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REVIEW ARTICLE

Indoleamine 2,3-dioxygenase (IDO)-activity in Severe Psychiatric Disorders: A Systemic Review

Frederike T. Fellendorf[1], Nina Bonkat[1], Nina Dalkner[1,*], Elena M.D. Schönthaler[1], Mirko Manchia[2,3], Dietmar Fuchs[4] and Eva Z. Reininghaus[1]

[1]Department of Psychiatry and Psychotherapeutic Medicine, Medical University Graz, Graz, Austria; [2]Section of Psychiatry, Department of Medical Sciences and Public Health, University of Cagliari, Cagliari, Italy; [3]Department of Pharmacology, Dalhousie University, Halifax, Nova Scotia, Canada, [4]Institute of Biological Chemistry, Biocenter, Medical University of Innsbruck, Innsbruck, Austria

Abstract: ***Background*:** Indoleamine 2,3-dioxygenase (IDO) activity is induced by cellular immune activation and therefore associated with inflammatory diseases, among others psychiatric disorders. This review aims to elucidate IDO activity reflected by kynurenine (KYN) to tryptophan (TRP) ratio in severe mental disorders.

***Methods*:** A systematic literature search in MEDLINE and EMBASE was conducted targeting clinical trials in English language measuring KYN/TRP in individuals with a diagnosis of depression, bipolar disorder, or schizophrenia.

***Results*:** Five out of 15 studies found higher levels of KYN/TRP in depression compared to a control group while the same amount found no difference. Moreover, three studies showed lower levels. In bipolar disorder, four out of six, and in psychotic disorders, three out of four trials found higher levels in patients compared to controls. There are only two studies comparing KYN/TRP in major depression and bipolar disorder, showing conflicting results. Eight studies focused on associations between KYN/TRP and clinical parameters, whereas two studies found positive correlations between KYN/TRP and severity of depressive symptoms. In contrast, four studies did not show an association. IDO activity during specific psychiatric treatment was analyzed by eight studies.

***Conclusion*:** In summary, this review demonstrates an inconsistency in the findings of studies investigating KYN/TRP in severe mental disorders. Although there are hints that inflammation associated with TRP catabolism towards the KYN pathway *via* elevated IDO activity seems likely, no conclusive statements can be drawn. Presumably, the consideration of influencing factors such as inflammatory processes, metabolic activities and psychological/neuropsychiatric symptoms are pivotal for a deeper understanding of the underlying mechanisms.

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1. INTRODUCTION

Indoleamine 2,3-dioxygenase (IDO)-1 and 2 and tryptophan 2,3-dioxygenase (TDO) are the enzymes which catabolize tryptophan to kynurenine [1, 2]. Tryptophan is an essential amino acid relevant to protein synthesis and the precursor for various catabolites, as illustrated in Fig. (**1**) [3]. In the first metabolic route, tryptophan is converted to the neurotransmitters 5-hydroxytryptamine (5-HT, serotonin), N-acetylserotonin and further to melatonin.

The second path is the kynurenine axis, in which tryptophan is more likely converted into kynurenine under pro-inflammatory conditions [4]. The activity of TDO is substrate-regulated and, in the absence of glucocorticoids, relatively stable. In contrast, the activity of IDO is strongly induced in monocyte-derived cells by pro-inflammatory cytokines, mainly interferon (IFN)-γ, but also interleukin (IL)-2 and IL-6 and tumor necrosis factor (TNF)-α and is inhibited by anti-inflammatory cytokines such as IL-4 [5, 6]. Additionally, IDO activity is increased in overweight and obesity [7] and shifts with age in women [8]. The serum/plasma kynurenine to tryptophan ratio (KYN/TRP) has been established as a proxy for IDO activity [9].

Further, kynurenine is metabolized into several neuroactive compounds, most significantly kynurenine acid, 3-hydroxykynurenine, and quinolinic acid. These kynurenine catabolites are associated with psychosocial stress [10], and

*Address correspondence to this author at the Department of Psychiatry and Psychotherapeutic Medicine, Medical University Graz, Graz, Austria; E-mail: nina.dalkner@medunigraz.at

