depression (Capuron et al., 2003); ^eNegative correlations between Kyn/Trp ratio and depression and anxiety (Botwinick et al., 2014); ^fHigher Kyn/Trp ratio was correlated with higher state anxiety scores (Hüfner et al., 2015); ^gHigher CRP and neopterin levels and Kyn/Trp ratio were correlated with higher levels of fatigue (Kurz et al., 2012); ^hHigher Kyn levels were correlated with higher depression levels, and IL-6 levels covaried with fatigue (Pertl et al., 2013).

because administration of Kyn alone can lead to depressive-like symptoms without Trp depletion.

As with the findings for Trp levels, some studies found that higher values for Kyn, the Kyn/Trp ratio, CRP, and neopterin were associated with increased fatigue, depression, or anxiety, while other studies did not find significant correlations. Researchers commonly use the Kyn/Trp ratio as a proxy for IDO activity levels (Raison et al., 2010), and increased IDO activity is associated with chronic immune activation, which is the putative mechanism for psychoneurological symptoms (Savitz et al., 2015). The Kyn/Trp ratio predicts overall survival among people with cancer (Wang et al., 2018; Zhai et al., 2015) and mortality rate among people with acquired immune deficiency syndrome (Wang et al., 2019). Studies with findings of significant correlations between the Kyn pathway and fatigue or depression (Fosså et al., 2020; Kurz et al., 2012; Schroecksnadel et al., 2007) tended to include more people with advanced disease and higher inflammatory activity than studies without significant findings (Lyon et al., 2018; Pertl et al., 2013). Therefore, it will be important to consider cancer stage and assess inflammatory and immune activity in future studies.

Meanwhile, Hüfner et al. (2015) found a weak association between neopterin and the Kyn/Trp ratio. This evidence suggests that IDO activity induced by immune activation is not the only way to activate the Kyn pathway. Other factors, such as stress and glucocorticoid-activated TDO, may also influence the Kyn pathway and psychoneurological symptoms. Because people with cancer experience tremendous stress during cancer diagnosis and treatment, it would be informative to measure

stress and cortisol levels while assessing metabolites in future studies.

Most studies in this review were focused on Trp and Kyn levels and did not measure downstream KYNA and QA. Only two studies measured KYNA and QA and examined the imbalance of neuroprotective and neurodegenerative effects of the Kyn pathway. Given the evidence that lower levels of KYNA and higher levels of QA are routinely observed in people with depression (Ogyu et al., 2018) and Alzheimer's disease (Zwilling et al., 2011), future studies are needed to evaluate QA and KYNA levels along with Kyn, Trp, and neopterin levels among people with cancer.

Study Limitations

It is important to acknowledge several limitations we noted across these studies. First, most of the studies had small sample sizes, did not control for fasting status, and had variation in the time of day of blood collection. Even though it is hard to control fasting status, collecting blood at fixed times would reduce the influence of circadian rhythms. Second, some studies did not control for the influence of confounding factors, including age, sex, cancer stage, and pharmacologic agents. Notably, some antidepressants can modulate Trp and Kyn metabolism (Eskelund et al., 2017), and sex is associated with different types of changes in Kyn/Trp ratios and neopterin (Reininghaus et al., 2019). These sources of variability might have impacted our findings of associations between metabolites and psychoneurological symptoms. Therefore, future studies are needed that look at larger homogenous populations stratified by tumor type, cancer treatment, and possible immunological status while controlling for confounding factors (i.e., age, sex, cancer stage, pharmacologic agents). Longitudinal studies are also needed to assess metabolites and psychoneurological changes during and after chemotherapy, radiation therapy, immune therapy and after major treatments. Given the coexistence of multiple psychoneurological symptoms among people living with cancer, future research should evaluate the cluster of psychoneurological symptoms and their relationships with Kyn metabolites.

Conclusion

In this systematic review we summarized the Kyn pathway and identified common metabolites of the Kyn pathway associated with multiple psychoneurological symptoms among adult cancer survivors. Evidence from eight studies showed that decreased Trp levels and increased values for Kyn and the Trp/Kyn and KYNA/Trp ratios in parallel with immune activation with increased CRP and neopterin may be correlated with certain psychoneurological symptoms among cancer survivors, although discrepancies still exist between studies. Thus, while Kyn pathway activation could be associated with psychoneurological symptoms among cancer survivors, determining its exact etiological role in relation to these symptoms will require further research. Future researchers should include the

metabolites we identified through this review in symptom studies to expand our understanding of the biological mechanisms underlying psychoneurological symptoms among adult cancer survivors. These metabolites may also serve as biomarkers for future individualized and/or targeted interventions aimed at reversing the negative symptoms associated with high levels of distress and/or maladaptive biobehavioral effects among adult cancer survivors.

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