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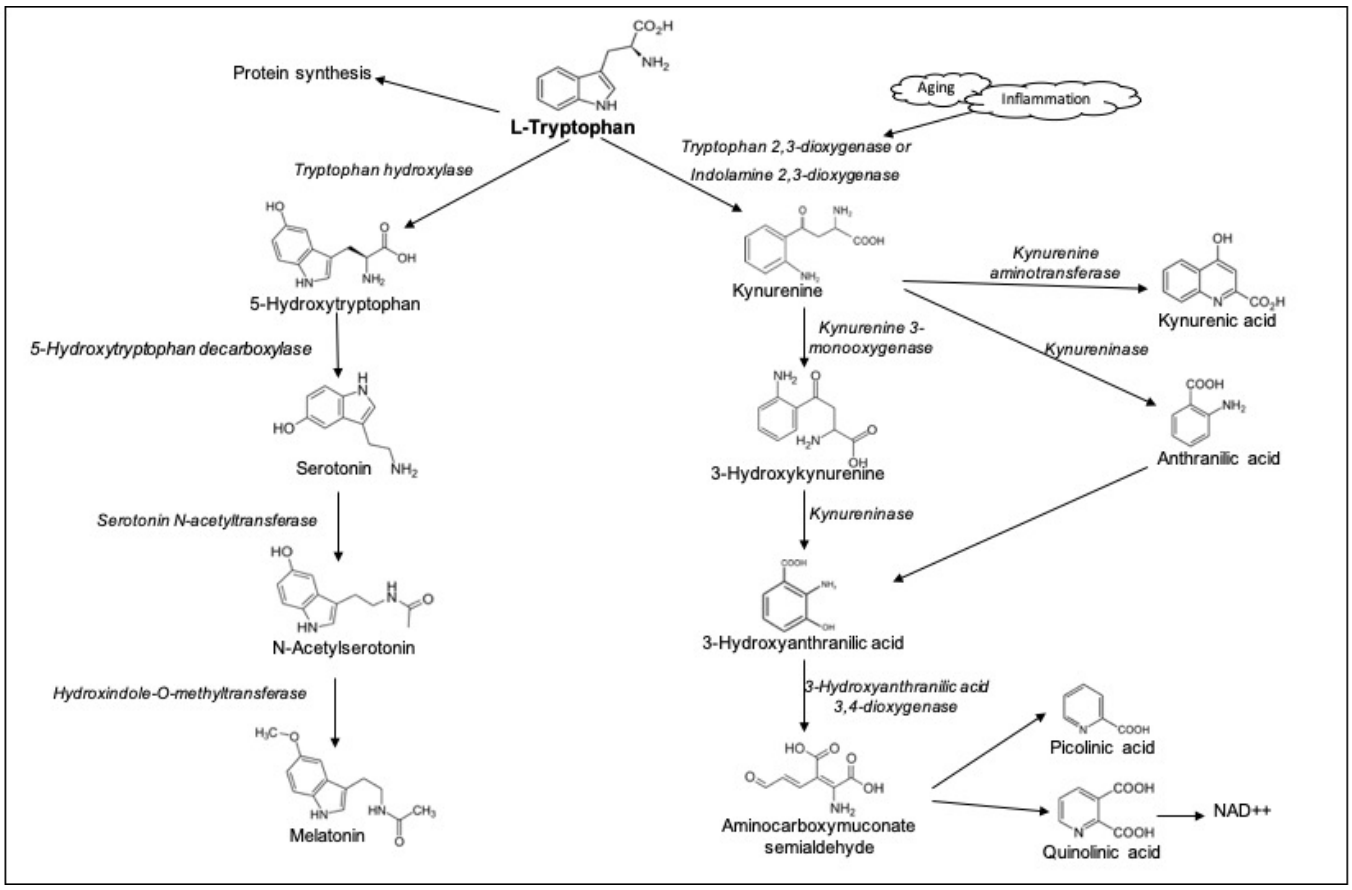

Fig. (1). Tryptophan catabolism.

cognitive dysfunction [11]. Consequently, the catabolites of kynurenine are involved in processes of neuropsychiatric disorders [12, 13] through their neurotoxic and neuroprotective features, but their exact etiological role is not yet fully explored [14].

An increased IDO activity has been found under conditions when the immune system is chronically over-activated, for example, in overweight and obesity [7], autoimmune disorders, chronic infectious diseases, malignancies [15], and cardiovascular disorders [16]. Additionally, relations between increased IDO activity and cognitive deficits in animals [17] and humans with Alzheimer's [18] were shown. Other neurodegenerative diseases such as Huntington's and Parkinson's showed alterations as well [19]. These immune-bio-chemical pathways are presumably also relevant to neuropsychiatric symptoms, including severe mood symptoms and cognitive deficits in particular such as those associated with chronic low-grade inflammation.

Severe mental illnesses (SMI) such as major depressive disorder (MDD), bipolar disorder (BD) and schizophrenia (SZ) have a high burden on affected persons, relatives, and the health system due to frequent chronic courses, which influence the quality of life and functional outcome. Next to psychopathology and psychosocial consequences (including decreased functioning due to amongst other cognitive impairment), psychiatric and somatic comorbidities lead to higher mortality compared to the general population [20]. Besides, a polygenetic predisposition, neurotransmitter imbalance, and the appearance of chronic and acute psychosocial stressors, inflammatory processes and immune system alterations are highly relevant in the etiopathogenesis of MDD [21], BD [22], and SZ [23]. Chronic low-grade inflammation with increased proinflammatory cytokines in acute illness episodes, but also in symptom-free periods, is found to be associated with MDD [24, 25], BD [25-27], and SZ [28, 29]. Additionally, as diagnosis and treatment considerations in psychiatry are often based on verbal anamneses and clinical symptomatology, a more objective method for measuring state and trait markers is highly desirable, and the analysis of biomarkers is particularly promising.

IDO activity might be involved in the etiopathogenesis and symptom presentation of SMI, although findings seem rare and inconsistent. In particular, the comparison of MDD, BD, and SZ and the association to psychiatric symptomatology are missing in reviews. Therefore, this review aims to elucidate IDO activity reflected by KYN/TRP and serum IDO in SMI by conducting systemic literature research.

2. MATERIALS AND METHODS

2.1. Systematic Search Strategy

We conducted a systematic search in November 2021 for peer-reviewed articles in the English language indexed in MEDLINE (*via* PubMed) and EMBASE without any tem-

poral restriction. The search keywords were "(tryptophan OR kynurenine OR IDO) AND (bipolar OR depressi* OR schizophrenia)" and targeted English language manuscripts only. Inclusion criteria were: 1) measuring IDO activity reflected by KYN/TRP levels (serum/plasma or cerebrospinal fluid (CSF)) in adult humans with a severe psychiatric disorder (MDD, BD; SZ) in comparison to a mentally healthy control group (HC) or another SMI or in psychiatric treatment 2) clinical trials (no case reports) and 3) published journal articles (no conference abstracts).

2.2. Data Management

The references found were downloaded from MEDLINE and EMBASE and inserted in the Rayyan web app [30]. This software consists of an online platform that facilitates the systematic review process by allowing to share the exclusion-inclusion decision of the potentially eligible studies among co-authors.

All findings were screened on title and abstract by the authors FF or NB initially, yielding 66 results. All publications possibly fulfilling eligibility criteria were retrieved as full manuscripts. The review and analysing of all full manuscripts were conducted by authors FF and NB.

3. RESULTS

We identified 3991 results in MEDLINE and 2344 results in EMBASE, with 1755 of them being duplicates. Of the remaining manuscripts, 33 records met the inclusion criteria and were further investigated.

The search found twelve publications about KYN/TRP reflecting IDO activity in MDD [31-42], six in BD [43-48], three in MDD and BD [49-51] and four in psychotic disorders [52-55] compared to an HC group. The details of the studies, including target group, sample size, and results, can be found in Table **1** for depressed cohorts, in Table **2** for individuals with BD, and in Table **3** for individuals with SZ and psychotic disorders. One study compared KYN/TRP in BD and MDD [56] and two additional studies analysed clinical associations in psychiatric cohorts [57, 58]. IDO activity during specific psychiatric treatment was investigated by nine studies [34, 42, 50, 59-64]. The results and discussions may be presented individually or combined in a single section with short and informative headings.

3.1. IDO in Major Depressive Disorder

Of the fifteen studies investigating cohorts with MDD and/or depressed BD, five found higher KNY/TRP levels [33, 39, 50] or serum IDO [34] in the patient group compared to HC, respectively higher levels in a suicidal subgroup [38]. Three studies found lower levels [35, 40, 51], whereas the study by Pompili *et al*. showed a higher TRP/KYN ratio in individuals with depression compared to HC, which indicates that the KYN/TRP ratio as well as the IDO activity was lower in depressed individuals [51]. Consequently, five studies found no differences between the groups [36, 37, 41, 42, 49]. Arteaga-Henriquez *et al*. showed increased levels only in a subgroup (Munich cohort); however, it should be noted that this cohort was less overweight, less medicated and more severely depressed, as measured with the Hamilton Depression Scale (HAMD) as a measure for depression severity [31] than the other cohort (Muenster cohort). Baranyi *et al*. observed a trend toward higher KYN/TRP in patients with MDD, which was not statistically significant, and further a positive correlation between tryptophan and kynurenine levels only in individuals with MDD. Interestingly, only tryptophan but not kynurenine differed between the MDD and HC group [32]. Maes *et al*. showed no significant difference in KYN/TRYP levels between MDD and HC, but elevated levels in the subgroup of individuals with somatization [37].

Both the publications by Quak *et al*. and Sorgdrager *et al*. used the study sample from the longitudinal cohort of the Netherlands Study of Depression and Anxiety and included therefore an overlapping cohort. Interestingly, they found different results concerning the KYN/TRP. Quak *et al*. focused more on associations to proinflammatory cytokines, and although an association between IL-6, as well as C-reactive protein (CRP), and depressive symptoms were found, this relation could statistically not be explained by KYN/TRP [40]. Sorgdrager *et al*. [41] investigated the relation between KYN/TRP and cortisol and found increased evening cortisol levels associated with decreased KYN/TRP, but only in recurrent depressive participants. In line with that, Zoga *et al*. showed statistically significant correlations of IDO with CRP, tumor necrosis factor (TNF)-α and TNF-γ [34].

3.2. IDO in Bipolar Disorder

Of the six studies investigating KYN/TRP in BD, four found higher levels in the BD group than in HC [43, 44, 47, 48] and two found no difference [45, 46]. Of note, our study group published pilot results in 2014 [47] and expanded the results with an enlarged sample size in 2021 [43]. In our studies, we focused on body mass index (BMI) and found higher KYN/TRP levels in overweight compared to normal weight persons.

Regarding inflammatory parameters, van den Ameele *et al*. found correlations of KYN/TRP with TNF- α only in the subgroup of patients during mania [45].

Even though Mukherjee *et al*. found no statistical difference between KYN/TRP ratio between BD and HC, the ratio correlated with the depression severity of the patients [46].

Poletti *et al*. found a negative correlation between the KYN/TRP ratio and the cortical thickness of several parietal and temporal brain regions, including the amygdala, the middle temporal gyrus, and the insula, in patients with BD [48].

3.3. IDO in Schizophrenia

Of the four trials studying IDO in psychotic disorders, three showed higher levels of KYN/TRP in patients with psychotic disorders diagnosed according to DSM-IV [52]

Table 1. Studies investigating kynurenine to tryptophan ratio in cohorts with depression in comparison to healthy controls.

Authors	Samples	Measured Variables	Results
Arteaga-Henriquez *et al*., 2021 [31]	Muenster cohort: 231 MDD, Munich cohort: 50 MDD, 206 HC	Serum KYN/TRP	• Munich MDD > HC, Muenster MDD (HC: $F(1,54)=7.94$, $p=.007$; Muenster: $F(1,228)=19.06$, $p<.001$) • Positive correlation between KYN/TRP and HAMD in MDD ($r=0.14$, $p=.029$)
Baranyi *et al*., 2017 [32]	71 MDD, 48 HC	Plasma KYN/TRP	• Statistical trend: MDD > HC (0.041±0.055 *vs* 0.038±0.011, $U=1338.0$, $p=.061$)
Chiu *et al*., 2021 [35]	33 first-episode drug-naïve MDD patient, 33 matched HC	KYN/TRP	• MDD < HC (0.02±0.01 *vs*. 0.03±0.02, $U=364.5$, $p=.02$)
Hestad *et al*., 2017 [36]	49 depressed, 31 controls with neurological symptoms	Serum and CSF KYN/TRP	• No group difference
Liu *et al*., 2018 [49]	33 depressed MDD, 20 depressed BD, 23 HC	Plasma KYN/TRP	• No difference between all three groups • Positive correlation between HAMD and KYN/TRP in MDD ($r=.12$ $p=.516$)
Maes *et al*., 2011 [37]	36 somatization, 36 MDD, 39 MDD+somatization 35 HC	Plasma KYN/TRP	• Somatization > MDD, MDD+somatization, HC (2.87±0.63 *vs* 2.62±0.64, 2.59±0.54, 2.44±0.51; $F=2.75$, $p=.04$)
Messaoud *et al*., 2019 [38]	73 MDD non-suicidal, 56 MDD suicidal, 40 HC	Plasma KYN/TRP	• Suicidal MDD > non-suicidal MDD ($F(2,165)=18.64$, $p<.001$), HC • Correlation with suicidal ideation ($r=0.33$, $p<.001$)
Myint el al., 2007 [39]	58 MDD, 189 HC	Plasma KYN/TRP	• MDD > HC (0.03±0.01, 0.02±0.01, $p=.036$)
Pompili *et al*., 2019 [51]	49 depressed (37 MDD, 12 BD), 78 HC	Plasma TRP/KYN #	• TRP/KYN: depressed > HC (18.4[16.1-20.7], 6.23[5.18-7.29], $t=10.5$, $p<.0001$); → TRP: depressed > HC; KYN: depressed < HC • no association to suicide attempt
Quak *et al*., 2014 [40]	1042 MDD, 1007 HC	Serum KYN/TRP	• MDD < HC ($31.1±9.1x10^3$ *vs*. $35.5±9.1x10^3$, $p=.015$)
Sorgdrager *et al*., 2017 [41]	1320 MDD, 406 HC (Overlapping cohort with Quak *et al*.)	Serum KYN/TRP	• No group difference
Umehara *et al*., 2017 [42]	33 medication-naïve MDD, 33 HC	Plasma KYN/TRP	• No group difference
Wu *et al*., 2018 [33]	170 late-life-MDD, 135 HC	Serum KYN/TRP	• MDD > HC (0.031±0.011 *vs*. 0.028±0.0054, $F=6.58$, $p=.011$)
Zhou *et al*., 2018 [50]	84 Depressed (MDD, BD), 60 HC	Serum KYN/TRP	• Depressed MDD/BD > HC ($F=19.33$, $p<.001$)
Zoga *et al*., 2014 [34]	40 female MDD, 40 female HC	Serum IDO	• MDD > HC (16.79±13.53 *vs*. 4.14±4.26; $p<.001$)

Abbreviations: BD=Bipolar disorder; CSF=Cerebrospinal fluid; HAMD=Hamilton Depression Scale; HC=Healthy controls; IDO=Indoleamine 2,3-dioxygenase; TRP=tryptophan, KYN/TRP=Kynurenine to tryptophan ratio; MDD=Major depressive disorder, # of note: tryptophan to kynurenine ratio.

Table 2. Studies investigating kynurenine to tryptophan ratio in cohorts with bipolar disorder in comparison to healthy controls.

Authors	Samples	Measured Variables	Results
Fellendorf *et al*., 2021 [43]	226 BD, 142 HC (overlapping cohort with Reininghaus *et al*., 2014)	Serum KYN/TRP; BMI	• BD > HC (F=19.17, p<.01) • Overweight > normal weight
Mukherjee *et al*., 2018 [46]	21 acute BD, 28 HC	KYN/TRP; Total sleep time	• No difference between BD and HC • KYN/TRP correlated with depressive severity (covariates BMI, sleep duration)
Poletti *et al*., 2019 [48]	55 depressed BD, 17 manic BD, 33 HC	Plasma KYN/TRP	BD > HC (depressed: 44.21±11.19, manic: 45.50±12.77 *vs*. 35.44±9.97; F=7.04, p<.001)
Reininghaus *et al*., 2014 [47]	78 euthymic BD, 156 HC	Serum KYN/TRP; BMI	BD > HC (52.80±12.89 *vs*. 45.23±11.26, F(1,202)=5.831 p<.025) • overweight > normal weight
Trepci *et al*., 2021 [44]	101 BD, 80 HC	CSF KYN/TRP	BD > HC (31.86 (23.0-39.8) *vs*. 22.2 (18.6-26.8), *p=.04)*
Van den Ameele *et al*., 2019 [45]	35 depressed BD, 32 (hypo)manic BD 35 HC	Plasma KYN/TRP	• No differences between the groups

Abbreviations: BD=Bipolar disorder; BMI=Body mass index; CSF=Cerebrospinal fluid; HC=Healthy controls; KYN/TRP=Kynurenine to tryptophan ratio.

Table 3. Studies investigating kynurenine to tryptophan ratio in cohorts with psychotic disorders in comparison to healthy controls.

Authors	Samples	Measured variables	Results
Barry *et al*., 2009 [52]	34 psychotic disorder, 36 HC	plasma KYN/TRP	• Psychotic patients > HC (0.06±0.003 *vs*. 0.05±0.002; t=2.02; p<.05)
Chiappelli *et al*., 2016 [55]	37 SZ, 38 HC	Plasma KYN/TRP	• SZ > HC (29.8±11.2 *vs*. 24.9±5.3; F(1,73)=5.85, p=.018)
Kindler *et al*., 2020 [54]	96 SZ 81 HC	Plasma KYN/TRP	SZ > HC (F(1,175)=5.1, p=.025)
Okamoto *et al*., 2021 [53]	30 SZ, 10 HC	Serum KYN/TRP	• No group difference (0.03[0.02∼0.06], 0.03[0.02∼0.05]; p=.93)

Abbreviations: HC=Healthy controls; KYN/TRP=Kynurenine to tryptophan ratio; SZ=Schizophrenia.

and in patients with SZ [54, 55] compared to HC. Another study found no significant difference between the groups [53].

Kindler *et al*. demonstrated a correlation between KYN/TRP and CRP, as well as IL-1ß mRNA only in individuals with SZ. Furthermore, they divided the patient group into a cohort with participants showing high proinflammatory cytokines (authors found IL-18, IL-1ß, IL-6 and IL-8 to be of interest) and a cohort without high proinflammatory cytokines. Significantly higher KYN/TRP has been seen in patients with SZ showing high cytokine levels [54]. Additionally, Okamoto *et al*. observed a significant correlation between KYN/TRP and TNF-α in individuals with SZ [53]. Concerning brain structure, Chiappelli *et al*. found an inverse relation between KYN/TRP and frontal white matter glutamate levels measured by diffusion tensor imaging [55]. Kindler *et al*. showed a negative correlation between KYN/TRP and the rostral middle frontal gyrus volume, as well as the cognitive performance subdomain attention [54].

3.4. Differences of IDO in Severe Mental Disorders

Differences in KYN/TRP levels between SMI were investigated by two studies. Comai *et al*. compared 100 patients with MDD to 66 BD patients and found higher levels of KYN/TRP in BD. Additionally, only in BD KYN/TRP was associated with diverse inflammatory markers (positively: IL-1ß, TNF-a, negatively: IL-2; IL-9) and to lower white matter microstructure of the inferior fronto-occipital fasciculus [56]. In contrast, Liu *et al*. included depressed MDD and BD individuals as well and did not observe a significant difference in KYN/TRP between the groups [49].

3.5. IDO and Clinical Symptomatology

3.5.1. IDO and Depressive Clinical Symptomatology

Eight Studies focused on associations of KNY/TRP and clinical parameters. Two studies found positive correlations between KYN/TRP and severity of depressive symptoms measured with the HAMD [31, 49]. In contrast, four studies observed no association between KYN/TRP and depressive symptomatology [33, 34, 36, 49]. Additionally, Hüfner *et al*. assessed the blood levels of ten depressed individuals on two study days, once with higher Montgomery Asberg Depression Rating Scale (MADRS) scores and once with lower MADRS scores and found a negative correlation between MADRS and KYN/TRP in the lower score range (r=.38, p=.016) [57]. Maes *et al*. showed a positive correlation between KYN/TRP and somatization severity but not with depressive symptomatology [37]. Interestingly, Wu *et al*. found an increased KYN/TRP only in MDD with late and not with early onset depression [33].

3.5.2. IDO and Suicidal Symptomatology

Messaoud *et al*. stated in one study [38], and confirmed it with a partly overlapping sample [58], that individuals with MDD who have currently suicidal ideations, exhibit higher KYN/TRP than non-suicidal ones. Additionally, KYN/TRP correlated with suicidal ideation, and additionally with a proinflammatory index (including IL-1, IL-6, IL-12, IL-20 and cortisol. In contrast, Pompili *et al*. observed no effect of KYN/TRP on suicidal history [51].

3.5.3. IDO and Bipolar Clinical Symptomatology

In BD, one trial found an association between IDO and depressive symptom severity (measured with HAMD) controlling for sleep duration and BMI [46], whereas another study found no association [45]. Accordingly, another study revealed no alterations in IDO over time, and no correlations with illness episodes were demonstrated [43].

3.5.4. IDO and Psychotic Clinical Symptomatology

Barry *et al*. showed an association between KYN/TRP and illness duration in a psychotic subgroup (r=.36, p=.04), but no relations to other clinical parameters measured with the Scale for Assessment of Positive Symptoms (SAPS), the Scale for Assessment for Negative Symptoms (SANS), and the Calgary Depression Scale for Schizophrenia (CDSS) were found [52].

3.6. IDO During Treatment

Umehara *et al*. studied ten initially drug naïve individuals with MDD at baseline and after eight weeks of monotherapy of antidepressive medication and found no significant change in KYN/TRP due to treatment [42]. In contrast, Zoga *et al*. showed a significant decrease in IDO from baseline (one week without medication) after six weeks of treatment with either antidepressant drugs or electroconvulsive therapy (ECT) [34]. In line with that, Reininghaus *et al*. observed a significant decrease in KYN/TRP within a six-week psychiatric rehabilitation program, but only in individuals with MDD who showed a significant treatment response and not in non-responders [60]. In further investigations, the same study group found sex specificities in a partly overlapping sample, with an increase in KYN/TRP only in men over time [64].

Two trials investigated KYN/TRP levels during times of treatment with ketamine. Kadriu *et al*. found lower IDO levels 230 minutes, one day and three days after single ketamine injection, compared to a baseline measurement, in 39 individuals with treatment resistant bipolar depression [59]. Zhou *et al*. administered six ketamine infusions over twelve days to 84 unipolar and bipolar depressed individuals and found neither KYN/TRP alterations over time nor changes in dependency of treatment response [50].

Guloksuz *et al*. analysed kynurenine catabolites in patients with either MDD or BD who received a six-week ECT twice a week because of a depressive episode and found an increase in KYN/TRP and a negative correlation with the HAMD score at the end compared to baseline [61].

Two studies investigated repetitive transcranial magnetic stimulation (rTMS) in patients with treatment resistant depression. Tateishi *et al*. found an improvement in depressive symptomatology but no change in KNY/TRP in 13 subjects receiving 30 rTMS stimulations over a six-week period, while TRP levels significantly increased [63]. Leblhuber *et al*. showed a trend towards a decrease in KYN/TRP in 21 participants who received ten rTMS treatments associated with a significant reduction in depressive symptomatology. However, these alterations were not found in a control group of 17 participants receiving sham stimulation [62].

4. DISCUSSION

The aim of this systemic literature review in two databases was to elucidate the IDO activity reflected by KYN/TRP in SMI and its association to clinical parameters in individuals with MDD, BD and SZ. Importantly, many studies observed changes in KYN/TRP in individuals with SMI and associations with clinical characteristics such as depressive symptoms, somatization, suicidality, and cognitive performance [37, 38, 54, 57]. Nevertheless, looking at all results as a whole, the conclusion of inconsistency in findings can be drawn.

Most of the found studies investigated KYN/TRP in MDD or currently depressed patients with BD. However, only five out of 15 studies found higher levels of KYN/TRP in these patient groups compared to HC and the same amount of studies found no significant difference between patients and HC. In contrast, three studies showed lower levels of KYN/TRP. In BD, four out of six trials revealed higher levels of KYN/TRP in patients than in HC and only two studies observed no difference between groups. In psychotic disorders, three out of four studies found higher levels of KYN/TRP and only one study found no significant difference between patients and HC. However, it is important to point out that the number of existing studies is quite small. There are only two studies comparing MDD and BD in KYN/TRP levels, showing conflicting results

with either higher levels in BD than in MDD [56] or no difference between groups [49]. Marx and colleagues conducted a meta-analysis on tryptophan catabolites and also highlighted the shift in tryptophan metabolism from serotonin to the kynurenine pathway in SMI [65]. They demonstrated that tryptophan and kynurenine were decreased across MDD, BD and SZ, however, there were cross-diagnostic differences: Kynurenic acid and the kynurenic acid to quinolinic acid ratio were decreased in affective disorders (*i.e.*, MDD and BD), whereas kynurenic acid was not altered in SZ; kynurenic acid to 3-hydroxykynurenine ratio was decreased in MDD but not SZ. Kynurenic acid to kynurenine ratio was decreased in MDD and SZ, and the KYN/TRP was increased in MDD and SZ [65]. Further, it was shown that quinolinic acid was associated with cognitive deficits in SZ but not MDD [66]. With regards to our results, it might be concluded that a different pattern between affective disorders and psychotic disorders exists. This conclusion is corroborated by recent studies revealing cross-diagnostic differences in the clinical correlates of kynurenine metabolites [56, 65, 66].

Presumably, factors influencing both IDO activity and SMI play a significant role in their interaction. For instance, sex [67] and age [68] were shown to have an impact on IDO activity. Furthermore, most of the study findings lead to the assumption that the tryptophan metabolism towards the kynurenine breakdown is associated with a pro-inflammatory state [34, 53, 54]. However, it is possible that this inflammation triggered alteration of IDO activity is influenced by the psychiatric state, as revealed in the study by van den Ameele *et al*. (2019), which found associations between KYN/TRP and inflammatory markers only in manic BD patients [45]. Furthermore, the results of four studies indicate that BMI impacts IDO activity [31, 43, 46, 47]. However, BMI has not been included as a co-variable in most of the existing studies. Additionally, psychiatric and psychological aspects such as somatization [37], relapses/recurrent depressive episodes [41], late onset of depression [33], suicidality [38, 58], or illness duration [52] can have an effect on IDO activity. Some of the studies refer to an influencing effect of psychotropics, but in most of the studies, the sample size was too small to further analyze these effects.

Furthermore, no sufficient conclusion can be drawn concerning differences between peripheral blood samples and CSF, as only one study measured KYN/TRP in CSF. Interestingly, the authors compared both serum and CSF data and did not report any relevant differences [44]. However, further catabolites such as kynurenic acid were increased only in CSF and not in peripheral plasma in individuals with BD and previous psychosis compared to HC, while the CSF kynurenic acid concentrations were unchanged in patients with BD with acute depression [69]. These results indicate the complexity of catabolism and its clinical associations. Of note, the availability of CSF is usually limited.

Accelerated breakdown of serum tryptophan to kynurenine may lead to reduced circulating tryptophan available for the production of serotonin. According to the monoamine-deficit hypothesis, a shortage of cerebral serotonin is involved in neuropsychiatric symptomatology of depression, mania, and psychosis [70, 71]. It can therefore be hypothesized that a more severe depressive symptomatology is associated with higher KYN/TRP and IDO activity. Nevertheless, in clinical cohorts, results are not that clear. In predominant depressive cohorts, some studies reported a positive correlation between KYN/TRP and depressive symptomatology [31, 49], one found a negative correlation between KYN/TRP and MADRS score, but only in the lower score range, while others did not find an association [33, 34, 36, 49]. In BD, one trial found an association between KYN/TRP with depressive severity when sleep duration and BMI were included as covariates [46], while another study showed no such association [45]. Additionally, there were no alterations over time and no correlation with illness episodes [43]. Two studies detected a positive correlation between suicidal ideation [38, 58] and KYN/TRP ratio, while another one did not find an association between suicidality and KYN/TRP [51]. Therefore, the findings are inconsistent regarding the clinical aspects of IDO activity.

Additionally, inconsistent results were found regarding the effect of treatment on KYN/TRP. In most studies, the KYN/TRP ratio decreased after various different treatments like antidepressant medication in general, ketamine injection, ECT, and rTMS [34, 59, 60, 72]. Some studies, however, did not detect any change after treatment, and one study even revealed an increase in the KYN/TRP ratio after a six-week ECT in patients [61]. One possible explanation for these varying results is that only effective treatment leads to a decrease in IDO activity. This was supported by a study by Reininghaus *et al*., who showed a significant reduction in the KYN/TRP ratio only in treatment responders compared to non-responders [60]. Effective treatment of mental disorders could lead to a decrease in proinflammatory markers, which could then affect the IDO activity [34, 73]. The participants in studies that showed no effect or an increase in IDO activity might not have been significant responders to the treatment. For example, the study by Zhou *et al*., which found no KYN/TRP alterations after ketamine infusions, also did not analyse the respective treatment response in the participants [50]. However, the study by Kadriu *et al*. contradicts this theory, as their participants were treatment resistant patients with BD, who showed a reduction in the IDO levels after ketamine injection [59]. In the study by Guloksuz *et al*., the authors hypothesized that the increase in KYN/TRP ratios in patients with MDD and BD after treatment with ECT resulted from a decrease in the further breakdown of KYN and not from an increased TRP degradation and therefore increased IDO activity [61]. These results show that it cannot be predicted how IDO activity and tryptophan breakdown are affected by treatment in patients with SMI. The effect might differ with the type of mental illness, the treatment received, and the response to the treatment.

Although findings are inconsistent, increased tryptophan catabolism along the kynurenine axis seems to be dependent

on an immune-mediated activation of IDO-1, at least under specific circumstances. Consequently, there might be a shift away from serotonin and melatonin. Both pathophysiological mechanisms might facilitate metabolic dysregulation. SMI is associated with higher rates of overweight and obesity than the general population, leading to metabolic and cardiovascular comorbidities, and overall increased mortality [74, 75]. These metabolic and cardiovascular diseases are also linked to immune- and inflammatory processes and oxidative stress. Some study results show that IDO activity in overweight participants negatively supports the association between SMI, overweight, and inflammation [31, 43, 46, 47]. Thus, future studies on this relationship should consider BMI and measures of obesity in their analyses. Recently, also the role of the gut-brain axis as a bi-directional system between the brain and gastrointestinal tract, linking emotional and cognitive centers of the brain, has been studied in this context [76]. Effects of nutrition and gut microbiome on tryptophan breakdown may have an influence on all these parameters but have not been explored to date.

Therefore, the normalization of inflammatory processes, *e.g*., tryptophan metabolism towards the kynurenine pathway, might positively impact symptomatology, cognitive impairment [77, 78], and comorbidities. Some studies investigated the effect of frequent psychopharmaceuticals on the degradation of tryptophan [79]. It was shown that escitalopram, but not venlafaxine treatment, was followed by a lower KYN/TRP [80]. Desipramine might impact IDO expression *via* IFN decrease [81]. It is suggested that lithium, as the most important mood-stabilizer in BD treatment, has anti-inflammatory properties [82] Furthermore, lithium and valproate were shown to have an antimanic effect *via* IDO inhibition in rats [83]. However, central processes and direct impact on tryptophan catabolism of known psychopharmaceutical have to be studied in the future. Additionally, other present drugs have an impact on tryptophan degradation., For example, studies showed a reduction in depressive symptomatology during an IFN- α therapy for cancer or hepatitis C was found through an effect of increased IDO [84, 85]. Furthermore, aspirine [86], Coenzyme Q10 [87] and glycyrrhizic acid [88] were shown to impact IDO activity. Potential targets for future pharmacological approaches might be cytokine syntheses or antagonism, inhibitory of cyclooxygenase and the inhibition of IDO [73, 79].

CONCLUSION

In summary, this review demonstrates an inconsistency of results in studies investigating KYN/TRP in SMI. Although there are hints that inflammation associated with tryptophan catabolism towards the kynurenine pathway *via* elevated IDO activity is connected to SMI, no conclusive statements can be drawn. Presumably, the consideration of influencing factors such as inflammatory processes, metabolic activities, and psychological/neuropsychiatric symptoms is pivotal for a deeper understanding of SMI. Therefore, future studies investigating IDO activity reflected by KYN/TRP in SMI should include clinical and metabolic factors in studying well-selected study cohorts with big sample sizes.

LIST OF ABBREVIATIONS

BD	=	Bipolar Disorder
BMI	=	Body Mass Index
HAMD	=	Hamilton Depression Scale
IDO	=	Indoleamine 2,3-Dioxygenase
KYN	=	Kynurenine
MDD	=	Major Depressive Disorder
SMI	=	Severe Mental Illnesses
TRP	=	Tryptophan

CONSENT FOR PUBLICATION

Not applicable.

STANDARDS OF REPORTING

PRISMA guidelines and methodology were followed.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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SUPPLEMENTARY MATERIAL

PRISMA checklist is available as supplementary material on the publisher's website along with the published article.

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